

BMJ Open

Assessing the Potential Return on Investment of the Proposed NHS Diabetes Prevention Programme in Different Population Subgroups: An Economic Evaluation

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| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2016-014953 |
| Article Type: | Research |
| Date Submitted by the Author: | 31-Oct-2016 |
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| Primary Subject Heading: | Health economics |
| Secondary Subject Heading: | Diabetes and endocrinology, Public health |
| Keywords: | PUBLIC HEALTH, DIABETES & ENDOCRINOLOGY, HEALTH ECONOMICS |
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3 Assessing the Potential Return on Investment of the Proposed NHS Diabetes Prevention Programme
4 in Different Population Subgroups: An Economic Evaluation
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Contributors

CT contributed to planning the project, carried out the model adaptation and wrote the manuscript. She is guarantor. SS contributed to planning the project, adapting the model and writing the manuscript. PB developed the model and revised the draft paper. HS contributed to the conceptual development of the model adaptation and revised the draft paper. MG provided specialist knowledge around model inputs and revised the draft paper. AB was principle investigator for the project and contributed to the analysis and manuscript.

Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that the only support for the submitted work was from the funders mentioned below. The authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years other than Public Health England and NHS England and no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval

Ethical approval was not needed for this study because the model is based on publicly available data and analysis of secondary data.

Funding

This abstract presents independent research commissioned and funded by Public Health England (PHE) with support from NHS England, Diabetes UK and the Department of Health. Model development was funded by the National Institute for Health Research (NIHR)'s School for Public Health Research (SPHR). The views expressed are those of the authors and not necessarily those of PHE, NHS England, Diabetes UK, the NIHR or the Department of Health.

Role of the Sponser

Public Health England commissioned the work with the following objective: 'To model the potential cost-effectiveness of the NHS DPP for different sub-groups of the population (for example by gender, BME groups, age profile, working age/retired, level of deprivation)'. PHE also specified the nature of the intervention including its expected cost, uptake and its proposed adherence to NICE guidelines. However, PHE did not have any influence over the findings of the analysis. The decision to submit the article for publication was made entirely independently of the funders.

Acknowledgements

We would like to thank the PHE steering group and stakeholders from the DPP demonstrator sites for advice about model parameters relating to the DPP intervention and useful outputs. Many thanks also to Maxine Johnson, Kelly Mackenzie, Tom Sanders and Elizabeth Goyder for their involvement in stakeholder workshops and advice about other aspects of the project. We are also extremely grateful to Pete Dodd and Mat Hall for their excellent quality assurance work with the SPHR Diabetes Prevention Model. Finally, this work could not have been carried out without the SPHR Diabetes Prevention Model, which was funded by the National Institute for Health Research's School for Public Health Research.

Transparency

The lead author (CT) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Patient Involvement

Patients were not involved in this study.

Data Sharing Agreement

Detailed results for each subgroup analysed in the model are available on request by email from the corresponding author.

ABSTRACT

Objectives

To evaluate the return on investment of the NHS Diabetes Prevention Programme (DPP) in England, and estimate which population subgroups are likely to benefit most in terms of cost-effectiveness, cost-savings and health benefits.

Design

Economic Analysis using the School for Public Health Research Diabetes Prevention Model

Setting

England 2015-16

Population

Adults aged 16 or over with high risk of type 2 diabetes (HbA1c 6-6.4%). Population subgroups defined by age, sex, ethnicity, socioeconomic deprivation, baseline BMI, baseline HbA1c and working status.

Interventions

The proposed NHS DPP: An intensive lifestyle intervention focussing on dietary advice, physical activity and weight loss. Comparator: No diabetes prevention intervention.

Main outcome measures

Incremental costs, savings and return on investment, quality adjusted life years (QALYs), diabetes cases, cardiovascular cases and net monetary benefit from an NHS perspective.

Results

Intervention costs will be recouped through NHS savings within 12 years, with net NHS saving of £1.28 over 20 years for each £1 invested. Per 100,000 DPP interventions given, 3,552 QALYs are

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3 gained. The DPP is most cost-effective and cost-saving in obese individuals, those with baseline
4 HbA1c 6.2-6.4% and those aged 40-74. QALY gains are lower in minority ethnic and low
5 socioeconomic status subgroups. Probabilistic sensitivity analysis suggests that there is 97%
6
7 probability that the DPP will be cost-effective within 20 years. NHS savings are highly sensitive to
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9 intervention cost, effectiveness and duration of effect.
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12 13 **Conclusions**

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16 The DPP is likely to be cost-effective and cost-saving under current assumptions. Prioritising obese
17 individuals will create the most value for money and obtain the greatest health benefits per individual
18 targeted. Low socioeconomic status or ethnic minority groups may gain fewer QALYs per
19 intervention, so targeting strategies should ensure the DPP does not contribute to widening health
20 inequalities. Further evidence is needed around the differential responsiveness of population
21 subgroups to the DPP.
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ARTICLE SUMMARY

Strengths and Limitations of this Study:

- Strength: The study uses the SPHR Diabetes Prevention Model, which synthesises a broad range of evidence from published data about type 2 diabetes risk factors and the complex disease progression pathways that lead from a diabetes diagnosis.
- Strength: The individual patient level model structure allows the heterogeneity present within the population to be modelled, enabling detailed subgroup analysis.
- Limitation: The analysis uses a comparator of “no NHS DPP intervention”, which does not fully represent the current situation where some localities do have programmes for high risk individuals. These were not modelled due to limited evidence and heterogeneity of intervention implementation between localities.
- Limitation: Data about the long-term effectiveness of lifestyle interventions and the differential response of population subgroups to such interventions is limited. Further research is required to inform these parameters.

INTRODUCTION

Type-2 diabetes is a major public health priority in the UK. Currently there are over 2.9 million people with diabetes in England¹. Diabetes is estimated to directly cost the NHS in England about £5.6 billion per year², of which most contributes to treating complications of the disease such as amputation, blindness, kidney failure and cardiovascular disease (CVD). To help tackle this problem, Public Health England (PHE), NHS England and Diabetes UK are together implementing the NHS Diabetes Prevention Programme (DPP)³. The NHS DPP consists of intensive lifestyle management programmes aimed at those at high risk of diabetes due to impaired glucose regulation (IGR), defined as HbA1c 6-6.4% (42-47 mmol/mol) or fasting plasma glucose of 5.5-6.9 mmol/l. It is expected that IGR individuals will be identified through a mixture of NHS Health Checks and opportunistic or targeted screening processes, and that 100,000 individuals will be referred to the DPP each year once the programme is running.

Previous economic evaluations indicate that lifestyle interventions such as that planned for the NHS DPP can be cost-effective^{4,5}. However, there is evidence that diabetes prevention interventions may be differentially effective in different population subgroups⁶⁻¹⁰, thereby potentially leading to differential cost-effectiveness. Given a limited number of available interventions, analysis of potential disparities in cost-effectiveness of the DPP between different subgroups is important not only to maximise potential health benefits and cost-savings, but also to ensure that health benefits are distributed in the population in a fair and equitable manner, which is an important consideration for public health interventions.

This study aims to (a) model the potential cost-effectiveness of the proposed NHS DPP in the English population using an adaptation of the National Institute for Health Research (NIHR) School for Public Health Research (SPHR) Diabetes Prevention Model¹¹, and (b) investigate in which subgroups, defined by age, gender, ethnicity, socioeconomic deprivation, baseline BMI, baseline HbA1c and working status the DPP is likely to have the most benefit in terms of cost-effectiveness, cost-savings and health benefits.

METHODS

Model Structure

The SPHR Diabetes Prevention Model was developed to forecast long-term health and health care costs under alternative scenarios for diabetes prevention. A detailed description of the methodology and assumptions used in the model can be found in the supplementary appendix.

The model is an individual patient simulation model based upon the evolution of personalised trajectories for metabolic factors including body mass index (BMI), systolic blood pressure (SBP), cholesterol and measures of blood glucose (including HbA1c)¹². The baseline population consists of a representative sample of the English population obtained from the Health Survey for England (HSE)¹³. HSE 2011 was chosen to inform the baseline population in the model due to its focus on diabetes and cardiovascular disease, meaning it incorporates information about relevant metabolic factors. Individuals aged below 16 were excluded from the analysis.

The model runs in annual cycles (see schematic in Figure S1 of the supplementary material). For each person, their BMI, cholesterol, SBP and HbA1c progress from year to year. Every year in the model, an individual may visit their GP or undergo a health check, and be diagnosed with and treated for hypertension, high cardiovascular risk, diabetes, microvascular complications of diabetes, cardiovascular disease (CVD), congestive heart failure, osteoarthritis, depression and breast or colon cancer, or may die. Utility of each individual in each year of the model is dependent upon their age, gender and medical conditions. Each condition is associated with a utility (health related quality of life) decrement and a healthcare cost. Model costs are at 2014/15 values. The model perspective is that of the NHS in England.

Intervention

The NHS DPP is an intensive lifestyle intervention focussing on dietary advice, physical activity and weight loss, aimed at individuals in England at high risk of diabetes. The model begins at the point where individuals eligible for the DPP (HbA1c 6-6.4%/42-47 mmol/mol; aged ≥ 16) have been

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3 identified and does not incorporate any local costs or utility change associated with identification or
4 referral. Table S1 of the supplementary material details baseline characteristics for the 1,492 high risk
5 individuals in the HSE 2011.
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10 An intervention uptake rate of 32% was assumed in consultation with Public Health England. It was
11 assumed that those who did not take up the intervention incurred no extra costs or benefits.
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14 Effectiveness evidence came from a recent PHE commissioned evidence review and meta-analysis of
15 pragmatic diabetes prevention interventions, carried out specifically to inform the likely effectiveness
16 of the NHS DPP⁶. PHE, NHS England and Diabetes UK have specified that in order to maximise
17 intervention effectiveness, they wish the commissioned DPP to fulfil 9-12 guidelines as recommended
18 in NICE guidance for diabetes prevention (PH38)¹⁴. NICE guidelines include using particular
19 strategies associated with increased effectiveness, specifying the minimum amount of contact time
20 and follow-up sessions, and delivering the programme through qualified practitioners. In line with
21 this, a mean weight loss of 3.24kg was assumed, taken from the meta-analysis of interventions
22 fulfilling 9-12 NICE guidelines⁶. Data about concomitant reduction in blood pressure, cholesterol and
23 HbA1c was not available from the PHE evidence review and so was linearly extrapolated from an
24 earlier review and meta-analysis¹⁵ (see Table S2 and supplementary methods for details).
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37 There is some evidence to indicate that effectiveness of lifestyle interventions to prevent type 2
38 diabetes differs between population subgroups, although study quality varies⁶⁻¹⁰. Stratification of
39 intervention effectiveness by baseline BMI was implemented into the model, again using data from
40 the PHE meta-analysis⁶. There was insufficient evidence around differential effectiveness for other
41 subgroups to incorporate into the model. In practice, some individuals who start the intervention will
42 not complete it. Most of the studies used to derive the estimate of effectiveness in the PHE meta-
43 analysis used intention to treat analysis, but two have not (personal communication from N. Ashra). It
44 is likely therefore that the effectiveness estimate used in the model only partially accounts for non-
45 completion and therefore may be higher than is realistic in practice. Sensitivity analysis was carried
46 out to account for this possibility. A linear rate of weight regain was assumed over five years in line
47 with the assumptions used to produce the NICE guidelines for diabetes prevention (PH38)¹⁶.
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3 The cost of the NHS DPP was determined through the DPP procurement process in 2016. As this was
4 still undergoing at the time of this analysis, the average cost from the PHE impact assessment of £270
5 per participant was used (personal communication from P. Zerdevas, PHE). This is the cost per person
6 starting the intervention and incorporates expected retention rates of participants. In the control
7 simulation, it was assumed that IGR individuals would not receive any intervention and would
8 therefore not incur any extra costs or changes to their metabolic trajectories.
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14 **Subgroups**

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19 Population subgroups were selected for analysis due to the potential influence of different
20 characteristics on diabetes risk and for equity implications. The following subgroups were chosen:
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- 23 • 4 Age groups (Age 16-40; Age 40-59; Age 60-74; Age \geq 75)
- 24 • 2 Gender groups (Male; Female)
- 25 • 2 Ethnicity groups (White; BME)
- 26 • 5 Deprivation groups (IMD quintiles 1-5)
- 27 • 3 Working status groups (Working; Retired; Other)
- 28 • 4 BMI groups (BMI $<$ 25 kg/m²; BMI 25-29.9 kg/m²; BMI 30-34.9 kg/m²; BMI \geq 35 kg/m²)
- 29 • 2 HbA1c groups (HbA1c 6-6.19%; HbA1c 6.2-6.49%)

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39 The analysis models a single year of NHS DPP intervention and all the downstream cost savings and
40 health benefits (including life years, QALYs, and reduction in diabetes and CVD cases) that this
41 produces over the subsequent 20 years. 1000 model runs were performed for each of the 1,492 HSE
42 2011 individuals in the deterministic analysis and model outcomes for each subgroup extracted from
43 the total results. All costs were discounted by 3.5% and QALYs by 1.5%, as per Department of Health
44 guidelines¹⁷.
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Sensitivity Analysis

Four deterministic one-way sensitivity analyses were performed to investigate the sensitivity of the results to a more conservative set of intervention parameters. The assumptions around intervention specification for each of these scenarios are shown in Table S2 of the supplementary materials.

1. Uniform intervention effectiveness (no stratification by BMI)
2. 25% lower mean effectiveness
3. Three year duration of intervention effect (instead of five years)
4. Higher intervention cost of £350 (instead of £270).

Probabilistic sensitivity analysis (PSA) was also carried out to describe the uncertainty in parameter inputs of the model and how this translates into uncertainty in the outcomes of the model. A suitable distribution was selected for each parameter, based upon its mean and standard error. Random sampling simultaneously across all input parameter distributions allowed parameter uncertainty to be quantified. 5000 different random samples of parameter values were selected, and each was applied to the 1,492 individuals in the simulation. A list of model parameters, their distribution for PSA and their source is provided in the supplementary appendix.

RESULTS

Population Results

Model results suggest that a year of DPP implementation in the English IGR population is likely to start saving money for the NHS from the first year of implementation, recoup intervention costs within 12 years (by the end of 2027/28) and be cost-effective compared with no DPP intervention (at a willingness to pay threshold of £20,000 per QALY gained) within 6 years (by the end of 2021/22) (Figure 1). For every 100,000 interventions given, the DPP is expected to prevent or delay 4,147 cases of diabetes and 413 cases of CVD (Table 1).

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3 The subdivision of NHS costs/savings by disease area is shown in Table 1. This indicates that most
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5 cost-savings arise due to reductions in the cost of treating diabetes or CVD, with high savings also
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7 accrued through a reduction in other primary care costs including GP visits and prescription of statins
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9 and anti-hypertensives. The timing of cost-savings varies depending upon disease area, with cost-
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11 savings in CVD care, diagnostics and other primary care accumulating in the short-term, whilst cost-
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13 savings in diabetes treatment, microvascular disease and other complications accumulate more slowly.
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15 This indicates that one year of the DPP implemented now is likely to continue saving money in the
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17 NHS for many years in the future despite a fairly transient (diminishing over five years) effect on
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19 metabolic risk factors, due to knock-on delays in progression to more complex diabetes (requiring
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21 insulin) and to expensive microvascular complications of diabetes.
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24 Return on investment is calculated by dividing total savings or monetised benefit (excluding
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26 intervention costs) by the cost of the intervention to work out the gain obtained for each £1 invested in
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28 the DPP. The model estimates that at 20 years following intervention implementation, for every £1
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30 invested in the DPP, £1.28 of NHS savings and £9.21 worth of total net monetary benefit (calculated
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32 using £60,000 as the value of a QALY) will be produced (Figure 1 and Table 1).
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34 35 36 37 38 **Subgroup Results**

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41 Across the subgroup dimensions examined, the biggest differentials in cost-effectiveness are seen in
42
43 the subgroups defined by baseline BMI (Figure 1). The NHS DPP is estimated to be most cost-
44
45 effective in individuals with BMI ≥ 35 kg/m² (12% of the eligible population). For this subgroup,
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47 NHS savings outweigh initial investment within five years and rise to a net value of £520 per person
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49 within 20 years (Figure 2). QALYs gained over 20 years are also highest (6,377 per 100,000
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51 individuals), and there are the largest reductions in diabetes and CVD cases (maximum reduction of
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53 diabetes cases = 5,484 at year 6, and maximum reduction of CVD cases = 846 at year 7 – see Figure
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55 S2 of the supplementary materials). The 20 year return on investment is estimated to be £2.93 per £1
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57 spent on intervention (Figure 1), and over £17 per £1 spent if monetised health benefits are included
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3 at £60,000 per QALY. The second most cost-saving group is those who have BMI 30-34 kg/m². In
4
5 contrast, the non-obese subgroups have substantially worse estimated return on investment, with the
6
7 BMI < 25 kg/m² subgroup not recouping intervention costs within the 20 year modelled period.
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10 Across the other dimensions for defining subgroups, IMD deprivation quintile makes a relatively
11
12 small difference to return on investment. Age makes a much larger difference with the middle age
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14 groups (40-59, and 60-74) showing better return on investment than the younger (<40) and older (≥
15
16 75) groups. Estimated return on investment is marginally better for females than males, marginally
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18 different between working, retired and other, and marginally better for a white versus BME subgroup.
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20 The other large subgroup difference is between those above or below 6.2% HbA1c at baseline, with
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22 the higher HbA1c subgroup showing a larger return on investment than the lower HbA1c subgroup.
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25 There are three subgroups to which net mean cost-savings do not accrue within the 20 years following
26
27 intervention implementation. These include the oldest age group (≥75), individuals who are normal
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29 weight or underweight (BMI <25) and individuals with HbA1c 6-6.19. Note that subgroup
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31 characteristics are not mutually exclusive, so although on average the intervention is not cost-saving
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33 in people of normal weight, it may be cost-saving in certain individuals with other characteristics
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35 which correlate with cost-savings, such as high HbA1c.
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38 In general, subgroups that obtain the highest cost-savings also obtain the highest QALY gains and are
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40 the most cost-effective, as cost savings relate to preventing disease progression. However, the DPP
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42 also reduces mortality of older individuals, resulting in higher QALYs than might otherwise be
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44 expected in subgroups containing higher numbers of older people. Equally subgroups containing
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46 younger individuals (including the BME group and the most socioeconomically deprived group) gain
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48 fewer incremental QALYs and life years; their disease and mortality risk is reduced due to their lower
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50 age so the NHS DPP is less effective, suggesting that the health benefits of the DPP may not be
51
52 equitably distributed (Figure 3).
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55 In all subgroups, numbers of incremental diabetes/CVD cases drop in the short-term whilst the
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57 intervention effect is operating and then rise again at the point when weight has been fully regained.
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3 This indicates that most cases of diabetes/CVD are likely to be delayed rather than prevented entirely
4 based upon current assumptions about long term effectiveness of the interventions.
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7 8 **Sensitivity Analyses** 9

10 The PSA estimation of mean incremental total cost savings per person is £131 and of mean
11 incremental QALYs is 0.0388 at 20 years following intervention implementation in England (Table
12 S3 of the supplementary materials). This is higher for both cost-savings and QALY gains than found
13 during deterministic analysis; the difference is due to non-linearity in the model, which is likely to be
14 particularly important around the BMI stratified estimation of intervention effect. The probability that
15 the NHS DPP will be cost-effective in 20 years compared with no DPP intervention, at a willingness
16 to pay threshold of £20,000 per QALY is 97% (see Figure 4), and the probability that the DPP will be
17 cost-saving for the NHS 20 years after intervention implementation is 70%. As in the deterministic
18 analysis, BMI is the most important criteria for determining cost-effectiveness, with the two highest
19 BMI subgroups being more cost-saving and cost-effective than other population subgroups (Table S3
20 of the supplementary materials and Figure 4).
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33 One-way sensitivity analysis indicates that under conservative scenarios of higher intervention cost
34 (£350 instead of £270), 25% lower intervention effectiveness or lower duration of intervention effect
35 (three year decline instead of five year) the NHS DPP would take longer than 20 years to recoup
36 initial intervention costs in the majority of subgroups (Table S4 of the supplementary materials). The
37 intervention is still likely to be cost-effective (at a threshold of £20,000 per QALY) within a 10 year
38 time horizon in all but the least cost-effective subgroups. Of these scenarios, reducing duration of
39 intervention effect has the most significant impact on outcomes, with only the BMI ≥ 35 subgroup
40 remaining cost-saving. However, in all three scenarios, the relative cost-effectiveness of subgroups
41 remains unchanged compared with the basecase analysis.
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53 If intervention effect is no longer stratified by BMI, the difference between subgroups of a particular
54 population characteristic is reduced compared with the base case scenario. Whilst for some subgroups,
55 such as those defined by BMI, a clear gradient is still apparent, for other groups such as those defined
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3 by IMD quintile or ethnicity the difference in outcomes is minimal, suggesting that stratification of
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5 intervention effectiveness by BMI is a key driver of differential cost-effectiveness in those groups in
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7 the base case analysis.
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DISCUSSION

The NHS DPP is highly likely to be cost-effective and cost-saving over the medium to long-term using current assumptions around intervention cost, effectiveness and duration of effect, and will start to save costs for the NHS from the first year of implementation, recouping the initial investment in the intervention by year 12. However, the number of potential individuals at high risk of type 2 diabetes in England (estimated to be about 5 million¹⁸) far exceeds the 100,000 interventions that NHS England plans to offer each year³. Prioritising obese individuals in particular (BMI \geq 30 kg/m²), plus those with the highest baseline HbA1c and focussing on those aged between 40 and 74 (the ages covered in any case by the NHS Health Check) is likely to create the most value for money in the programme by obtaining both the greatest cost-savings for the NHS and the highest health benefits per individual targeted.

This study does suggest that care may have to be taken when implementing the DPP to ensure that it does not lead to greater health inequalities in some groups at high risk of type 2 diabetes and its complications, including individuals from minority ethnic or socioeconomically deprived backgrounds. The analysis shows a tendency for the NHS DPP to provide fewer QALYs to these subgroups than to individuals from more socioeconomically advantaged or white ethnic backgrounds. Given that the model does not incorporate (nor is there any clear evidence for) differential effectiveness of the DPP by socioeconomic status or ethnicity, these differences are likely to occur for two main reasons. Firstly; disease risk is influenced by subgroup - for example, both ethnicity and socioeconomic status are parameters in the QRISK equations that are used in the model to determine CVD risk¹⁹. This means that even if a given individual reduces their metabolic risk factors through the DPP, they may still be at high risk of disease due to environmental or genetic factors outside the scope of the intervention. Secondly, subgroups differ in key personal characteristics associated with intervention efficacy – for example, mean age and baseline BMI are lower than average in the BME subgroup, and mean age is lower than average in the most socioeconomically deprived quintile. Low mean age and BMI confer lower mortality and disease risks, and therefore the NHS DPP will make less of a difference to risk reduction. Given that these subgroups also tend to suffer from low uptake

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3 of lifestyle interventions ^{20,21}, it is important that DPP providers make particular efforts to engage
4
5 individuals from these groups if exacerbation of health inequalities is to be avoided.
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8 A major strength of this analysis is the synthesis of a broad range of evidence using the SPHR
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10 Diabetes Prevention Model ¹¹. This is an individual patient simulation model that incorporates a large
11
12 amount of evidence from published data about type 2 diabetes risk factors and the complex disease
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14 progression pathways that lead from a diabetes diagnosis, and is able to represent the heterogeneity
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16 present within the English population and thereby model population subgroups. However, the model
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18 only takes healthcare costs into account, meaning that wider societal costs and benefits cannot be
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20 calculated, and even within healthcare does not incorporate diseases such as dementia that may impact
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22 upon long-term healthcare costs. A more important limitation is that the comparator of “no NHS DPP
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24 intervention” used for this analysis does not fully represent the current situation where some localities
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26 do have programmes for high risk individuals. These were not modelled due to limited evidence and
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28 heterogeneity of intervention implementation between localities. Subgroup analysis has also been
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30 limited by the relatively small number of IGR individuals in the HSE data, meaning that smaller
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32 subgroups (such as individual minority ethnic groups) or subgroup combinations, both of which
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34 would provide useful information for those implementing the DPP, cannot be accurately modelled.
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38 The study uses the most recent estimates of intervention effectiveness from a PHE evidence review
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40 designed specifically to inform the development of the DPP ⁶, and therefore is likely to provide a
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42 more accurate estimate of DPP cost-effectiveness than previous economic analyses of diabetes
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44 prevention interventions. However, data about the long-term effectiveness of lifestyle interventions
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46 and the differential response of population subgroups to such interventions is limited and represents
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48 the most important limitation of this study. Deterministic sensitivity analysis indicates that the cost-
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50 effectiveness of the DPP is substantially influenced by parameters such as intervention effectiveness
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52 and duration of intervention effect. Future research should therefore focus primarily on improving
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54 estimates of subgroup effectiveness, and gathering evidence about initial weight loss and weight
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56 regain rates due to the NHS DPP, which could be added to the model. The biggest challenges in
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58 performing good quality subgroup analysis are sufficiently powering the clinical studies to account for
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3 subgroups that may only comprise a small proportion of the population, and taking into account
4 potential interaction between personal characteristics that could lead to confounding across subgroups
5 in intervention uptake rates or effectiveness. Large scale analysis of the first year of DPP roll-out
6 using careful statistical design and long-term follow-up should enable these challenges to be
7 overcome successfully and provide high quality data for updating and improving the accuracy of
8 model predictions.
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For peer review only

Table 1: Mean cumulative incremental outcomes per person given the intervention in England. Costs and cost-ineffective returns are shown in red whereas savings and cost-effective returns are shown in black. Costs are discounted at 3.5% whereas QALYs are discounted at 1.5%.

| | Year 1 2016/17 | Year 2 2017/18 | Year 3 2018/19 | Year 4 2019/20 | Year 5 2020/21 | Year 10 2025/26 | Year 15 2030/31 | Year 20 2035/36 |
|---|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|--------------------|--------------------|
| TOTAL COSTS | £240 | £218 | £195 | £173 | £150 | £23 | -£43 | -£75 |
| DPP Costs | £270 | £270 | £270 | £270 | £270 | £270 | £270 | £270 |
| NHS Costs | -£30 | -£52 | -£75 | -£97 | -£120 | -£247 | -£313 | -£345 |
| <i>Diabetes Treatment</i> | -£1 | -£3 | -£6 | -£9 | -£17 | -£79 | -£106 | -£115 |
| <i>CVD Treatment</i> | -£11 | -£18 | -£25 | -£32 | -£37 | -£56 | -£65 | -£69 |
| <i>Microvascular Complications¹</i> | -£1 | -£3 | -£5 | -£7 | -£10 | -£27 | -£46 | -£60 |
| <i>Other Complications²</i> | -£2 | -£5 | -£8 | -£12 | -£15 | -£30 | -£40 | -£45 |
| <i>Diagnostics³</i> | -£4 | -£4 | -£5 | -£5 | -£4 | -£3 | -£2 | -£2 |
| <i>Other Primary Care⁴</i> | -£11 | -£19 | -£26 | -£32 | -£37 | -£52 | -£54 | -£54 |
| Life Years ⁵ | 6 | 41 | 130 | 281 | 486 | 1,795 | 2,838 | 3,487 |
| QALYs ⁵ | 50 | 133 | 269 | 457 | 686 | 1,986 | 2,966 | 3,552 |
| Diabetes Cases ⁵ | -1043 | -1995 | -3000 | -3788 | -4147 | -1812 | -766 | -654 |
| CVD Cases ⁵ | -183 | -273 | -344 | -396 | -413 | -394 | -325 | -282 |
| ICER (£/QALY) | £475,625 | £163,636 | £72,715 | £37,870 | £21,860 | £1,162 | -£1,446 | -£2,120 |
| Net Monetary Benefit ⁶ | -£209 | -£138 | -£34 | £101 | £262 | £1,169 | £1,822 | £2,207 |
| RoI: Total Savings ⁷ | £0.11 | £0.19 | £0.28 | £0.36 | £0.44 | £0.91 | £1.16 | £1.28 |
| RoI: NMB ⁷ | £0.22 | £0.49 | £0.87 | £1.37 | £1.97 | £5.33 | £7.75 | £9.17 |
| DPP Diabetes Prevention Programme; NHS National Health Service; QALY Quality Adjusted Life Year; CVD Cardiovascular Disease; ICER Incremental Cost-Effectiveness Ratio; RoI Return on Investment; NMB Net Monetary Benefit. | | | | | | | | |
| ¹ Includes costs of nephropathy, ulcer, amputation and retinopathy | | | | | | | | |
| ² Includes costs of osteoarthritis, depression, breast and colon cancer | | | | | | | | |
| ³ Diagnosis of diabetes, high CVD risk and hypertension | | | | | | | | |
| ⁴ Includes costs of GP visits and prescription of statins and anti-hypertensives | | | | | | | | |
| ⁵ Per 100,000 individuals given the DPP intervention | | | | | | | | |
| ⁶ Value of a QALY assumed to be £60,000 for net monetary benefit analysis ¹⁷ | | | | | | | | |
| ⁷ Return on Investment per £1 invested in the DPP | | | | | | | | |

Figure 1: Bar charts showing: A) the year that the NHS DPP becomes cost-saving (recoups intervention costs); B) the year that the NHS DPP becomes cost-effective; C) the total NHS return on investment within 20 years per £1 spent on the NHS DPP for each of the population subgroups. Vertical arrows indicate that the DPP is not cost-saving within the 20 year period modelled.

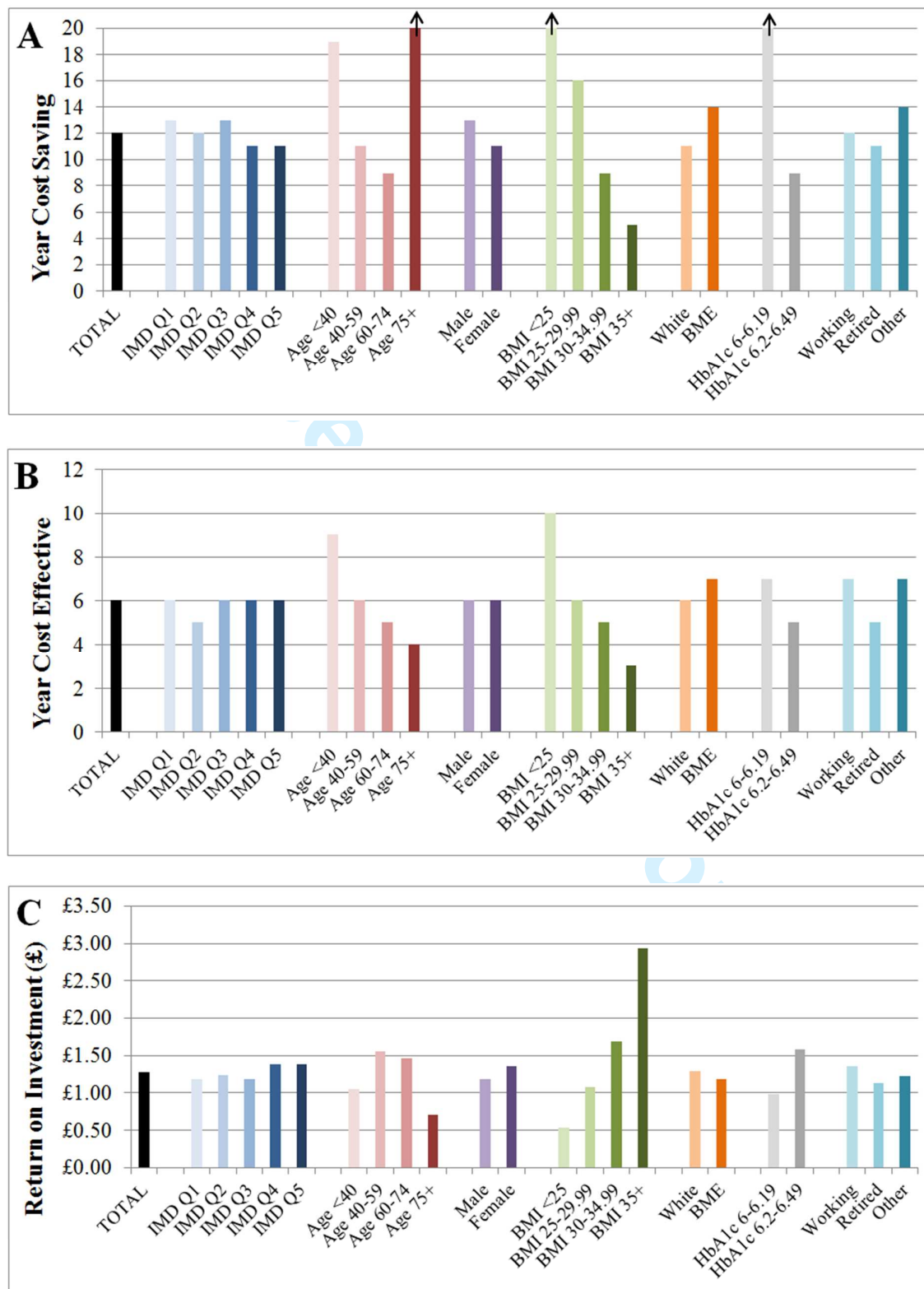
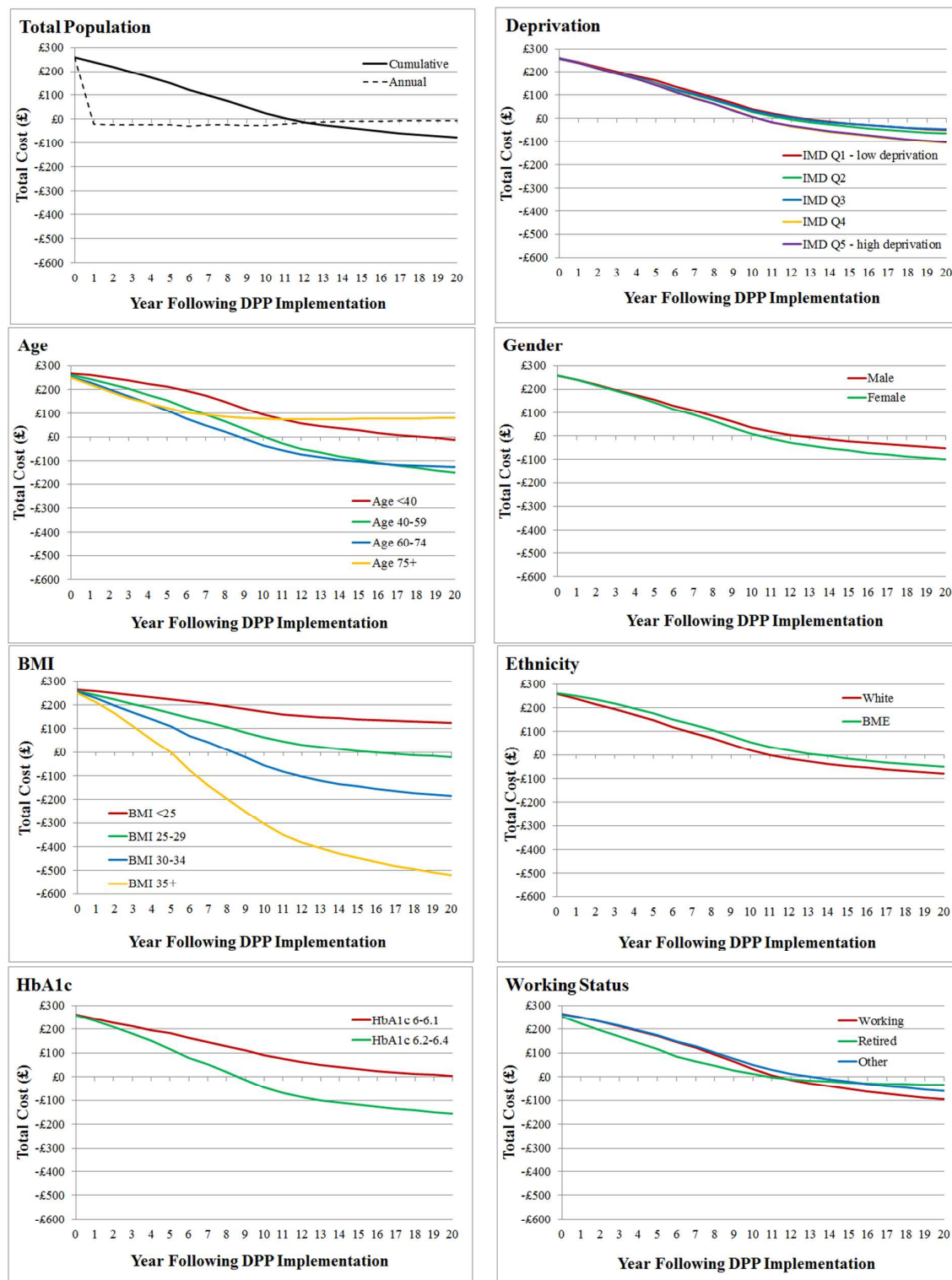


Figure 2: Graphs showing cumulative incremental (net) costs per person given the intervention over a 20 year time horizon for each subgroup and for the total population. Annual incremental costs per person are shown as a dotted line on the total population graph. Costs are discounted at 3.5%.



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Figure 3: Graphs showing: A) cumulative incremental QALY gain; B) incremental reduction in diabetes cases and C) incremental reduction in CVD cases per 100,000 individuals in different deprivation quintiles (i) and ethnic groups (ii)

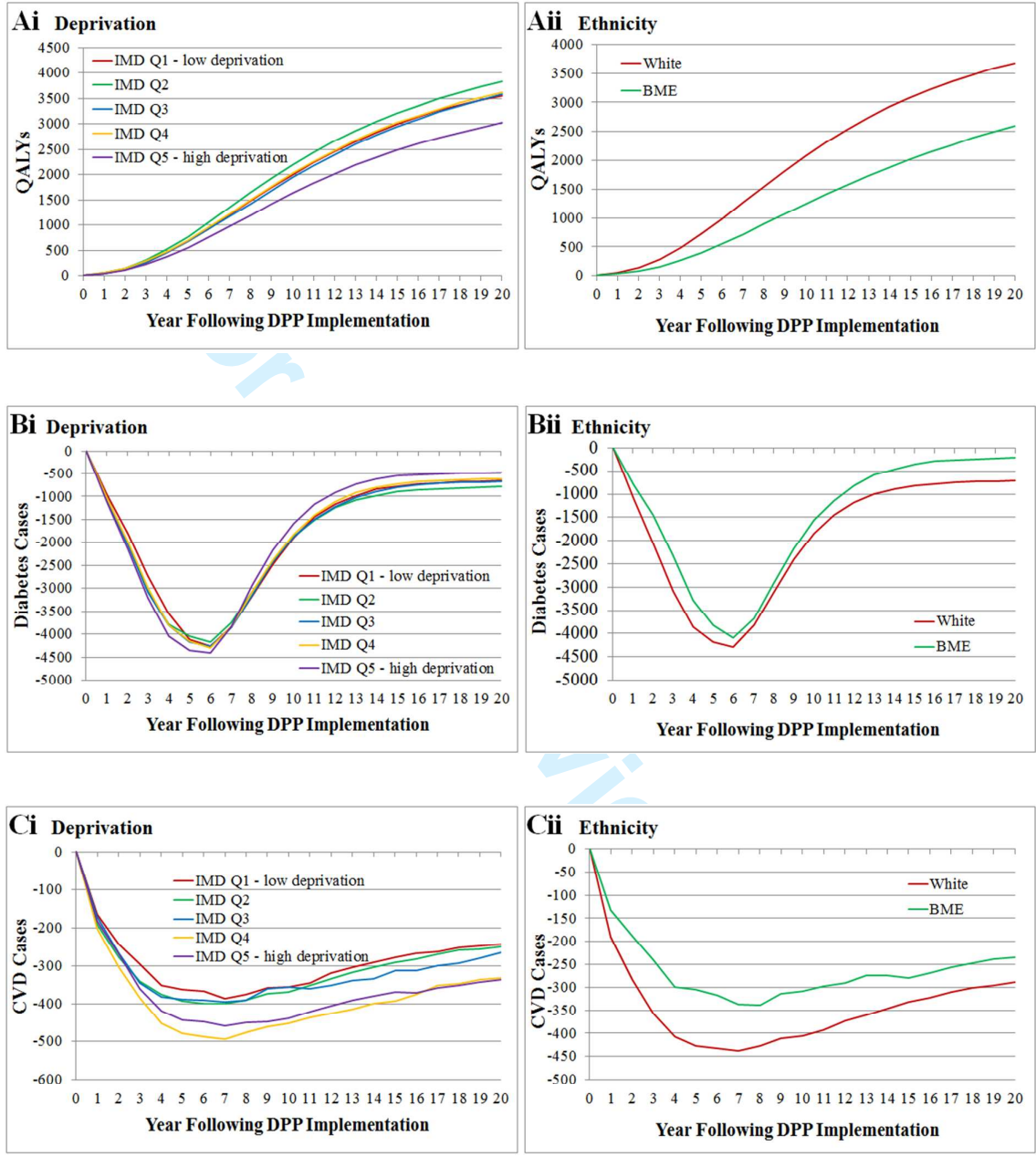
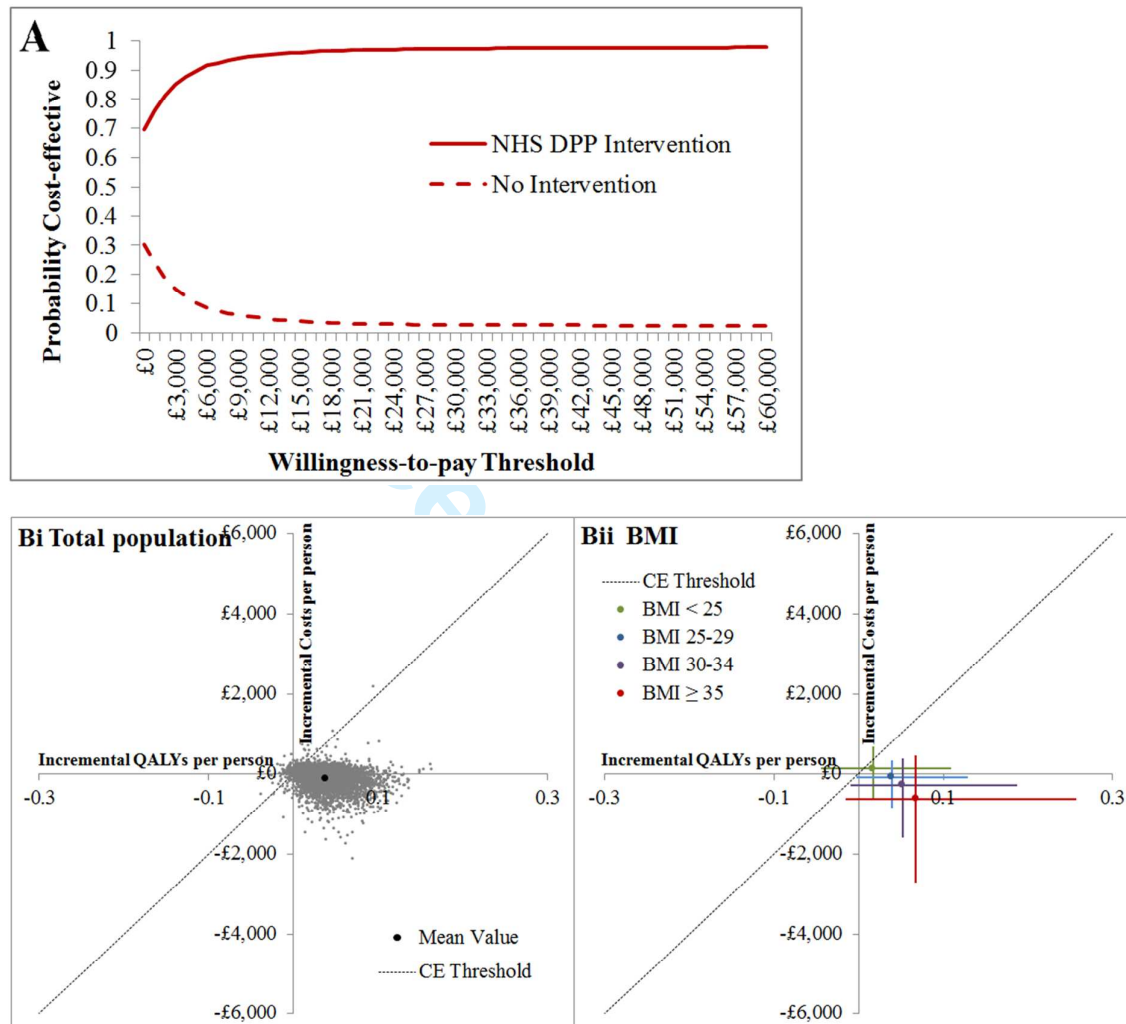


Figure 4: PSA Results. A) Cost-effectiveness acceptability curve showing the probability that the DPP or no intervention will be cost-effective over a range of different willingness to pay thresholds. B) Distribution of PSA results for i) the total population and ii) BMI subgroups on the cost-effectiveness plane. Error bars represent 95% confidence intervals for incremental total costs and incremental QALYs. The cost-effectiveness (CE) threshold is £20,000/QALY. Note that the size of the 95% confidence intervals and therefore the probability that the intervention will be cost-effective or cost-saving is partially related to the size of each subgroup within the total IGR population of England, in addition to being related to the distribution of results on the cost-effectiveness plane.



Reference List

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3 ONLINE ONLY SUPPLEMENTAL MATERIAL
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5 Full Title: Assessing the Potential Return on Investment of the Proposed NHS Diabetes
6 Prevention Programme in Different Population Subgroups: An Economic Evaluation
7

8 Running Title: Return on Investment of the NHS DPP
9

10 Chloe Thomas, Susi Sadler, Penny Breeze, Hazel Squires, Michael Gillett, Alan Brennan
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A) SUPPLEMENTARY TABLES & FIGURES

| CHARACTERISTIC | NUMBER | PERCENTAGE | |
|---|--------|--------------------|--------|
| Male | 644 | 43.2% | |
| Female | 848 | 56.8% | |
| White | 1332 | 89.3% | |
| BME | 160 | 10.7% | |
| <i>Indian</i> | 46 | 3.1% | |
| <i>Pakistani</i> | 23 | 1.5% | |
| <i>Bangladeshi</i> | 5 | 0.3% | |
| <i>Other Asian</i> | 19 | 1.3% | |
| <i>Caribbean</i> | 16 | 1.1% | |
| <i>African</i> | 28 | 1.9% | |
| <i>Chinese</i> | 4 | 0.3% | |
| <i>Other</i> | 19 | 1.3% | |
| Age1 < 40 | 279 | 18.7% | |
| Age2 40-59 | 482 | 32.3% | |
| Age3 60-74 | 453 | 30.4% | |
| Age4 75+ | 278 | 18.6% | |
| IMD 1 (least deprived) | 339 | 22.7% | |
| IMD 2 | 436 | 29.2% | |
| IMD 3 | 177 | 11.9% | |
| IMD 4 | 297 | 19.9% | |
| IMD 5 (most deprived) | 243 | 16.3% | |
| Working | 679 | 45.5% | |
| Retired | 584 | 39.1% | |
| Other | 229 | 15.3% | |
| BMI1 < 25 kg/m ² | 409 | 27.4% | |
| BMI2 25-29 kg/m ² | 586 | 39.3% | |
| BMI3 30-34 kg/m ² | 324 | 21.7% | |
| BMI4 ≥ 35 kg/m ² | 173 | 11.6% | |
| HbA1c 6-6.1 % (42-44 mmol/mol) | 763 | 51.1% | |
| HbA1c 6.2-6.4 % (45-47 mmol/mol) | 729 | 48.9% | |
| | MEAN | STANDARD DEVIATION | MEDIAN |
| Age (years) | 57.1 | 17.8 | 58.0 |
| BMI (kg/m ²) | 28.4 | 5.7 | 27.8 |
| Total Cholesterol (mmol/l) | 5.7 | 1.0 | 5.7 |
| HDL Cholesterol (mmol/l) | 1.5 | 0.4 | 1.5 |
| HbA1c (%) | 6.19 | 0.14 | 6.19 |
| Systolic Blood Pressure (mm Hg) | 129.7 | 17.2 | 128.5 |
| EQ-5D (TTO) | 0.739 | 0.307 | 0.796 |
| BME Black and Minority Ethnic; BMI Body Mass Index; IMD Index of Multiple Deprivation; CVD Cardiovascular Disease; IGR Impaired Glucose Regulation; HDL High Density Lipoprotein; EQ-5D 5 dimensions Euroqol (health related quality of life index); TTO Time Trade-Off | | | |

Table S1: Baseline characteristics of the IGR individuals from HSE 2011, following imputation of missing metabolic data (N=1,492).

| SPECIFICATION | BASE-CASE | SA 1 | SA 2 | SA 3 | SA 4 |
|---|-----------|-------------|--------------|----------------|-------------|
| Intervention Uptake* | 32% | 32% | 32% | 32% | 32% |
| Intervention Effectiveness ^{6,15} : | | | | | |
| Mean weight change (kg) | -3.24 | -3.24 | -2.43 | -3.24 | -3.24 |
| Mean BMI change (kg/m ²) | -1.47 | -1.47 | -1.10 | -1.47 | -1.47 |
| Mean SBP change (mmHg) | -6.57 | -6.57 | -0.15 | -6.57 | -6.57 |
| Mean cholesterol change (mmol/l) | -0.28 | -0.28 | -4.93 | -0.28 | -0.28 |
| Mean HbA1c change (%) | -0.20 | -0.20 | -0.21 | -0.20 | -0.20 |
| Stratification of Intervention Effectiveness (kg) ^{6 **} | -0.23 | None | -0.23 | -0.23 | -0.23 |
| Intervention Cost* | £270 | £270 | £270 | £270 | £350 |
| Time to Weight Regain* | 5 years | 5 years | 5 years | 3 years | 5 years |
| * PHE estimates of expected values | | | | | |
| ** extra weight loss per unit increase in baseline BMI above 31.5 kg/m ² , or weight gain per unit decrease in baseline BMI below 31.5 kg/m ² | | | | | |

Table S2: Key intervention specification parameters in the basecase and one-way sensitivity analysis (SA) scenarios. Values in bold indicate differences from basecase.

| | TOTAL COST | QALYS | NET MONETARY BENEFIT* | PROBABILITY COST-EFFECTIVE** | PROBABILITY COST-SAVING |
|--|------------|-------|-----------------------|------------------------------|-------------------------|
| Total Population | -£131 | 0.038 | -£3,376 | 97% | 70% |
| <i>IMD Q1: low deprivation</i> | -£110 | 0.041 | -£2,638 | 83% | 57% |
| <i>IMD Q2</i> | -£121 | 0.039 | -£3,034 | 87% | 60% |
| <i>IMD Q3</i> | -£141 | 0.039 | -£3,608 | 71% | 53% |
| <i>IMD Q4</i> | -£138 | 0.039 | -£3,543 | 83% | 58% |
| <i>IMD Q5: high deprivation</i> | -£159 | 0.033 | -£4,760 | 78% | 60% |
| <i>Age <40</i> | -£35 | 0.019 | -£1,811 | 64% | 46% |
| <i>Age 40-59</i> | -£215 | 0.036 | -£5,909 | 89% | 72% |
| <i>Age 60-74</i> | -£194 | 0.054 | -£3,591 | 91% | 66% |
| <i>Age 75+</i> | £24 | 0.043 | £563 | 81% | 40% |
| <i>Male</i> | -£105 | 0.041 | -£2,529 | 91% | 59% |
| <i>Female</i> | -£156 | 0.036 | -£4,303 | 94% | 68% |
| <i>BMI <25</i> | £123 | 0.016 | £7,396 | 51% | 26% |
| <i>BMI 25-29</i> | -£83 | 0.039 | -£2,130 | 89% | 55% |
| <i>BMI 30-34</i> | -£277 | 0.051 | -£5,360 | 92% | 74% |
| <i>BMI 35+</i> | -£627 | 0.067 | -£9,286 | 93% | 83% |
| <i>White</i> | -£132 | 0.039 | -£3,311 | 97% | 70% |
| <i>BME</i> | -£121 | 0.030 | -£4,045 | 61% | 51% |
| <i>HbA1c 6-6.1</i> | -£39 | 0.029 | -£1,305 | 87% | 49% |
| <i>HbA1c 6.2-6.4</i> | -£226 | 0.048 | -£4,706 | 96% | 76% |
| <i>Working</i> | -£150 | 0.036 | -£4,090 | 91% | 68% |
| <i>Retired</i> | -£102 | 0.048 | -£2,088 | 93% | 58% |
| <i>Other</i> | -£101 | 0.025 | -£3,915 | 68% | 52% |
| *Value of a QALY assumed to be £60,000 for net monetary benefit analysis ¹⁷ | | | | | |
| **At a willingness to pay threshold of £20,000 per QALY | | | | | |

Table S3: Summary table showing incremental PSA results for each subgroup compared with no DPP intervention. All results are reported per person given the intervention at 20 years following intervention implementation. Costs are discounted at 3.5% and QALYs at 1.5%. Higher cost savings, QALY gains and net monetary benefit are shown in deeper shades of red, whereas lowest cost savings, QALY gains and net monetary benefit are shown in blue.

| | BASECASE* | | SA1 | | SA2 | | SA3 | | SA4 | |
|------------------|-----------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| | Year CS | Year CE | Year CS | Year CE | Year CS | Year CE | Year CS | Year CE | Year CS | Year CE |
| Total Population | 12 | 6 | 10 | 5 | 20 | 7 | NCS | 8 | NCS | 7 |
| IMD Q1 | 13 | 6 | 10 | 5 | NCS | 7 | NCS | 8 | NCS | 7 |
| IMD Q2 | 12 | 5 | 10 | 5 | NCS | 6 | NCS | 7 | NCS | 6 |
| IMD Q3 | 13 | 6 | 10 | 5 | NCS | 7 | NCS | 8 | NCS | 7 |
| IMD Q4 | 11 | 6 | 10 | 5 | 16 | 6 | NCS | 8 | 17 | 7 |
| IMD Q5 | 11 | 6 | 9 | 5 | 16 | 7 | NCS | 9 | 17 | 7 |
| Age <40 | 19 | 9 | 11 | 8 | NCS | 11 | NCS | 17 | NCS | 11 |
| Age 40-59 | 11 | 6 | 9 | 6 | 14 | 7 | NCS | 9 | 14 | 7 |
| Age 60-74 | 9 | 5 | 8 | 4 | 12 | 6 | NCS | 6 | 13 | 6 |
| Age 75+ | NCS | 4 | NCS | 4 | NCS | 5 | NCS | 5 | NCS | 5 |
| Male | 13 | 6 | 10 | 5 | NCS | 6 | NCS | 8 | NCS | 7 |
| Female | 11 | 6 | 10 | 5 | 16 | 7 | NCS | 8 | 18 | 7 |
| BMI <25 | NCS | 10 | 11 | 6 | NCS | 13 | NCS | NCE | NCS | 13 |
| BMI 25-29 | 16 | 6 | 10 | 5 | NCS | 7 | NCS | 8 | NCS | 7 |
| BMI 30-34 | 9 | 5 | 9 | 5 | 11 | 6 | NCS | 6 | 11 | 6 |
| BMI 35+ | 5 | 3 | 7 | 4 | 6 | 4 | 8 | 4 | 7 | 4 |
| White | 11 | 6 | 10 | 5 | 19 | 6 | NCS | 7 | NCS | 6 |
| BME | 14 | 7 | 10 | 6 | NCS | 9 | NCS | 11 | NCS | 9 |
| HbA1c 6-6.1 | NCS | 7 | 14 | 6 | NCS | 8 | NCS | 10 | NCS | 9 |
| HbA1c 6.2-6.4 | 9 | 5 | 8 | 4 | 12 | 6 | NCS | 6 | 12 | 6 |
| Working | 12 | 7 | 10 | 6 | 17 | 8 | NCS | 9 | 19 | 8 |
| Retired | 11 | 5 | 9 | 4 | NCS | 5 | NCS | 6 | NCS | 5 |
| Other | 14 | 7 | 10 | 6 | NCS | 8 | NCS | 11 | NCS | 9 |

CS Cost-Saving; CE Cost-Effective; NCS Not Cost-Saving within 20 years; NCE Not Cost-Effective within 20 years
*Stratified intervention effect by BMI, 5 year duration of intervention effect, intervention cost £270.

Table S4: Comparison of the year that the intervention becomes cost-saving and cost-effective (using a threshold of £20,000 per QALY) between different population subgroups for each deterministic sensitivity analysis. Depth of shading represents how early cost-savings/cost-effectiveness occur, with darker grey representing earlier years.

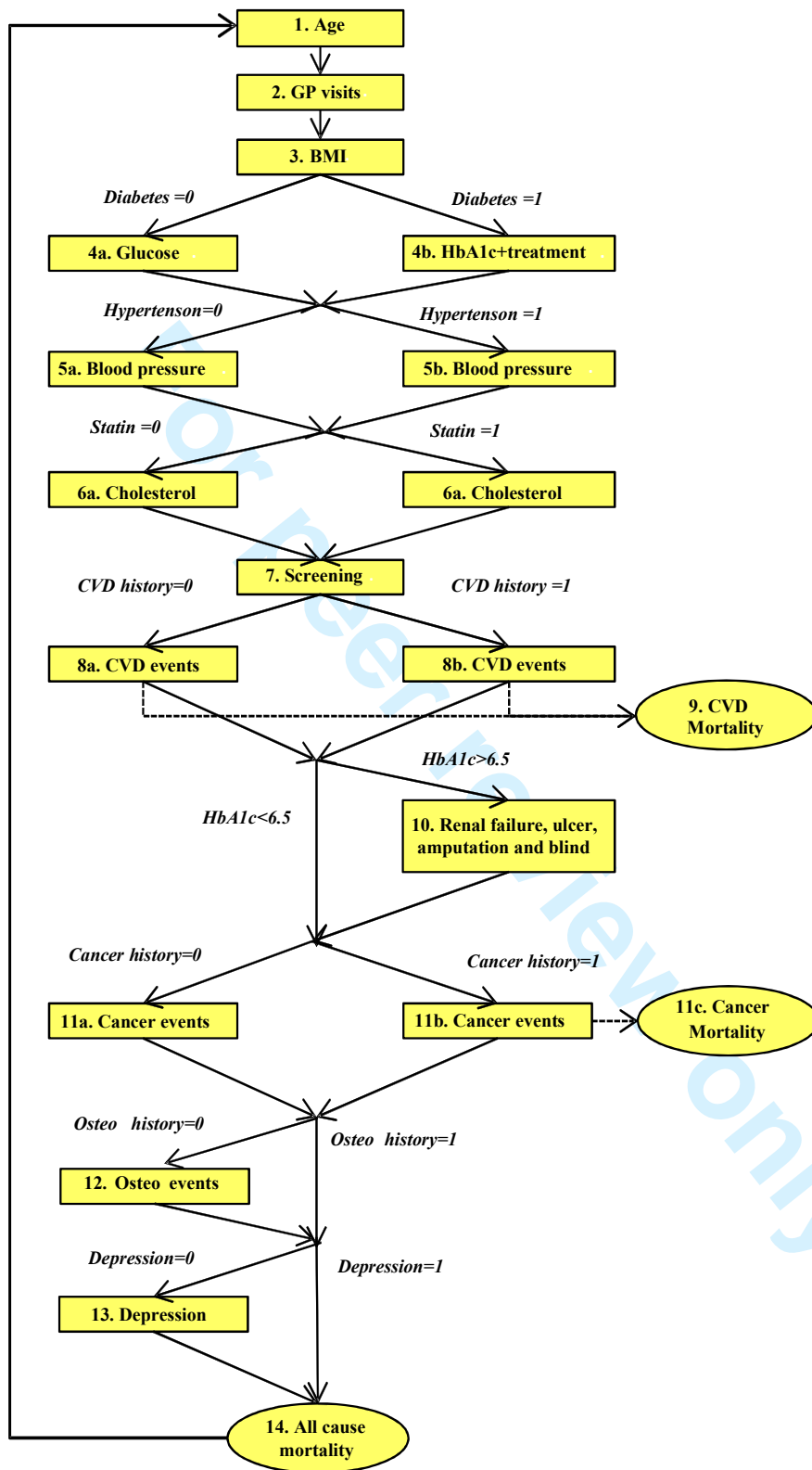


Figure S1: Model schematic showing what happens in each yearly cycle.

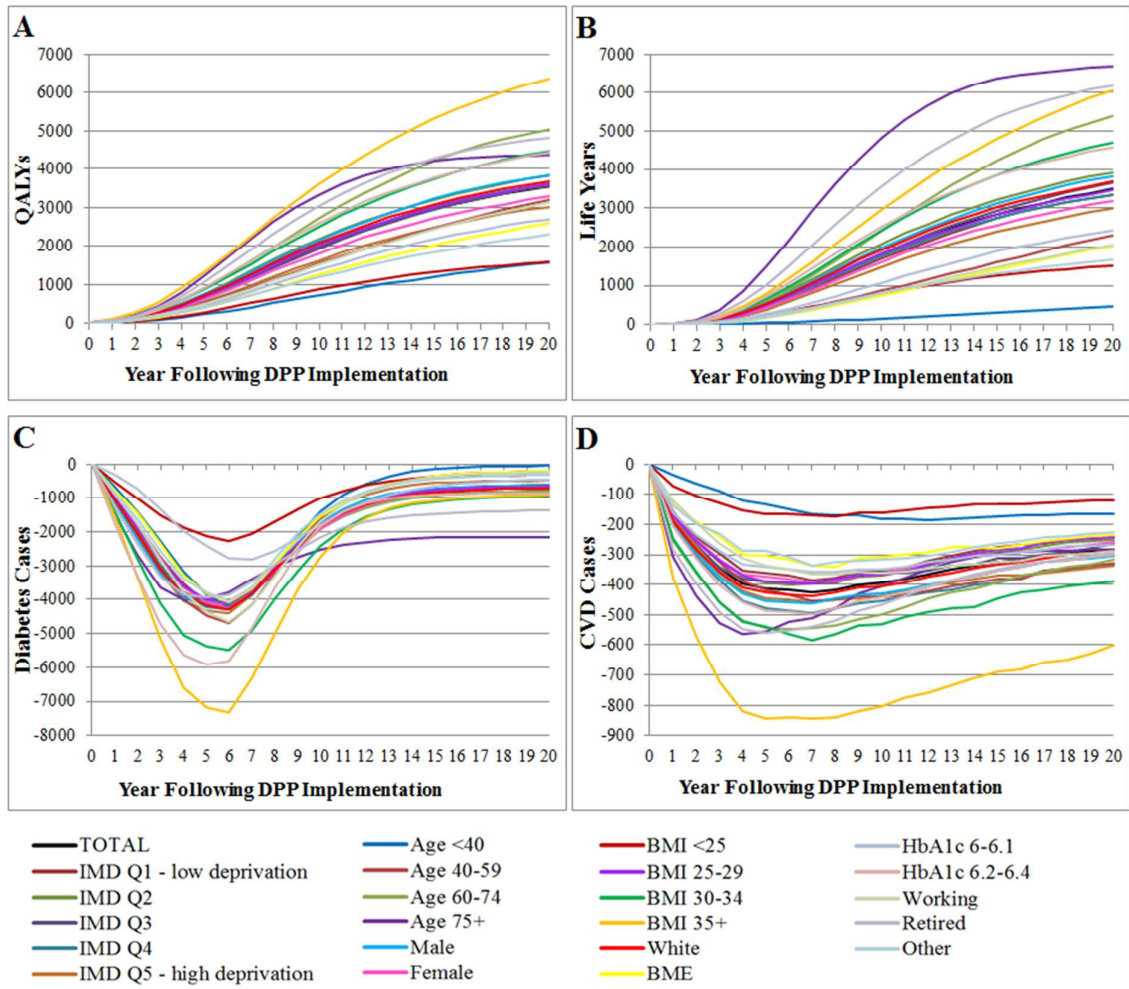


Figure S2: Graphs showing cumulative gain of A) QALYs and B) life years; and reduction in C) incremental diabetes cases and D) incremental CVD cases, per 100,000 individuals across all subgroups over 20 years.

B) SUPPLEMENTARY METHODS

CONCEPTUAL MODELLING

A conceptual model of the problem and a model-based conceptual model were developed according to a new conceptual modelling framework for complex public health models (1). In line with this framework the conceptual models were developed in collaboration with a project stakeholder group comprising health economists, public health specialists, research collaborators from other SPHR groups, diabetologists, local commissioners and lay members. The conceptual model of the problem mapped out all relevant factors associated with diabetes based upon iterative literature searches. Key initial sources were reports of two existing diabetes prevention models used for National Institute for Health and Care Excellence public health guidance (2;3). This conceptual model of the problem was presented at a Stakeholder Workshop. Discussion at the workshop led to modifications of the model, identifying additional outcomes such as depression and helping to identify a suitable conceptual model boundary for the cost-effectiveness model structure.

MODEL STRUCTURE

The model is based upon individual longitudinal trajectories of metabolic risk factors (BMI, systolic blood pressure [SBP], cholesterol and HbA1c [measure of blood glucose]). For each individual, yearly changes in these risk factors occur, dependent upon the individuals' baseline characteristics. Figure 1 in the main article illustrates the sequence of updating clinical characteristics and clinical events that are estimated within a cycle of the model. This sequence is repeated for every annual cycle of the model. The first stage of the sequence updates the age of the individual. The second stage estimates how many times the individual attends the GP. The third stage estimates the change in BMI of the individual from the previous period. In the fourth stage, if the individual has not been diagnosed as diabetic (Diabetes_Dx=0) their change in glycaemia is estimated using the Whitehall II model. If they are diabetic (Diabetes_Dx=1), it is estimated using the UKPDS model. In stages five and six the individual's blood pressure and cholesterol are updated using the Whitehall II model if the individual is not identified as hypertensive or receiving statins. In stage seven, the individual may undergo assessment for diabetes, hypertension and dyslipidaemia during a GP consultation. From stage eight onwards the individual may experience cardiovascular outcomes, diabetes related complications, cancer, osteoarthritis or depression. If the individual has a history of cardiovascular disease (CVD history=1), they follow a different pathway in stage eight to those without a history of cardiovascular disease (CVD history=0). Individuals with HbA1c greater than 6.5 are assumed to be at risk of diabetes related complications. Individuals who do not have a history of cancer (Cancer history=0) are

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3 at risk of cancer diagnosis, whereas those with a diagnosis of cancer (Cancer history=1) are at risk of
4 mortality due to cancer. Individuals without a history of osteoarthritis or depression may develop
5 these conditions in stages 12 and 13. Finally, all individuals are at risk of dying due to causes other
6 than cardiovascular or cancer mortality. Death from renal disease is included in the estimate of other-
7 cause mortality.
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10 11 12 13 14 **DATA SELECTION**

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16 Having developed and agreed the model structure and boundary with the stakeholder group the
17 project team sought suitable sources of data for the baseline population, GP attendance, metabolic risk
18 trajectories, treatment algorithms, and risk models for long term health outcomes, health care and
19 health related. Given the complexity of the model it was not possible to use systematic review
20 methods to identify all sources of data for these model inputs. As a consequence we used a series of
21 methods to identify the most appropriate sources of data within the time constraints of the project.
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26 Firstly, we discussed data sources with the stakeholder groups and identified key studies in the UK
27 that have been used to investigate diabetes and its complications and comorbidities. The stakeholder
28 group included experts in the epidemiology of non-communicable disease who provided useful
29 insight into the strengths and limitations of prominent cohort studies and trials that have studies the
30 risks of long term health outcomes included in the model. The stakeholder group also included
31 diabetes prevention cost-effectiveness modellers, whose understanding of studies that could be used to
32 inform risk parameters, costs and health related quality of life estimates. Secondly, we used a review
33 of economic evaluations of diabetes prevention and weight management cost-effectiveness studies to
34 identify sources of data used in similar economic evaluations (4). Thirdly, we conducted targeted
35 literature searches where data could not be identified from large scale studies of a UK population, or
36 could be arguably described as representative of a UK population through processes described above.
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46 47 **BASELINE POPULATION**

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49 The model required demographic, anthropometric and metabolic characteristics that would be
50 representative of the UK general population. The Heath Survey for England (HSE) was suggested by
51 the stakeholder group because it collects up-to-date cross-sectional data on the characteristics of all
52 ages of the English population. It also benefits from being a reasonably good representation of the
53 socioeconomic profile of England. A major advantage of this dataset is that includes important
54 clinical risk factors such as HbA1c, SBP, and cholesterol. The characteristics of individuals included
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3 in the cost-effectiveness model were based sampled from the HSE 2011 dataset (5). The HSE 2011
4 focused on CVD and associated risk factors. The whole dataset was obtained from the UK Data
5 Service. The total sample size of the HSE 2011 is 10,617 but individuals aged under 16 were excluded
6 resulting in 8,610 in total.
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10 Only a subset of variables reported in the HSE 2011 cohort was needed to inform the baseline
11 characteristics in the economic model. A list of model baseline characteristics and the corresponding
12 variable name and description from the HSE 2011 are listed below in Table 1. Two questions for
13 smoking were combined to describe smoking status according to the QRISK2 algorithm in which
14 former smokers and the intensity of smoking are recorded within one measure. The number of
15 missing data for each observation in the HSE data is detailed in Table 1 and summary statistics for the
16 data extracted from the HSE2011 dataset are reported in Table 2.
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Table 1: HSE variable names and missing data summary

| Model requirements | HSE 2011 variable name | HSE 2011 variable description | No. Missing data entries |
|-----------------------------------|------------------------|--|--------------------------|
| Age | Age | Age last birthday | 0 |
| Sex | Sex | Sex | 0 |
| Ethnicity | Origin | Ethnic origin of individual | 36 |
| Deprivation (Townsend) | qimd | Quintile of IMD SCORE | 0 |
| Weight | wtval | Valid weight (Kg) inc. estimated>130kg | 1284 |
| Height | htval | Valid height (cm) | 1207 |
| BMI | bmival | Valid BMI | 1431 |
| Waist circumference | wstval | Valid Mean Waist (cm) | 2871 |
| Waist-Hip ratio | whval | Valid Mean Waist/Hip ratio | 2882 |
| Total Cholesterol | cholval | Valid Total Cholesterol Result | 4760 |
| HDL cholesterol | hdlval | Valid HDL Cholesterol Result | 4760 |
| HbA1c | glyhbval | Valid Glycated HB Result | 4360 |
| FPG | | | N/A |
| 2-hr glucose | | | N/A |
| Systolic Blood pressure | omsysval | Omron Valid Mean Systolic BP | 3593 |
| Hypertension treatment | medcinbp | Currently taking any medicines, tablets or pills for high BP | 6050 |
| Gestational diabetes | pregdi | Whether pregnant when told had diabetes | 8008 |
| Anxiety/depression | Anxiety | Anxiety/Depression | 930 |
| Smoking | cigsta3 | Cigarette Smoking Status: Current/Ex-Reg/Never-Reg | 75 |
| | cigst2 | Cigarette Smoking Status - Banded current smokers | 74 |
| Statins | lipid | Lipid lowering (Cholesterol/Fibrinogen) - prescribed | 5804 |
| Rheumatoid Arthritis | compm12 | XIII Musculoskeletal system | 5 |
| Atrial Fibrillation | murmur1 | Doctor diagnosed heart murmur (excluding pregnant) | 2008 |
| Family history diabetes | | | N/A |
| History of Cardiovascular disease | cvdis2 | Had CVD (Angina, Heart Attack or Stroke) | 3 |
| Economic Activity | econact | Economic status | 37 |

Table 2: Characteristics of final sample from HSE 2011 (N=8610)

| Characteristic | Number | Percentage | |
|---|-------------|---------------------------------------|---------------|
| Male | 3822 | 44.4% | |
| White | 7719 | 89.7% | |
| Indian | 206 | 2.4% | |
| Pakistani | 141 | 1.6% | |
| Bangladeshi | 46 | 0.5% | |
| Other Asian | 97 | 1.1% | |
| Caribbean | 78 | 0.9% | |
| African | 120 | 1.4% | |
| Chinese | 35 | 0.4% | |
| Other | 168 | 2.0% | |
| IMD 1 (least deprived) | 1774 | 20.6% | |
| IMD 2 | 1823 | 21.2% | |
| IMD 3 | 1830 | 21.3% | |
| IMD 4 | 1597 | 18.5% | |
| IMD 5 (most deprived) | 1586 | 18.4% | |
| Non-smoker | 4550 | 52.8% | |
| Past smoker | 2353 | 27.3% | |
| Current smoker | 1707 | 19.8% | |
| Anti-hypertensive treatment | 1544 | 17.9% | |
| Statins | 929 | 10.8% | |
| Pre-existing CVD | 639 | 7.4% | |
| Diagnosed diabetes | 572 | 6.6% | |
| Missing HbA1c data | 4706 | 54.7% | |
| Undiagnosed diabetes (HbA1c \geq 6.5) before imputation HbA1c | 98 | 1.1% (2.5% those with HbA1c data) | |
| Undiagnosed diabetes (HbA1c \geq 6.5) after imputation HbA1c | 761 | 8.8% | |
| IGR (HbA1c 6-6.4%) before imputation HbA1c | 529 | 6.1% (13.6% those with HbA1c data) | |
| IGR (HbA1c 6-6.4%) after imputation HbA1c | 1492 | 17.3% | |
| | Mean | Standard deviation | Median |
| Age (years) | 49.6 | 18.7 | 49.0 |
| BMI (kg/m ²) | 27.4 | 5.4 | 26.6 |
| Total Cholesterol (mmol/l) | 5.4 | 1.1 | 5.4 |
| HDL Cholesterol (mmol/l) | 1.5 | 0.4 | 1.5 |
| HbA1c (%) | 5.7 | 0.8 | 5.6 |
| Systolic Blood Pressure (mm Hg) | 126.3 | 17.0 | 124.5 |
| EQ-5D (TTO) | 0.825 | 0.244 | 0.848 |
| BMI Body Mass Index; IMD Index of Multiple Deprivation; CVD Cardiovascular Disease; IGR Impaired Glucose Regulation; HDL High Density Lipoprotein; EQ-5D 5 dimensions EuroQol (health related quality of life index) ; TTO Time Trade-Off | | | |

A complete dataset was required for all individuals at baseline. However, no measurements for Fasting Plasma Glucose (FPG) or 2 hour glucose were obtained for the HSE 2011 cohort. In addition,

the questionnaire did not collect information about individual family history of diabetes or family history of Cardiovascular Disease (CVD). These variables were imputed from other datasets.

Many individuals were lacking responses to some questions but had data for others. One way of dealing with this is to exclude all individuals with incomplete data from the sample. However, this would have reduced the sample size dramatically, which would have been detrimental to the analysis. It was decided that it would be better to make use of all the data available to represent a broad range of individuals within the UK population. With this in mind, we decided to use assumptions and imputation models to estimate missing data.

MISSING DATA IMPUTATION

Ethnicity

Only a small number of individuals had missing data for ethnicity. In the QRISK2 algorithm the indicator for white includes individuals for whom ethnicity is not recorded. In order to be consistent with the QRISK2 algorithm we assumed that individuals with missing ethnicity data were white.

Anthropometric data

A large proportion of anthropometric data was missing in the cohort. Table 3 reports the number of individuals with two or more anthropometric records missing. This illustrates that only 758 individuals had no anthropometric data at all. Imputation models for anthropometric data were developed utilising observations from other measures to help improve their accuracy.

Table 3: Multi-way assessment of missing data

| Conditions | Number of individuals |
|--------------------------------------|-----------------------|
| No weight and no height | 1060 |
| No weight and no waist circumference | 907 |
| No weight and no hip circumference | 906 |
| No height and no waist circumference | 818 |
| No height and no hip circumference | 817 |
| No hip and no waist | 2865 |
| No anthropometric data | 758 |

Two imputation models were generated for each of the following anthropometric measures: weight, height, waist circumference and hip circumference. The first imputation method included an alternative anthropometric measure to improve precision. The second included only age and/or sex, to be used if the alternative measure was also missing. Simple ordinary least squares (OLS) regression models were used to predict missing data. Summary data for each measure confirmed that the data were approximately normally distributed. Covariate selection was made by selecting the

anthropometric measure that maximised the Adjusted R-squared statistic, and age and sex were included if the coefficients were statistically significant ($P < 0.1$).

The imputation models for weight are reported in Table 4. Individuals' sex and age were included in both models. A quadratic relationship between age and weight was identified. Waist circumference had a positive and significant relationship with weight. The R^2 for model 1 suggested that 80% of the variation in weight is described by the model. The R^2 for model 2 was much lower as only 18% of the variation in weight was described by age and sex. The residual standard error is reported for both models.

Table 4: Imputation model for weight

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | -17.76 | 50.249 |
| Sex | 2.614 | 13.036 |
| Age | 0.064 | 0.903 |
| Age*Age | -0.0027 | -0.0086 |
| Waist circumference | 1.060 | |
| R-squared | 0.7981 | 0.1831 |
| Residual standard error | 7.483 | 15.31 |

The imputation models for height are reported in Table 5. Individuals' sex and age were included in both models. A quadratic relationship between age and height was identified. Waist circumference had a positive and significant relationship with height. The R^2 for model 1 suggested that 53% of the variation in height is described by the model suggesting a fairly good fit. The R^2 for model 2 was slightly lower in which 52% of the variation in height was described by age and sex. The residual standard error is reported for both models.

Table 5: Imputation model for height

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | 157.4 | 162.1 |
| Sex | 12.82 | 13.43 |
| Age | 0.081 | 0.1291 |
| Age*Age | -0.0021 | -0.0025 |
| Waist circumference | 0.071 | |
| R-squared | 0.532 | 0.5244 |
| Residual standard error | 6.617 | 6.682 |

The imputation models for waist circumference are reported in Table 6. Individuals' sex and age were included in both models. A quadratic relationship between age and waist circumference fit to the data better than a linear relationship. Weight had a positive and significant relationship with waist circumference. The R^2 for model 1 suggested that 81% of the variation in waist circumference is described by the model suggesting a very good fit. The R^2 for model 2 was much lower in which only

22% of the variation in waist circumference was described by age and sex which is a moderately poor fit. The residual standard error is reported for both models.

Table 6: Imputation model for waist

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | 28.73 | 65.327 |
| Sex | 0.5754 | 9.569 |
| Age | 0.1404 | 0.7617 |
| Age*Age | 0.0007 | -0.0053 |
| Weight | 0.7098 | |
| R-squared | 0.8096 | 0.2196 |
| Residual standard error | 6.122 | 12.44 |

The imputation models for hip circumference are reported in Table 7. Individuals' sex and age were included in both models. A quadratic relationship between age and hip circumference fit to the data better than a linear relationship. Weight had a positive and significant relationship with hip circumference. The R^2 for model 1 suggested that 80% of the variation in hip circumference is described by the model suggesting a very good fit. The R^2 for model 2 was much lower in which only 2% of the variation in hip circumference was described by age and sex which is a very poor fit. The residual standard error is reported for both models.

Table 7: Imputation model for hip

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | 66.9145 | 96.891 |
| Sex | -8.3709 | -0.9783 |
| Age | -0.1714 | 0.3528 |
| Age*Age | 0.0021 | -0.0029 |
| Weight | 0.5866 | |
| R-squared | 0.7949 | 0.023 |
| Residual standard error | 4.539 | 10.1 |

Metabolic data

A large proportion of metabolic data was missing in the cohort, ranging from 2997-4309 observations for each metabolic measurement. Table 8 reports the number of individuals with two or more metabolic records missing. This illustrates that 2987 individuals have no metabolic data. Imputation models for metabolic data were developed utilising observations from other measures to help improve their accuracy.

Table 8: Multi-way assessment of missing data

| Conditions | Number of individuals |
|--------------------------------------|-----------------------|
| No HbA1c and no cholesterol | 4309 |
| No HbA1c and no blood pressure | 2997 |
| No cholesterol and no blood pressure | 3050 |
| No metabolic data | 2987 |

Two imputation models were generated for each of the following metabolic measures: total cholesterol, high density lipoprotein (HDL) cholesterol, HbA1c and systolic blood pressure (SBP) and. The first imputation method included an alternative metabolic measure to improve precision. The second included only age and/or sex, to be used if the alternative measure was also missing. Simple ordinary least squares (OLS) regression models were used to predict missing data. Summary data for each measure confirmed that the data were approximately normally distributed. Covariate selection was made by selecting the metabolic measure that maximised the adjusted R-squared statistic, and age and sex were included if the coefficients were statistically significant ($P < 0.1$).

These imputation models were developed to estimate metabolic data from information collected in the HSE. An alternative approach would have been to use estimates of these measures from the natural history statistical models. At the time of the analysis it was uncertain what form and design the natural history models would take, therefore the HSE imputation models were developed for use until a better alternative was found.

The imputation models for total cholesterol are reported in Table 9. Individuals' age was included in both models. A quadratic relationship between age and weight was identified. Diastolic blood pressure had a positive and significant relationship with total cholesterol. The R^2 for model 1 suggested that 20% of the variation in total cholesterol is described by the model. The R^2 for model 2 was lower in which only 18% of the variation in total cholesterol was described by age. The residual standard error is reported for both models.

Table 9: Imputation model for total cholesterol

| Coefficient | Model 1 | Model 2 |
|--------------------------|---------|---------|
| Intercept | 1.973 | 2.821 |
| Age | 0.0774 | 0.0904 |
| Age*Age | -0.0006 | -0.0007 |
| Diastolic blood pressure | 0.0159 | |
| R-squared | 0.2035 | 0.1792 |
| Residual standard error | 0.9526 | 0.9741 |

The imputation models for HDL cholesterol are reported in Table 10. Individuals' sex and age were included in both models. A quadratic relationship between age and height was identified. Diastolic blood pressure had a negative and significant relationship with HDL cholesterol. The R^2 for model 1

suggested that only 13% of the variation in HDL cholesterol is described by the model suggesting a relatively poor fit. The R^2 for model 2 suggested that 12% of the variation in HDL cholesterol was described by age and sex. The residual standard error is reported for both models.

Table 10: Imputation model for HDL Cholesterol

| Coefficient | Model 1 | Model 2 |
|--------------------------|---------|----------|
| Intercept | 1.501 | 1.383 |
| Sex | -0.279 | -0.274 |
| Age | 0.0086 | 0.0075 |
| Age*Age | -0.0001 | -0.00004 |
| Diastolic blood pressure | -0.0018 | |
| R-squared | 0.1198 | 0.1157 |
| Residual standard error | 0.4122 | 0.417 |

The imputation models for HbA1c are reported in Table 11. Individuals' age was included in both models. A quadratic relationship between age and HbA1c fit to the data better than a linear relationship. SBP had a positive and significant relationship with HbA1c. The R^2 for model 1 suggested that only 19% of the variation in HbA1c is described by the model, suggesting a modest fit. The R^2 for model 2 described 18% of the variation in HbA1c by age alone. The residual standard error is reported for both models.

Table 11: Imputation model for HbA1c

| Coefficient | Model 1 | Model 2 |
|-------------------------|----------|----------|
| Intercept | 4.732 | 4.962 |
| Age | 0.0141 | 1.422 |
| Age*Age | -0.00003 | -0.00003 |
| Systolic blood pressure | 0.002 | |
| R-squared | 0.1941 | 0.1835 |
| Residual standard error | 0.4243 | 0.4228 |

The imputation models for SBP are reported in Table 12. Individuals' sex and age were included in both models. A linear relationship between age and SBP fit to the data better than a quadratic relationship. Total cholesterol and HbA1c had a positive and significant relationship with SBP, whereas HDL cholesterol had a negative significant relationship with SBP. The R^2 for model 1 suggested that 22% of the variation in SBP is described by the model suggesting a modest fit. The R^2 for model 2 was similar in which only 20% of the variation in SBP was described by age and sex. The residual standard error is reported for both models.

Table 12: Imputation model for Systolic Blood Pressure

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | 84.983 | 104.132 |
| Sex | 6.982 | 6.396 |
| Age | 0.330 | 0.380 |
| Total cholesterol | 2.093 | |
| HDL cholesterol | -0.746 | |
| HbA1c | 1.986 | |
| R-squared | 0.2235 | 0.2047 |
| Residual standard error | 14.59 | 15.1 |

Treatment for Hypertension and Statins

A large proportion of individuals had missing data for questions relating to whether they received treatment for hypertension or high cholesterol. The majority of non-responses to these questions were coded to suggest that the question was not applicable to the individual. As a consequence it was assumed that individuals with missing treatment data were not taking these medications.

Gestational Diabetes

Only 30 respondents without current diabetes reported that they had been diagnosed with diabetes during a pregnancy in the past. Most individuals had missing data for this question due to it not being applicable. The missing data was assumed to indicate that individuals had not had gestational diabetes.

Anxiety/Depression

Most individuals who had missing data for anxiety and depression did so because the question was not applicable. A small sample N=69 refused to answer the question. We assumed that individuals with missing data for anxiety and depression did not have severe anxiety/depression.

Smoking

Individuals with missing data for smoking status were assumed to be non-smokers, without a history of smoking.

Rheumatoid Arthritis and Atrial Fibrillation

A very small sample of individuals had missing data for musculoskeletal illness (N=5) and atrial fibrillation (N=1). These individuals were assumed to not suffer from these illnesses.

Family history of diabetes

No questions in the HSE referred to the individual having a family history of diabetes, so this data had to be imputed. It was important that data was correlated with other risk factors for diabetes, such as HbA1c and ethnicity. We analysed a cross-section of the Whitehall II dataset to generate a logistic

regression to describe the probability that an individual has a history of diabetes conditional on their HbA1c and ethnic origin. The model is described in Table 13.

Table 13: Imputation model for history of diabetes

| | Coefficient |
|-----------------|--------------------|
| Intercept | -3.29077 (0.4430) |
| HbA1c | 0.28960 (0.0840) |
| HDL Cholesterol | 0.81940 (0.13878) |

Economic Activity

Individuals without information about their employment status were assumed to be retired if aged 65 or over and in employment if under 65.

POPULATION SELECTION

The DPP is only eligible to individuals with impaired glucose regulation (IGR), defined as HbA1c 6-6.4% in the model. The process of identifying eligible individuals or referring them to the DPP was not explicitly modelled. Instead, all individuals from the HSE 2011 with actual or imputed HbA1c levels between 6-6.4% are assumed to have been previously identified by a variety of means, and only these IGR individuals are included in the simulation. This means that the costs of identifying IGR individuals or referring them to the DPP intervention are not included.

GP ATTENDANCE IN THE GENERAL POPULATION

Frequency of GP visits (separate from NHS health checks) was simulated in the dataset for two reasons; firstly, to estimate the healthcare utilisation for the ID population without diabetes and cardiovascular disease and secondly, to predict the likelihood that individuals participate in opportunistic screening for diabetes and vascular risks. It was assumed that GP attendance in the ID population occurs at the same frequency as in the general population. However, for cost purposes, consultations were assumed to take 40% longer than the general population average (see Costs section).

GP attendance conditional on age, sex, BMI, ethnicity, and health outcomes was derived from analysis of wave 1 of the Yorkshire Health Study (11). The analysis used a negative binomial regression model to estimate self-reported rate of GP attendance per 3 months (Table 14). The estimated number of GP visits was multiplied by 4 to reflect the annual number of visits per year.

Table 14: GP attendance reported in the Yorkshire Health Study (N= 18,437)

| | Model 1 | | Model 2 | |
|-----------------------|---------|----------------|---------|----------------|
| | Mean | Standard error | Mean | Standard error |
| Age | 0.0057 | 0.0005 | 0.0076 | 0.0005 |
| Male | -0.1502 | 0.0155 | -0.1495 | 0.0159 |
| BMI | 0.0020 | 0.0015 | 0.0110 | 0.0015 |
| IMD score 2010 | 0.0043 | 0.0005 | | |
| Ethnicity (Non-white) | 0.1814 | 0.0370 | 0.2620 | 0.0375 |
| Heart Disease | 0.1588 | 0.0281 | 0.2533 | 0.0289 |
| Depression | 0.2390 | 0.0240 | 0.6127 | 0.0224 |
| Osteoarthritis | 0.0313 | 0.0240 | 0.2641 | 0.0238 |
| Diabetes | 0.2023 | 0.0270 | 0.2702 | 0.0278 |
| Stroke | 0.0069 | 0.0460 | 0.1659 | 0.0474 |
| Cancer | 0.1908 | 0.0400 | 0.2672 | 0.0414 |
| Intercept | 0.6275 | 0.0590 | -0.5014 | 0.0468 |
| Alpha | 0.3328 | 0.0097 | 0.3423 | 0.0108 |

LONGITUDINAL TRAJECTORIES OF METABOLIC RISK FACTORS

A detailed description of the statistical analysis behind the personalised metabolic risk factor trajectories that underlie disease risk in the SPHR Diabetes Prevention model has previously been published (12), so this report provides only a brief summary.

A statistical analysis of the Whitehall II cohort study (13) was developed to describe correlated longitudinal changes in metabolic risk factors including BMI, latent blood glucose (an underlying, unobservable propensity for diabetes), total cholesterol, HDL cholesterol and systolic blood pressure. Parallel latent growth modelling was used to estimate the unobservable latent glycaemia and from this identify associations with test results for HbA1c, FPG, and 2-hour glucose. The growth factors (longitudinal changes) for BMI, glycaemia, systolic blood pressure, total and HDL cholesterol could then be estimated through statistical analysis. These growth factors are conditional on several individual characteristics including age, sex, ethnicity, smoking, family history of CVD, and family history of type 2 diabetes. Deprivation was excluded from the final analysis because it was not associated with the growth models, and it estimated counter-intuitive coefficients.

Unobservable heterogeneity between individual growth factors not explained by patient characteristics was incorporated into the growth models as random error terms. Correlation between the random error terms for glycaemia, total cholesterol, HDL cholesterol and systolic blood pressure was estimated from the Whitehall II cohort. This means that in the simulation, an individual with a higher growth rate for glycaemia is more likely to have a higher growth rate of total cholesterol and systolic blood pressure.

The baseline observations for BMI, HbA1c, systolic blood pressure, cholesterol and HDL cholesterol were extracted from the Health Survey for England 2011 in order to simulate a representative sample. The predicted intercept for these metabolic risk factors was estimated using the Whitehall II analysis to give population estimates of the individuals' starting values, conditional on their characteristics. The difference between the simulated and observed baseline risk factors was taken to estimate the individuals' random deviation from the population expectation. The individual random error in the slope trajectory was sampled from a conditional multivariate normal distribution to allow correlation between the intercept and slope random errors.

Following a diagnosis of diabetes in the simulation all individuals experience an initial fall in HbA1c due to changes in diet and lifestyle as observed in the UKPDS trial (14). The expected change in HbA1c conditional on HbA1c at diagnosis was estimated by fitting a simple linear regression to three aggregate outcomes reported in the study. These showed that the change in HbA1c increases for higher HbA1c scores at diagnosis. The regression parameters to estimate change in HbA1c are reported in Table 15.

Table 15: Estimated change in HbA1c following diabetes diagnosis

| | Mean | Standard error |
|---------------------------|---------|----------------|
| Change in HbA1c Intercept | -2.9465 | 0.0444513 |
| HbA1c at baseline | 0.5184 | 0.4521958 |

After this initial reduction in HbA1c the longitudinal trajectory of HbA1c is estimated using the UKPDS outcomes model (15) rather than the Whitehall II statistical analysis. The UKPDS dataset is made up of a newly diagnosed diabetic population. As part of the UKPDS Outcomes model, longitudinal trial data were analysed using a random effects model, which means that unobservable differences between individuals are accounted for in the analysis. The model can be used to predict HbA1c over time from the point of diagnosis. The coefficients of the model are reported in Table 16.

Table 16: Coefficient estimates for HbA1c estimated from UKPDS data

| | Mean Coefficient | Coefficient standard error |
|--|------------------|----------------------------|
| Intercept | -0.024 | 0.017 |
| Log transformation of year since diagnosis | 0.144 | 0.009 |
| Binary variable for year after diagnosis | -0.333 | 0.05 |
| HbA1c score in last period | 0.759 | 0.004 |
| HbA1c score at diagnosis | 0.085 | 0.004 |

It was important to maintain heterogeneity in the individual glycaemic trajectories before and after diagnosis. Therefore, the random error terms used to determine individual trajectories in glycaemia before diagnosis were used to induce random noise in the trajectory after diagnosis. We sampled the

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3 expected random error term for each individual after diagnosis conditional on pre-diagnosis slope,
4 assuming a 0.8 correlation between these values.
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7 The epidemiological literature for many of the health outcomes included in the model treats diabetes
8 diagnosis as a discrete health state, rather than a continuous risk function conditional on HbA1c. This
9 poses two methodological challenges in type 2 diabetes modelling. Firstly, diabetes diagnosis is
10 complex with several tests and a high proportion of undetected diagnoses. Therefore, it is not
11 necessarily an appropriate indicator of risk in the model. Secondly, we would prefer to model the
12 relationship on a continuous scale to avoid artificial steps in risk; however the evidence is not always
13 available to describe risk on a continuous scale. We took two main steps to reduce the impact of this
14 on our model. Firstly, we used the HbA1c threshold of 6.5% to indicate type-2 diabetes regardless of
15 detection, and to ensure consistency in natural history across interventions and counterfactuals.
16 Secondly, the QRISK2 model was adapted to incorporate continuous risk by HbA1c.
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25 **METABOLIC RISK FACTOR SCREENING, DIAGNOSIS AND TREATMENT**

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27
28 It is assumed that individuals eligible for anti-hypertensive treatment or statins will be identified
29 through opportunistic screening if they meet certain criteria and attend the GP for at least one visit in
30 the simulation period.
31

- 32
33 1. Individuals with a history of cardiovascular disease;
- 34 2. Individuals with a major microvascular event (foot ulcer, blindness, renal failure or
35 amputation);
- 36 3. Individuals with diagnosed diabetes;
- 37 4. Individuals with systolic blood pressure greater than 160mmHg.
38
39
40

41
42 Individuals may also be detected with diabetes through opportunistic screening if the following
43 criteria are met.
44

- 45 1. Individuals with a history of cardiovascular disease;
- 46 2. Individuals with a major microvascular event (foot ulcer, blindness, renal failure or
47 amputation);
- 48 3. At baseline individuals are assigned an HbA1c threshold above which diabetes is detected
49 opportunistically, individuals with an HbA1c above their individual threshold will attend the
50 GP to be diagnosed with diabetes. The threshold is sampled from the distribution of HbA1c
51 tests in a cohort of recently diagnosed patients in clinical practice (16).
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3 The base case has been designed to represent a health system with moderate levels of screening for
4 hypertension, diabetes, and dyslipidaemia.
5

6
7 It is assumed that there are three, non-mutually exclusive outcomes from the vascular checks or
8 opportunistic screening. Firstly, that the patient receives statins to reduce cardiovascular risk.
9
10 Secondly, that the patient has high blood pressure and should be treated with anti-hypertensive
11 medication. Thirdly, the model evaluates whether the blood glucose test indicates a diagnosis with
12 type 2 diabetes. The following threshold estimates were used to determine these outcomes.
13

- 14
15 1. Statins are initiated if the individual has greater than or equal to 20% 10 year CVD risk
16 estimated from the QRISK2 2012 algorithm (17).
17
- 18 2. Anti-hypertensive treatment is initiated if systolic blood pressure is greater than 160. If the
19 individual has a history of CVD, diabetes or a CVD risk >20%, the threshold for systolic
20 blood pressure is 140 (18).
21
- 22 3. Type 2 diabetes is diagnosed if the individual has an HbA1c test greater than 6.5. In the base
23 case it is assumed that FPG and 2-hr glucose are not used for diabetes diagnosis. However,
24 future adaptations of the model could use these tests for diagnosis.
25
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29 It is assumed within the model that if initiated, statins are effective in reducing an individual's total
30 cholesterol, and so an average effect is applied to all patients being prescribed them. A recent HTA
31 reviewed the literature on the effectiveness and cost-effectiveness of statins in individuals with acute
32 coronary syndrome (20). This report estimated the change in LDL cholesterol for four statin
33 treatments and doses compared with placebo from a Bayesian meta-analysis. The analysis estimated a
34 reduction in LDL cholesterol of -1.45 for simvastatin. This estimate was used to describe the effect of
35 statins in reducing total cholesterol. It was assumed that the effect was instantaneous upon receiving
36 statins and maintained as long as the individual receives statins. It was also assumed that individuals
37 receiving statins no longer experienced annual changes in cholesterol. HDL cholesterol was assumed
38 constant over time if patients received statins.
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45 Non-adherence to statin treatment is a common problem. Two recent HTAs reviewed the literature on
46 continuation and compliance with statin treatment. They both concluded that there was a lack of
47 adequate reporting, but that the proportion of patients fully compliant with treatment appears to
48 decrease with time, particularly in the first 12 months after initiating treatment, and can fall below
49 60% after five years (20;21). Although a certain amount of non-compliance is included within trial
50 data, clinical trials are not considered to be representative of continuation and compliance in general
51 practice. A yearly reduction in statin compliance used in the HTA analysis is reported in Table 17. It
52 is based on the published estimate of compliance for the first five years of statin treatment for primary
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prevention in general clinical practice (21). Compliance declines to a minimum of 65% after five years of treatment. It is assumed that there is no further drop after five years.

Table 17: Proportion of patients assumed to be compliant with statin treatment, derived from Table 62 in (20)

| Year after statin initiation | 1 | 2 | 3 | 4 | 5 |
|------------------------------|-----|-----|------|------|------|
| Proportion compliant | 0.8 | 0.7 | 0.68 | 0.65 | 0.65 |

In the simulation, it is assumed in the base case that only 65% of individuals initiate statins when they are deemed eligible. However those that initiate statins remain on statins for their lifetime. Those who refuse statins may be prescribed them again at a later date.

The change in systolic blood pressure following antihypertensive treatment was obtained from a meta-analysis of anti-hypertensive treatments (22). This study identified an average change in systolic blood pressure of -8.4 mmHg for monotherapy with calcium channel blockers. It is assumed that this reduction in systolic blood pressure is maintained for as long as the individual receives anti-hypertensive treatment. For simplicity we do not assume that the individual switches between anti-hypertensive treatments over time. Once an individual is receiving anti-hypertensive treatment it is assumed that their systolic blood pressure is stable and does not change over time. Non-adherence and discontinuation are not modelled for anti-hypertensives.

COMORBID OUTCOMES AND MORTALITY

In every model cycle individuals within the model are evaluated to determine whether they have a clinical event, including mortality, within the cycle period. In each case the simulation estimates the probability that an individual has the event and uses a random number draw to determine whether the event occurred.

CARDIOVASCULAR DISEASE

First Cardiovascular event

Several statistical models for cardiovascular events were identified in a review of economic evaluations for diabetes prevention (4). The UKPDS outcomes model (23), Framingham risk equation (24) and QRISK2 (25) have all been used in previous models to estimate cardiovascular events. The Framingham risk equation was not adopted because, unlike the QRISK2 model, it is not estimated from a UK population. The UKPDS outcomes model would be ideally suited to estimate the risk of cardiovascular disease in a population diagnosed with type 2 diabetes. Whilst this is an important outcome of the cost-effectiveness model, there was concern that it would not be representative of individuals with normal glucose tolerance or impaired glucose regulation. It was important that

reductions in cardiovascular disease risk in these populations were represented to capture the population-wide benefits of public health interventions. The QRISK2 model was selected for use in the cost-effectiveness model because it is a validated model of cardiovascular risk in a UK population that could be used to generate probabilities for diabetic and non-diabetic populations. We considered using the UKPDS outcomes model specifically to estimate cardiovascular risk in patients with type 2 diabetes. However, it would not be possible to control for shifts in absolute risk generated by the different risk scores due to different baselines and covariates. This would lead to some individuals experiencing counterintuitive and favourable shifts in risk after onset of type 2 diabetes. Therefore, we decided to use diabetes as a covariate adjustment to the QRISK2 model to ensure that the change in individual status was consistent across individuals.

We accessed the 2012 version of the QRISK from the website (26). The QRISK2 equation estimates the probability of a cardiovascular event in the next year conditional on ethnicity, smoking status, age, BMI, ratio of total/HDL cholesterol, Townsend score, atrial fibrillation, rheumatoid arthritis, renal disease, hypertension, diabetes, and family history of cardiovascular disease. Data on all these variables was available from the HSE 2011. Table 18 reports the coefficient estimates for the QRISK2 algorithm. The standard errors were not reported within the open source code. Where possible, standard errors were imputed from a previous publication of the risk equation (27). Coefficients that were not reported in this publication were assumed to have standard errors of 20%.

Table 18: Coefficients from the 2012 QRISK2 risk equation and estimate standard errors

| Covariates | Estimated coefficients adjusting for individual characteristics | | | | | | | | | |
|------------------------|---|----------------|-----------|--------|-------------------------|---------|----------------|---------|----------------|--|
| | Women | | Men | | Interaction terms | Women | | Men | | |
| | Mean | Standard error | Mean | Mean | | Mean | Standard error | Mean | Standard error | |
| White | 0.0000 | 0.0000 | 0.0000 | 0.0000 | Age1*former smoker | 0.1774 | 0.035 | -3.881 | 0.776 | |
| Indian | 0.2163 | 0.0537 | 0.3163 | 0.0425 | Age1*light smoker | -0.3277 | 0.066 | -16.703 | 3.341 | |
| Pakistani | 0.6905 | 0.0698 | 0.6092 | 0.0547 | Age1*moderate smoker | -1.1533 | 0.231 | -15.374 | 3.075 | |
| Bangladeshi | 0.3423 | 0.1073 | 0.5958 | 0.0727 | Age1*Heavy smoker | -1.5397 | 0.308 | -17.645 | 3.529 | |
| Other Asian | 0.0731 | 0.1071 | 0.1142 | 0.0845 | Age1*AF | -4.6084 | 0.922 | -7.028 | 1.406 | |
| Caribbean | -0.0989 | 0.0619 | -0.3489 | 0.0641 | Age1*renal disease | -2.6401 | 0.528 | -17.015 | 3.403 | |
| Black African | -0.2352 | 0.1275 | -0.3604 | 0.1094 | Age1*hypertension | -2.2480 | 0.450 | 33.963 | 6.793 | |
| Chinese | -0.2956 | 0.1721 | -0.2666 | 0.1538 | Age1*Diabetes | -1.8452 | 0.369 | 12.789 | 2.558 | |
| Other | -0.1010 | 0.0793 | -0.1208 | 0.0734 | Age1*BMI | -3.0851 | 0.617 | 3.268 | 0.654 | |
| Non-smoker | 0.0000 | 0.0000 | 0.0000 | 0.0000 | Age1*family history CVD | -0.2481 | 0.050 | -17.922 | 3.584 | |
| Former smoker | 0.2033 | 0.0152 | 0.2684 | 0.0108 | Age1*SBP | -0.0132 | 0.003 | -0.151 | 0.030 | |
| Light smoker | 0.4820 | 0.0220 | 0.5005 | 0.0166 | Age1*Townsend | -0.0369 | 0.007 | -2.550 | 0.510 | |
| Moderate smoker | 0.6126 | 0.0178 | 0.6375 | 0.0148 | Age2*former smoker | -0.0051 | 0.001 | 7.971 | 1.594 | |
| Heavy smoker | 0.7481 | 0.0194 | 0.7424 | 0.0143 | Age2*light smoker | -0.0005 | 0.000 | 23.686 | 4.737 | |
| Age 1* | 5.0327 | | 47.3164 | | Age2*moderate smoker | 0.0105 | 0.002 | 23.137 | 4.627 | |
| Age 2* | -0.0108 | | -101.2362 | | Age2*Heavy smoker | 0.0155 | 0.003 | 26.867 | 5.373 | |
| BMI* | -0.4724 | 0.0423 | 0.5425 | 0.0299 | Age2*AF | 0.0507 | 0.010 | 14.452 | 2.890 | |
| Ratio Total / HDL chol | 0.1326 | 0.0044 | 0.1443 | 0.0022 | Age2*renal disease | 0.0343 | 0.007 | 28.270 | 5.654 | |
| SBP | 0.0106 | 0.0045 | 0.0081 | 0.0046 | Age2*hypertension | 0.0258 | 0.005 | -18.817 | 3.763 | |
| Townsend | 0.0597 | 0.0068 | 0.0365 | 0.0048 | Age2*Diabetes | 0.0180 | 0.004 | 0.963 | 0.193 | |
| AF | 1.3261 | 0.0310 | 0.7547 | 0.1018 | Age2*BMI | 0.0345 | 0.007 | 10.551 | 2.110 | |

| | | | | | | | | | |
|--|--------|--------|--------|--------|----------------------------|---------|-------|--------|-------|
| Rheumatoid arthritis | 0.3626 | 0.0319 | 0.3089 | 0.0445 | Age2*family history CVD | -0.0062 | 0.001 | 26.605 | 5.321 |
| Renal disease | 0.7636 | 0.0639 | 0.7441 | 0.0702 | Age2*SBP | 0.0000 | 0.000 | 0.291 | 0.058 |
| Hypertension | 0.5421 | 0.0115 | 0.4978 | 0.0112 | Age2*Townsend | -0.0011 | 0.000 | 3.007 | 0.601 |
| Diabetes | 0.8940 | 0.0199 | 0.7776 | 0.0175 | | | | | |
| Family history of CVD | 0.5997 | 0.0122 | 0.6965 | 0.0111 | | | | | |
| AF Atrial Fibrillation CVD Cardiovascular disease SBP systolic blood pressure * covariates transformed with fractional polynomials | | | | | | | | | |

The QRISK2 risk equation can be used to calculate the probability of a cardiovascular event including coronary heart disease (angina or myocardial infarction), stroke, transient ischaemic attacks and fatality due to cardiovascular disease. The equation estimates the probability of a cardiovascular event in the next period conditional on the coefficients listed in Table 18. The equation for the probability of an event in the next period is calculated as

$$p(Y = 1) = 1 - S(1)^\theta$$

$$\theta = \sum \beta X$$

The probability of an event is calculated from the survival function at 1 year raised to the power of θ , where θ is the sum product of the coefficients reported in Table 18 multiplied by the individual's characteristics. Underlying survival curves for men and women were extracted from the QRISK2 open source file. Mean estimates for the continuous variables were also reported in the open source files.

We modified the QRISK assumptions regarding the relationship between IGR, diabetes and cardiovascular disease. Firstly, we assumed that individuals with HbA1c > 6.5 have an increased risk of cardiovascular disease even if they have not received a formal diagnosis. Secondly, risk of cardiovascular disease was assumed to increase with HbA1c for test results greater than 6.5 to reflect observations from the UKPDS that HbA1c increases the risk of MI and Stroke (23). Thirdly, prior to type 2 diabetes (HbA1c > 6.5) HbA1c is linearly associated with cardiovascular disease. A study from the EPIC Cohort has found that a unit increase in HbA1c increases the risk of coronary heart disease by a hazard ratio of 1.25, after adjustment for other risk factors (28). Individuals with an HbA1c greater than the mean HbA1c observed in the HSE 2011 cohort were at greater risk of CVD than those with an HbA1c lower than the HSE mean.

The QRISK algorithm identifies which individuals experience a cardiovascular event but does not specify the nature of the event. The nature of the cardiovascular event was determined independently. A targeted search of recent Health Technology appraisals of cardiovascular disease was performed to identify a model for the progression of cardiovascular disease following a first event. All QRISK events are assigned to a specific diagnosis according to age and sex specific distributions of

cardiovascular events used in a previous Health Technology Assessment (HTA) (21). Table 19 reports the probability of cardiovascular outcomes by age and gender.

Table 19: The probability distribution of cardiovascular events by age and gender

| | Age | Stable angina | Unstable angina | MI rate | Fatal CHD | TIA | Stroke | Fatal CVD |
|-------|-------|---------------|-----------------|---------|-----------|-------|--------|-----------|
| Men | 45-54 | 0.307 | 0.107 | 0.295 | 0.071 | 0.060 | 0.129 | 0.030 |
| | 55-64 | 0.328 | 0.071 | 0.172 | 0.086 | 0.089 | 0.206 | 0.048 |
| | 65-74 | 0.214 | 0.083 | 0.173 | 0.097 | 0.100 | 0.270 | 0.063 |
| | 75-84 | 0.191 | 0.081 | 0.161 | 0.063 | 0.080 | 0.343 | 0.080 |
| | 85+ | 0.214 | 0.096 | 0.186 | 0.055 | 0.016 | 0.351 | 0.082 |
| Women | 45-54 | 0.325 | 0.117 | 0.080 | 0.037 | 0.160 | 0.229 | 0.054 |
| | 55-64 | 0.346 | 0.073 | 0.092 | 0.039 | 0.095 | 0.288 | 0.067 |
| | 65-74 | 0.202 | 0.052 | 0.121 | 0.081 | 0.073 | 0.382 | 0.090 |
| | 75-84 | 0.149 | 0.034 | 0.102 | 0.043 | 0.098 | 0.464 | 0.109 |
| | 85+ | 0.136 | 0.029 | 0.100 | 0.030 | 0.087 | 0.501 | 0.117 |

Subsequent Cardiovascular events

After an individual has experienced a cardiovascular event, it is not possible to predict the transition to subsequent cardiovascular events using QRISK2. Instead, as with assigning first CVD events, the probability of subsequent events was estimated from the HTA evaluating statins (21). This study reported the probability of future events, conditional on the nature of the previous event. Table 20 to Table 24 report the probabilities within a year of transitioning from stable angina, unstable angina, myocardial infarction (MI), transient ischemic attack (TIA) or stroke for individuals in different age groups. The tables suggest that, for example 99.46% of individuals with stable angina will remain in the stable angina state, but 0.13%, 0.32% and 0.01% will progress to unstable angina, MI or death from coronary heart disease (CHD) respectively.

Table 20: Probability of cardiovascular event conditional on age and status of previous event (age 45-54)

| Age 45-54 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9946 | 0.0013 | 0 | 0.0032 | 0 | 0 | 0 | 0 | 0.0009 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.9127 | 0.0495 | 0 | 0 | 0 | 0 | 0.0362 | 0.0016 |
| | Unstable angina (subsequent) | 0 | 0 | 0.9729 | 0.0186 | 0 | 0 | 0 | 0 | 0.0081 | 0.0004 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.128 | 0.8531 | 0 | 0.0015 | 0 | 0.0167 | 0.0007 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0162 | 0.978 | 0 | 0.0004 | 0 | 0.0052 | 0.0002 |
| | TIA | 0 | 0 | 0 | 0.0016 | 0 | 0.9912 | 0.0035 | 0 | 0.0024 | 0.0013 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0016 | 0 | 0 | 0.0431 | 0.9461 | 0.0046 | 0.0046 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0016 | 0 | 0 | 0.0144 | 0.9798 | 0.0021 | 0.0021 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Table 21: Probability of cardiovascular event conditional on age and status of previous event (age 55-64)

| Age 55-64 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9880 | 0.0033 | 0 | 0.0057 | 0 | 0 | 0 | 0 | 0.0030 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.8670 | 0.0494 | 0 | 0 | 0 | 0 | 0.0800 | 0.0036 |
| | Unstable angina (subsequent) | 0 | 0 | 0.9415 | 0.0471 | 0 | 0 | 0 | 0 | 0.0109 | 0.0005 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.1087 | 0.8409 | 0 | 0.0047 | 0 | 0.0439 | 0.0019 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0183 | 0.9678 | 0 | 0.0015 | 0 | 0.0119 | 0.0005 |
| | TIA | 0 | 0 | 0 | 0.0029 | 0 | 0.9666 | 0.0159 | 0 | 0.0079 | 0.0068 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0029 | 0 | 0 | 0.0471 | 0.9159 | 0.0171 | 0.0171 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0029 | 0 | 0 | 0.0205 | 0.9622 | 0.0072 | 0.0072 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Table 22: Probability of cardiovascular event conditional on age and status of previous event (age 65-74)

| Age 65-74 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9760 | 0.0060 | 0 | 0.0110 | 0 | 0 | 0 | 0 | 0.0070 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.8144 | 0.0479 | 0 | 0 | 0 | 0 | 0.1319 | 0.0059 |
| | Unstable angina (subsequent) | 0 | 0 | 0.9021 | 0.0844 | 0 | 0 | 0 | 0 | 0.0129 | 0.0006 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.0948 | 0.8106 | 0 | 0.0098 | 0 | 0.0811 | 0.0036 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0183 | 0.9585 | 0 | 0.0032 | 0 | 0.0191 | 0.0008 |
| | TIA | 0 | 0 | 0 | 0.0055 | 0 | 0.9174 | 0.0423 | 0 | 0.0185 | 0.0163 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0055 | 0 | 0 | 0.0485 | 0.8673 | 0.0393 | 0.0393 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0055 | 0 | 0 | 0.0237 | 0.9412 | 0.0148 | 0.0148 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Table 23: Probability of cardiovascular event conditional on age and status of previous event (age 75-84)

| Age 75-84 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9680 | 0.0087 | 0 | 0.0163 | 0 | 0 | 0 | 0 | 0.0070 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.7366 | 0.0448 | 0 | 0 | 0 | 0 | 0.2093 | 0.0093 |
| | Unstable angina (subsequent) | 0 | 0 | 0.8360 | 0.1484 | 0 | 0 | 0 | 0 | 0.0149 | 0.0007 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.0794 | 0.7502 | 0 | 0.0200 | 0 | 0.1440 | 0.0064 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0171 | 0.9466 | 0 | 0.0066 | 0 | 0.0286 | 0.0013 |
| | TIA | 0 | 0 | 0 | 0.0082 | 0 | 0.8514 | 0.0878 | 0 | 0.0185 | 0.0342 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0082 | 0 | 0 | 0.0471 | 0.7736 | 0.0856 | 0.0856 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0082 | 0 | 0 | 0.0251 | 0.9107 | 0.0280 | 0.0280 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Table 24: Probability of cardiovascular event conditional on age and status of previous event (age 85-94)

| Age 85-94 | | To | | | | | | | | | |
|-----------|--|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9600 | 0.0114 | 0 | 0.0216 | 0 | 0 | 0 | 0 | 0.0070 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.6315 | 0.0396 | 0 | 0 | 0 | 0 | 0.3149 | 0.0140 |
| | Unstable angina (subsequent) | 0 | 0 | 0.7255 | 0.2568 | 0 | 0 | 0 | 0 | 0.0170 | 0.0008 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.0623 | 0.6498 | 0 | 0.0380 | 0 | 0.2393 | 0.0106 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0148 | 0.9311 | 0 | 0.0124 | 0 | 0.0399 | 0.0018 |
| | TIA | 0 | 0 | 0 | 0.0108 | 0 | 0.7967 | 0.1286 | 0 | 0.0185 | 0.0453 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0108 | 0 | 0 | 0.0409 | 0.6153 | 0.1665 | 0.1665 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0108 | 0 | 0 | 0.0248 | 0.8655 | 0.0494 | 0.0494 |
| | MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease | | | | | | | | | | |

Congestive Heart Failure

The review of previous economic evaluations of diabetes prevention cost-effectiveness studies found that only a small number of models had included congestive heart failure as a separate outcome. Discussion with the stakeholder group identified that the UKPDS Outcomes model would be an appropriate risk model for congestive heart failure in type 2 diabetes patients. However, it was suggested that this would not be an appropriate risk equation for individuals with normal glucose tolerance or impaired glucose tolerance. The Framingham risk equation was suggested as an alternative. The main limitation of this equation is that it is quite old and is based on a non-UK population. However, a citation search of this article did not identify a more recent or UK based alternative.

Congestive heart failure was included as a separate cardiovascular event because it was not included as an outcome of the QRISK2. The Framingham Heart Study has reported logistic regressions to estimate the 4 year probability of congestive heart failure for men and women (29). The equations included age, diabetes diagnosis (either formal diagnosis or HbA1c>6.5), BMI and systolic blood pressure to adjust risk based on individual characteristics. We used this risk equation to estimate the probability of congestive heart failure in the SPHR diabetes prevention model. Table 25 describes the covariates for the logit models to estimate the probability of congestive heart failure in men and women.

Table 25: Logistic regression coefficients to estimate the 4-year probability of congestive heart failure from the Framingham study

| Variables | Units | Regression Coefficient | OR (95% CI) | P |
|---|-------------------|------------------------|------------------|-------|
| Men | | | | |
| Intercept | | -9.2087 | | |
| Age | 10 y | 0.0412 | 1.51 (1.31-1.74) | <.001 |
| Left ventricular hypertrophy | Yes/no | 0.9026 | 2.47 (1.31-3.77) | <.001 |
| Heart rate | 10 bpm | 0.0166 | 1.18 (1.08-1.29) | <.001 |
| Systolic blood pressure | 20 mm Hg | 0.00804 | 1.17 (1.04-1.32) | 0.007 |
| Congenital heart disease | Yes/no | 1.6079 | 4.99 (3.80-6.55) | <.001 |
| Valve disease | Yes/no | 0.9714 | 2.64 (1.89-3.69) | <.001 |
| Diabetes | Yes/no | 0.2244 | 1.25 (0.89-1.76) | 0.2 |
| Women | | | | |
| Intercept | | -10.7988 | | |
| Age | 10 y | 0.0503 | 1.65 (1.42-1.93) | <.001 |
| left ventricular hypertrophy | Yes/no | 1.3402 | 3.82 (2.50-5.83) | <.001 |
| Heart rate | 100 cL | 0.0105 | 1.11 (1.01-1.23) | 0.03 |
| Systolic blood pressure | 10 bpm | 0.00337 | 1.07 (0.96-1.20) | 0.24 |
| congenital heart disease | 20 mm Hg | 1.5549 | 4.74 (3.49-6.42) | <.001 |
| Valve disease | Yes/no | 1.3929 | 4.03 (2.86-5.67) | <.001 |
| Diabetes | Yes/no | 1.3857 | 4.00 (2.78-5.74) | <.001 |
| BMI | kg/m ² | 0.0578 | 1.06 (1.03-1.09) | <.001 |
| Valve disease and diabetes | Yes/no | -0.986 | 0.37 (0.18-0.78) | 0.009 |
| *OR indicates odds ratio; CI, confidence interval; LVH, left ventricular hypertrophy; CHD, congenital heart disease; and BMI, body mass index. Predicted probability of heart failure can be calculated as: $p = 1/(1+\exp(-x\beta))$, where $x\beta = \text{Intercept} + \text{Sum (of regression coefficient*value of risk factor)}$ | | | | |

Many of the risk factors included in this risk equation were not simulated in the diabetes model. We adjusted the baseline odds of CHD to reflect the expected prevalence of these symptoms in a UK population.

The proportion of the UK population with left ventricular hypertrophy was assumed to be 5% in line with previous analyses of the Whitehall II cohort (30). The heart rate for men was assumed to be 63.0bpm and for women 65.6bpm based on data from previous Whitehall II cohort analyses (31). The prevalence of congenital heart disease was estimated from an epidemiology study in the North of England. The study reports the prevalence of congenital heart disease among live births which was used to estimate the adult prevalence (32). This may over-estimate the prevalence, because the life expectancy of births with congenital heart disease is reduced compared with the general population. However, given the low prevalence it is unlikely to impact on the results. The prevalence of valve disease was estimated from the Echocardiographic Heart of England Screening study (33).

Using the estimated population values, the intercept values were adjusted to account for the population risk in men and women. This resulted in a risk equation with age, systolic blood pressure, diabetes and BMI in women to describe the risk of congestive heart failure.

MICROVASCULAR COMPLICATIONS

The review of previous economic evaluations identified that the UKPDS data was commonly used to estimate the incidence of microvascular complications (4). This data has the advantage of being estimated from a UK diabetic population. Given that the events described in the UKPDS outcomes model are indicative of late stage microvascular complications, we did not believe it was necessary to seek an alternative model that would be representative of an impaired glucose tolerance population.

We adopted a simple approach to modelling microvascular complications. We used both versions of the UKPDS Outcomes model to estimate the occurrence of major events relating to these complications, including renal failure, amputation, foot ulcer, and blindness (15;23). These have the greatest cost and utility impact compared with earlier stages of microvascular complications, so are more likely to have an impact on the SPHR diabetes prevention outcomes. As a consequence, we assumed that microvascular complications only occur in individuals with HbA1c>6.5. Whilst some individuals with hyperglycaemia (HbA1c>6.0) may be at risk of developing microvascular complications, it is unlikely that they will progress to renal failure, amputation or blindness before a diagnosis of diabetes. Importantly, we did not assume that only individuals who have a formal diagnosis of diabetes are at risk of these complications. This allows us to incorporate the costs of undetected diabetes into the simulation.

The UKPDS includes four statistical models to predict foot ulcers, amputation with no prior ulcer, amputation with prior ulcer and a second amputation (23). In order to simplify the simulation of neuropathy outcomes we consolidated the models for first amputation with and without prior ulcer into a single equation. The parametric survival models were used to generate estimates of the cumulative hazard in the current and previous period. From which the probability of organ damage being diagnosed was estimated.

$$p(\text{Death}) = 1 - \exp(H(t) - H(t - 1))$$

The functional form for the microvascular models included exponential and Weibull. The logistic model was also used to estimate the probability of an event over the annual time interval.

Retinopathy

We used the UKPDS outcomes model v2 to estimate the incidence of blindness in individuals with HbA1c>6.5. The exponential model assumes a baseline hazard λ , which can be calculated from the model coefficients reported in Table 26 and the individual characteristics for \mathbf{X} .

$$\lambda = \exp(\beta_0 + X\beta_k)$$

Table 26: Parameters of the UKPDS2 Exponential Blindness survival model

| | Mean coefficient | Standard error | Modified mean coefficient |
|-------------------|------------------|----------------|---------------------------|
| Lambda | -11.607 | 0.759 | -10.967 |
| Age at diagnosis | 0.047 | 0.009 | 0.047 |
| HbA1c | 0.171 | 0.032 | 0.171 |
| Heart rate | 0.080 | 0.039 | |
| SBP | 0.068 | 0.032 | 0.068 |
| White Blood Count | 0.052 | 0.019 | |
| CHF History | 0.841 | 0.287 | 0.841 |
| IHD History | 0.0610 | 0.208 | 0.061 |

The age at diagnosis coefficient was multiplied by age in the current year if the individual had not been diagnosed with diabetes or by the age at diagnosis if the individual had received a diagnosis. The expected values for the risk factors not included in the SPHR model (heart rate and white blood count) were taken from Figure 3 of the UKPDS publication in which these are described (23). Assuming these mean values, it was possible to modify the baseline risk without simulating heart rate and white blood cell count.

Neuropathy

We used the UKPDS outcomes model v2 to estimate the incidence of ulcer and amputation in individuals with HbA1c > 6.5. The parameters of the ulcer and first amputation models are reported in Table 27.

Table 27: Parameters of the UKPDS2 Exponential model for Ulcer, Weibull model for first amputation with no prior ulcer and exponential model for 1st amputation with prior ulcer

| | Ulcer | | 1 st Amputation no prior ulcer | | 1 st Amputation prior ulcer | | 2 nd Amputation | |
|---------------------|----------|----------------|---|----------------|--|----------------|----------------------------|----------------|
| | Logistic | | Weibull | | Exponential | | Exponential | |
| | Mean | Standard error | Mean | Standard error | Mean | Standard error | Mean | Standard error |
| lambda | -11.295 | 1.130 | -14.844 | 1.205 | -0.881 | 1.39 | -3.455 | 0.565 |
| Rho | | | 2.067 | 0.193 | | | | |
| Age at diagnosis | 0.043 | 0.014 | 0.023 | 0.011 | -0.065 | 0.027 | | |
| Female | -0.962 | 0.255 | -0.0445 | 0.189 | | | | |
| Atrial fibrillation | | | 1.088 | 0.398 | | | | |
| BMI | 0.053 | 0.019 | | | | | | |
| HbA1c | 0.160 | 0.056 | 0.248 | 0.042 | | | 0.127 | 0.06 |
| HDL | | | -0.059 | 0.032 | | | | |
| Heart rate | | | 0.098 | 0.050 | | | | |
| MMALB | | | 0.602 | 0.180 | | | | |
| PVD | 0.968 | 0.258 | 1.010 | 0.189 | 1.769 | 0.449 | | |
| SBP | | | 0.086 | 0.043 | | | | |
| WBC | | | 0.040 | 0.017 | | | | |
| Stroke History | | | 1.299 | 0.245 | | | | |

The exponential model assumes a baseline hazard λ , which can be calculated from the model coefficients reported in Table 27 and the individual characteristics for \mathbf{X} .

$$\lambda = \exp(\beta_0 + \mathbf{X}\boldsymbol{\beta})$$

The Weibull model for amputation assumes a baseline hazard:

$$h(t) = \rho t^{\rho-1} \exp(\lambda)$$

where λ is also conditional on the coefficients and individual characteristics at time t . The logistic model for ulcer is described below.

$$\Pr(y = 1|\mathbf{X}) = \frac{\exp(\mathbf{X}\boldsymbol{\beta})}{1 + \exp(\mathbf{X}\boldsymbol{\beta})}$$

The ulcer and amputation models include a number of covariates that were not included in the simulation. As such it was necessary to adjust the statistical models to account for these measures. We estimated a value for the missing covariates and added the value multiplied by the coefficient to the baseline hazard.

The expected values for the risk factors not included in the SPHR diabetes prevention model (heart rate, white blood count, micro-/macroalbuminuria, peripheral vascular disease and atrial fibrillation)

were taken from Figure 3 of the UKPDS publication in which these are described (23). In the ulcer model we assumed that 2% of the population had peripheral vascular disease.

The amputation risk model with a history of ulcer was not included in the simulation, but was used to estimate an additional log hazard ratio to append onto the amputation model without a history of ulcer. The log hazard was estimated for each model assuming the same values for other covariates. The difference in the log hazard between the two models was used to approximate the log hazard ratio for a history of ulcer in the amputation model (10.241). The final model specifications are reported in Table 28.

Table 28: Coefficients estimates for Ulcer and 1st Amputation

| | Ulcer | | 1 st Amputation | | 2 nd Amputation | |
|------------------|----------|----------------|----------------------------|----------------|----------------------------|----------------|
| | Logistic | | Weibull | | Exponential | |
| | Mean | Standard error | Mean | Standard error | Mean | Standard error |
| Lambda | -11.276 | 1.13 | -13.954 | 1.205 | -3.455 | 0.565 |
| Rho | | | 2.067 | 0.193 | | |
| Age at Diagnosis | 0.043 | 0.014 | 0.023 | 0.011 | | |
| Female | -0.962 | 0.255 | -0.445 | 0.189 | | |
| BMI | 0.053 | 0.019 | | | | |
| HbA1c | 0.160 | 0.056 | 0.248 | 0.042 | 0.127 | 0.06 |
| HDL | | | -0.059 | 0.032 | | |
| Stroke | | | 1.299 | 0.245 | | |
| Foot Ulcer | | | 10.241 | | | |

Nephropathy

We used the UKPDS outcomes model v1 to estimate the incidence of renal failure in individuals with HbA1c > 6.5. Early validation analyses identified that the UKPDS v2 model implemented in the SPHR model substantially overestimated the incidence of renal failure. The Weibull model for renal failure assumes a baseline hazard:

$$h(t) = \rho t^{\rho-1} \exp(\lambda)$$

where λ is also conditional on the coefficients and individual characteristics at time t . The parameters of the renal failure risk model are reported in Table 29.

Table 29: Parameters of the UKPDS2 Weibull renal failure survival model

| | Mean | Standard error |
|-----------------|---------|----------------|
| Lambda | -10.016 | 0.939 |
| Shape parameter | 1.865 | 0.387 |
| SBP | 0.404 | 0.106 |
| BLIND History | 2.082 | 0.551 |

CANCER

The conceptual model identified breast cancer and colorectal cancer risk as being related to BMI. However, these outcomes were not frequently included in previous cost-effectiveness models for diabetes prevention. Discussion with stakeholders identified the EPIC Norfolk epidemiology cohort study as a key source of information about cancer risk in a UK population. Therefore, we searched publications from this cohort to identify studies reporting the incidence of these risks. In order to obtain the best quality evidence for the relationship between BMI and cancer risk we searched for a recent systematic review and meta-analysis using key terms ‘Body Mass Index’ and ‘Cancer’, filtering for meta-analysis studies.

Breast cancer

Incidence rates for breast cancer in the UK were estimated from the European Prospective Investigation of Cancer (EPIC) cohort. This is a large multi-centre cohort study looking at diet and cancer. In 2004 the UK incidence of breast cancer by menopausal status was reported in a paper from this study investigating the relationship between body size and breast cancer (34). The estimates of the breast cancer incidence in the UK are reported in Table 30.

Table 30: UK breast cancer incidence

| | Number of Cases | Person Years | Mean BMI | Incidence Rate of per person-year | Reference |
|-------------------|-----------------|--------------|----------|-----------------------------------|-----------|
| UK pre-menopause | 102 | 103114.6 | 24 | 0.00099 | (34) |
| UK post-menopause | 238 | 84214.6 | 24 | 0.00283 | (34) |

A large meta-analysis that included 221 prospective observational studies has reported relative risks of cancers per unit increase in BMI, including breast cancer by menopausal status (35). We included a risk adjustment in the model so that individuals with higher BMI have a higher probability of pre- and post-menopausal breast cancer (35). In the simulation we adjusted the incidence of breast cancer by multiplying the linear relative risk by the difference in the individual’s BMI and the average BMI reported in the EPIC cohort. The relative risk and confidence intervals per 5mg/m² increase in BMI are reported in Table 31.

Table 31: Relative risk of Breast cancer by BMI

| | Mean Relative risk | 2.5 th Confidence Interval | 97.5 th Confidence Interval | Reference |
|-------------------|--------------------|---------------------------------------|--|-----------|
| UK pre-menopause | 0.89 | 0.84 | 0.94 | (35) |
| UK post-menopause | 1.09 | 1.04 | 1.14 | (35) |

Colorectal cancer

Incidence rates for colorectal cancer in the UK were reported from the European Prospective Investigation of Cancer (EPIC) cohort. The UK incidence of colorectal cancer is reported by gender in a paper from this study investigating the relationship between body size and colon and rectal cancer (34). The estimates of the colorectal cancer incidence are reported in Table 32.

Table 32: UK colorectal cancer incidence

| | Number of Cases | Person Years | Mean Age | Mean BMI | Incidence Rate of per person-year | Reference |
|--------|-----------------|--------------|----------|----------|-----------------------------------|-----------|
| Male | 125 | 118468 | 53.1 | 25.4 | 0.00106 | (36) |
| Female | 145 | 277133 | 47.7 | 24.5 | 0.00052 | (36) |

The risk of colorectal cancer has been linked to obesity. We included a risk adjustment in the model to reflect observations that the incidence of breast cancer is increased in individuals with higher BMI. A large meta-analysis that included 221 prospective observational studies has reported relative risks of BMI and cancers, including colon cancer by gender (35). We selected linear relative risk estimates estimated from pooled European and Australian populations. In the simulation we adjusted the incidence of colorectal cancer by multiplying the relative risk by the difference in the individual's BMI and the average BMI reported in the EPIC cohort. The relative risk and confidence intervals per 5mg/m² increase in BMI are reported in Table 33.

Table 33: Relative risk of colon cancer by BMI

| | Mean Relative risk | 2.5 th Confidence Interval | 97.5 th Confidence Interval | Reference |
|-------------------|--------------------|---------------------------------------|--|-----------|
| UK pre-menopause | 1.21 | 1.18 | 1.24 | (35) |
| UK post-menopause | 1.04 | 1 | 1.07 | (35) |

OSTEOARTHRITIS

The stakeholder group requested that BMI and diabetes be included as independent risk factors for osteoarthritis based on recent evidence (37). Osteoarthritis had not been included as a health state in previous cost-effectiveness models. A search for studies using key words 'Diabetes', 'Osteoarthritis' and 'Cohort Studies' did not identify a UK based study with diabetes and BMI included as independent covariates in the risk model. The Bruneck cohort, a longitudinal study of inhabitants of a town in Italy reported diabetes and BMI as independent risk factors for osteoarthritis (37). The cohort may not be representative of the UK. However, the individuals are from a European country, the study has a large sample size and has estimated the independent effects of BMI and diabetes on the risk of osteoarthritis. No UK based studies identified in our searches met these requirements. The data used to estimate the incidence of osteoarthritis is reported in Table 34.

Table 34: Incidence of osteoarthritis and estimated risk factors

| | No cases | Person years | Mean BMI | Incidence rate | Reference |
|-------------|--------------|--------------|----------|----------------|-----------------------------|
| No diabetes | 73 | 13835 | 24.8 | 0.0053 | (37) |
| | Hazard ratio | 2.5th | 97.5th | | Reference |
| HR Diabetes | 2.06 | 1.11 | 3.84 | | (37) |
| HR BMI | 1.076 | 1.023 | 1.133 | | (37) Personal communication |

DEPRESSION

Depression was not included as a health state in previous cost-effectiveness models for diabetes prevention. However, a member of the stakeholder group identified that a relationship between diabetes and depression was included in the CORE diabetes treatment model (38). With this in mind, we decided to include depression as a health state in the model, but not to model its severity.

Some individuals enter the simulation with depression at baseline according to individual responses in the Health Survey for England 2011 questionnaire. Depression is described as a chronic state from which individuals do not completely remit. We did not estimate the effect of depression on the longitudinal changes for BMI, glycaemia, systolic blood pressure and cholesterol. As a consequence it was not possible to relate the impact of depression to the incidence of diabetes and CVD risk.

In the simulation, individuals can develop depression in any cycle of the model. The baseline incidence of depression among all individuals without a history of depression was estimated from a study examining the bidirectional association between depressive symptoms and type 2 diabetes (39). Although the study was not from a UK population, the US cohort included ethnically diverse men and women aged 45 to 84 years. We assumed that diagnosis of diabetes and/or cardiovascular disease increases the incidence of depression in individuals who do not have depression at baseline. We identified a method for inflating risk of depression for individuals with diabetes from the US cohort study described above (39). The risk of depression in individuals who have had a stroke was also inflated according to a US cohort study (40). Odds of depression and odds ratios for inflated risk of depression due to diabetes or stroke are presented in Table 35.

Table 35: Baseline incidence of depression

| Baseline Risk of depression | Mean | 2.5 th CI | 97.5 th |
|------------------------------|--------|----------------------|--------------------|
| Depression cases in NGT | 336 | | |
| Person years | 9139 | | |
| Odds of depression | 0.0382 | | |
| Log odds of depression | -3.266 | | |
| Inflated risk for Diabetes | | | |
| Odds ratio of diabetes | 1.52 | 1.09 | 2.12 |
| Log odds ratio of diabetes | 0.419 | | |
| Inflate risk of stroke | | | |
| Odds ratio of stroke | 6.3 | 1.7 | 23.2 |
| Log odds ratio stroke | 1.8406 | | |
| NGT Normal Glucose Tolerance | | | |

MORTALITY

Cardiovascular Mortality

Cardiovascular mortality is included as an event within the QRISK2 and the probability of subsequent cardiovascular events obtained from an HTA assessing statins (21) as described in the cardiovascular disease section above.

Cancer Mortality

Cancer mortality rates were obtained from the Office of National statistics (41). The ONS report one and five year net survival rates for various cancer types, by age group and gender. Net survival was an estimate of the probability of survival from the cancer alone. It can be interpreted as the survival of cancer patients after taking into account the background mortality that the patients would have experienced if they had not had cancer.

The age-adjusted 5-year survival rate for breast cancer and colorectal cancer were used to estimate an annual risk of mortality assuming a constant rate of mortality. We assume that the mortality rate does not increase due to cancer beyond 5 years after cancer diagnosis. The five year survival rate for breast cancer is 84.3%, which translated into a 3.37% annual probability of death from breast cancer. The five year survival rate for persons with colorectal cancer is 55.3%, which translated into an 11.16% annual probability of death from colorectal cancer.

Other cause Mortality (including diabetes risk)

Other cause mortality describes the risk of death from any cause except cardiovascular disease and cancer. All-cause mortality rates by age and sex were extracted from the Office of National Statistics (42). The mortality statistics report the number of deaths by ICD codes for 5-year age groups. We subtracted the number of cardiovascular disease, breast and colorectal cancer related deaths from the all-cause mortality total to estimate other cause mortality rates by age and sex (Table 33).

Table 36: All cause and derived other cause mortality from the Office of National statistics

| | All cause | | Other cause | | | All cause | | Other cause | |
|----|-----------|--------|-------------|--------|-----|-----------|--------|-------------|--------|
| | Men | Women | Men | Women | | Men | Women | Men | Women |
| 1 | 0.0004 | 0.0003 | 0.0003 | 0.0003 | 51 | 0.0034 | 0.0024 | 0.0025 | 0.0017 |
| 2 | 0.0002 | 0.0002 | 0.0002 | 0.0002 | 52 | 0.0039 | 0.0026 | 0.0029 | 0.0019 |
| 3 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 53 | 0.0044 | 0.0028 | 0.0032 | 0.0020 |
| 4 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 54 | 0.0045 | 0.0032 | 0.0034 | 0.0022 |
| 5 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 55 | 0.0051 | 0.0033 | 0.0037 | 0.0024 |
| 6 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 56 | 0.0057 | 0.0037 | 0.0041 | 0.0027 |
| 7 | 0.0001 | 0.0001 | 0.0001 | 0.0000 | 57 | 0.0061 | 0.0041 | 0.0044 | 0.0030 |
| 8 | 0.0001 | 0.0001 | 0.0001 | 0.0000 | 58 | 0.0069 | 0.0041 | 0.0050 | 0.0030 |
| 9 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 59 | 0.0071 | 0.0050 | 0.0052 | 0.0036 |
| 10 | 0.0001 | 0.0000 | 0.0001 | 0.0000 | 60 | 0.0081 | 0.0054 | 0.0059 | 0.0040 |
| 11 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 61 | 0.0086 | 0.0057 | 0.0063 | 0.0042 |
| 12 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 62 | 0.0096 | 0.0062 | 0.0070 | 0.0046 |
| 13 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 63 | 0.0104 | 0.0067 | 0.0076 | 0.0050 |
| 14 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 64 | 0.0108 | 0.0072 | 0.0079 | 0.0053 |
| 15 | 0.0002 | 0.0001 | 0.0002 | 0.0001 | 65 | 0.0125 | 0.0082 | 0.0091 | 0.0061 |
| 16 | 0.0002 | 0.0001 | 0.0002 | 0.0001 | 66 | 0.0141 | 0.0090 | 0.0103 | 0.0067 |
| 17 | 0.0003 | 0.0002 | 0.0003 | 0.0002 | 67 | 0.0148 | 0.0097 | 0.0108 | 0.0072 |
| 18 | 0.0004 | 0.0002 | 0.0004 | 0.0002 | 68 | 0.0162 | 0.0107 | 0.0118 | 0.0079 |
| 19 | 0.0004 | 0.0002 | 0.0004 | 0.0002 | 69 | 0.0181 | 0.0118 | 0.0132 | 0.0087 |
| 20 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 70 | 0.0218 | 0.0138 | 0.0157 | 0.0101 |
| 21 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 71 | 0.0234 | 0.0145 | 0.0168 | 0.0106 |
| 22 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 72 | 0.0252 | 0.0167 | 0.0182 | 0.0122 |
| 23 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 73 | 0.0269 | 0.0173 | 0.0193 | 0.0127 |
| 24 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 74 | 0.0310 | 0.0200 | 0.0223 | 0.0147 |
| 25 | 0.0006 | 0.0003 | 0.0006 | 0.0002 | 75 | 0.0327 | 0.0222 | 0.0233 | 0.0157 |
| 26 | 0.0006 | 0.0003 | 0.0005 | 0.0002 | 76 | 0.0375 | 0.0249 | 0.0267 | 0.0176 |
| 27 | 0.0006 | 0.0004 | 0.0005 | 0.0003 | 77 | 0.0411 | 0.0284 | 0.0293 | 0.0202 |
| 28 | 0.0007 | 0.0003 | 0.0006 | 0.0003 | 78 | 0.0458 | 0.0321 | 0.0326 | 0.0228 |
| 29 | 0.0007 | 0.0003 | 0.0006 | 0.0003 | 79 | 0.0523 | 0.0358 | 0.0372 | 0.0254 |
| 30 | 0.0007 | 0.0004 | 0.0006 | 0.0003 | 80 | 0.0585 | 0.0411 | 0.0418 | 0.0289 |
| 31 | 0.0008 | 0.0004 | 0.0007 | 0.0004 | 81 | 0.0652 | 0.0456 | 0.0465 | 0.0321 |
| 32 | 0.0007 | 0.0005 | 0.0007 | 0.0004 | 82 | 0.0745 | 0.0530 | 0.0531 | 0.0372 |
| 33 | 0.0008 | 0.0005 | 0.0007 | 0.0004 | 83 | 0.0833 | 0.0606 | 0.0594 | 0.0426 |
| 34 | 0.0009 | 0.0005 | 0.0008 | 0.0004 | 84 | 0.0931 | 0.0678 | 0.0664 | 0.0476 |
| 35 | 0.0010 | 0.0006 | 0.0008 | 0.0005 | 85 | 0.1040 | 0.0760 | 0.0738 | 0.0537 |
| 36 | 0.0011 | 0.0006 | 0.0010 | 0.0005 | 86 | 0.1147 | 0.0872 | 0.0814 | 0.0617 |
| 37 | 0.0013 | 0.0006 | 0.0011 | 0.0005 | 87 | 0.1300 | 0.0977 | 0.0923 | 0.0692 |
| 38 | 0.0013 | 0.0007 | 0.0011 | 0.0006 | 88 | 0.1468 | 0.1106 | 0.1042 | 0.0782 |
| 39 | 0.0013 | 0.0007 | 0.0011 | 0.0006 | 89 | 0.1643 | 0.1242 | 0.1166 | 0.0879 |
| 40 | 0.0015 | 0.0009 | 0.0012 | 0.0006 | 90 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 41 | 0.0016 | 0.0010 | 0.0013 | 0.0007 | 91 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 42 | 0.0018 | 0.0010 | 0.0015 | 0.0008 | 92 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 43 | 0.0018 | 0.0012 | 0.0015 | 0.0009 | 93 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 44 | 0.0020 | 0.0012 | 0.0017 | 0.0009 | 94 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 45 | 0.0022 | 0.0014 | 0.0017 | 0.0010 | 95 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 46 | 0.0023 | 0.0016 | 0.0018 | 0.0011 | 96 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 47 | 0.0023 | 0.0015 | 0.0018 | 0.0011 | 97 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 48 | 0.0027 | 0.0017 | 0.0021 | 0.0012 | 98 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 49 | 0.0028 | 0.0019 | 0.0022 | 0.0014 | 99 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 50 | 0.0030 | 0.0021 | 0.0023 | 0.0015 | 100 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |

The rate of other cause mortality by age and sex was treated as the baseline hazard. Following input from stakeholders, an increased risk of mortality was assigned to individuals with diabetes using data

1
2
3 from a published meta-analysis (43). This study used data from 820,900 people from 97 prospective
4 studies to calculate hazard ratios for cause-specific death, according to baseline diabetes status (43).
5 Cause of death was separated into vascular disease, cancer and other cause mortality. From this study
6 we estimated that individuals with a diagnosis of diabetes have a fixed increased risk of other cause
7 mortality (Hazard ratio 1.8 (95% CI 1.71-1.9)). The estimates reported in the meta-analysis include
8 increased risk of death from renal disease, therefore mortality from renal disease was not simulated
9 separately to avoid double counting of benefits.
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14 UTILITIES

15 **Baseline Utility**

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18
19 Baseline utilities for all individuals in the cohort were extracted from the HSE 2011. The tariffs for
20 the responses to the 3 level EQ-5D were derived from a UK population study (44). Baseline utility
21 was assumed to decline due to ageing. In the simulation, utility declines by an absolute decrement of
22 0.004 per year. This estimate is based on previous HTA modelling in cardiovascular disease (21).
23
24
25

26 **Utility Decrements**

27
28 The utility decrements for long term chronic conditions were applied to the age and BMI adjusted
29 EQ-5D score. It was assumed that a diagnosis of diabetes was not associated with a reduction in EQ-
30 5D independent of the utility decrements associated with complications, comorbidities or depression.
31 Cardiovascular disease, renal failure, amputation, foot ulcers, blindness, cancer, osteoarthritis and
32 depression were all assumed to result in utility decrements. The utility decrements are measured as a
33 factor which is applied to the individual's age and BMI adjusted baseline. If individuals have multiple
34 chronic conditions the utility decrements are multiplied together to give the individual's overall utility
35 decrement from comorbidities and complications, in line with current NICE guidelines for combining
36 comorbidities (45).
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43 Due to the number of health states it was not practical to conduct a systematic review to identify
44 utility decrements for all health states. A pragmatic approach was taken to search for health states
45 within existing health technology assessments for the relevant disease area or by considering studies
46 used in previous economic models for diabetes prevention. Discussions with experts in health
47 economic modelling were also used to identify prominent sources of data for health state utilities.
48
49
50

51 Two sources of data were identified for diabetes related complications. A recent study from the
52 UKPDS estimated the impact of changes in health states from a longitudinal cohort (46). They
53 estimated the impact of myocardial infarction, ischaemic heart disease, stroke, heart failure,
54 amputation and blindness on quality of life using seven rounds of EQ-5D questionnaires administered
55 between 1997 and 2007. This data was used to estimate the utility decrement for amputation and
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3 congestive heart failure. The absolute decrement for amputation was converted into utility decrement
4 factors that could be multiplied by the individuals' current EQ-5D to estimate the relative effect of the
5 complication.
6

7
8 Utility decrements for renal failure and foot ulcers were not available from the UKPDS study
9 described above. A study by Coffey et al. (2000) was used to estimate utility decrements for renal
10 failure and foot ulcers (47). In this study, 2,048 subjects with type 1 and type 2 diabetes were
11 recruited from specialty clinics. The Self-Administered Quality of Well Being index (QWB-SA) was
12 used to calculate a health utility score.
13

14
15
16 Utility decrements for cardiovascular events were taken from an HTA assessing statins to reflect the
17 utility decrements in all patients (21) rather than using the UKPDS, which is only representative of a
18 diabetic population. The study conducted a literature review to identify appropriate utility multipliers
19 for stable angina, unstable angina, myocardial infarction and stroke. We used these estimates in the
20 model and assume that transient ischaemic attack is not associated with a utility decrement in line
21 with this HTA.
22
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25
26 A systematic review of breast cancer utility studies was identified following consultation with
27 colleagues with experience in this area. The review highlighted a single burden of illness study with a
28 broad utility decrement for cancer (48), rather than utilities by cancer type or disease status. This
29 study was most compatible with the structure of the cost-effectiveness structure. Within this study
30 1823 cancer survivors and 5469 age-, sex-, and educational attainment-matched control subjects
31 completed EQ-5D questionnaires to estimate utility with and without cancer.
32
33

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36 The utility decrement for osteoarthritis was taken from a Health Technology Assessment that assessed
37 the clinical effectiveness and cost-effectiveness of glucosamine sulphate/hydrochloride and
38 chondroitin sulphate in modifying the progression of osteoarthritis of the knee (49).
39
40

41
42 A review of cost-effectiveness studies highlights the scarcity of studies of health-related quality of life
43 in depression (50). The utility studies identified in the review described depression states by severity
44 and did not adjust for comorbid conditions. Furthermore, the valuations were variable between studies
45 suggesting poor consistency in the estimations. Therefore, it was difficult to apply these in the model.
46 We decided to use a study which had used the EQ-5D in an RCT, for consistency with our utility
47 measure (51). They report an average post treatment utility of 0.67, from which we estimated the
48 utility decrement compared with the average utility reported in the HSE dataset. The decrement was
49 then converted into a relative utility reduction.
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54 Table 37 reports the multiplicative utility factors that are used in the model to describe health utility
55 decrements from comorbid complications. The mean absolute decrement estimated in each study is
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reported alongside the baseline utility for each study. The utility factor was estimated by dividing the implied health utility with the comorbidity by the baseline utility.

Table 37: Utility decrement factors

| | Mean Absolute decrement | St. error absolute decrement | Baseline Utility | Multiplicative Utility Factor | Source |
|---|-------------------------|------------------------------|------------------|-------------------------------|----------------|
| Foot ulcer | -0.099 | 0.013 | 0.689 | 0.856 | Coffey (47) |
| Amputation | -0.172 | 0.045 | 0.807 | 0.787 | UKPDS (52) |
| Blind | 0.033 | 0.027 | 0.807 | 1.041 | UKPDS (52) |
| Renal failure | -0.078 | 0.026 | 0.689 | 0.887 | Coffey (47) |
| Stable Angina | | | | 0.801 | Ward HTA (21) |
| Unstable Angina y1 | | | | 0.770 | Ward HTA (21) |
| Unstable Angina y2 | | | | 0.770 | Ward HTA (21) |
| Myocardial Infarction y1 | | | | 0.760 | Ward HTA (21) |
| Myocardial Infarction y2 | | | | 0.760 | Ward HTA (21) |
| Transient Ischaemic Attack | | | | 1.000 | Ward HTA (21) |
| Stroke y1 | | | | 0.629 | Ward HTA (21) |
| Stroke y2 | | | | 0.629 | Ward HTA (21) |
| Breast Cancer | -0.060 | | 0.800 | 0.913 | Yabroff (48) |
| Colorectal Cancer | -0.060 | | 0.800 | 0.913 | Yabroff (48) |
| Osteoarthritis | -0.101 | | | | Black HTA (49) |
| Depression | -0.116 | | 0.7905 | 0.875 | Benedict (51) |
| Congestive Heart Failure | -0.101 | 0.032 | | 0.875 | UKPDS (52) |
| UKPDS baseline utility 0.807; HSE baseline 0.7905 | | | | | |

COSTS

At any given time period of the model individuals can have multiple health complications that incur direct healthcare costs. Some of the health states are mutually exclusive; however an individual can accrue multiple complications within the model. Each health state is associated with an average cost, which is accrued by all individuals for every time period for which the state is indicated. Resource use for each comorbidity is added together and no savings are assumed to be made from the use of the same resources for two or more comorbidities for an individual. An exception to this is an assumed adjustment to the utilisation of GP services for individuals with chronic diseases. In the majority of cases it is assumed that the unit costs of healthcare for someone with ID would be the same as the unit costs for an individual in the general population. The exception was cost for a GP appointment, which was expected to be 40% higher than in the general population due to increased length of consultation. All costs were inflated to 2014/15 values using the retail price index where necessary, from the Personal Social Services Research Unit (PSSRU) sources of information (53). Table 38 shows a summary of all the unit costs used in the model and their sources.

Table 38: Summary of all drug, treatment, care and resource costs included in the model

| | Drug, Treatment, Care and Resource Costs of | Cost per year/ incident in 2014/15 prices (* 2006 prices) | Source |
|--|---|--|------------|
| Screening and Intervention costs | | | |
| | Intervention per person | £270 | PHE |
| First line diabetes treatment - low cost diabetes monotherapy | | | |
| | Ongoing costs of diabetes monotherapy – made up of... | £79.06 | |
| | Metformin 500 mg <i>bid</i> standard (85% of patients) or modified release (15%) tablets | £18.83 | BNF (54) |
| | Nurse at GP (consultation) | £25.52 | PSSRU (53) |
| | Health care assistant (10 mins) | £3.40 | PSSRU (53) |
| | Urine sample | £1.00 | (55) |
| | Eye screening | £24.31 | (56) |
| | Lab tests – made up of... | £6.00 | |
| | <i>HbA1c test</i> | £3.00 | (55) |
| | <i>Lipids test</i> | £1.00 | (55) |
| | <i>Liver function test</i> | £1.00 | (55) |
| | <i>B12 test</i> | £1.00 | (55) |
| | Additional first year costs of diabetes monotherapy – made up of... | £103 | |
| | Nurse at GP (2 x consultations) | £51.03 | PSSRU (53) |
| | Health care assistant (2 x 10 mins) | £6.80 | PSSRU (53) |
| | Urine sample (x2) | £2.00 | (55) |
| | Lab tests as above (x2) | £12.00 | (55) |
| | Smoking cessation (central estimate of cost of nicotine replacement therapy) taken up by 50% of the assumed 20% of population who smoke | £30.90 | PSSRU (53) |
| | Second line diabetes treatment - Metformin and Gliptins– made up of... | £529 | |
| | Sitagliptin 100 mg daily | £434 | BNF (54) |
| | Metformin 500 mg <i>bid</i> standard (85% of patients) or modified release (15%) tablets | £85 | BNF (54) |
| | Self-monitoring strips (82 per annum) (57) | £16.36 | BNF (54) |
| | Nurse at GP (consultation) | £25.52 | (53) |
| | Health care assistant (10 mins) | £3.40 | (53) |
| | Urine sample | £1.00 | (55) |
| | Eye screening | £24.31 | (56) |
| | Lab tests as for first line treatment | £6.00 | (55) |
| | Third line diabetes treatment - Insulin and oral anti-diabetics – made up of... | £1,503 | |
| | Nurse at GP (3 x consultations) | £76.55 | PSSRU (53) |
| | Health care assistant (3 x 10 mins) | £10.21 | PSSRU (53) |
| | Urine sample (x3) | £3.00 | (55) |
| | Eye screening | £24.31 | (56) |
| | Lab tests as for first line treatment (x3) | £18.00 | (55) |
| | Insulin treatment costs – made up of... | £1,376 | |
| | <i>Glargine</i> | £830.83 | (58) |
| | <i>Oral anti-diabetics</i> | £57.75 | (58) |
| | <i>Reagent test strips</i> | £292.74 | (58) |
| | <i>Hypoglycaemic rescue</i> | £30.98 | (58) |
| | <i>Pen delivery devices</i> | £72.44 | (58) |
| | <i>Sharps</i> | £90.98 | (58) |

| | | | |
|--|--|---------|------------|
| Other primary care costs | | | |
| | GP visit (17 minutes) | £46.95 | PSSRU (53) |
| | Diagnosis of hypertension (including ambulatory blood pressure monitoring) | £56.51 | (19) |
| | Annual treatment with statins (simvastatin 20 mg <i>bid</i>) | £26.59 | BNF (54) |
| | Annual treatment with anti-hypertensives | £195.94 | (59) |
| Cardiovascular disease costs | | | |
| | Unstable Angina year 1: <i>Secondary care costs: 100% hospitalisation, 50% revascularisation procedure, three outpatient appointments.</i> <i>Primary care costs (three GP visits) and medications</i> | £4,674 | (20) |
| | Myocardial infarction year 1 <i>Secondary care costs: 100% hospitalisation, 50% revascularisation procedure, three outpatient appointments.</i> <i>Primary care costs (three GP visits) and medications.</i> | £4,813 | (20) |
| | Subsequent ACS care costs <i>Secondary care costs (one outpatient appointment).</i> <i>Primary care costs (three GP visits) and medications.</i> | £410 | (20) |
| | Stroke year 1 (NHS costs) <i>Costs of acute events reported in Youman et al. (60) weighted by the distribution of severity of stroke (21).</i> | £9,716 | (60) |
| | Social care costs of stroke in subsequent years <i>The costs of ongoing care at home or in an institution weighted by the distribution of severity of stroke and discharge locations.</i> | £2,730 | (20) |
| | Fatal coronary heart disease <i>Assumed that 50% of fatalities incurred cost.</i> | £713 | (61) |
| | Fatal non cardiac vascular event <i>Assumed that 50% of fatalities incurred cost.</i> | £4,443 | (60) |
| | Congestive heart failure | £3,091 | UKPDS (62) |
| Other complications of diabetes costs | | | |
| | Renal failure – weighted composite of... | £25,046 | |
| | <i>Haemodialysis with overheads</i> | £42,049 | (63) |
| | <i>Automated peritoneal dialysis</i> | £27,217 | (63) |
| | <i>Continuous ambulatory peritoneal dialysis</i> | £19,742 | (63) |
| | <i>Transplant (year 1)</i> | £23,660 | (64) |
| | <i>Immunosuppressant (10 years)</i> | £6,959 | (64) |
| | Foot ulcers | £216 | (65) |
| | Amputation first year | £10,101 | UKPDS (66) |
| | Amputation subsequent years | £1,896 | UKPDS (66) |
| | Blindness first year | £1,434 | UKPDS (66) |
| | Blindness subsequent years | £479 | UKPDS (66) |
| | Breast cancer | £13,818 | (67) |
| | Colorectal cancer | £18,729 | (68) |
| | Osteoarthritis | £962 | (69) |
| | Depression - made up of... | £137 | (70) |
| | <i>Practice nurse at surgery</i> | £13.70 | |
| | <i>Practice nurse at home visit</i> | £0.54 | |
| | <i>Practice nurse telephone</i> | £0.99 | |
| | <i>Health visitor</i> | £1.94 | |
| | <i>District nurse</i> | £0.38 | |
| | <i>Other nurse</i> | £1.17 | |
| | <i>HCA phlebotomist</i> | £1.05 | |

| | | | | |
|--|--|-------------------------------|-------|--|
| | | <i>Other primary care</i> | £4.85 | |
| | | <i>Out of hours</i> | £6.18 | |
| | | <i>NHS direct</i> | £2.28 | |
| | | <i>Walk-in centre</i> | £8.15 | |
| | | <i>Prescribed medications</i> | £74 | |
| | | <i>Secondary care</i> | £21 | |
| Assumed 20% smoking prevalence and 50% uptake of smoking cessation services SANG Stable angina; UANG unstable angina; MI myocardial infarction; TIA transient ischemic attack; CHD congestive heart failure; ACS acute Coronary Syndrome; UKPDS United Kingdom prospective Diabetes Study. Assume | | | | |

Opportunistic screening

Recent guidelines for hypertension have recommended that hypertension be confirmed with ambulatory blood pressure monitoring (ABPM) (18). The cost of ABPM assessment is included in the cost of diagnosis (£53.40) (19), however, we assume that the test does not alter the initial diagnosis.

A cost of diabetes diagnosis is included in the model based on the cost of an HbA1c test.

The cost of screening for high cardiovascular risk was not included as a cost associated with initiation with statins because most GP practices in the UK routinely commission and use cardiovascular risk scores that are easy to access within a normal consultation.

Diabetes

A three stage diabetes treatment regimen is applied in the model as a trade-off between model simplicity and capturing key cost differences between the interventions. At diagnosis all patients are prescribed low cost treatments, represented by Metformin (weighted average of standard and modified release) to describe the average cost of these medications. If HbA1c increases above 7.4% the individual is prescribed the more expensive Gliptins in addition to Metformin, based on a recent HTA (71). For costing purposes the second drug to be added to Metformin was assumed to be Sitagliptin. The individual continues to receive Metformin plus Gliptins for a period of time until they require insulin. Within the model the individual is switched to insulin in the first annual cycle at which HbA1c exceeds 8.5% (71). The insulin Glargine was chosen to represent insulin treatment in the UK. The cost of diabetes in the year of diagnosis is assumed to be greater than subsequent years because the individual will receive more contact time whilst their diabetes is being controlled.

Other Primary Care Costs

Individuals who are prescribed statins receive a daily dose of 40mg of generic Simvastatin. The individual remains on statins for the rest of their life. A unit cost of anti-hypertensives was obtained from a 2004 study (59) and inflated to 2014/15 prices. Due to the number of different anti-hypertensive treatments available and possibilities for combination therapies, using the cost from this study of prescriptions was preferred to using costs directly from the BNF. The stakeholder group

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3 advised that attendance at visits to monitor cardiovascular risk on statins and anti-hypertensives are
4 not perfect. Therefore, the costs of GP attendance to monitor blood pressure and cardiovascular risk
5 are assumed to be accounted for within the model for GP attendance.
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8 **Cardiovascular costs**

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10 Costs for cardiovascular disease were obtained from a 2009 HTA for high dose lipid-lowering therapy
11 (20). Table 38 shows the details of included costs. The costs of fatal stroke and MI were obtained
12 from two separate studies (60;61), and it was assumed that 50% of individuals would incur these costs.
13 The costs of congestive heart failure were estimated from the UKPDS costing study for complications
14 related to diabetes (62).
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18 **Microvascular costs**

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20 The cost of renal failure was estimated from three studies reporting the costs of dialysis type (63), the
21 costs of transplantation (64) and the prevalence of dialysis and transplant (72). The overall cost was
22 estimated as a weighted average of the treatment outcomes.
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26 The cost of foot ulcers was estimated from a US Cost of Illness study (65). A search of the literature
27 did not identify any UK based studies. The costs were converted from dollars to pounds using
28 Purchasing Power Parities reported by the OECD (73).
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30

31 The costs of amputation and blindness in the first year of surgery and in subsequent years were
32 reported in a recent UKPDS costing study (66).
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34

35 **Costs of Other Comorbidities**

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37 Disease progression for breast cancer and colorectal cancer was not included in the model. Therefore,
38 a lifetime cost of cancer care was imposed at diagnosis in the model. Costs for breast and colon cancer
39 were taken from two screening appraisals (67;68). Breast cancer costs were estimated as a weighted
40 average depending on the prognosis at diagnosis, whereas colon cancer costs were estimated as a
41 weighted average depending on the Dukes tumour stage.
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46 The annual cost of osteoarthritis was estimated in a costing study (69). In this report the authors
47 estimated the expected cost of osteoarthritis from three previous costing studies. The costs include GP
48 attendance, nurse consultations, replacement surgery, help at home and prescription medications.
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51 A recent trial to prevent secondary depressive episodes collected comprehensive cost data from a
52 sample of individuals with depression (70). The resource uses identified in the control arm were
53 extracted to estimate the costs of depression. The costs from this data were not implemented directly
54 into the model; this would have over-estimated the number of GP visits as the model already accounts
55 for GP attendance due to depression. Therefore, a revised estimate of the cost of depression,
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3 excluding GP consultation was estimated using updated unit costs. Given that this cost captures the
4 costs of depression following the first acute episode we assumed that this cost adequately described
5 the ongoing healthcare costs for individuals with a history of depression. It is possible that this will
6 overestimate costs for patients who successfully remit and avoid future depression. However, there is
7 evidence from the literature to suggest that individuals with a history of depression have a high
8 utilisation of healthcare resources to support this assumption (74).
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12 **INTERVENTION**

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16 The subgroup analysis estimates the per person cost savings and health outcomes of delivering the
17 DPP lifestyle intervention in the 22 chosen subgroups. Interventions will be commissioned from a
18 handful of national providers and will include a mixture of dietary educational advice and physical
19 activity, with the aim of reducing both weight and diabetes risk.
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23 The SPHR Diabetes Prevention Model does not explicitly model changes in diet or physical activity.
24 Instead interventions are assumed to impact directly upon individual risk factors such as BMI, blood
25 pressure, cholesterol and HbA1c. In the model these changes then impact upon incidence rates of type
26 2 diabetes and related diseases. This section of the technical appendix describes the assumptions
27 around the intervention that are used as default settings in the model.
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31 **Intervention Uptake**

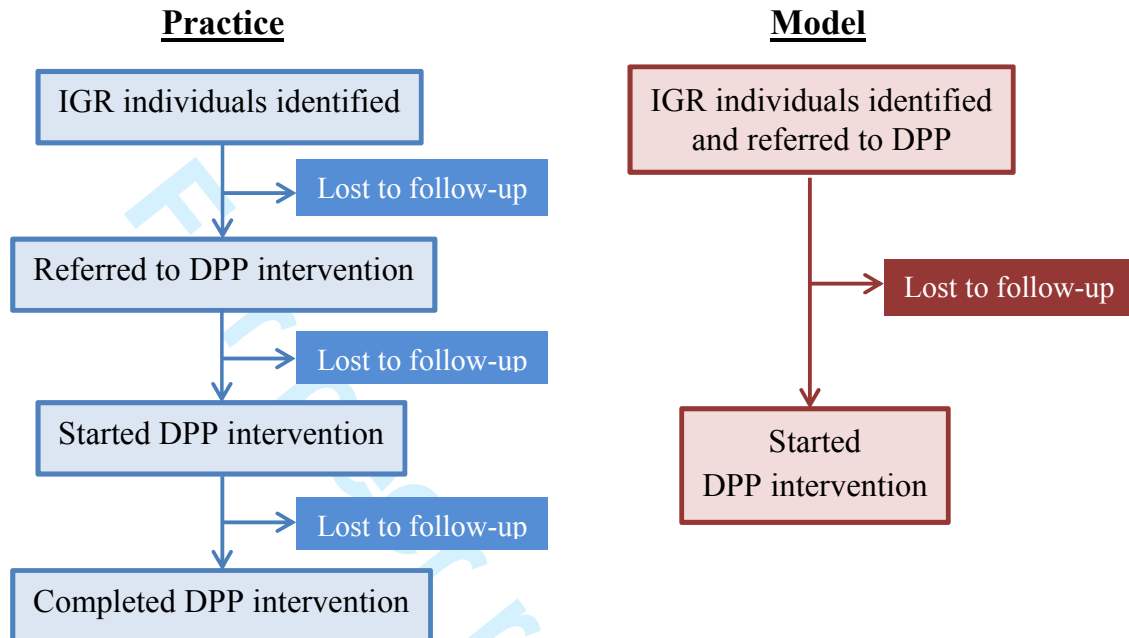
32
33 In practice, of the IGR individuals identified through HbA1c testing, only a proportion will receive
34 the intervention. Some individuals may not be referred for intervention. Of those referred, some will
35 choose not to take up the intervention, and of those that do attend the first intervention session, some
36 will not complete the intervention (Figure 2).
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40 Referral rates are not directly modelled, and instead it is assumed that all individuals are identified
41 and referred for intervention prior to the model start. This is partly because of lack of data around
42 referral rates and partly because referral rates are a function of the number of available intervention
43 places.
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47 Intervention uptake is defined as the proportion of those referred to the intervention who decide to
48 take up the intervention. The original aim of the analysis was to include data around differential
49 uptake of interventions in different population subgroups. However, good quality data could not be
50 identified and instead a uniform uptake rate of 32% has been used. It is assumed that those who
51 decided not to take up the intervention incur no costs and no benefits of intervention. No costs of
52 identifying or referring individuals to intervention are modelled. In practice, some individuals who
53 start the intervention will not complete it and therefore not gain full benefit. However, non-
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completion is partially accounted for in the estimate of effectiveness used in the model (74), so has not been explicitly built in. This is discussed further below.

Figure 2: Schematic showing intervention uptake and completion in practice and in the model



Intervention Effectiveness

The effectiveness data used in the model comes from a PHE evidence review of pragmatic lifestyle interventions for prevention of type 2 diabetes (75). This updates a previous review by Dunkley and others (76). Both reviews incorporate meta-analyses of a wide range of different lifestyle interventions aimed at reducing type-2 diabetes, and report a variety of outcomes including type-2 diabetes incidence rate and weight loss. The PHE evidence review also includes some analysis of differential effectiveness in population subgroups and for different intervention characteristics.

PHE, NHS England and Diabetes UK have specified that they wish the commissioned DPP intervention to fulfil 9-12 NICE guidelines as recommended in PH38 (3). NICE guidelines include using particular strategies that are associated with increased effectiveness, specifying the minimum amount of contact time and follow-up sessions, and delivering the programme through qualified practitioners. Both the PHE evidence review and the Dunkley meta-analysis indicate that interventions have increased effectiveness if they fulfil a greater number of NICE guidelines (75;76). In line with this, the model uses the results from the subgroup analysis of interventions fulfilling 9-12 NICE guidelines as the mean effectiveness (weight loss of 3.24kg – Table 12 in the PHE Evidence Review (75)).

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3 Unlike the Dunkley meta-analysis, the PHE evidence review does not report differences in HbA1c,
4 systolic blood pressure (SBP) or cholesterol for this subgroup of interventions. However, it is clear
5 from the Dunkley analysis that there will be concurrent reductions in these other metabolic factors,
6 and that the effectiveness of the intervention would be underestimated in the model if they were not
7 included. To incorporate these changes, the differences in HbA1c, SBP and cholesterol were
8 extrapolated from the Dunkley analysis to reflect the updated weight loss used from the PHE evidence
9 review. This assumes that relationships between changes in metabolic factors are linear. The
10 intervention effectiveness for each metabolic factor used in the model is reported in Table 39.
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16 **Table 39: Mean intervention effectiveness used in the model**

| | Mean values from Dunkley et al supplementary Table 7 (76) | Used in the DPP analysis: Default Mean weight loss from Table 12 of PHE evidence review for 9-12 NICE guidelines (75) | Used in the DPP analysis: Sensitivity analysis - 25% Lower |
|--------------------------------|---|---|--|
| Weight (kg) | -2.12 | -3.24 | -2.43 |
| BMI (kg/m ²) | -0.96 | -1.47 | -1.10 |
| HbA1c (%) | -0.13 | -0.20 | -0.15 |
| Systolic Blood Pressure (mmHg) | -4.3 | -6.57 | -4.93 |
| Total Cholesterol (mmol/l) | -0.18 | -0.28 | -0.21 |

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32 There is good evidence from the PHE evidence review and other studies that intervention
33 effectiveness is unlikely to be uniform across the population, and in particular varies according to the
34 baseline BMI of individuals, those with higher baseline BMI reporting increased weight loss and
35 diabetes risk reduction than those with lower baseline BMI (75;77-79). A differential intervention
36 effect by baseline BMI was therefore implemented in the model. Again this was taken from the PHE
37 evidence review as shown in Table 40 (75).
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42 **Table 40: Weight change results per unit baseline BMI from the PHE Evidence Review (75)**

| Subgroup | Weight change | Unit | Study Median |
|----------|--------------------------|-------------------------------------|------------------------|
| BMI | -0.23 kg (-0.53 to 0.07) | Per unit increase in mean study BMI | 31.5 kg/m ² |

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Personalised intervention effects for each individual, dependent upon their baseline BMI were
calculated using the following equation:

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|--|--|
| Personalised Intervention Effect = Mean Intervention Effect | |
| + BMI Effect * (Individual BMI – Median BMI) | |
| Where: | Mean Intervention Effect = -3.24 kg |
| | BMI Effect = -0.23 kg |
| | Individual BMI = the baseline BMI of each individual in the population |
| | Median BMI = 31.5 kg/m ² (the median of the mean BMI from each study included in the PHE meta-analysis) |

For example, for an individual with baseline BMI of 30, the personalised intervention effect would correspond to a weight loss of 2.895kg (smaller than the mean intervention effect), whereas for an individual with baseline BMI of 35, the personalised intervention effect would correspond to a weight loss of 4.045kg (larger than the mean intervention effect). Note that in individuals with BMI < 17.5, the effect of the intervention would be to actually increase weight. However, there are very few such IGR individuals in the model and an intervention focussing on weight loss may not in any case be the best option for individuals who are already underweight.

From this personalised change in weight due to the intervention, individualised changes in BMI, HbA1c, SBP and cholesterol were derived. Individuals in the intervention arm of the model who take up the intervention were assumed to receive this reduction in their metabolic factors instantaneously at the start of the model.

In practice, some individuals who start the intervention will not complete it. The PHE evidence review contains a mixture of studies that have used either intention to treat or complete case analysis (75). Intention to treat analysis takes non-completion into account, whereas complete case analysis does not. However, it is unclear which studies have been used to derive the estimate of effectiveness for 9-12 NICE guidelines. It is likely therefore that the effectiveness estimate used in the model only partially accounts for non-completion and therefore may be higher than is realistic in practice.

The Whitehall II BMI trajectory model estimates an indirect relationship between BMI change and changes in metabolic risk factors. The changes to HbA1c, systolic blood pressure and cholesterol were adjusted to avoid double counting of the indirect effects through BMI and direct effects of the intervention.

Intervention Costs

The actual intervention cost of the DPP will be determined through the DPP procurement process in early 2016. As this was still undergoing at the time of this analysis, PHE suggested that the mid average cost from their impact assessment of £270 per participant should be used as the default cost. This incorporates expected retention rates of participants, but does not include any local costs of identifying or referring individuals for intervention.

Duration of Intervention Effect

There is very little published information about how long the effectiveness of intensive lifestyle interventions is likely to endure in participants before weight is regained. In the model, default intervention effectiveness is assumed to decline linearly from its peak at the start of the model until individuals reach the BMI/SBP/HbA1c/cholesterol level that they would have been without intervention. It has been assumed for the analysis that this process takes five years.

MODEL PARAMETERS

All parameters used in the model, their distributions for PSA and their sources are documented here.

GP Attendance in the General Population

GP attendance is estimated from statistical analysis of the Yorkshire Health Study (11). In the PSA, the parameters are sampled from a multivariate normal distribution, using the mean estimates described in Table 41 and covariance matrix in Table 42.

Table 41: GP attendance reported in the Yorkshire Health Study (N= 18,437) ⁽¹¹⁾

| | Mean | Standard error | Uncertainty Distribution |
|-----------------------|---------|----------------|--------------------------|
| Age | 0.0076 | 0.0005 | MULTIVARIATE NORMAL |
| Male | -0.1495 | 0.0159 | MULTIVARIATE NORMAL |
| BMI | 0.0110 | 0.0015 | MULTIVARIATE NORMAL |
| Ethnicity (Non-white) | 0.2620 | 0.0375 | MULTIVARIATE NORMAL |
| Heart Disease | 0.2533 | 0.0289 | MULTIVARIATE NORMAL |
| Depression | 0.6127 | 0.0224 | MULTIVARIATE NORMAL |
| Osteoarthritis | 0.2641 | 0.0238 | MULTIVARIATE NORMAL |
| Diabetes | 0.2702 | 0.0278 | MULTIVARIATE NORMAL |
| Stroke | 0.1659 | 0.0474 | MULTIVARIATE NORMAL |
| Cancer | 0.2672 | 0.0414 | MULTIVARIATE NORMAL |
| Intercept | -0.5014 | 0.0468 | MULTIVARIATE NORMAL |
| Alpha | 0.3423 | 0.0108 | MULTIVARIATE NORMAL |

Table 42: Variance-covariance matrix for GP attendance regression

| | Age | Male | BMI | Ethnicity (Non-white) | Heart Disease | Depression | Osteoarthritis | Diabetes | Stroke | Cancer | Intercept | Alpha |
|-----------------------|--------|--------|--------|-----------------------|---------------|------------|----------------|----------|---------|--------|-----------|-------|
| Age | 0.0000 | | | | | | | | | | | |
| Male | 0.0000 | 0.0003 | | | | | | | | | | |
| BMI | 0.0000 | 0.0000 | 0.0000 | | | | | | | | | |
| Ethnicity (Non-white) | 0.0000 | 0.0000 | 0.0000 | 0.0014 | | | | | | | | |
| Heart Disease | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0008 | | | | | | | |
| Depression | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0005 | | | | | | |
| Osteoarthritis | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0006 | | | | | |
| Diabetes | 0.0000 | 0.0000 | 0.0000 | 0.0000 | -0.0001 | 0.0000 | 0.0000 | 0.0008 | | | | |
| Stroke | 0.0000 | 0.0000 | 0.0000 | 0.0000 | -0.0002 | -0.0001 | 0.0000 | -0.0001 | 0.0022 | | | |
| Cancer | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | -0.0001 | 0.0017 | | |

| | | | | | | | | | | | | |
|-----------|--------|--------|---------|---------|--------|--------|--------|--------|--------|--------|--------|--------|
| Intercept | 0.0000 | 0.0000 | -0.0001 | -0.0002 | 0.0002 | 0.0000 | 0.0002 | 0.0003 | 0.0000 | 0.0001 | 0.0022 | |
| Alpha | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0010 |

Whitehall II Statistical Model of Metabolic Trajectories

The metabolic trajectories used in the model are derived from statistical analysis of the longitudinal Whitehall II cohort (13). The parameters derived from this model are described in the following tables.

Table 43: Coefficient estimates for metabolic risk factor parallel growth models

| | Parameter Description | Estimated Mean | Standard error | p-value |
|-----------------------------|---|----------------|----------------|---------|
| BMI Intercept | | | | |
| α_{10} | Population mean BMI intercept | 2.2521 | 0.045 | <0.001 |
| γ_{10} | Age at baseline coefficient for BMI intercept | 0.0056 | 0.001 | <0.001 |
| | Sex coefficient for BMI intercept | -0.0311 | 0.012 | 0.009 |
| | Family history of CVD coefficient for BMI intercept | -0.0079 | 0.012 | 0.515 |
| v_{10} | Random error term for BMI intercept | 0.1165 | 0.003 | <0.001 |
| BMI linear slope | | | | |
| α_{11} | Population mean BMI linear slope | 0.6409 | 0.042 | <0.001 |
| γ_{11} | Age at baseline coefficient for BMI linear slope | -0.0084 | 0.001 | <0.001 |
| | Sex coefficient for BMI linear slope | -0.0285 | 0.011 | 0.009 |
| | Family history of CVD coefficient for BMI linear slope | -0.0155 | 0.010 | 0.117 |
| v_{11} | Random error term for BMI linear slope | 0.0222 | <0.001 | <0.001 |
| BMI quadratic slope | | | | |
| α_{12} | Population mean BMI quadratic slope | -0.2007 | 0.023 | <0.001 |
| γ_{12} | Age at baseline coefficient for quadratic slope | 0.0026 | <0.001 | <0.001 |
| | Sex coefficient for quadratic slope | 0.0089 | 0.006 | 0.147 |
| | Family history of CVD coefficient for quadratic slope | 0.0104 | 0.006 | 0.061 |
| ε_1 | Random error term for BMI | 0.0104 | <0.001 | <0.001 |
| Glyc Intercept | | | | |
| α_{20} | Population mean glyc intercept | 0 | NA | NA |
| γ_{20} | Smoker coefficient for glyc intercept | -0.1388 | 0.029 | <0.001 |
| τ_{20} | Association between BMI intercept and glyc intercept | 0.2620 | 0.024 | <0.001 |
| v_{20} | Random error term for glyc intercept | 0.0851 | 0.008 | <0.001 |
| Glyc linear slope | | | | |
| α_{21} | Population mean glyc linear slope | -0.4255 | 0.071 | <0.001 |
| γ_{21} | Sex coefficient for glyc linear slope | 0.1486 | 0.045 | 0.001 |
| | Ethnicity coefficient for glyc linear slope | -0.0218 | 0.081 | 0.786 |
| | Family history of T2DM coefficient for glyc linear slope | -0.0512 | 0.054 | 0.345 |
| | Smoker coefficient for glyc linear slope | 0.1796 | 0.066 | 0.007 |
| τ_{21} | Association between BMI intercept and glyc linear slope | 0.0821 | 0.024 | 0.001 |
| τ_{22} | Association between BMI linear slope and glyc linear slope | 0.1984 | 0.073 | 0.007 |
| v_{21} | Random error term for glyc linear slope | 0.0222 | 0.011 | 0.053 |
| Glyc quadratic slope | | | | |
| α_{22} | Population mean glyc quadratic slope | 0.1094 | 0.025 | <0.001 |
| γ_{22} | Sex coefficient for glyc quadratic slope | -0.0855 | 0.027 | 0.002 |
| | Ethnicity coefficient for glyc quadratic slope | 0.0899 | 0.049 | 0.067 |
| | Family history of T2DM coefficient for glyc quadratic slope | 0.0633 | 0.033 | 0.052 |
| | Smoker coefficient for glyc quadratic slope | -0.0390 | 0.040 | 0.330 |
| v_{22} | Random error term for glyc quadratic slope | 0.0107 | 0.003 | 0.002 |
| ε_2 | Glyc measurement error | 0.0707 | 0.005 | <0.001 |
| SBP Intercept | | | | |
| α_{30} | Population mean SBP intercept | 0.6934 | 0.021 | <0.001 |
| γ_{30} | Age at baseline coefficient for SBP intercept | 0.0043 | <0.001 | <0.001 |

| | | | | |
|------------------|---|---------|--------|--------|
| | Sex coefficient for SBP intercept | 0.0380 | 0.004 | <0.001 |
| | Smoking coefficient for SBP intercept | -0.0243 | 0.006 | <0.001 |
| | Ethnicity coefficient for SBP intercept | 0.0078 | 0.007 | 0.300 |
| | Family history of CVD coefficient for SBP intercept | 0.0061 | 0.004 | 0.160 |
| τ_{31} | Association between BMI intercept and SBP intercept | 0.1080 | 0.006 | <0.001 |
| u_{30} | Random error term for SBP intercept | 0.0085 | 0.00 | <0.001 |
| SBP linear slope | | | | |
| α_{31} | Population mean SBP linear slope | -0.0227 | 0.021 | 0.278 |
| γ_{31} | Age at baseline coefficient for SBP linear slope | 0.0024 | <0.001 | <0.001 |
| | Sex coefficient for SBP linear slope | -0.0004 | 0.004 | 0.927 |
| | Smoking coefficient for SBP linear slope | 0.0205 | 0.005 | <0.001 |
| | Ethnicity coefficient for SBP linear slope | 0.0224 | 0.007 | 0.001 |
| | Family history of CVD coefficient for SBP linear slope | -0.0013 | 0.004 | 0.748 |
| τ_{31} | Association between BMI intercept and SBP linear slope | -0.0396 | 0.006 | <0.001 |
| | Association between BMI linear slope and SBP linear slope | 0.2325 | 0.019 | <0.001 |
| u_{31} | Random error term for SBP linear slope | 0.0024 | <0.001 | <0.001 |
| ε_3 | SBP measurement error variance | 0.0093 | <0.001 | <0.001 |
| TC Intercept | | | | |
| α_{40} | Population mean TC intercept | 2.9956 | 0.176 | <0.001 |
| γ_{40} | Age at baseline coefficient for TC intercept | 0.0456 | 0.003 | <0.001 |
| | Sex coefficient for TC intercept | 0.0660 | 0.036 | 0.070 |
| τ_{40} | Association between BMI intercept and TC intercept | 0.4459 | 0.049 | <0.001 |
| u_{40} | Random error term for TC intercept | 0.8960 | 0.025 | <0.001 |
| TC linear slope | | | | |
| α_{41} | Population mean TC linear slope | 2.1216 | 0.128 | <0.001 |
| γ_{41} | Age at baseline coefficient for TC linear slope | -0.0316 | 0.002 | <0.001 |
| | Sex coefficient for TC linear slope | -0.2677 | 0.026 | <0.001 |
| τ_{41} | Association between BMI intercept and TC linear slope | -0.4808 | 0.035 | <0.001 |
| τ_{42} | Association between BMI linear slope and TC linear slope | 0.9802 | 0.108 | <0.001 |
| u_{41} | Random error term for TC linear slope | 0.1583 | 0.011 | <0.001 |
| ε_4 | TC measurement error variance | 0.3426 | 0.006 | <0.001 |
| HDL Intercept | | | | |
| α_{50} | Population mean HDL intercept | 2.4124 | 0.054 | <0.001 |
| γ_{50} | Age at baseline coefficient for HDL intercept | 0.0032 | 0.011 | <0.001 |
| | Sex coefficient for HDL intercept | -0.3710 | 0.001 | <0.001 |
| τ_{51} | Association between BMI intercept and HDL intercept | -0.3514 | 0.015 | <0.001 |
| u_{50} | Random error term for HDL intercept | 0.0827 | -0.040 | <0.001 |
| HDL linear slope | | | | |
| α_{51} | Population mean HDL linear slope | 0.1241 | 0.034 | <0.001 |
| γ_{51} | Age at baseline coefficient for HDL linear slope | 0.0020 | 0.001 | <0.001 |
| | Sex coefficient for HDL linear slope | 0.0041 | 0.007 | 0.558 |
| τ_{51} | Association between BMI intercept and HDL linear slope | -0.0400 | 0.010 | <0.001 |
| u_{51} | Random error term for HDL linear slope | 0.0090 | 0.001 | <0.001 |
| ε_5 | HDL measurement error variance | 0.0333 | 0.001 | <0.001 |

Table 44: Coefficient estimates for latent glycaemic measurement model

| | Parameter Description | Estimated Mean | Standard error | p-value |
|-----------------|-----------------------------------|----------------|----------------|---------|
| μ_0 | FPG intercept | 4.2903 | 0.089 | <0.001 |
| θ_{01} | Glycaemic factor to FPG | 1 | NA | NA |
| θ_{02} | Age to FPG | 0.0031 | 0.001 | 0.022 |
| θ_{03} | Sex to FPG | 0.2129 | 0.021 | <0.001 |
| θ_{04} | Ethnicity to FPG | 0.0100 | 0.037 | 0.786 |
| θ_{05} | Family history of diabetes to FPG | 0.1168 | 0.025 | <0.001 |
| ε_0 | FPG measurement error variance | 0.1649 | 0.007 | <0.001 |
| μ_1 | 2-hr Glucose intercept | 0.5707 | 0.223 | 0.011 |
| θ_{11} | Glycaemic factor to 2-hr glucose | 2.4384 | 0.078 | <0.001 |
| θ_{12} | Age to 2-hr glucose | 0.0716 | 0.003 | <0.001 |

| | | | | |
|-----------------|--|---------|-------|--------|
| θ_{13} | Sex to 2-hr glucose | -0.1411 | 0.058 | 0.014 |
| θ_{14} | Ethnicity to 2-hr glucose | 0.3047 | 0.100 | 0.002 |
| θ_{15} | Family history of diabetes to 2-hr glucose | 0.3496 | 0.068 | <0.001 |
| ε_1 | 2-hr measurement error variance | 2.3679 | 0.054 | <0.001 |
| μ_2 | HbA1c intercept | 4.4769 | 0.073 | <0.001 |
| θ_{21} | Glycaemic factor to HBA1c | 0.5074 | 0.016 | <0.001 |
| θ_{22} | Age to HBA1c | 0.0101 | 0.001 | <0.001 |
| θ_{23} | Sex to HBA1c | -0.0457 | 0.001 | <0.001 |
| θ_{24} | Ethnicity to HBA1c | 0.1854 | 0.030 | <0.001 |
| θ_{25} | Family history of diabetes to HBA1c | 0.0563 | 0.020 | 0.004 |
| ε_2 | HbA1c measurement error variance | 0.1166 | 0.003 | <0.001 |

Table 45: Covariance matrix Ω for individual random error

| | v_{10} | v_{11} | v_{20} | v_{21} | v_{22} | v_{30} | v_{31} | v_{40} | v_{41} | v_{50} | v_{51} |
|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| v_{10} | 0.1165 | | | | | | | | | | |
| v_{11} | 0.0095 | 0.0131 | | | | | | | | | |
| v_{20} | <0.0010 | <0.0010 | 0.0851 | | | | | | | | |
| v_{21} | <0.0010 | <0.0010 | 0.0222 | 0.0209 | | | | | | | |
| v_{22} | <0.0010 | <0.0010 | <0.0010 | <0.0010 | 0.0107 | | | | | | |
| v_{30} | <0.0010 | <0.0010 | 0.0080 | <0.0010 | <0.0010 | 0.0085 | | | | | |
| v_{31} | <0.0010 | <0.0010 | <0.0010 | 0.0018 | <0.0010 | <0.0017 | 0.0024 | | | | |
| v_{40} | <0.0010 | <0.0010 | 0.0324 | <0.0010 | <0.0010 | 0.0031 | <0.0010 | 0.8960 | | | |
| v_{41} | <0.0010 | <0.0010 | <0.0010 | <0.0012 | <0.0010 | <0.0010 | 0.0066 | -0.2229 | 0.1583 | | |
| v_{50} | <0.0010 | <0.0010 | -0.0118 | <0.0010 | <0.0010 | 0.0010 | <0.0010 | 0.0273 | <0.0010 | 0.0827 | |
| v_{51} | <0.0010 | <0.0010 | <0.0010 | -0.0059 | <0.0010 | <0.0010 | 0.0020 | <0.0010 | 0.0159 | 0.0061 | 0.0090 |

HbA1c trajectory in individuals diagnosed with type 2 diabetes

The input parameters for the initial reduction in HbA1c and long term trend in HbA1c following diagnosis, derived from analysis of the UKPDS outcomes model (15), are reported in Table 46 and Table 47 respectively.

Table 46: Estimated change in HbA1c in first year following diabetes diagnosis

| | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|---------------------------|--------------|-------------|-------------|------------------|
| Change in HbA1c Intercept | NORMAL | -2.9465 | 0.0444513 | -2.9465 |
| HbA1c at baseline | NORMAL | 0.5184 | 0.4521958 | 0.5184 |

Table 47: Estimated change in HbA1c following diabetes diagnosis over long term

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|---|--------------|-------------|-------------|------------------|
| Longitudinal HbA1c for diabetes intercept | NORMAL | -0.024 | 0.017 | -0.024 |
| Longitudinal HbA1c for diabetes log(time since diagnosis) | NORMAL | 0.144 | 0.009 | 0.144 |
| Longitudinal HbA1c for diabetes Second year | NORMAL | -0.333 | 0.05 | -0.333 |
| Longitudinal HbA1c for diabetes lag HbA1c | NORMAL | 0.759 | 0.004 | 0.759 |
| Longitudinal HbA1c for diabetes HbA1c at diagnosis | NORMAL | 0.085 | 0.004 | 0.0896 |

Systolic blood pressure and cholesterol trajectory following treatment

The changes in systolic blood pressure and total cholesterol following treatment with anti-hypertensives or statins, and statin uptake are reported in Table 48.

Table 48: Treatment effects following treatment

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|------------------------------------|--------------|-------------|-------------|------------------|--------|
| Simvastatin treatment effects | NORMAL | -1.45 | 0.11 | -1.45 | (20) |
| Anti-hypertensive treatment effect | NORMAL | -8.4 | 0.638 | -8.4 | (22) |
| Statin Uptake | UNIFORM | 0.65 | (0.4-0.9) | 0.65 | (21) |

Metabolic Risk Factor screening

The distribution for the HbA1c threshold at which opportunistic screening for type 2 Diabetes is initiated even if the individual does not have a history of cardiovascular disease, microvascular disease or identified impaired glucose regulation is reported in Table 49.

Table 49: Threshold for HbA1c opportunistic diagnosis

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|-----------------------|--------------|-------------|-------------|------------------|--------|
| HbA1c at diagnosis | NORMAL | 8.1 | 0.073 | 8.1 | (16) |

COMORBID OUTCOMES AND MORTALITY

Cardiovascular Disease

Cardiovascular risk is estimated using the QRISK2 model (25). Parameter distributions for men and women are reported in Table 50.

Table 50: Input parameters of the QRISK2 risk model

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|--------------------------|--------------|-------------|-------------|------------------|
| QRISK female ethnicity 2 | NORMAL | 0.2163 | 0.0537 | 0.2163 |
| QRISK female ethnicity 3 | NORMAL | 0.6905 | 0.069 | 0.6905 |
| QRISK female ethnicity 4 | NORMAL | 0.3423 | 0.1073 | 0.3423 |
| QRISK female ethnicity 5 | NORMAL | 0.0731 | 0.1071 | 0.0731 |
| QRISK female ethnicity 6 | NORMAL | -0.0989 | 0.0619 | -0.0989 |
| QRISK female ethnicity 7 | NORMAL | -0.2352 | 0.1275 | -0.2352 |
| QRISK female ethnicity 8 | NORMAL | -0.2956 | 0.1721 | -0.2956 |
| QRISK female ethnicity 9 | NORMAL | -0.1010 | 0.0793 | -0.1010 |
| QRISK female smoke 2 | NORMAL | 0.2033 | 0.0152 | 0.2033 |
| QRISK female smoke 3 | NORMAL | 0.48200 | 0.0220 | 0.4820 |
| QRISK female smoke 4 | NORMAL | 0.6126 | 0.0178 | 0.6126 |
| QRISK female smoke 5 | NORMAL | 0.7481 | 0.0194 | 0.7481 |
| QRISK female age 1 | NORMAL | 5.0373 | 1.0065 | 5.0327 |
| QRISK female age 2 | NORMAL | -0.0108 | 0.0022 | -0.0108 |
| QRISK female bmi | NORMAL | 0.4724 | 0.0423 | 0.4724 |
| QRISK female cholesterol | NORMAL | 0.6375 | 0.0143 | 0.6375 |

| | | | | | |
|----|--|----------|-----------|----------|-----------|
| 1 | QRISK female sbp | NORMAL | 0.0106 | 0.0045 | 0.0106 |
| 2 | QRISK female townsend | NORMAL | 0.060 | 0.0068 | 0.060 |
| 3 | QRISK female fibrillation | NORMAL | 1.3261 | 0.0310 | 1.3261 |
| 4 | QRISK female RA | NORMAL | 0.3626 | 0.0319 | 0.3626 |
| 5 | QRISK female Renal | NORMAL | 0.7636 | 0.0639 | 0.7636 |
| 6 | QRISK female Hypertension | NORMAL | 0.5421 | 0.0115 | 0.5421 |
| 7 | QRISK female diabetes | NORMAL | 0.8940 | 0.0199 | 0.8940 |
| 8 | QRISK female family history cvd | NORMAL | 0.5997 | 0.0122 | 0.5997 |
| 9 | QRISK female age1 * smoke 1 | NORMAL | 0.1774 | 0.0355 | 0.1774 |
| 10 | QRISK female age 1 * smoke 2 | NORMAL | -0.3277 | 0.0655 | -0.3277 |
| 11 | QRISK age1 * smoke 3 | NORMAL | -1.1533 | 0.2307 | -1.1533 |
| 12 | QRISK female age 1 * smoke 4 | NORMAL | -1.5397 | 0.3079 | -1.5397 |
| 13 | QRISK female age 1 * atrial fibrillation | NORMAL | -4.6084 | 0.922 | -4.6084 |
| 14 | QRISK female age 1 * renal | NORMAL | -2.6401 | 0.5280 | -2.6401 |
| 15 | QRISK female age 1 * hypertension | NORMAL | -2.2480 | 0.4496 | -2.2480 |
| 16 | QRISK female age 1 * diabetes | NORMAL | -1.8452 | 0.3690 | -1.8452 |
| 17 | QRISK female age 1 * bmi | NORMAL | -3.0851 | 0.6170 | -3.0851 |
| 18 | QRISK female age 1 * family history cvd | NORMAL | -0.2481 | 0.0496 | -0.2481 |
| 19 | QRISK female age 1 * sbp | NORMAL | -0.0132 | 0.0026 | -0.0132 |
| 20 | QRISK female age 1 * town | NORMAL | -0.0369 | 0.0074 | -0.0369 |
| 21 | QRISK female age 2 * smoke 1 | NORMAL | -0.0053 | 0.0001 | -0.0053 |
| 22 | QRISK female age 2 * smoke 2 | NORMAL | -0.0005 | 0.0001 | -0.0005 |
| 23 | QRISK female age 2 * smoke 3 | NORMAL | -0.0105 | 0.0021 | -0.0105 |
| 24 | QRISK female age 2 * smoke 4 | NORMAL | -0.0155 | 0.0031 | -0.0155 |
| 25 | QRISK female age 2 * fibrillation | NORMAL | -0.0507 | 0.0101 | -0.0507 |
| 26 | QRISK female age 2 * renal | NORMAL | 0.0343 | 0.0069 | 0.0343 |
| 27 | QRISK female age 2 * hypertension | NORMAL | 0.0258 | 0.0051 | 0.0258 |
| 28 | QRISK female age 2 * diabetes | NORMAL | 0.0180 | 0.0036 | 0.0180 |
| 29 | QRISK female age 2 * bmi | NORMAL | 0.0345 | 0.0069 | 0.0345 |
| 30 | QRISK female age 2 * family history cardiovascular | NORMAL | -0.0062 | 0.0012 | -0.0062 |
| 31 | QRISK female age 2 * sbp | NORMAL | -0.000029 | 0.000006 | -0.000029 |
| 32 | QRISK female age 2 * townsend | NORMAL | -0.0011 | 0.0002 | -0.0011 |
| 33 | QRISK female 1 year survival | CONSTANT | 0.9983 | NA | NA |
| 34 | QRISK male ethnicity 2 | NORMAL | 0.3163 | 0.0425 | 0.3163 |
| 35 | QRISK male ethnicity 3 | NORMAL | 0.6092 | 0.0547 | 0.6092 |
| 36 | QRISK male ethnicity 4 | NORMAL | 0.5958 | 0.0727 | 0.5958 |
| 37 | QRISK male ethnicity 5 | NORMAL | 0.1142 | 0.0845 | 0.1142 |
| 38 | QRISK male ethnicity 6 | NORMAL | -0.3489 | 0.0641 | -0.3489 |
| 39 | QRISK male ethnicity 7 | NORMAL | -0.3604 | 0.1094 | -0.3604 |
| 40 | QRISK male ethnicity 8 | NORMAL | -0.2666 | 0.1538 | -0.2666 |
| 41 | QRISK male ethnicity 9 | NORMAL | -0.1208 | 0.0734 | -0.1208 |
| 42 | QRISK male SMOKE 2 | NORMAL | 0.2033 | 0.0152 | 0.2033 |
| 43 | QRISK male SMOKE 3 | NORMAL | 0.4820 | 0.0220 | 0.4820 |
| 44 | QRISK male SMOKE 4 | NORMAL | 0.6126 | 0.0178 | 0.6126 |
| 45 | QRISK male SMOKE 5 | NORMAL | 0.7481 | 0.0194 | 0.7481 |
| 46 | QRISK male age 1 | NORMAL | 47.316 | 9.4630 | 47.316 |
| 47 | QRISK male age 2 | NORMAL | -101.236 | 20.247 | -101.236 |
| 48 | QRISK male bmi | NORMAL | 0.5425 | 0.0299 | 0.5425 |
| 49 | QRISK male cholesterol | NORMAL | 0.14425 | 0.0022 | 0.14425 |
| 50 | QRISK male sbp | NORMAL | 0.0081 | 0.0046 | 0.0081 |
| 51 | QRISK male townsend | NORMAL | 0.0365 | 0.0048 | 0.0365 |
| 52 | QRISK male fibrillation | NORMAL | 0.7547 | 0.1018 | 0.7547 |
| 53 | QRISK male RA | NORMAL | 0.3089 | 0.0445 | 0.3089 |
| 54 | QRISK male renal | NORMAL | 0.7441 | 0.0702 | 0.7441 |
| 55 | QRISK male hypertension | NORMAL | 0.6965 | 0.011 | 0.6965 |
| 56 | QRISK male age 1 smoke 1 | NORMAL | -3.8805 | 0.7761 | -3.8805 |
| 57 | QRISK male age 1 smoke 2 | NORMAL | -16.703 | 3.3406 | -16.703 |
| 58 | QRISK male age 1 smoke 3 | NORMAL | -15.3738 | 3.5291 | -15.3738 |
| 59 | QRISK male age 1 smoke 4 | NORMAL | -17.6453 | 3.5291 | -17.6453 |

| | | | | |
|-------------------------------|----------|----------|--------|----------|
| QRISK male age 1 fibrillation | NORMAL | -7.0146 | 1.4056 | -7.0282 |
| QRISK male age 1 renal | NORMAL | -17.015 | 3.4029 | -17.015 |
| QRISK male age 1 hypertension | NORMAL | 33.9625 | 6.7925 | 33.9625 |
| QRISK male age 1 diabetes | NORMAL | 12.7886 | 2.5577 | 12.7886 |
| QRISK male age 1 bmi | NORMAL | 3.2680 | 0.6536 | 3.2680 |
| QRISK male age 1 fxcd | NORMAL | -17.9219 | 3.5844 | -17.9219 |
| QRISK male age 1 sbp | NORMAL | -0.1511 | 0.030 | -0.1511 |
| QRISK male age 1 town | NORMAL | -2.5502 | 0.5100 | -2.5502 |
| QRISK male age 2 SMOKE 1 | NORMAL | 7.9709 | 1.5942 | 7.9709 |
| QRISK male age 2 SMOKE 2 | NORMAL | 23.6859 | 4.7372 | 23.6859 |
| QRISK male age 2 SMOKE 3 | NORMAL | 23.1371 | 4.6274 | 23.1371 |
| QRISK male age 2 SMOKE 4 | NORMAL | 26.8674 | 5.3735 | 26.8674 |
| QRISK male age 2 Fibrillation | NORMAL | 14.4518 | 2.8904 | 14.4518 |
| QRISK male age 2 renal | NORMAL | 28.2702 | 5.654 | 28.2702 |
| QRISK male age 2 hypertension | NORMAL | -18.8167 | 3.7633 | -18.8167 |
| QRISK male age 2 diabetes | NORMAL | 0.9630 | 0.1926 | 0.963 |
| QRISK male age 2 bmi | NORMAL | 10.5517 | 2.1103 | 10.5517 |
| QRISK male age 2 FXCD | NORMAL | 26.6047 | 5.3209 | 26.6047 |
| QRISK male age 2 sbp | NORMAL | 0.2911 | 0.0582 | 0.2911 |
| QRISK male age 2 town | NORMAL | 3.007 | 0.6014 | 3.007 |
| QRISK2 male 1 year survival | CONSTANT | 0.997 | NA | NA |

The QRISK2 model was modified to allow a linear relationship between HbA1c and the risk of cardiovascular disease for individuals with IGR and type 2 Diabetes (HbA1c>42 mmol/mol). The parameter distributions for these additional inputs are reported in Table 51.

Table 51: Additional parameters for linear relationship between HbA1c and cardiovascular disease

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|---|--------------|-------------|-------------|------------------|-----------------|
| Female RR of MI due to HbA1c in diabetics | LOGNORMAL | 0.078 | 0.030 | 1.08 | ⁽²⁵⁾ |
| Male RR of MI due to HbA1c in diabetics | LOGNORMAL | 0.108 | 0.023 | 1.11 | ⁽²⁵⁾ |
| RR of stroke due to HbA1c in diabetics | LOGNORMAL | 0.092 | 0.026 | 1.096 | ⁽²⁵⁾ |
| Log(RR) of cvd due to IGR | NORMAL | 0.223 | 0.043 | 1.25 | ⁽²⁸⁾ |

Congestive Heart Failure

The parameter distributions for congestive heart failure based on the Framingham Heart Study (29) are reported in Table 52.

Table 52: Input parameters for Congestive Heart Failure Risk model for men and women

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|--|--------------|-------------|-------------|------------------|
| Male Heart failure baseline hazard | NORMAL | -9.2087 | 0.9209 | -9.2087 |
| Male Heart failure Age | NORMAL | 0.0412 | 0.0278 | 0.0412 |
| Male Heart failure LVH | NORMAL | 0.9026 | 1.0359 | 0.9026 |
| Male Heart failure Heart rate | NORMAL | 0.0166 | 0.0174 | 0.0166 |
| Male Heart failure Systolic blood pressure | NORMAL | 0.00804 | 0.0117 | 0.00804 |
| Male Heart failure CHD | NORMAL | 1.6079 | 0.5336 | 1.6079 |
| Male Heart failure Valve disease | NORMAL | 0.9714 | 0.6557 | 0.9714 |
| Male Heart failure Diabetes | NORMAL | 0.2244 | 0.6682 | 0.2244 |
| Female Heart failure baseline hazard | NORMAL | -10.7988 | 1.0799 | -10.7988 |

| | | | | |
|---|--------|---------|--------|---------|
| Female Heart failure Age | NORMAL | 0.0503 | 0.0301 | 0.0503 |
| Female Heart failure LVH | NORMAL | 1.3402 | 0.8298 | 1.3402 |
| Female Heart failure Heart rate | NORMAL | 0.0105 | 0.0193 | 0.0105 |
| Female Heart failure Systolic blood pressure | NORMAL | 0.00337 | 0.0109 | 0.00337 |
| Female Heart failure CHD | NORMAL | 1.5549 | 0.5973 | 1.5549 |
| Female Heart failure Valve disease | NORMAL | 1.3929 | 0.6707 | 1.3929 |
| Female Heart failure Diabetes | NORMAL | 1.3857 | 0.7105 | 1.3857 |
| Female Heart failure BMI | NORMAL | 0.0578 | 0.0555 | 0.0578 |
| Female Heart failure Valve disease & Diabetes | NORMAL | -0.986 | 1.4370 | -0.986 |

Microvascular Complications

The parameter distributions for the risk models for foot ulcer, blindness, renal failure, first amputation and second amputation are reported in Table 53. Parameters for renal failure were based on the UKPDS Outcomes Model 1 (15), whereas parameters for other microvascular complications were based on the UKPDS Outcomes Model 2 (23).

Table 53: Input parameters for microvascular complications

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|--|--------------|-------------|-------------|------------------|
| Renal failure baseline hazard | NORMAL | -10.016 | 0.939 | -10.016 |
| Renal failure Weibull shape | NORMAL | 1.865 | 1.4352 | 1.865 |
| Renal failure systolic blood pressure | NORMAL | 0.404 | 0.106 | 0.404 |
| Renal failure blindness | NORMAL | 2.082 | 0.551 | 2.082 |
| Foot ulcer baseline hazard | NORMAL | -11.295 | 1.13 | -11.295 |
| Foot ulcer age at diagnosis | NORMAL | 0.043 | 0.014 | 0.043 |
| Foot ulcer female | NORMAL | -0.962 | 0.255 | -0.962 |
| Foot ulcer BMI | NORMAL | 0.053 | 0.019 | 0.053 |
| Foot ulcer HbA1c | NORMAL | 0.16 | 0.056 | 0.16 |
| Foot ulcer PVD | NORMAL | 0.968 | 0.258 | 0.968 |
| Amputation baseline hazard | NORMAL | -14.844 | 1.205 | -14.844 |
| Amputation age at diagnosis | NORMAL | 0.023 | 0.011 | 0.023 |
| Amputation female | NORMAL | -0.445 | 0.189 | -0.445 |
| Amputation atrial fibrillation | NORMAL | 1.088 | 0.398 | 1.088 |
| Amputation HbA1c | NORMAL | 0.248 | 0.042 | 0.248 |
| Amputation HDL | NORMAL | -0.059 | 0.032 | -0.059 |
| Amputation heart rate | NORMAL | 0.098 | 0.05 | 0.098 |
| Amputation MMALB | NORMAL | 0.602 | 0.18 | 0.602 |
| Amputation peripheral vascular disease | NORMAL | 1.01 | 0.189 | 1.01 |
| Amputation white blood count | NORMAL | 0.04 | 0.017 | 0.04 |
| Amputation Stroke | NORMAL | 1.299 | 0.245 | 1.299 |
| Amputation shape | NORMAL | 2.067 | 0.193 | 2.067 |
| Amputation with Ulcer lambda | NORMAL | -0.881 | 0.139 | -0.881 |
| Amputation with Ulcer age at diagnosis | NORMAL | -0.065 | 0.027 | -0.065 |
| Amputation with Ulcer PVD | NORMAL | 1.769 | 0.449 | 1.769 |
| Second Amputation baseline hazard | NORMAL | -3.455 | 0.565 | -3.455 |
| Second Amputation HbA1c | NORMAL | 0.127 | 0.06 | 0.127 |
| Blindness baseline hazard | NORMAL | -10.6774 | 0.759 | -10.6774 |
| Blindness age at diagnosis | NORMAL | 0.047 | 0.009 | 0.047 |
| Blindness HbA1c | NORMAL | 0.171 | 0.032 | 0.171 |
| Blindness heart rate | NORMAL | 0.08 | 0.039 | 0.08 |
| Blindness systolic blood pressure | NORMAL | 0.068 | 0.032 | 0.068 |
| Blindness white blood cells | NORMAL | 0.052 | 0.019 | 0.052 |

| | | | | |
|---------------|--------|-------|-------|-------|
| Blindness CHF | NORMAL | 0.841 | 0.287 | 0.841 |
| Blindness IHD | NORMAL | 0.61 | 0.208 | 0.61 |

Cancer

The parameter distributions for the incidence and hazard ratios for breast cancer and colorectal cancer are reported in Table 54.

Table 54: Input parameters for breast cancer and colorectal cancer risk models

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|--|--------------|-------------|-------------|------------------|--------|
| Colorectal cancer men | NORMAL | 0.0011 | 0.0001 | 0.0011 | (36) |
| Colorectal cancer women | NORMAL | 0.0005 | 0.0000 | 0.0005 | (36) |
| Breast cancer pre-menopause | NORMAL | 0.0010 | 0.0001 | 0.0010 | (34) |
| Breast cancer post-menopause | NORMAL | 0.0028 | 0.0002 | 0.0028 | (34) |
| Colorectal cancer BMI relative risk for men | LOGNORMAL | 0.1906 | 0.0111 | 1.21 | (35) |
| Colorectal cancer BMI relative risk for women | LOGNORMAL | 0.0392 | 0.0151 | 1.04 | (35) |
| Breast cancer BMI relative risk for pre-menopause | LOGNORMAL | -0.1165 | 0.0251 | 0.89 | (35) |
| Breast cancer BMI relative risk for post-menopause | LOGNORMAL | 0.0862 | 0.0205 | 1.09 | (35) |

The parameter distributions for breast and colorectal cancer mortality are reported in Table 55.

Table 55: Input parameters for breast cancer and colorectal cancer mortality (41)

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|-----------------------------------|--------------|-------------|-------------|------------------|
| Breast cancer 5 year survival | BETA | 439.69 | 2354.44 | 0.157 |
| Colorectal cancer 5 year survival | BETA | 1457.56 | 1806.35 | 0.447 |

Osteoarthritis

The parameter distributions for the incidence and hazard ratios for osteoarthritis are reported below.

Table 56: Input parameters for the osteoarthritis risk model (37)

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|-------------------------------|--------------|-------------|-------------|------------------|
| Osteoarthritis incidence | NORMAL | 0.0053 | 0.0000004 | 0.0053 |
| Osteoarthritis RR of diabetes | LOGNORMAL | 0.723 | 0.317 | 2.06 |
| Osteoarthritis RR of BMI | LOGNORMAL | 0.073 | 0.026 | 1.076 |

Depression

The parameter distributions for the incidence and hazard ratios for depression are reported below.

Table 57: Input parameters for the depression risk model

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|-------------------------|--------------|-------------|-------------|------------------|--------|
| Odds of depression | BETA | 336 | 8803 | 0.0397 | (39) |
| Odds ratio for diabetes | LOGNORMAL | 0.4187 | 0.1483 | 1.52 | (39) |
| Odds ratio for stroke | LOGNORMAL | 1.8406 | 0.5826 | 6.3 | (40) |

UTILITIES

The parameter distributions used to estimate health state utilities in the model are reported below.

Table 58: Utility input parameters

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|---|--------------|-------------|-------------|------------------|--------|
| Renal/ulcer baseline utility | NORMAL | 0.689 | 0.014 | 0.689 | (47) |
| Renal dialysis | NORMAL | -0.078 | 0.026 | -0.078 | (47) |
| Foot ulcer | NORMAL | -0.099 | 0.013 | -0.099 | (47) |
| Amputation/heart failure baseline utility | NORMAL | 0.807 | 0.005 | 0.807 | (23) |
| Heart failure | NORMAL | -0.101 | 0.032 | -0.101 | (23) |
| Amputation | NORMAL | -0.172 | 0.045 | -0.172 | (23) |
| Stable angina multiplicative factor decrement | NORMAL | 0.801 | 0.038 | 0.801 | (21) |
| Unstable angina multiplicative factor decrement | NORMAL | 0.77 | 0.038 | 0.77 | (21) |
| MI multiplicative factor decrement | NORMAL | 0.76 | 0.018 | 0.76 | (21) |
| Stroke multiplicative factor decrement | NORMAL | 0.629 | 0.04 | 0.629 | (21) |
| Cancer baseline utility | NORMAL | 0.8 | 0.0026 | 0.8 | (48) |
| Cancer decrement | NORMAL | -0.06 | 0.008 | -0.06 | (48) |
| Osteoarthritis utility | NORMAL | 0.69 | 0.069 | 0.69 | (49) |
| Depression baseline utility | NORMAL | 0.48 | 0.048 | 0.48 | (51) |
| Depression remitters | NORMAL | 0.31 | 0.031 | 0.31 | (51) |
| Depression responders | NORMAL | 0.20 | 0.020 | 0.20 | (51) |
| Depression non-responders | NORMAL | 0.070 | 0.007 | 0.070 | (51) |
| Depression drop-outs | NORMAL | 0.050 | 0.005 | 0.050 | (51) |
| Age utility decrement | NORMAL | -0.004 | 0.0001 | -0.004 | (21) |

UNIT HEALTH CARE COSTS

The parameter distributions used to estimate health state utilities in the model are reported below.

Table 59: Cost input parameters

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|---------------------------|--------------|-------------|-------------|------------------|--------|
| DPP Intervention | GAMMA | | | £270 | PHE |
| DIABETES COSTS | | | | | |
| Insulin (annual cost) | GAMMA | 3.367 | 408.6 | £1375.72 | (58) |
| Metformin (annual cost) | CONSTANT | NA | NA | £18.83 | (54) |
| Sitagliptin (annual cost) | CONSTANT | NA | NA | £433.77 | (54) |

| | | | | | |
|---------------------------------------|----------|----------|----------|-----------|------|
| Nurse appointment (Advanced) | GAMMA | 100 | 0.26 | £25.52 | (53) |
| Health care assistant appointment | GAMMA | 100 | 0.03 | £3.40 | (53) |
| Eye screening | GAMMA | 15.3664 | 1.58219 | £24.31 | (56) |
| HbA1c test | GAMMA | 100 | 0.03 | £3.00 | (55) |
| Lipids test | GAMMA | 100 | 0.01 | £1.00 | (55) |
| LfT test | GAMMA | 100 | 0.01 | £1.00 | (55) |
| B12 test | GAMMA | 100 | 0.01 | £1.00 | (55) |
| Urine test | GAMMA | 100 | 0.01 | £1.00 | (55) |
| Nicotine replacement therapy | GAMMA | 100 | 1.03 | £103.00 | (53) |
| CVD COSTS | | | | | |
| Unstable Angina hospital admission | GAMMA | 100 | 12.75591 | £1275.59 | (20) |
| Revascularisation in hospital | GAMMA | 100 | 60.36846 | £6036.85 | (20) |
| MI Hospital admission | GAMMA | 100 | 15.54896 | £1554.90 | (20) |
| First Outpatient appointment | GAMMA | 100 | 1.653571 | £165.36 | (20) |
| Subsequent outpatient appointments | GAMMA | 100 | 1.100574 | £110.06 | (20) |
| Fatal CHD | GAMMA | 100 | 7.125001 | £712.50 | (38) |
| Fatal Stroke | GAMMA | 100 | 44.42562 | £4442.56 | (60) |
| First year stroke | GAMMA | 100 | 97.15908 | £9715.91 | (60) |
| Subsequent year stroke | GAMMA | 100 | 27.29644 | £2729.64 | (20) |
| Glytrin Spray | CONSTANT | NA | NA | £12.61 | (20) |
| Isosorbide mononitrate | CONSTANT | NA | NA | £13.54 | (20) |
| Verapamil | CONSTANT | NA | NA | £50.57 | (20) |
| Atenolol | CONSTANT | NA | NA | £36.42 | (20) |
| Aspirin | CONSTANT | NA | NA | £8.01 | (20) |
| Ramipril | CONSTANT | NA | NA | £90.45 | (20) |
| ARB | CONSTANT | NA | NA | £253.28 | (20) |
| Clopidogrel | CONSTANT | NA | NA | £554.41 | (20) |
| Congestive Heart Failure | GAMMA | 67.20788 | 45.99274 | £3091.07 | (62) |
| MICROVASCULAR COSTS | | | | | |
| Blindness year 1 | GAMMA | 10.26317 | 139.7079 | £1433.85 | (66) |
| Blindness subsequent years | GAMMA | 11.31099 | 42.37999 | £479.36 | (66) |
| Amputation year 1 | GAMMA | 19.37193 | 521.4492 | £10101.48 | (66) |
| Amputation subsequent years | GAMMA | 4.597909 | 412.4212 | £1896.28 | (66) |
| Renal Haemodialysis | GAMMA | 100 | 420.49 | £42049.00 | (63) |
| Renal Automated Peritoneal dialysis | GAMMA | 100 | 272.1714 | £27217.14 | (63) |
| Renal Ambulatory peritoneal dialysis | GAMMA | 100 | 197.4225 | £19742.25 | (63) |
| Renal transplant | GAMMA | 100 | 236.5973 | £23659.73 | (64) |
| Immunosuppressants | GAMMA | 100 | 69.58745 | £6958.75 | (64) |
| Foot ulcer not infected | GAMMA | 100 | 1.677526 | £167.75 | (65) |
| Foot ulcer with cellulitis | GAMMA | 100 | 4.431003 | £443.10 | (65) |
| Foot ulcer with osteomyelitis | GAMMA | 100 | 8.215817 | £821.58 | (65) |
| OTHER DISEASE COSTS | | | | | |
| Breast Cancer | GAMMA | 100 | 138.1811 | £13818.11 | (67) |
| Colorectal cancer Dukes A | GAMMA | 100 | 100.9135 | £10091.35 | (68) |
| Colorectal cancer Dukes B | GAMMA | 100 | 173.1532 | £17315.32 | (68) |
| Colorectal cancer Dukes C | GAMMA | 100 | 265.5026 | £26550.26 | (68) |
| Colorectal cancer Dukes D | GAMMA | 100 | 166.2553 | £16625.53 | (68) |
| Osteoarthritis | GAMMA | 100 | 9.616886 | £961.69 | (69) |
| Depression – Practice nurse surgery | GAMMA | 100 | 0.090154 | £9.02 | (70) |
| Depression – Practice nurse home | GAMMA | 100 | 0.270463 | 27.05 | (70) |
| Depression – Practice nurse telephone | GAMMA | 100 | 0.090154 | 9.02 | (70) |
| Depression – Health visitor | GAMMA | 100 | 0.387834 | 38.78 | (70) |
| Depression – District nurse | GAMMA | 100 | 0.377628 | 37.76 | (70) |
| Depression – Other nurse | GAMMA | 100 | 0.090154 | 9.02 | (70) |
| Depression – HCA phlebotomist | GAMMA | 100 | 0.034021 | 3.40 | (70) |
| Depression – Other primary care | GAMMA | 100 | 0.255154 | 25.52 | (70) |
| Depression – Out of Hours | GAMMA | 100 | 0.268661 | 26.87 | (70) |
| Depression – NHS Direct | GAMMA | 100 | 0.25295 | 25.30 | (70) |
| Depression – Walk-in Centre | GAMMA | 100 | 0.388316 | 38.83 | (70) |
| Depression – Prescribed medicines | GAMMA | 100 | 0.096144 | 9.61 | (70) |

| | | | | | |
|-----------------------------|----------|-----|------|---------|------|
| Depression – Secondary Care | GAMMA | 100 | 0.81 | 81.00 | (70) |
| DIAGNOSIS AND OTHER COSTS | | | | | |
| GP appointment | GAMMA | 100 | 0.47 | £46.95 | (53) |
| Diabetes diagnosis | GAMMA | 100 | 0.12 | £14.81 | (55) |
| Hypertension diagnosis | GAMMA | 100 | 0.57 | £56.51 | (19) |
| Anti-hypertensives | GAMMA | 100 | 1.96 | £195.94 | (59) |
| Simvastatin | CONSTANT | NA | NA | £26.59 | (54) |

QUALITY ASSURANCE

Within ScHARR, research is conducted within a framework of standards and systems that ensure high quality science and governance. This includes ensuring staff receive appropriate training and operate within a culture of high quality research, building sufficient time into each project for quality assurance (including error checking and validation), internal and external review of models and ideally external peer review through publication in academic journals.

The SPHR Diabetes Prevention Model has undergone an extensive process of quality assurance and error checking, both during its development and during the adaptations required for this analysis. Face validity around the model structure and assumptions was provided during model development by means of regular input from a group of stakeholders, including clinicians, diabetes researchers, patients and public health commissioners, and during model adaptation by a group of stakeholders representing the seven DPP demonstrator sites.

A guide to checking, avoiding and identifying errors in health economic models has recently been developed within ScHARR (81). Where possible, the suggested black box verification tests were carried out as part of model development. A more complex set of internal validations were also carried out to ensure that the model was behaving as planned (e.g. that metabolic trajectories and risk equations work in the intended way). The model has also undergone a series of validations against external data (82), and the structure and model assumptions have undergone formal peer review for a publications associated with the model (12). Finally, in addition to ScHARR's own process of model quality assurance and error checking, the model code was externally reviewed and refactored as part of the PHE project adaptation by Dr Mat Hall, a software engineer from the Department of Computer Science at the University of Sheffield.

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Table

Table 1| CHEERS checklist—Items to include when reporting economic evaluations of health interventions

| Section/Item | Item No | Recommendation | Reported on page No/line No |
|--|---------|---|-----------------------------|
| Title and abstract | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared. | P1, L1 |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | P5-6 |
| Introduction | | | |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study. | P8, para 1 |
| | | Present the study question and its relevance for health policy or practice decisions. | P8, para 3 |
| Methods | | | |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | P9, L8-12 P11, L7-16 |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | P9, L23-25 |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | P9, L21 |
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | P10-11 |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | P11, L19 L19 |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | P11, L21 L21 |
| Choice of health outcomes | 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | P11, L18 |
| Measurement of effectiveness | 11a | <i>Single study-based estimates</i> : Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. | P10, L6-8 |
| | 11b | <i>Synthesis-based estimates</i> : Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data. | N/A |
| Measurement and valuation of preference based outcomes | 12 | If applicable, describe the population and methods used to elicit preferences for outcomes. | N/A |
| Estimating resources and costs | 13a | <i>Single study-based economic evaluation</i> : Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | N/A |
| | 13b | <i>Model-based economic evaluation</i> : Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | P11, L2-3 |
| Currency, price date, and conversion | 14 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | P9, L20 |
| Choice of model | 15 | Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended. | P9, L6 Fig S1 |
| Assumptions | 16 | Describe all structural or other assumptions underpinning the decision-analytical model. | P9 + Supp. Methods |
| Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty. | Supp. Methods |
| Results | | | |
| Study parameters | 18 | Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended. | Supp. Methods |
| Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | P12-13 Table 1 |
| Characterising uncertainty | 20a | <i>Single study-based economic evaluation</i> : Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). | N/A |

RESEARCH METHODS & REPORTING

(continued)

| Section/item | Item No | Recommendation | Reported on page No/line No |
|--|---------|--|-----------------------------|
| | 20b | <i>Model-based economic evaluation</i> : Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | P 15 |
| Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | P 13-15 |
| Discussion | | | |
| Study findings, limitations, generalisability, and current knowledge | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | P 17-19 |
| Other | | | |
| Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | P 3, L 5-9 |
| Conflicts of interest | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | P 2, L 18-23 |

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

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BMJ Open

Assessing the Potential Return on Investment of the Proposed UK NHS Diabetes Prevention Programme in Different Population Subgroups: An Economic Evaluation

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|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2016-014953.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 09-May-2017 |
| Complete List of Authors: | Thomas, Chloe; University of Sheffield, School of Health and Related Research Sadler, Susannah; University of Sheffield Breeze, Penny; University of Sheffield, Squires, Hazel; University of Sheffield, School of Health and Related Research Gillett, Michael; UNIVERSITY OF SHEFFIELD, SCHOOL OF HEALTH AND RELATED RESEARCH Brennan, Alan; University of Sheffield, School of Health and Realated Research (SchARR) |
| Primary Subject Heading: | Health economics |
| Secondary Subject Heading: | Diabetes and endocrinology, Public health |
| Keywords: | PUBLIC HEALTH, DIABETES & ENDOCRINOLOGY, HEALTH ECONOMICS |
| | |

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3 1 Assessing the Potential Return on Investment of the Proposed UK NHS Diabetes Prevention
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10 above.

11 **Contributors**

12 CT contributed to planning the project, carried out the model adaptation and wrote the manuscript.
13 She is guarantor. SS contributed to planning the project, adapting the model and writing the
14 manuscript. PB developed the model and revised the draft paper. HS contributed to the conceptual
15 development of the model adaptation and revised the draft paper. MG provided specialist knowledge
16 around model inputs and revised the draft paper. AB was principle investigator for the project and
17 contributed to the analysis and manuscript.

18 **Competing Interests**

19 All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf
20 and declare that the only support for the submitted work was from the funders mentioned below. The
21 authors have no financial relationships with any organisations that might have an interest in the
22 submitted work in the previous three years other than Public Health England and NHS England and
23 no other relationships or activities that could appear to have influenced the submitted work.

1 **Ethical Approval**

2 Ethical approval was not needed for this study because the model is based on publicly available data
3 and analysis of secondary data.

4 **Funding**

5 This abstract presents independent research commissioned and funded by Public Health England
6 (PHE) with support from NHS England, Diabetes UK and the Department of Health. Model
7 development was funded by the National Institute for Health Research (NIHR)'s School for Public
8 Health Research (SPHR). The views expressed are those of the authors and not necessarily those of
9 PHE, NHS England, Diabetes UK, the NIHR or the Department of Health.

10 **Role of the Sponser**

11 Public Health England commissioned the work with the following objective: 'To model the potential
12 cost-effectiveness of the NHS DPP for different sub-groups of the population (for example by gender,
13 BME groups, age profile, working age/retired, level of deprivation)'. PHE also specified the nature of
14 the intervention including its expected cost, uptake and its proposed adherence to NICE guidelines.
15 However, PHE did not have any influence over the findings of the analysis. The decision to submit
16 the article for publication was made entirely independently of the funders.

17 **Acknowledgements**

18 We would like to thank the PHE steering group and stakeholders from the DPP demonstrator sites for
19 advice about model parameters relating to the DPP intervention and useful outputs. Many thanks also
20 to Maxine Johnson, Kelly Mackenzie, Tom Sanders and Elizabeth Goyder for their involvement in
21 stakeholder workshops and advice about other aspects of the project. We are also extremely grateful
22 to Pete Dodd and Mat Hall for their excellent quality assurance work with the SPHR Diabetes
23 Prevention Model. Finally, this work could not have been carried out without the SPHR Diabetes
24 Prevention Model, which was funded by the National Institute for Health Research's School for
25 Public Health Research.

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3 **1 Transparency**
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6 2 The lead author (CT) affirms that the manuscript is an honest, accurate, and transparent account of the
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8 3 study being reported; that no important aspects of the study have been omitted; and that any
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10 4 discrepancies from the study as planned have been explained.
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13 **5 Patient Involvement**
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19 **7 Data Sharing Agreement**
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22 8 Detailed results for each subgroup analysed in the model are available on request by email from the
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24 9 corresponding author.
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3 **1 ABSTRACT**

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To evaluate potential return on investment of the NHS Diabetes Prevention Programme (DPP) in England, and estimate which population subgroups are likely to benefit most in terms of cost-effectiveness, cost-savings and health benefits.

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Economic Analysis using the School for Public Health Research Diabetes Prevention Model

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Adults aged 16 or over with high risk of type 2 diabetes (HbA1c 6-6.4%). Population subgroups defined by age, sex, ethnicity, socioeconomic deprivation, baseline BMI, baseline HbA1c and working status.

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14 Interventions

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The proposed NHS DPP: An intensive lifestyle intervention focussing on dietary advice, physical activity and weight loss. Comparator: No diabetes prevention intervention.

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17 Main outcome measures

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Incremental costs, savings and return on investment, quality adjusted life years (QALYs), diabetes cases, cardiovascular cases and net monetary benefit from an NHS perspective.

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20 Results

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Intervention costs will be recouped through NHS savings within 12 years, with net NHS saving of £1.28 over 20 years for each £1 invested. Per 100,000 DPP interventions given, 3,552 QALYs are

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3 1 gained. The DPP is most cost-effective and cost-saving in obese individuals, those with baseline
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5 2 HbA1c 6.2-6.4% and those aged 40-74. QALY gains are lower in minority ethnic and low
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7 3 socioeconomic status subgroups. Probabilistic sensitivity analysis suggests that there is 97%
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9 4 probability that the DPP will be cost-effective within 20 years. NHS savings are highly sensitive to
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11 5 intervention cost, effectiveness and duration of effect.
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13 14 **Conclusions**

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17 7 The DPP is likely to be cost-effective and cost-saving under current assumptions. Prioritising obese
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19 8 individuals could create the most value for money and obtain the greatest health benefits per
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21 9 individual targeted. Low socioeconomic status or ethnic minority groups may gain fewer QALYs per
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23 10 intervention, so targeting strategies should ensure the DPP does not contribute to widening health
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25 11 inequalities. Further evidence is needed around the differential responsiveness of population
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27 12 subgroups to the DPP.
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3 **1 ARTICLE SUMMARY**
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6 **2 Strengths and Limitations of this Study:**
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- Strength: The study uses the SPHR Diabetes Prevention Model, which synthesises a broad range of evidence from published data about type 2 diabetes risk factors and the complex disease progression pathways that lead from a diabetes diagnosis.
 - Strength: The individual patient level model structure allows the heterogeneity present within the population to be modelled, enabling detailed subgroup analysis.
 - Limitation: The NHS DPP has recently begun national implementation and direct data collection on its effectiveness in practice in England has not yet been obtained, therefore the analysis assumes that effectiveness will be similar to that obtained in pragmatic trials of intensive lifestyle interventions aimed at preventing type 2 diabetes, whilst also undertaking sensitivity analysis around this assumption.
 - Limitation: The analysis uses a comparator of “no NHS DPP intervention”, which does not fully represent the current situation where some localities do have programmes for high risk individuals. These were not modelled due to limited evidence and heterogeneity of intervention implementation between localities.
 - Limitation: Data about the long-term effectiveness of lifestyle interventions and the differential response of population subgroups to such interventions is limited. Further research is required to inform these parameters.

1 INTRODUCTION

2 Type-2 diabetes is a major public health priority in the UK. Currently there are over 2.9 million
3 people with diabetes in England ¹, and estimated to be a further 5 million at high risk of developing
4 the disease ². Diabetes is estimated to directly cost the NHS in England about £5.6 billion per year ³,
5 of which most contributes to treating complications of the disease such as amputation, blindness,
6 kidney failure and cardiovascular disease (CVD). To help tackle this problem, Public Health England
7 (PHE), NHS England and Diabetes UK are together implementing the NHS Diabetes Prevention
8 Programme (DPP) ⁴. The NHS DPP consists of intensive lifestyle management programmes aimed at
9 those at high risk of diabetes due to impaired glucose regulation (IGR), defined as HbA1c 6-6.4%
10 (42-47 mmol/mol) or fasting plasma glucose of 5.5-6.9 mmol/l. It is expected that IGR individuals
11 will be identified through a mixture of NHS Health Checks and opportunistic or targeted screening
12 processes, and that 100,000 individuals will be referred to the DPP each year once the programme is
13 running.

14 Previous economic evaluations indicate that lifestyle interventions such as that planned for the NHS
15 DPP can be cost-effective ⁵⁻⁸. However, there is evidence that diabetes prevention interventions may
16 be differentially effective in different population subgroups ⁹⁻¹³, thereby potentially leading to
17 differential cost-effectiveness. Given the limited number of available interventions, analysis of
18 potential disparities in cost-effectiveness of the DPP between different subgroups is important not
19 only to maximise potential health benefits and cost-savings, but also to ensure that health benefits are
20 distributed in the population in a fair and equitable manner, which is an important consideration for
21 public health interventions.

22 This study aims to (a) model the potential cost-effectiveness of the proposed NHS DPP in the English
23 population using an adaptation of the National Institute for Health Research (NIHR) School for Public
24 Health Research (SPHR) Diabetes Prevention Model ^{7,14}, and (b) investigate in which subgroups,
25 defined by age, gender, ethnicity, socioeconomic deprivation, baseline BMI, baseline HbA1c and

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3 1 working status the DPP is likely to have the most benefit in terms of cost-effectiveness, cost-savings
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5 2 and health benefits.
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8 **METHODS**

9 10 **Model Structure**

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13 5 The SPHR Diabetes Prevention Model was developed to forecast long-term health and health care
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15 6 costs under alternative scenarios for diabetes prevention. A detailed description of the methodology
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17 7 and assumptions used in the model can be found in the supplementary appendix.
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21 8 The model is an individual patient simulation model based upon the evolution of personalised
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23 9 trajectories for metabolic factors including body mass index (BMI), systolic blood pressure (SBP),
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25 10 cholesterol and measures of blood glucose (including HbA1c)¹⁵. The baseline population consists of a
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27 11 representative sample of the English population obtained from the Health Survey for England (HSE)
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29 12 ¹⁶. HSE 2011 was chosen to inform the baseline population in the model due to its focus on diabetes
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31 13 and cardiovascular disease, meaning it incorporates information about relevant metabolic factors.
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33 14 Individuals aged below 16 were excluded from the analysis.
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37 15 The model runs in annual cycles (see schematic in Figure S1 of the supplementary material). For each
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39 16 person, their BMI, cholesterol, SBP and HbA1c progress from year to year. Every year in the model,
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41 17 an individual may visit their GP or undergo a health check, and be diagnosed with and treated for
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43 18 hypertension, high cardiovascular risk, diabetes, microvascular complications of diabetes,
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45 19 cardiovascular disease (CVD), congestive heart failure, osteoarthritis, depression and breast or colon
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47 20 cancer, or may die. Utility of each individual in each year of the model is dependent upon their age,
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49 21 gender and medical conditions. Each condition is associated with a utility (health related quality of
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51 22 life) decrement and a healthcare cost. Total costs and QALYs are aggregated over all individuals in
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53 23 the model. Costs are at 2014 values in English pounds. The model perspective is that of the NHS in
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55 24 England.
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57 **Intervention**

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1 The NHS DPP is an intensive lifestyle intervention focussing on dietary advice, physical activity and
2 weight loss, aimed at individuals in England at high risk of diabetes. The model begins at the point
3 where individuals eligible for the DPP (HbA1c 6-6.4%/42-47 mmol/mol; aged ≥ 16) have been
4 identified and does not incorporate any local costs or utility change associated with identification or
5 referral. Table S1 of the supplementary material details baseline characteristics for the 1,492 high risk
6 individuals in the HSE 2011.

7 An intervention uptake rate of 32% was assumed in consultation with Public Health England. It was
8 assumed that those who did not take up the intervention incurred no extra costs or benefits.
9 Effectiveness evidence came from a recent PHE commissioned evidence review and meta-analysis of
10 pragmatic diabetes prevention interventions, carried out specifically to inform the likely effectiveness
11 of the NHS DPP⁹. PHE, NHS England and Diabetes UK have specified that in order to maximise
12 intervention effectiveness, they wish the commissioned DPP to fulfil at least 9-12 guidelines as
13 recommended in NICE guidance for diabetes prevention (PH38)¹⁷. NICE guidelines include using
14 particular strategies associated with increased effectiveness, specifying the minimum amount of
15 contact time and follow-up sessions, and delivering the programme through qualified practitioners. In
16 line with this, a mean weight loss of 3.24kg was assumed, taken from the meta-analysis of
17 interventions fulfilling 9-12 NICE guidelines⁹. Data about concomitant reduction in systolic blood
18 pressure, total cholesterol and HbA1c was not available from the PHE evidence review and so was
19 linearly extrapolated from an earlier review and meta-analysis¹⁸ (see Table S2 and supplementary
20 methods for details). Current evidence indicates that whilst there may potentially be a small number
21 of adverse musculoskeletal events associated with intensive lifestyle intervention compared with
22 control, these are not significant so were not incorporated into the analysis¹¹.

23 There is some evidence to indicate that effectiveness of lifestyle interventions to prevent type 2
24 diabetes differs between population subgroups, although study quality varies⁹⁻¹³. Stratification of
25 intervention effectiveness by baseline BMI was implemented into the model, again using data from
26 the PHE meta-analysis⁹. There was insufficient evidence around differential effectiveness for other
27 subgroups to incorporate into the model. In practice, some individuals who start the intervention will

1 not complete it. Most of the studies used to derive the estimate of effectiveness in the PHE meta-
2 analysis used intention to treat analysis, but two have not (personal communication from N. Ashra). It
3 is likely therefore that the effectiveness estimate used in the model only partially accounts for non-
4 completion and therefore may be higher than is realistic in practice. Sensitivity analysis was carried
5 out to account for this possibility. A linear rate of weight regain (plus reduction in the intervention
6 effects on HbA1c, SBP and cholesterol) was assumed over the first five years in line with the
7 assumptions used to produce the NICE guidelines for diabetes prevention (PH38)¹⁹. This meant that
8 individuals' metabolic trajectories returned to where they would have been without intervention,
9 within five years of intervention implementation.

10 The cost of the NHS DPP was determined through the DPP procurement process in 2016. As this was
11 still undergoing at the time of this analysis, the average cost from the NHS England impact
12 assessment of £270 per participant was used²⁰. This is the price that the NHS is willing to pay per
13 person starting the intervention and incorporates expected retention rates of participants. Due to the
14 NHS perspective taken, potential out of pocket costs for intervention attendees were not included. In
15 the control simulation, it was assumed that IGR individuals would not receive any intervention and
16 would therefore not incur any extra costs or changes to their metabolic trajectories.

17 **Subgroups**

18 Population subgroups were selected for analysis due to the potential influence of different
19 characteristics on diabetes risk and for equity implications. The following subgroups were chosen:

- 20 • 4 Age groups (Age 16-40; Age 40-59; Age 60-74; Age \geq 75)
- 21 • 2 Gender groups (Male; Female)
- 22 • 2 Ethnicity groups (White; BME)
- 23 • 5 Deprivation groups (IMD quintiles 1-5)
- 24 • 3 Working status groups (Working; Retired; Other)
- 25 • 4 BMI groups (BMI < 25 kg/m²; BMI 25-29.9 kg/m²; BMI 30-34.9 kg/m²; BMI \geq 35 kg/m²)
- 26 • 2 HbA1c groups (HbA1c 6-6.19%; HbA1c 6.2-6.49%)

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3 1 The analysis models a single year of NHS DPP intervention and all the downstream cost savings and
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5 2 health benefits (including life years, QALYs, and reduction in diabetes and CVD cases) that this
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7 3 produces over the subsequent 20 years. 1000 model runs were performed for each of the 1,492 HSE
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9 4 2011 individuals in the deterministic analysis and model outcomes for each subgroup extracted from
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11 5 the total results. All costs were discounted by 3.5% and QALYs by 1.5%, as per Department of Health
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13 6 guidelines²¹.

7 **Sensitivity Analysis**

8 Four deterministic one-way sensitivity analyses were performed to investigate the sensitivity of the
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10 9 results to a more conservative set of intervention parameters. The assumptions around intervention
11
12 10 specification for each of these scenarios are shown in Table S2 of the supplementary materials.

- 11 1. Uniform intervention effectiveness (no stratification by BMI)
- 12 2. 25% lower mean effectiveness
- 13 3. Three year duration of intervention effect (instead of five years)
- 14 4. Higher intervention cost of £350 (instead of £270).

15 A fifth sensitivity analysis was also carried out in which a series of combinatorial subgroups were
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17 16 modelled, defined by both BMI and age, or BMI and HbA1c, in order to observe the interaction
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19 17 between characteristics.

20 Probabilistic sensitivity analysis (PSA) was carried out to describe the uncertainty in parameter inputs
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22 19 of the model and how this translates into uncertainty in the outcomes of the model. A suitable
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24 20 distribution was selected for each parameter, based upon its mean and standard error. Random
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26 21 sampling simultaneously across all input parameter distributions allowed parameter uncertainty to be
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28 22 quantified. 5000 different random samples of parameter values were selected, and each was applied to
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30 23 the 1,492 individuals in the simulation. A list of model parameters, their distribution for PSA and their
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32 24 source is provided in Tables 42-60 in the supplementary appendix.

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3 1 **RESULTS**

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5 2 **Population Results**

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8 3 **MODEL RESULTS SUGGEST THAT A YEAR OF DPP**

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10 4 **REDUCE HEALTHCARE COSTS FROM THE FIRST YEAR OF**
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12 5 **YEARS (BY THE END OF 2027/28) AND BE COST-EFFECTIVE**
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14 6 **WILLINGNESS TO PAY THRESHOLD OF £20,000 PER QALY**
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16 7 **GAINED) WITHIN 6 YEARS (BY THE END OF 2021/22) (FIGURE**
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18 8 **LEGENDS**

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21 9 Figure 1). For every 100,000 interventions given, the DPP is expected to prevent or delay 4,147 cases
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23 10 of diabetes and 413 cases of CVD (Table 1).

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26 11 The subdivision of NHS costs/savings by disease area is shown in Table 1. This indicates that most
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28 12 cost-savings arise due to reductions in the cost of treating diabetes or CVD, with high savings also
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30 13 accrued through a reduction in other primary care costs including GP visits and prescription of statins
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32 14 and anti-hypertensives. The timing of cost-savings varies depending upon disease area, with cost-
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34 15 savings in CVD care, diagnostics and other primary care accumulating in the short-term, whilst cost-
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36 16 savings in diabetes treatment, microvascular disease and other complications accumulate more slowly.
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38 17 This indicates that one year of the DPP implemented now is likely to continue saving money in the
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40 18 NHS for many years in the future despite a fairly transient (diminishing over five years) effect on
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42 19 metabolic risk factors, due to knock-on delays in progression to more complex diabetes (requiring
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44 20 insulin) and to expensive microvascular complications of diabetes.

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47 21 **RETURN ON INVESTMENT IS CALCULATED BY DIVIDING TOTAL**
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49 22 **INTERVENTION COSTS) BY THE COST OF THE INTERVENTION**
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51 23 **THE DPP. THE MODEL ESTIMATES THAT AT 20 YEARS**
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53 24 **INVESTED IN THE DPP, £1.28 OF NHS SAVINGS AND £9.21 WORTH**
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55 25 **USING £60,000 AS THE VALUE OF A QALY) WILL BE PRODUCED**
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57 26 **(FIGURE LEGENDS**

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3 1 Figure 1 and Table 1).
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3 Subgroup Results

4 Across the subgroup dimensions examined, the biggest differentials in cost-effectiveness are seen in
5 the subgroups defined by baseline BMI (FIGURE LEGENDS

6 **FIGURE 1). THE NHS DPP IS ESTIMATED TO BE MOST COST-
7 EFFECTIVE IN INDIVIDUALS WITH BMI \geq 35 KG/M² (12% OF THE
8 NHS SAVINGS OUTWEIGH INITIAL INVESTMENT WITHIN FIVE
9 WITHIN 20 YEARS (FIGURE 2). QALYS GAINED OVER 20 YEARS
10 ARE ALSO HIGHEST (6,377 PER 100,000 INDIVIDUALS), AND
11 THERE ARE THE LARGEST REDUCTIONS IN DIABETES AND CVD
12 CASES (MAXIMUM REDUCTION OF DIABETES CASES = 5,484 AT
13 YEAR 6, AND MAXIMUM REDUCTION OF CVD CASES = 846 AT
14 YEAR 7 – SEE FIGURE S2 OF THE SUPPLEMENTARY MATERIALS).
15 THE 20 YEAR RETURN ON INVESTMENT IS ESTIMATED TO BE
16 £2.93 PER £1 SPENT ON INTERVENTION (FIGURE LEGENDS**

17 Figure 1), and over £17 per £1 spent if monetised health benefits are included at £60,000 per QALY.
18 The second most cost-saving group is those who have BMI 30-34 kg/m². In contrast, the non-obese
19 subgroups have substantially worse estimated return on investment, with the BMI < 25 kg/m²
20 subgroup not recouping intervention costs within the 20 year modelled period.

21 Across the other dimensions for defining subgroups, IMD deprivation quintile makes a relatively
22 small difference to return on investment. Age makes a much larger difference with the middle age
23 groups (40-59, and 60-74) showing better return on investment than the younger (<40) and older (\geq
24 75) groups. Estimated return on investment is marginally better for females than males, marginally
25 different between working, retired and other, and marginally better for a white versus BME subgroup.
26 The other large subgroup difference is between those above or below 6.2% HbA1c at baseline, with
27 the higher HbA1c subgroup showing a larger return on investment than the lower HbA1c subgroup.

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3 1 There are three subgroups to which net mean cost-savings do not accrue within the 20 years following
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5 2 intervention implementation. These include the oldest age group (≥ 75), individuals who are normal
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7 3 weight or underweight (BMI < 25) and individuals with HbA1c 6-6.19. Note that subgroup
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9 4 characteristics are not mutually exclusive, so although on average the intervention is not cost-saving
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11 5 in people of normal weight, it may be cost-saving in certain individuals with other characteristics
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13 6 which correlate with cost-savings, such as high HbA1c.

16 7 In general, subgroups that obtain the highest cost-savings also obtain the highest QALY gains and are
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18 8 the most cost-effective, as cost savings relate to preventing disease progression. However, the DPP
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20 9 also reduces mortality of older individuals, resulting in higher QALYs than might otherwise be
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22 10 expected in subgroups containing higher numbers of older people. Equally subgroups containing
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24 11 younger individuals (including the BME group and the most socioeconomically deprived group) gain
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26 12 fewer incremental QALYs and life years; their disease and mortality risk is reduced due to their lower
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28 13 age so the NHS DPP is less effective, suggesting that the health benefits of the DPP may not be
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30 14 equitably distributed (Figure S2 and S3 in the supplementary appendix)**Error! Reference source not**
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32 15 **found..**

35 16 In all subgroups, numbers of incremental diabetes/CVD cases drop in the short-term whilst the
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37 17 intervention effect is operating and then rise again at the point when weight has been fully regained.
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39 18 This indicates that most cases of diabetes/CVD are likely to be delayed rather than prevented entirely
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41 19 based upon current assumptions about long term effectiveness of the interventions.

44 20 **Sensitivity Analyses**

47 21 The PSA estimation of mean incremental total cost savings per person is £131 and of mean
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49 22 incremental QALYs is 0.0388 at 20 years following intervention implementation in England (Table
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51 23 S3 of the supplementary materials). This is higher for both cost-savings and QALY gains than found
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53 24 during deterministic analysis; the difference is due to non-linearity in the model, which is likely to be
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55 25 particularly important around the BMI stratified estimation of intervention effect. The probability that
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57 26 the NHS DPP will be cost-effective in 20 years compared with no DPP intervention, at a willingness
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1 to pay threshold of £20,000 per QALY is 97% (see Figure 3), and the probability that the DPP will be
2 cost-saving for the NHS 20 years after intervention implementation is 70%. As in the deterministic
3 analysis, BMI is the most important criteria for determining cost-effectiveness, with the two highest
4 BMI subgroups being more cost-saving and cost-effective than other population subgroups (Table S3
5 of the supplementary materials and Figure 3).

6 One-way sensitivity analysis indicates that under conservative scenarios of higher intervention cost
7 (£350 instead of £270), 25% lower intervention effectiveness or lower duration of intervention effect
8 (three year decline instead of five year) the NHS DPP would take longer than 20 years to recoup
9 initial intervention costs in the majority of subgroups (Table S4 of the supplementary materials). The
10 intervention is still likely to be cost-effective (at a threshold of £20,000 per QALY) within a 10 year
11 time horizon in all but the least cost-effective subgroups. Of these scenarios, reducing duration of
12 intervention effect has the most significant impact on outcomes, with only the BMI ≥ 35 subgroup
13 remaining cost-saving. However, in all three scenarios, the relative cost-effectiveness of subgroups
14 remains unchanged compared with the basecase analysis.

15 If intervention effect is no longer stratified by BMI, the difference between subgroups of a particular
16 population characteristic is reduced compared with the base case scenario. Whilst for some subgroups,
17 such as those defined by BMI, a clear gradient is still apparent, for other groups such as those defined
18 by IMD quintile or ethnicity the difference in outcomes is minimal, suggesting that stratification of
19 intervention effectiveness by BMI is a key driver of differential cost-effectiveness in those groups in
20 the base case analysis.

21 Combinatorial analysis indicates that the high return on investment in the BMI 35+ subgroup is
22 mitigated in individuals who are also aged 75+ and reduced to only £1.54 per £1 spent, whereas in
23 individuals aged 40-59 it is improved even further to £3.20 (Figure 4). An even higher return on
24 investment of £3.52 could potentially be obtained if individuals who have both BMI 35+ and HbA1c
25 6.2-6.4% are selected for the NHS DPP intervention. This suggests that subgroups with high benefits
26 can be combined to potentially increase the return on investment even further.

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For peer review only

1 DISCUSSION

2 It is essential with large-scale and expensive national programmes such as the NHS DPP that a cost-
3 effectiveness analysis using the best currently available data is carried out prior to implementation:
4 firstly, to determine whether the intervention should be carried out at all; secondly, to enable effective
5 budgeting; and thirdly, where interventions are limited, to estimate who is likely to benefit most and
6 therefore should be prioritised. This analysis suggests that the NHS DPP is highly likely to be cost-
7 effective and cost-saving over the medium to long-term using current assumptions around
8 intervention cost, effectiveness and duration of effect, and should start to save costs for the NHS from
9 the first year of implementation, recouping the initial investment in the intervention by year 12. The
10 number of potential individuals at high risk of type 2 diabetes in England (estimated to be about 5
11 million²) far exceeds the 100,000 interventions that NHS England plans to offer each year³. This
12 analysis indicates that prioritising obese individuals in particular (BMI ≥ 30 kg/m²), combined with
13 those with the highest baseline HbA1c and focussing on those aged between 40 and 74 (the ages
14 covered in any case by the NHS Health Check) is likely to create the most value for money in the
15 programme by obtaining both the greatest cost-savings for the NHS and the highest health benefits per
16 individual targeted.

17 This study does suggest that care may have to be taken when implementing the NHS DPP to ensure
18 that it does not lead to greater health inequalities in some groups at high risk of type 2 diabetes and its
19 complications, including individuals from minority ethnic or socioeconomically deprived
20 backgrounds. The analysis shows a tendency for the NHS DPP to provide fewer QALYs to these
21 subgroups than to individuals from more socioeconomically advantaged or white ethnic backgrounds.

22 Given that the model does not incorporate (nor is there any clear evidence for) differential
23 effectiveness of the NHS DPP by socioeconomic status or ethnicity, these differences are likely to
24 occur for two main reasons. Firstly; disease risk is influenced by subgroup - for example, both
25 ethnicity and socioeconomic status are parameters in the QRISK equations that are used in the model
26 to determine CVD risk²². This means that even if a given individual reduces their metabolic risk
27 factors through the DPP, they may still be at high risk of disease due to environmental or genetic

1 factors outside the scope of the intervention. Secondly, subgroups differ in key personal
2 characteristics associated with intervention efficacy – for example, mean age is lower than average in
3 the BME subgroup and in the most socioeconomically deprived quintile. Low mean age results in
4 lower health benefits and return on investment from the NHS DPP than high age due to the lower
5 absolute risks of disease and mortality in such individuals and therefore lower ability to benefit .
6 Given that BME and low socioeconomic status subgroups also tend to suffer from low uptake of
7 lifestyle interventions ^{23;24}, it is important that NHS DPP providers make particular efforts to engage
8 individuals from these groups if exacerbation of health inequalities is to be avoided.

9 A major strength of this analysis is the synthesis of a broad range of evidence using the SPHR
10 Diabetes Prevention Model ^{7;14}. This is an individual patient simulation model that incorporates a
11 large amount of evidence from published data about type 2 diabetes risk factors and the complex
12 disease progression pathways that lead from a diabetes diagnosis, and is able to represent the
13 heterogeneity present within the English population and thereby model population subgroups.
14 However, the model only takes healthcare costs into account, meaning that wider societal costs and
15 benefits cannot be calculated, and even within healthcare does not incorporate diseases such as
16 dementia that may impact upon long-term healthcare costs. A more important limitation is that the
17 comparator of “no NHS DPP intervention” used for this analysis does not fully represent the current
18 situation where some localities do have programmes for high risk individuals. These were not
19 modelled due to limited evidence and heterogeneity of intervention implementation between
20 localities. Subgroup analysis has also been limited by the relatively small number of IGR individuals
21 in the HSE data, meaning that smaller subgroups (such as individual minority ethnic groups) or a
22 larger variety of subgroup combinations, both of which would provide useful information for those
23 implementing the NHS DPP, cannot be accurately modelled.

24 Whilst this study is not based on actual clinical data from the NHS DPP, because such data does not
25 yet exist as the national programme implementation is just beginning, it does use the most recently
26 published estimates of intervention effectiveness from a PHE evidence review designed specifically to
27 inform the development of the NHS DPP ⁹, and therefore is likely to provide a more accurate estimate

1 of NHS DPP cost-effectiveness than previous economic analyses of diabetes prevention interventions.
2 However, data about the long-term effectiveness of lifestyle interventions and the differential
3 response of population subgroups to such interventions is limited and represents the most important
4 limitation of this study. Deterministic sensitivity analysis indicates that the cost-effectiveness of the
5 NHS DPP is substantially influenced by parameters such as intervention effectiveness and duration of
6 intervention effect, which could also impact on the ordering of subgroups. Future research should
7 therefore focus primarily on improving estimates of subgroup effectiveness, and gathering evidence
8 about initial weight loss and weight regain rates due to the NHS DPP, which could be added to the
9 model. The biggest challenges in performing good quality subgroup analysis are sufficiently powering
10 the clinical studies to account for subgroups that may only comprise a small proportion of the
11 population, and taking into account potential interaction between personal characteristics that could
12 lead to confounding across subgroups in intervention uptake rates or effectiveness. The National
13 Institute for Health Research (NIHR) is commissioning a formal evaluation of the NHS DPP which
14 will include cost-effectiveness analysis. Careful statistical design of this analysis and long-term
15 follow-up of participants should enable these challenges to be overcome successfully and provide
16 high quality data for updating and improving the accuracy of model predictions.

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Table 1: Mean cumulative incremental outcomes per person given the intervention in England. Costs and cost-ineffective returns are shown in red whereas savings and cost-effective returns are shown in black. Costs are discounted at 3.5% whereas QALYs are discounted at 1.5%.

| | Year 1 2016/17 | Year 2 2017/18 | Year 3 2018/19 | Year 4 2019/20 | Year 5 2020/21 | Year 10 2025/26 | Year 15 2030/31 | Year 20 2035/36 |
|---|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|--------------------|--------------------|
| TOTAL COSTS | £240 | £218 | £195 | £173 | £150 | £23 | -£43 | -£75 |
| DPP Costs | £270 | £270 | £270 | £270 | £270 | £270 | £270 | £270 |
| NHS Costs | -£30 | -£52 | -£75 | -£97 | -£120 | -£247 | -£313 | -£345 |
| <i>Diabetes Treatment</i> | -£1 | -£3 | -£6 | -£9 | -£17 | -£79 | -£106 | -£115 |
| <i>CVD Treatment</i> | -£11 | -£18 | -£25 | -£32 | -£37 | -£56 | -£65 | -£69 |
| <i>Microvascular Complications¹</i> | -£1 | -£3 | -£5 | -£7 | -£10 | -£27 | -£46 | -£60 |
| <i>Other Complications²</i> | -£2 | -£5 | -£8 | -£12 | -£15 | -£30 | -£40 | -£45 |
| <i>Diagnostics³</i> | -£4 | -£4 | -£5 | -£5 | -£4 | -£3 | -£2 | -£2 |
| <i>Other Primary Care⁴</i> | -£11 | -£19 | -£26 | -£32 | -£37 | -£52 | -£54 | -£54 |
| Life Years ⁵ | 6 | 41 | 130 | 281 | 486 | 1,795 | 2,838 | 3,487 |
| QALYs ⁵ | 50 | 133 | 269 | 457 | 686 | 1,986 | 2,966 | 3,552 |
| Diabetes Cases ⁵ | -1043 | -1995 | -3000 | -3788 | -4147 | -1812 | -766 | -654 |
| CVD Cases ⁵ | -183 | -273 | -344 | -396 | -413 | -394 | -325 | -282 |
| ICER (£/QALY) | £475,625 | £163,636 | £72,715 | £37,870 | £21,860 | £1,162 | -£1,446 | -£2,120 |
| Net Monetary Benefit ⁶ | -£209 | -£138 | -£34 | £101 | £262 | £1,169 | £1,822 | £2,207 |
| RoI: Total Savings ⁷ | £0.11 | £0.19 | £0.28 | £0.36 | £0.44 | £0.91 | £1.16 | £1.28 |
| RoI: NMB ⁷ | £0.22 | £0.49 | £0.87 | £1.37 | £1.97 | £5.33 | £7.75 | £9.17 |
| DPP Diabetes Prevention Programme; NHS National Health Service; QALY Quality Adjusted Life Year; CVD Cardiovascular Disease; ICER Incremental Cost-Effectiveness Ratio; RoI Return on Investment; NMB Net Monetary Benefit. | | | | | | | | |
| ¹ Includes costs of nephropathy, ulcer, amputation and retinopathy | | | | | | | | |
| ² Includes costs of osteoarthritis, depression, breast and colon cancer | | | | | | | | |
| ³ Diagnosis of diabetes, high CVD risk and hypertension | | | | | | | | |
| ⁴ Includes costs of GP visits and prescription of statins and anti-hypertensives | | | | | | | | |
| ⁵ Per 100,000 individuals given the DPP intervention | | | | | | | | |
| ⁶ Value of a QALY assumed to be £60,000 for net monetary benefit analysis ¹⁷ | | | | | | | | |
| ⁷ Return on Investment per £1 invested in the DPP | | | | | | | | |

1 **FIGURE LEGENDS**

2 Figure 1: Bar charts showing: A) the year that the NHS DPP becomes cost-saving (recoups
3 intervention costs); B) the year that the NHS DPP becomes cost-effective; C) the total NHS return on
4 investment within 20 years per £1 spent on the NHSDPP for each of the population subgroups.
5 Vertical arrows indicate that the DPP is not cost-saving within the 20 year period modelled.

6 Figure 2: Graphs showing cumulative incremental (net) costs per person given the intervention over a
7 20 year time horizon for each subgroup and for the total population. Annual incremental costs per
8 person are shown as a dotted line on the total population graph. Costs are discounted at 3.5%

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21 Figure 3: PSA Results. A) Cost-effectiveness acceptability curve showing the probability that the DPP
22 or no intervention will be cost-effective over a range of different willingness to pay thresholds. B)
23 Distribution of PSA results for i) the total population and ii) BMI subgroups on the cost-effectiveness
24 plane. Error bars represent 95% confidence intervals for incremental total costs and incremental
25 QALYs. The cost-effectiveness (CE) threshold is £20,000/QALY. Note that the size of the 95%
26 confidence intervals and therefore the probability that the intervention will be cost-effective or cost-
27 saving is partially related to the size of each subgroup within the total IGR population of England, in
28 addition to being related to the distribution of results on the cost-effectiveness plane.
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38 Figure 4: Graphs showing the interaction between BMI and: A) age; B) HbA1c. Return on investment
39 in combinatorial subgroups defined using two personal characteristics.
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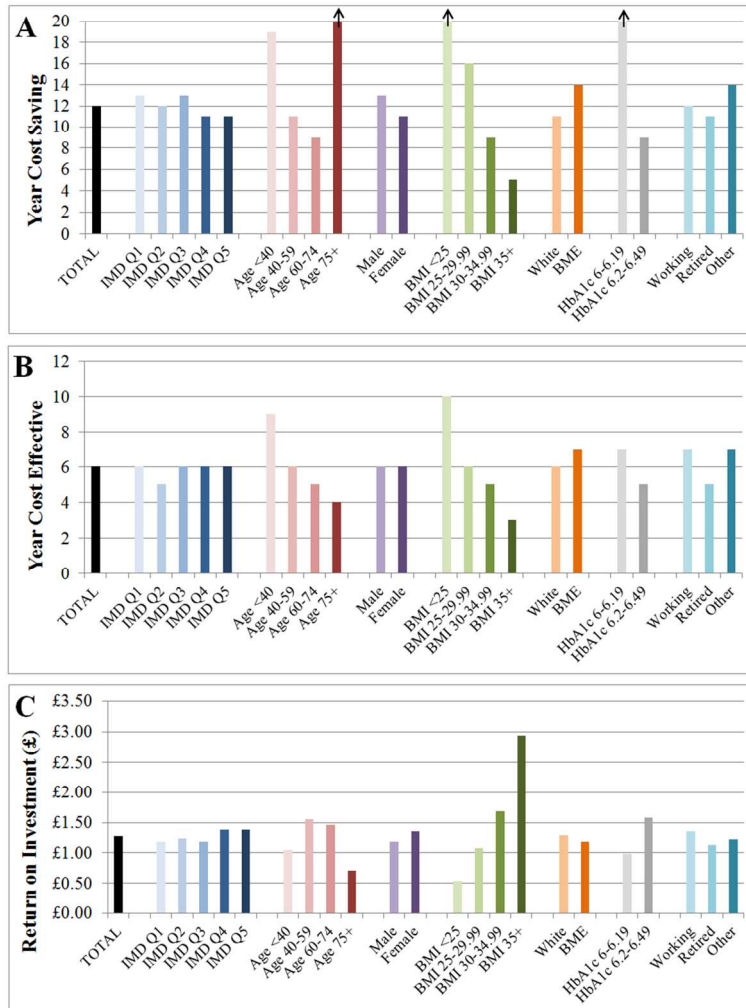


Figure 1: Bar charts showing: A) the year that the NHS DPP becomes cost-saving (recoups intervention costs); B) the year that the NHS DPP becomes cost-effective; C) the total NHS return on investment within 20 years per £1 spent on the NHS DPP for each of the population subgroups. Vertical arrows indicate that the DPP is not cost-saving within the 20 year period modelled.

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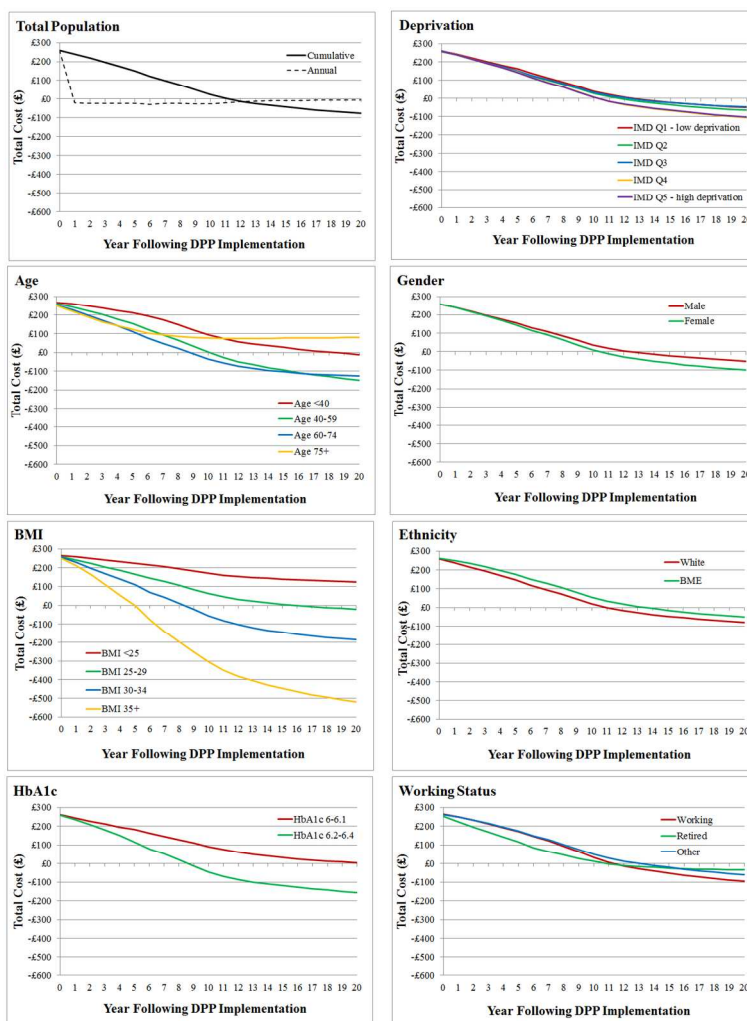


Figure 2: Graphs showing cumulative incremental (net) costs per person given the intervention over a 20 year time horizon for each subgroup and for the total population. Annual incremental costs per person are shown as a dotted line on the total population graph. Costs are discounted at 3.5%.

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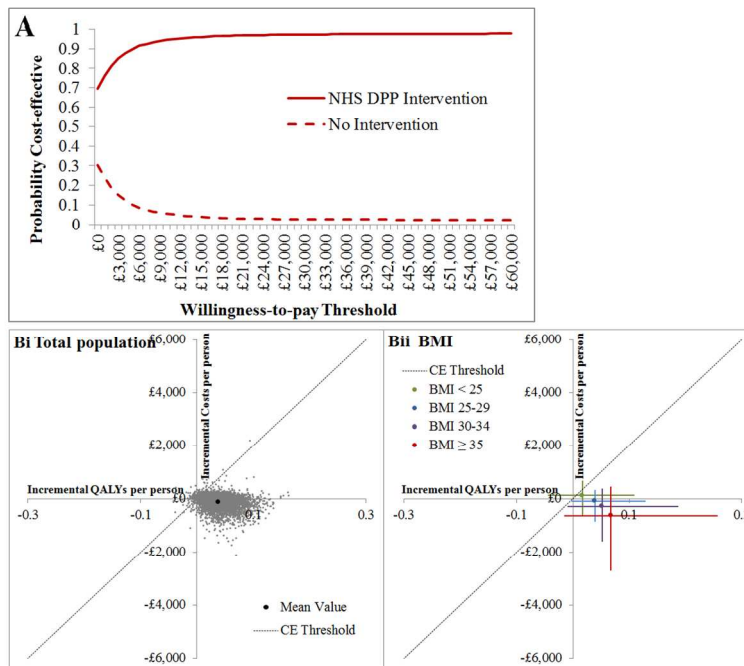


Figure 3: PSA Results. A) Cost-effectiveness acceptability curve showing the probability that the DPP or no intervention will be cost-effective over a range of different willingness to pay thresholds. B) Distribution of PSA results for i) the total population and ii) BMI subgroups on the cost-effectiveness plane. Error bars represent 95% confidence intervals for incremental total costs and incremental QALYs. The cost-effectiveness (CE) threshold is £20,000/QALY. Note that the size of the 95% confidence intervals and therefore the probability that the intervention will be cost-effective or cost-saving is partially related to the size of each subgroup within the total IGR population of England, in addition to being related to the distribution of results on the cost-effectiveness plane.

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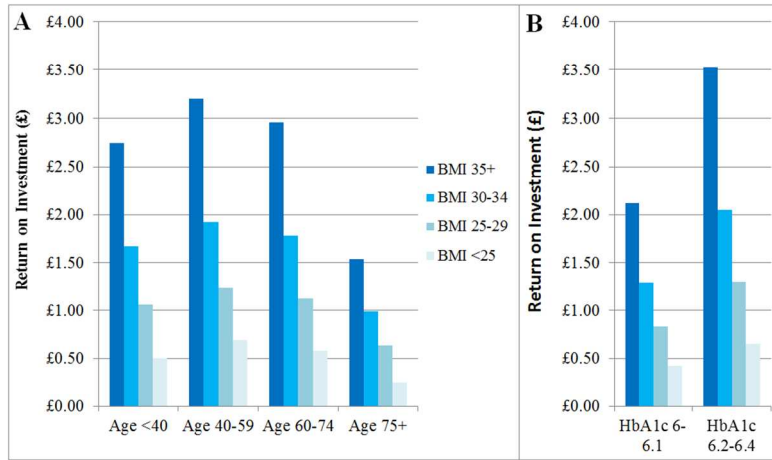


Figure 4: Graphs showing the interaction between BMI and: A) age; B) HbA1c. Return on investment in combinatorial subgroups defined using two personal characteristics.

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3 ONLINE ONLY SUPPLEMENTAL MATERIAL
4

5 Full Title: Assessing the Potential Return on Investment of the Proposed NHS Diabetes
6 Prevention Programme in Different Population Subgroups: An Economic Evaluation
7

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9 Running Title: Return on Investment of the NHS DPP
10

11 Chloe Thomas, Susi Sadler, Penny Breeze, Hazel Squires, Michael Gillett, Alan Brennan
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15 B) SUPPLEMENTARY METHODS
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A) SUPPLEMENTARY TABLES & FIGURES

| CHARACTERISTIC | NUMBER | PERCENTAGE | |
|---|--------|--------------------|--------|
| Male | 644 | 43.2% | |
| Female | 848 | 56.8% | |
| White | 1332 | 89.3% | |
| BME | 160 | 10.7% | |
| <i>Indian</i> | 46 | 3.1% | |
| <i>Pakistani</i> | 23 | 1.5% | |
| <i>Bangladeshi</i> | 5 | 0.3% | |
| <i>Other Asian</i> | 19 | 1.3% | |
| <i>Caribbean</i> | 16 | 1.1% | |
| <i>African</i> | 28 | 1.9% | |
| <i>Chinese</i> | 4 | 0.3% | |
| <i>Other</i> | 19 | 1.3% | |
| Age1 < 40 | 279 | 18.7% | |
| Age2 40-59 | 482 | 32.3% | |
| Age3 60-74 | 453 | 30.4% | |
| Age4 75+ | 278 | 18.6% | |
| IMD 1 (least deprived) | 339 | 22.7% | |
| IMD 2 | 436 | 29.2% | |
| IMD 3 | 177 | 11.9% | |
| IMD 4 | 297 | 19.9% | |
| IMD 5 (most deprived) | 243 | 16.3% | |
| Working | 679 | 45.5% | |
| Retired | 584 | 39.1% | |
| Other | 229 | 15.3% | |
| BMI1 < 25 kg/m ² | 409 | 27.4% | |
| BMI2 25-29 kg/m ² | 586 | 39.3% | |
| BMI3 30-34 kg/m ² | 324 | 21.7% | |
| BMI4 ≥ 35 kg/m ² | 173 | 11.6% | |
| HbA1c 6-6.1 % (42-44 mmol/mol) | 763 | 51.1% | |
| HbA1c 6.2-6.4 % (45-47 mmol/mol) | 729 | 48.9% | |
| | MEAN | STANDARD DEVIATION | MEDIAN |
| Age (years) | 57.1 | 17.8 | 58.0 |
| BMI (kg/m ²) | 28.4 | 5.7 | 27.8 |
| Total Cholesterol (mmol/l) | 5.7 | 1.0 | 5.7 |
| HDL Cholesterol (mmol/l) | 1.5 | 0.4 | 1.5 |
| HbA1c (%) | 6.19 | 0.14 | 6.19 |
| Systolic Blood Pressure (mm Hg) | 129.7 | 17.2 | 128.5 |
| EQ-5D (TTO) | 0.739 | 0.307 | 0.796 |
| BME Black and Minority Ethnic; BMI Body Mass Index; IMD Index of Multiple Deprivation; CVD Cardiovascular Disease; IGR Impaired Glucose Regulation; HDL High Density Lipoprotein; EQ-5D 5 dimensions Euroqol (health related quality of life index); TTO Time Trade-Off | | | |

Table S1: Baseline characteristics of the IGR individuals from HSE 2011, following imputation of missing metabolic data (N=1,492).

| SPECIFICATION | BASE-CASE | SA 1 | SA 2 | SA 3 | SA 4 |
|---|-----------|-------------|--------------|----------------|-------------|
| Intervention Uptake* | 32% | 32% | 32% | 32% | 32% |
| Intervention Effectiveness ^{6,15} : | | | | | |
| <i>Mean weight change (kg)</i> | -3.24 | -3.24 | -2.43 | -3.24 | -3.24 |
| <i>Mean BMI change (kg/m²)</i> | -1.47 | -1.47 | -1.10 | -1.47 | -1.47 |
| <i>Mean SBP change (mmHg)</i> | -6.57 | -6.57 | -0.15 | -6.57 | -6.57 |
| <i>Mean cholesterol change (mmol/l)</i> | -0.28 | -0.28 | -4.93 | -0.28 | -0.28 |
| <i>Mean HbA1c change (%)</i> | -0.20 | -0.20 | -0.21 | -0.20 | -0.20 |
| Stratification of Intervention Effectiveness (kg) ^{6 **} | -0.23 | None | -0.23 | -0.23 | -0.23 |
| Intervention Cost* | £270 | £270 | £270 | £270 | £350 |
| Time to Weight Regain* | 5 years | 5 years | 5 years | 3 years | 5 years |
| * PHE estimates of expected values | | | | | |
| ** extra weight loss per unit increase in baseline BMI above 31.5 kg/m ² , or weight gain per unit decrease in baseline BMI below 31.5 kg/m ² | | | | | |

Table S2: Key intervention specification parameters in the basecase and one-way sensitivity analysis (SA) scenarios. Values in bold indicate differences from basecase.

| | TOTAL COST | QALYS | NET MONETARY BENEFIT* | PROBABILITY COST-EFFECTIVE** | PROBABILITY COST-SAVING |
|--|------------|-------|-----------------------|------------------------------|-------------------------|
| Total Population | -£131 | 0.038 | -£3,376 | 97% | 70% |
| <i>IMD Q1: low deprivation</i> | -£110 | 0.041 | -£2,638 | 83% | 57% |
| <i>IMD Q2</i> | -£121 | 0.039 | -£3,034 | 87% | 60% |
| <i>IMD Q3</i> | -£141 | 0.039 | -£3,608 | 71% | 53% |
| <i>IMD Q4</i> | -£138 | 0.039 | -£3,543 | 83% | 58% |
| <i>IMD Q5: high deprivation</i> | -£159 | 0.033 | -£4,760 | 78% | 60% |
| <i>Age <40</i> | -£35 | 0.019 | -£1,811 | 64% | 46% |
| <i>Age 40-59</i> | -£215 | 0.036 | -£5,909 | 89% | 72% |
| <i>Age 60-74</i> | -£194 | 0.054 | -£3,591 | 91% | 66% |
| <i>Age 75+</i> | £24 | 0.043 | £563 | 81% | 40% |
| <i>Male</i> | -£105 | 0.041 | -£2,529 | 91% | 59% |
| <i>Female</i> | -£156 | 0.036 | -£4,303 | 94% | 68% |
| <i>BMI <25</i> | £123 | 0.016 | £7,396 | 51% | 26% |
| <i>BMI 25-29</i> | -£83 | 0.039 | -£2,130 | 89% | 55% |
| <i>BMI 30-34</i> | -£277 | 0.051 | -£5,360 | 92% | 74% |
| <i>BMI 35+</i> | -£627 | 0.067 | -£9,286 | 93% | 83% |
| <i>White</i> | -£132 | 0.039 | -£3,311 | 97% | 70% |
| <i>BME</i> | -£121 | 0.030 | -£4,045 | 61% | 51% |
| <i>HbA1c 6-6.1</i> | -£39 | 0.029 | -£1,305 | 87% | 49% |
| <i>HbA1c 6.2-6.4</i> | -£226 | 0.048 | -£4,706 | 96% | 76% |
| <i>Working</i> | -£150 | 0.036 | -£4,090 | 91% | 68% |
| <i>Retired</i> | -£102 | 0.048 | -£2,088 | 93% | 58% |
| <i>Other</i> | -£101 | 0.025 | -£3,915 | 68% | 52% |
| *Value of a QALY assumed to be £60,000 for net monetary benefit analysis ¹⁷ | | | | | |
| **At a willingness to pay threshold of £20,000 per QALY | | | | | |

Table S3: Summary table showing incremental PSA results for each subgroup compared with no DPP intervention. All results are reported per person given the intervention at 20 years following intervention implementation. Costs are discounted at 3.5% and QALYs at 1.5%. Higher cost savings, QALY gains and net monetary benefit are shown in deeper shades of red, whereas lowest cost savings, QALY gains and net monetary benefit are shown in blue.

| | BASECASE* | | SA1 | | SA2 | | SA3 | | SA4 | |
|----------------------|-----------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| | Year CS | Year CE | Year CS | Year CE | Year CS | Year CE | Year CS | Year CE | Year CS | Year CE |
| Total Population | 12 | 6 | 10 | 5 | 20 | 7 | NCS | 8 | NCS | 7 |
| <i>IMD Q1</i> | 13 | 6 | 10 | 5 | NCS | 7 | NCS | 8 | NCS | 7 |
| <i>IMD Q2</i> | 12 | 5 | 10 | 5 | NCS | 6 | NCS | 7 | NCS | 6 |
| <i>IMD Q3</i> | 13 | 6 | 10 | 5 | NCS | 7 | NCS | 8 | NCS | 7 |
| <i>IMD Q4</i> | 11 | 6 | 10 | 5 | 16 | 6 | NCS | 8 | 17 | 7 |
| <i>IMD Q5</i> | 11 | 6 | 9 | 5 | 16 | 7 | NCS | 9 | 17 | 7 |
| <i>Age <40</i> | 19 | 9 | 11 | 8 | NCS | 11 | NCS | 17 | NCS | 11 |
| <i>Age 40-59</i> | 11 | 6 | 9 | 6 | 14 | 7 | NCS | 9 | 14 | 7 |
| <i>Age 60-74</i> | 9 | 5 | 8 | 4 | 12 | 6 | NCS | 6 | 13 | 6 |
| <i>Age 75+</i> | NCS | 4 | NCS | 4 | NCS | 5 | NCS | 5 | NCS | 5 |
| <i>Male</i> | 13 | 6 | 10 | 5 | NCS | 6 | NCS | 8 | NCS | 7 |
| <i>Female</i> | 11 | 6 | 10 | 5 | 16 | 7 | NCS | 8 | 18 | 7 |
| <i>BMI <25</i> | NCS | 10 | 11 | 6 | NCS | 13 | NCS | NCE | NCS | 13 |
| <i>BMI 25-29</i> | 16 | 6 | 10 | 5 | NCS | 7 | NCS | 8 | NCS | 7 |
| <i>BMI 30-34</i> | 9 | 5 | 9 | 5 | 11 | 6 | NCS | 6 | 11 | 6 |
| <i>BMI 35+</i> | 5 | 3 | 7 | 4 | 6 | 4 | 8 | 4 | 7 | 4 |
| <i>White</i> | 11 | 6 | 10 | 5 | 19 | 6 | NCS | 7 | NCS | 6 |
| <i>BME</i> | 14 | 7 | 10 | 6 | NCS | 9 | NCS | 11 | NCS | 9 |
| <i>HbA1c 6-6.1</i> | NCS | 7 | 14 | 6 | NCS | 8 | NCS | 10 | NCS | 9 |
| <i>HbA1c 6.2-6.4</i> | 9 | 5 | 8 | 4 | 12 | 6 | NCS | 6 | 12 | 6 |
| <i>Working</i> | 12 | 7 | 10 | 6 | 17 | 8 | NCS | 9 | 19 | 8 |
| <i>Retired</i> | 11 | 5 | 9 | 4 | NCS | 5 | NCS | 6 | NCS | 5 |
| <i>Other</i> | 14 | 7 | 10 | 6 | NCS | 8 | NCS | 11 | NCS | 9 |

CS Cost-Saving; CE Cost-Effective; NCS Not Cost-Saving within 20 years; NCE Not Cost-Effective within 20 years
 *Stratified intervention effect by BMI, 5 year duration of intervention effect, intervention cost £270.

Table S4: Comparison of the year that the intervention becomes cost-saving and cost-effective (using a threshold of £20,000 per QALY) between different population subgroups for each deterministic sensitivity analysis. Depth of shading represents how early cost-savings/cost-effectiveness occur, with darker grey representing earlier years.

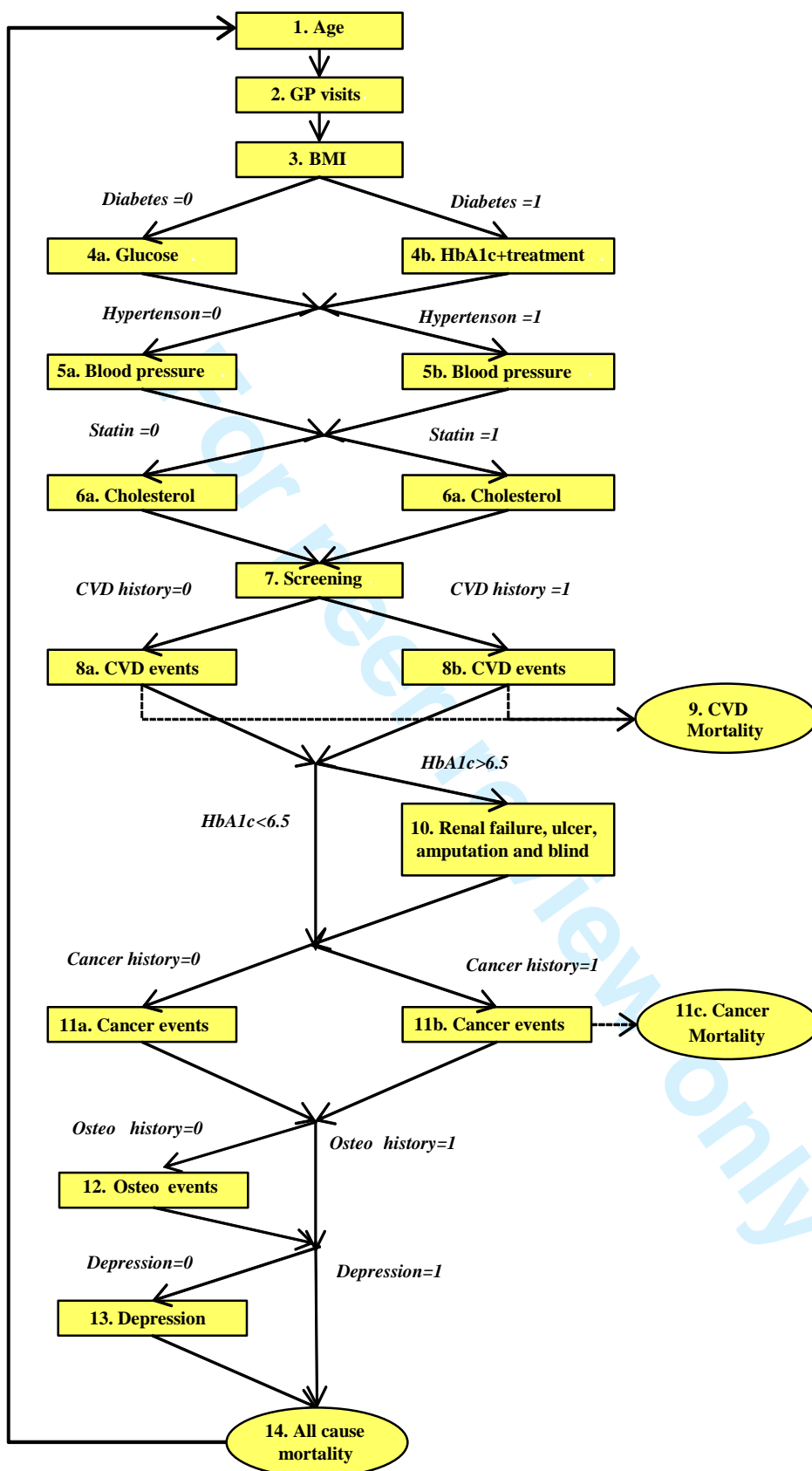


Figure S1: Model schematic showing what happens in each yearly cycle.

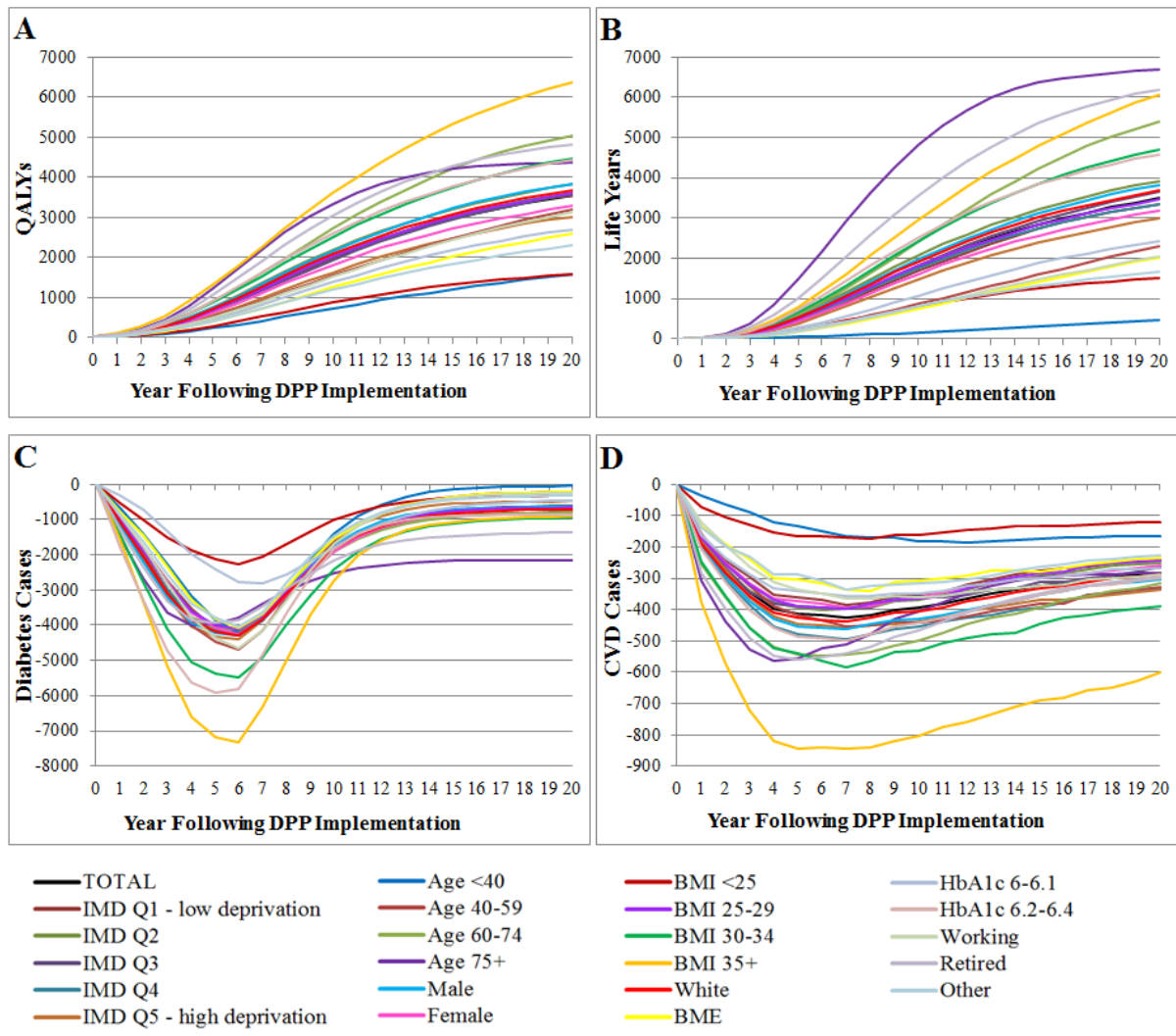


Figure S2: Graphs showing cumulative gain of A) QALYs and B) life years; and reduction in C) incremental diabetes cases and D) incremental CVD cases, per 100,000 individuals across all subgroups over 20 years.

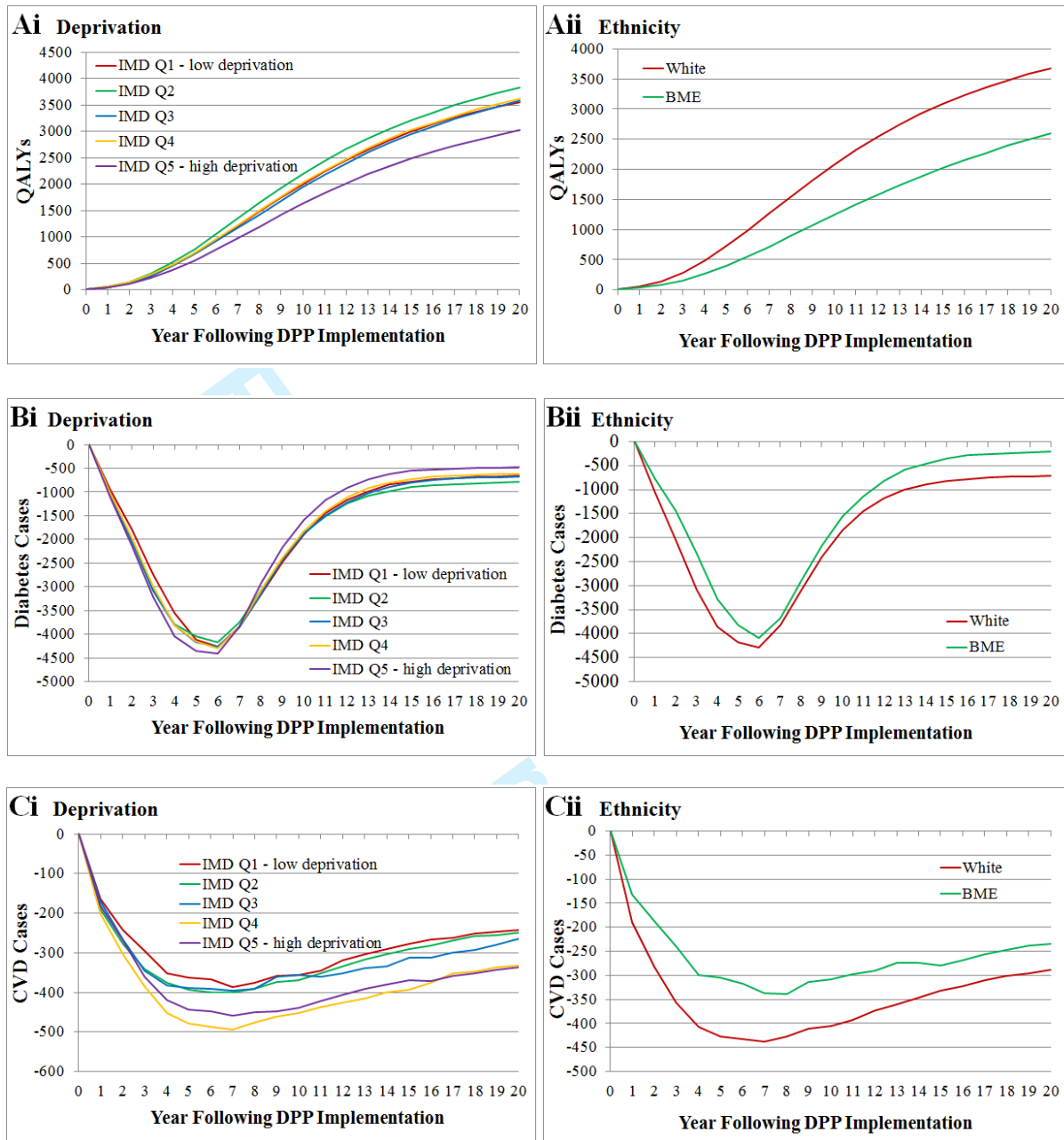


Figure S3: Graphs showing: A) cumulative incremental QALY gain; B) incremental reduction in diabetes cases and C) incremental reduction in CVD cases per 100,000 individuals in different deprivation quintiles (i) and ethnic groups (ii)

B) SUPPLEMENTARY METHODS

CONCEPTUAL MODELLING

A conceptual model of the problem and a model-based conceptual model were developed according to a new conceptual modelling framework for complex public health models (1). In line with this framework the conceptual models were developed in collaboration with a project stakeholder group comprising health economists, public health specialists, research collaborators from other SPHR groups, diabetologists, local commissioners and lay members. The conceptual model of the problem mapped out all relevant factors associated with diabetes based upon iterative literature searches. Key initial sources were reports of two existing diabetes prevention models used for National Institute for Health and Care Excellence public health guidance (2;3). This conceptual model of the problem was presented at a Stakeholder Workshop. Discussion at the workshop led to modifications of the model, identifying additional outcomes such as depression and helping to identify a suitable conceptual model boundary for the cost-effectiveness model structure.

MODEL STRUCTURE

The model is based upon individual longitudinal trajectories of metabolic risk factors (BMI, systolic blood pressure [SBP], cholesterol and HbA1c [measure of blood glucose]). For each individual, yearly changes in these risk factors occur, dependent upon the individuals' baseline characteristics. Figure 1 in the main article illustrates the sequence of updating clinical characteristics and clinical events that are estimated within a cycle of the model. This sequence is repeated for every annual cycle of the model. The first stage of the sequence updates the age of the individual. The second stage estimates how many times the individual attends the GP. The third stage estimates the change in BMI of the individual from the previous period. In the fourth stage, if the individual has not been diagnosed as diabetic (Diabetes_Dx=0) their change in glycaemia is estimated using the Whitehall II model. If they are diabetic (Diabetes_Dx=1), it is estimated using the UKPDS model. In stages five and six the individual's blood pressure and cholesterol are updated using the Whitehall II model if the individual is not identified as hypertensive or receiving statins. In stage seven, the individual may undergo assessment for diabetes, hypertension and dyslipidaemia during a GP consultation. From stage eight onwards the individual may experience cardiovascular outcomes, diabetes related complications, cancer, osteoarthritis or depression. If the individual has a history of cardiovascular disease (CVD history=1), they follow a different pathway in stage eight to those without a history of cardiovascular disease (CVD history=0). Individuals with HbA1c greater than 6.5 are assumed to be at risk of diabetes related complications. Individuals who do not have a history of cancer (Cancer history=0) are

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3 at risk of cancer diagnosis, whereas those with a diagnosis of cancer (Cancer history=1) are at risk of
4 mortality due to cancer. Individuals without a history of osteoarthritis or depression may develop
5 these conditions in stages 12 and 13. Finally, all individuals are at risk of dying due to causes other
6 than cardiovascular or cancer mortality. Death from renal disease is included in the estimate of other-
7 cause mortality.
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11 12 13 14 15 **DATA SELECTION**

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18 Having developed and agreed the model structure and boundary with the stakeholder group the
19 project team sought suitable sources of data for the baseline population, GP attendance, metabolic risk
20 trajectories, treatment algorithms, and risk models for long term health outcomes, health care and
21 health related. Given the complexity of the model it was not possible to use systematic review
22 methods to identify all sources of data for these model inputs. As a consequence we used a series of
23 methods to identify the most appropriate sources of data within the time constraints of the project.
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29 Firstly, we discussed data sources with the stakeholder groups and identified key studies in the UK
30 that have been used to investigate diabetes and its complications and comorbidities. The stakeholder
31 group included experts in the epidemiology of non-communicable disease who provided useful
32 insight into the strengths and limitations of prominent cohort studies and trials that have studied the
33 risks of long term health outcomes included in the model. The stakeholder group also included
34 diabetes prevention cost-effectiveness modellers, whose understanding of studies that could be used to
35 inform risk parameters, costs and health related quality of life estimates. Secondly, we used a review
36 of economic evaluations of diabetes prevention and weight management cost-effectiveness studies to
37 identify sources of data used in similar economic evaluations (4). Thirdly, we conducted targeted
38 literature searches where data could not be identified from large scale studies of a UK population, or
39 could be arguably described as representative of a UK population through processes described above.
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50 **BASELINE POPULATION**

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52 The model required demographic, anthropometric and metabolic characteristics that would be
53 representative of the UK general population. The Health Survey for England (HSE) was suggested by
54 the stakeholder group because it collects up-to-date cross-sectional data on the characteristics of all
55 ages of the English population. It also benefits from being a reasonably good representation of the
56 socioeconomic profile of England. A major advantage of this dataset is that includes important
57 clinical risk factors such as HbA1c, SBP, and cholesterol. The characteristics of individuals included
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3 in the cost-effectiveness model were based sampled from the HSE 2011 dataset (5). The HSE 2011
4 focused on CVD and associated risk factors. The whole dataset was obtained from the UK Data
5 Service. The total sample size of the HSE 2011 is 10,617 but individuals aged under 16 were excluded
6 resulting in 8,610 in total.
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10 Only a subset of variables reported in the HSE 2011 cohort was needed to inform the baseline
11 characteristics in the economic model. A list of model baseline characteristics and the corresponding
12 variable name and description from the HSE 2011 are listed below in Table 1. Two questions for
13 smoking were combined to describe smoking status according to the QRISK2 algorithm in which
14 former smokers and the intensity of smoking are recorded within one measure. The number of
15 missing data for each observation in the HSE data is detailed in Table 1 and summary statistics for the
16 data extracted from the HSE2011 dataset are reported in Table 2.
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Table 1: HSE variable names and missing data summary

| Model requirements | HSE 2011 variable name | HSE 2011 variable description | No. Missing data entries |
|-----------------------------------|------------------------|--|--------------------------|
| Age | Age | Age last birthday | 0 |
| Sex | Sex | Sex | 0 |
| Ethnicity | Origin | Ethnic origin of individual | 36 |
| Deprivation (Townsend) | qimd | Quintile of IMD SCORE | 0 |
| Weight | wtval | Valid weight (Kg) inc. estimated>130kg | 1284 |
| Height | htval | Valid height (cm) | 1207 |
| BMI | bmival | Valid BMI | 1431 |
| Waist circumference | wstval | Valid Mean Waist (cm) | 2871 |
| Waist-Hip ratio | whval | Valid Mean Waist/Hip ratio | 2882 |
| Total Cholesterol | cholval | Valid Total Cholesterol Result | 4760 |
| HDL cholesterol | hdlval | Valid HDL Cholesterol Result | 4760 |
| HbA1c | glyhbval | Valid Glycated HB Result | 4360 |
| FPG | | | N/A |
| 2-hr glucose | | | N/A |
| Systolic Blood pressure | omsysval | Omron Valid Mean Systolic BP | 3593 |
| Hypertension treatment | medcinbp | Currently taking any medicines, tablets or pills for high BP | 6050 |
| Gestational diabetes | pregdi | Whether pregnant when told had diabetes | 8008 |
| Anxiety/depression | Anxiety | Anxiety/Depression | 930 |
| Smoking | cigsta3 | Cigarette Smoking Status: Current/Ex-Reg/Never-Reg | 75 |
| | cigst2 | Cigarette Smoking Status - Banded current smokers | 74 |
| Statins | lipid | Lipid lowering (Cholesterol/Fibrinogen) - prescribed | 5804 |
| Rheumatoid Arthritis | compm12 | XIII Musculoskeletal system | 5 |
| Atrial Fibrillation | murmur1 | Doctor diagnosed heart murmur (excluding pregnant) | 2008 |
| Family history diabetes | | | N/A |
| History of Cardiovascular disease | cvdis2 | Had CVD (Angina, Heart Attack or Stroke) | 3 |
| Economic Activity | econact | Economic status | 37 |

Table 2: Characteristics of final sample from HSE 2011 (N=8610)

| Characteristic | Number | Percentage | |
|---|-------------|---------------------------------------|---------------|
| Male | 3822 | 44.4% | |
| White | 7719 | 89.7% | |
| Indian | 206 | 2.4% | |
| Pakistani | 141 | 1.6% | |
| Bangladeshi | 46 | 0.5% | |
| Other Asian | 97 | 1.1% | |
| Caribbean | 78 | 0.9% | |
| African | 120 | 1.4% | |
| Chinese | 35 | 0.4% | |
| Other | 168 | 2.0% | |
| IMD 1 (least deprived) | 1774 | 20.6% | |
| IMD 2 | 1823 | 21.2% | |
| IMD 3 | 1830 | 21.3% | |
| IMD 4 | 1597 | 18.5% | |
| IMD 5 (most deprived) | 1586 | 18.4% | |
| Non-smoker | 4550 | 52.8% | |
| Past smoker | 2353 | 27.3% | |
| Current smoker | 1707 | 19.8% | |
| Anti-hypertensive treatment | 1544 | 17.9% | |
| Statins | 929 | 10.8% | |
| Pre-existing CVD | 639 | 7.4% | |
| Diagnosed diabetes | 572 | 6.6% | |
| Missing HbA1c data | 4706 | 54.7% | |
| Undiagnosed diabetes (HbA1c \geq 6.5) before imputation HbA1c | 98 | 1.1% (2.5% those with HbA1c data) | |
| Undiagnosed diabetes (HbA1c \geq 6.5) after imputation HbA1c | 761 | 8.8% | |
| IGR (HbA1c 6-6.4%) before imputation HbA1c | 529 | 6.1% (13.6% those with HbA1c data) | |
| IGR (HbA1c 6-6.4%) after imputation HbA1c | 1492 | 17.3% | |
| | Mean | Standard deviation | Median |
| Age (years) | 49.6 | 18.7 | 49.0 |
| BMI (kg/m ²) | 27.4 | 5.4 | 26.6 |
| Total Cholesterol (mmol/l) | 5.4 | 1.1 | 5.4 |
| HDL Cholesterol (mmol/l) | 1.5 | 0.4 | 1.5 |
| HbA1c (%) | 5.7 | 0.8 | 5.6 |
| Systolic Blood Pressure (mm Hg) | 126.3 | 17.0 | 124.5 |
| EQ-5D (TTO) | 0.825 | 0.244 | 0.848 |
| BMI Body Mass Index; IMD Index of Multiple Deprivation; CVD Cardiovascular Disease; IGR Impaired Glucose Regulation; HDL High Density Lipoprotein; EQ-5D 5 dimensions EuroQol (health related quality of life index) ; TTO Time Trade-Off | | | |

A complete dataset was required for all individuals at baseline. However, no measurements for Fasting Plasma Glucose (FPG) or 2 hour glucose were obtained for the HSE 2011 cohort. In addition,

the questionnaire did not collect information about individual family history of diabetes or family history of Cardiovascular Disease (CVD). These variables were imputed from other datasets.

Many individuals were lacking responses to some questions but had data for others. One way of dealing with this is to exclude all individuals with incomplete data from the sample. However, this would have reduced the sample size dramatically, which would have been detrimental to the analysis. It was decided that it would be better to make use of all the data available to represent a broad range of individuals within the UK population. With this in mind, we decided to use assumptions and imputation models to estimate missing data.

MISSING DATA IMPUTATION

Ethnicity

Only a small number of individuals had missing data for ethnicity. In the QRISK2 algorithm the indicator for white includes individuals for whom ethnicity is not recorded. In order to be consistent with the QRISK2 algorithm we assumed that individuals with missing ethnicity data were white.

Anthropometric data

A large proportion of anthropometric data was missing in the cohort. Table 3 reports the number of individuals with two or more anthropometric records missing. This illustrates that only 758 individuals had no anthropometric data at all. Imputation models for anthropometric data were developed utilising observations from other measures to help improve their accuracy.

Table 3: Multi-way assessment of missing data

| Conditions | Number of individuals |
|--------------------------------------|-----------------------|
| No weight and no height | 1060 |
| No weight and no waist circumference | 907 |
| No weight and no hip circumference | 906 |
| No height and no waist circumference | 818 |
| No height and no hip circumference | 817 |
| No hip and no waist | 2865 |
| No anthropometric data | 758 |

Two imputation models were generated for each of the following anthropometric measures: weight, height, waist circumference and hip circumference. The first imputation method included an alternative anthropometric measure to improve precision. The second included only age and/or sex, to be used if the alternative measure was also missing. Simple ordinary least squares (OLS) regression models were used to predict missing data. Summary data for each measure confirmed that the data were approximately normally distributed. Covariate selection was made by selecting the

anthropometric measure that maximised the Adjusted R-squared statistic, and age and sex were included if the coefficients were statistically significant ($P < 0.1$).

The imputation models for weight are reported in Table 4. Individuals' sex and age were included in both models. A quadratic relationship between age and weight was identified. Waist circumference had a positive and significant relationship with weight. The R^2 for model 1 suggested that 80% of the variation in weight is described by the model. The R^2 for model 2 was much lower as only 18% of the variation in weight was described by age and sex. The residual standard error is reported for both models.

Table 4: Imputation model for weight

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | -17.76 | 50.249 |
| Sex | 2.614 | 13.036 |
| Age | 0.064 | 0.903 |
| Age*Age | -0.0027 | -0.0086 |
| Waist circumference | 1.060 | |
| R-squared | 0.7981 | 0.1831 |
| Residual standard error | 7.483 | 15.31 |

The imputation models for height are reported in Table 5. Individuals' sex and age were included in both models. A quadratic relationship between age and height was identified. Waist circumference had a positive and significant relationship with height. The R^2 for model 1 suggested that 53% of the variation in height is described by the model suggesting a fairly good fit. The R^2 for model 2 was slightly lower in which 52% of the variation in height was described by age and sex. The residual standard error is reported for both models.

Table 5: Imputation model for height

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | 157.4 | 162.1 |
| Sex | 12.82 | 13.43 |
| Age | 0.081 | 0.1291 |
| Age*Age | -0.0021 | -0.0025 |
| Waist circumference | 0.071 | |
| R-squared | 0.532 | 0.5244 |
| Residual standard error | 6.617 | 6.682 |

The imputation models for waist circumference are reported in Table 6. Individuals' sex and age were included in both models. A quadratic relationship between age and waist circumference fit to the data better than a linear relationship. Weight had a positive and significant relationship with waist circumference. The R^2 for model 1 suggested that 81% of the variation in waist circumference is described by the model suggesting a very good fit. The R^2 for model 2 was much lower in which only

22% of the variation in waist circumference was described by age and sex which is a moderately poor fit. The residual standard error is reported for both models.

Table 6: Imputation model for waist

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | 28.73 | 65.327 |
| Sex | 0.5754 | 9.569 |
| Age | 0.1404 | 0.7617 |
| Age*Age | 0.0007 | -0.0053 |
| Weight | 0.7098 | |
| R-squared | 0.8096 | 0.2196 |
| Residual standard error | 6.122 | 12.44 |

The imputation models for hip circumference are reported in Table 7. Individuals' sex and age were included in both models. A quadratic relationship between age and hip circumference fit to the data better than a linear relationship. Weight had a positive and significant relationship with hip circumference. The R^2 for model 1 suggested that 80% of the variation in hip circumference is described by the model suggesting a very good fit. The R^2 for model 2 was much lower in which only 2% of the variation in hip circumference was described by age and sex which is a very poor fit. The residual standard error is reported for both models.

Table 7: Imputation model for hip

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | 66.9145 | 96.891 |
| Sex | -8.3709 | -0.9783 |
| Age | -0.1714 | 0.3528 |
| Age*Age | 0.0021 | -0.0029 |
| Weight | 0.5866 | |
| R-squared | 0.7949 | 0.023 |
| Residual standard error | 4.539 | 10.1 |

Metabolic data

A large proportion of metabolic data was missing in the cohort, ranging from 2997-4309 observations for each metabolic measurement. Table 8 reports the number of individuals with two or more metabolic records missing. This illustrates that 2987 individuals have no metabolic data. Imputation models for metabolic data were developed utilising observations from other measures to help improve their accuracy.

Table 8: Multi-way assessment of missing data

| Conditions | Number of individuals |
|--------------------------------------|-----------------------|
| No HbA1c and no cholesterol | 4309 |
| No HbA1c and no blood pressure | 2997 |
| No cholesterol and no blood pressure | 3050 |
| No metabolic data | 2987 |

Two imputation models were generated for each of the following metabolic measures: total cholesterol, high density lipoprotein (HDL) cholesterol, HbA1c and systolic blood pressure (SBP) and. The first imputation method included an alternative metabolic measure to improve precision. The second included only age and/or sex, to be used if the alternative measure was also missing. Simple ordinary least squares (OLS) regression models were used to predict missing data. Summary data for each measure confirmed that the data were approximately normally distributed. Covariate selection was made by selecting the metabolic measure that maximised the adjusted R-squared statistic, and age and sex were included if the coefficients were statistically significant ($P < 0.1$).

These imputation models were developed to estimate metabolic data from information collected in the HSE. An alternative approach would have been to use estimates of these measures from the natural history statistical models. At the time of the analysis it was uncertain what form and design the natural history models would take, therefore the HSE imputation models were developed for use until a better alternative was found.

The imputation models for total cholesterol are reported in Table 9. Individuals' age was included in both models. A quadratic relationship between age and weight was identified. Diastolic blood pressure had a positive and significant relationship with total cholesterol. The R^2 for model 1 suggested that 20% of the variation in total cholesterol is described by the model. The R^2 for model 2 was lower in which only 18% of the variation in total cholesterol was described by age. The residual standard error is reported for both models.

Table 9: Imputation model for total cholesterol

| Coefficient | Model 1 | Model 2 |
|--------------------------|---------|---------|
| Intercept | 1.973 | 2.821 |
| Age | 0.0774 | 0.0904 |
| Age*Age | -0.0006 | -0.0007 |
| Diastolic blood pressure | 0.0159 | |
| R-squared | 0.2035 | 0.1792 |
| Residual standard error | 0.9526 | 0.9741 |

The imputation models for HDL cholesterol are reported in Table 10. Individuals' sex and age were included in both models. A quadratic relationship between age and height was identified. Diastolic blood pressure had a negative and significant relationship with HDL cholesterol. The R^2 for model 1

suggested that only 13% of the variation in HDL cholesterol is described by the model suggesting a relatively poor fit. The R^2 for model 2 suggested that 12% of the variation in HDL cholesterol was described by age and sex. The residual standard error is reported for both models.

Table 10: Imputation model for HDL Cholesterol

| Coefficient | Model 1 | Model 2 |
|--------------------------|---------|----------|
| Intercept | 1.501 | 1.383 |
| Sex | -0.279 | -0.274 |
| Age | 0.0086 | 0.0075 |
| Age*Age | -0.0001 | -0.00004 |
| Diastolic blood pressure | -0.0018 | |
| R-squared | 0.1198 | 0.1157 |
| Residual standard error | 0.4122 | 0.417 |

The imputation models for HbA1c are reported in Table 11. Individuals' age was included in both models. A quadratic relationship between age and HbA1c fit to the data better than a linear relationship. SBP had a positive and significant relationship with HbA1c. The R^2 for model 1 suggested that only 19% of the variation in HbA1c is described by the model, suggesting a modest fit. The R^2 for model 2 described 18% of the variation in HbA1c by age alone. The residual standard error is reported for both models.

Table 11: Imputation model for HbA1c

| Coefficient | Model 1 | Model 2 |
|-------------------------|----------|----------|
| Intercept | 4.732 | 4.962 |
| Age | 0.0141 | 1.422 |
| Age*Age | -0.00003 | -0.00003 |
| Systolic blood pressure | 0.002 | |
| R-squared | 0.1941 | 0.1835 |
| Residual standard error | 0.4243 | 0.4228 |

The imputation models for SBP are reported in Table 12. Individuals' sex and age were included in both models. A linear relationship between age and SBP fit to the data better than a quadratic relationship. Total cholesterol and HbA1c had a positive and significant relationship with SBP, whereas HDL cholesterol had a negative significant relationship with SBP. The R^2 for model 1 suggested that 22% of the variation in SBP is described by the model suggesting a modest fit. The R^2 for model 2 was similar in which only 20% of the variation in SBP was described by age and sex. The residual standard error is reported for both models.

Table 12: Imputation model for Systolic Blood Pressure

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | 84.983 | 104.132 |
| Sex | 6.982 | 6.396 |
| Age | 0.330 | 0.380 |
| Total cholesterol | 2.093 | |
| HDL cholesterol | -0.746 | |
| HbA1c | 1.986 | |
| R-squared | 0.2235 | 0.2047 |
| Residual standard error | 14.59 | 15.1 |

Treatment for Hypertension and Statins

A large proportion of individuals had missing data for questions relating to whether they received treatment for hypertension or high cholesterol. The majority of non-responses to these questions were coded to suggest that the question was not applicable to the individual. As a consequence it was assumed that individuals with missing treatment data were not taking these medications.

Gestational Diabetes

Only 30 respondents without current diabetes reported that they had been diagnosed with diabetes during a pregnancy in the past. Most individuals had missing data for this question due to it not being applicable. The missing data was assumed to indicate that individuals had not had gestational diabetes.

Anxiety/Depression

Most individuals who had missing data for anxiety and depression did so because the question was not applicable. A small sample N=69 refused to answer the question. We assumed that individuals with missing data for anxiety and depression did not have severe anxiety/depression.

Smoking

Individuals with missing data for smoking status were assumed to be non-smokers, without a history of smoking.

Rheumatoid Arthritis and Atrial Fibrillation

A very small sample of individuals had missing data for musculoskeletal illness (N=5) and atrial fibrillation (N=1). These individuals were assumed to not suffer from these illnesses.

Family history of diabetes

No questions in the HSE referred to the individual having a family history of diabetes, so this data had to be imputed. It was important that data was correlated with other risk factors for diabetes, such as HbA1c and ethnicity. We analysed a cross-section of the Whitehall II dataset to generate a logistic

1
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3 regression to describe the probability that an individual has a history of diabetes conditional on their
4 HbA1c and ethnic origin. The model is described in Table 13.
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7 **Table 13: Imputation model for history of diabetes**
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| | Coefficient |
|-----------------|-------------------|
| Intercept | -3.29077 (0.4430) |
| HbA1c | 0.28960 (0.0840) |
| HDL Cholesterol | 0.81940 (0.13878) |

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16 **Economic Activity**

17 Individuals without information about their employment status were assumed to be retired if aged 65
18 or over and in employment if under 65.
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24 **POPULATION SELECTION**

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27 The DPP is only eligible to individuals with impaired glucose regulation (IGR), defined as HbA1c 6-
28 6.4% in the model. The process of identifying eligible individuals or referring them to the DPP was
29 not explicitly modelled. Instead, all individuals from the HSE 2011 with actual or imputed HbA1c
30 levels between 6-6.4% are assumed to have been previously identified by a variety of means, and only
31 these IGR individuals are included in the simulation. This means that the costs of identifying IGR
32 individuals or referring them to the DPP intervention are not included.
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41 **GP ATTENDANCE IN THE GENERAL POPULATION**

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43 Frequency of GP visits (separate from NHS health checks) was simulated in the dataset for two
44 reasons; firstly, to estimate the healthcare utilisation for the ID population without diabetes and
45 cardiovascular disease and secondly, to predict the likelihood that individuals participate in
46 opportunistic screening for diabetes and vascular risks. It was assumed that GP attendance in the ID
47 population occurs at the same frequency as in the general population. However, for cost purposes,
48 consultations were assumed to take 40% longer than the general population average (see Costs
49 section).
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55 GP attendance conditional on age, sex, BMI, ethnicity, and health outcomes was derived from
56 analysis of wave 1 of the Yorkshire Health Study (11). The analysis used a negative binomial
57 regression model to estimate self-reported rate of GP attendance per 3 months (Table 14). The
58 estimated number of GP visits was multiplied by 4 to reflect the annual number of visits per year.
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Table 14: GP attendance reported in the Yorkshire Health Study (N= 18,437)

| | Model 1 | | Model 2 | |
|-----------------------|---------|----------------|---------|----------------|
| | Mean | Standard error | Mean | Standard error |
| Age | 0.0057 | 0.0005 | 0.0076 | 0.0005 |
| Male | -0.1502 | 0.0155 | -0.1495 | 0.0159 |
| BMI | 0.0020 | 0.0015 | 0.0110 | 0.0015 |
| IMD score 2010 | 0.0043 | 0.0005 | | |
| Ethnicity (Non-white) | 0.1814 | 0.0370 | 0.2620 | 0.0375 |
| Heart Disease | 0.1588 | 0.0281 | 0.2533 | 0.0289 |
| Depression | 0.2390 | 0.0240 | 0.6127 | 0.0224 |
| Osteoarthritis | 0.0313 | 0.0240 | 0.2641 | 0.0238 |
| Diabetes | 0.2023 | 0.0270 | 0.2702 | 0.0278 |
| Stroke | 0.0069 | 0.0460 | 0.1659 | 0.0474 |
| Cancer | 0.1908 | 0.0400 | 0.2672 | 0.0414 |
| Intercept | 0.6275 | 0.0590 | -0.5014 | 0.0468 |
| Alpha | 0.3328 | 0.0097 | 0.3423 | 0.0108 |

LONGITUDINAL TRAJECTORIES OF METABOLIC RISK FACTORS

A detailed description of the statistical analysis behind the personalised metabolic risk factor trajectories that underlie disease risk in the SPHR Diabetes Prevention model has previously been published (12), so this report provides only a brief summary.

A statistical analysis of the Whitehall II cohort study (13) was developed to describe correlated longitudinal changes in metabolic risk factors including BMI, latent blood glucose (an underlying, unobservable propensity for diabetes), total cholesterol, HDL cholesterol and systolic blood pressure. Parallel latent growth modelling was used to estimate the unobservable latent glycaemia and from this identify associations with test results for HbA1c, FPG, and 2-hour glucose. The growth factors (longitudinal changes) for BMI, glycaemia, systolic blood pressure, total and HDL cholesterol could then be estimated through statistical analysis. These growth factors are conditional on several individual characteristics including age, sex, ethnicity, smoking, family history of CVD, and family history of type 2 diabetes. Deprivation was excluded from the final analysis because it was not associated with the growth models, and it estimated counter-intuitive coefficients.

Unobservable heterogeneity between individual growth factors not explained by patient characteristics was incorporated into the growth models as random error terms. Correlation between the random error terms for glycaemia, total cholesterol, HDL cholesterol and systolic blood pressure was estimated from the Whitehall II cohort. This means that in the simulation, an individual with a higher growth rate for glycaemia is more likely to have a higher growth rate of total cholesterol and systolic blood pressure.

The baseline observations for BMI, HbA1c, systolic blood pressure, cholesterol and HDL cholesterol were extracted from the Health Survey for England 2011 in order to simulate a representative sample. The predicted intercept for these metabolic risk factors was estimated using the Whitehall II analysis to give population estimates of the individuals' starting values, conditional on their characteristics. The difference between the simulated and observed baseline risk factors was taken to estimate the individuals' random deviation from the population expectation. The individual random error in the slope trajectory was sampled from a conditional multivariate normal distribution to allow correlation between the intercept and slope random errors.

Following a diagnosis of diabetes in the simulation all individuals experience an initial fall in HbA1c due to changes in diet and lifestyle as observed in the UKPDS trial (14). The expected change in HbA1c conditional on HbA1c at diagnosis was estimated by fitting a simple linear regression to three aggregate outcomes reported in the study. These showed that the change in HbA1c increases for higher HbA1c scores at diagnosis. The regression parameters to estimate change in HbA1c are reported in Table 15.

Table 15: Estimated change in HbA1c following diabetes diagnosis

| | Mean | Standard error |
|---------------------------|---------|----------------|
| Change in HbA1c Intercept | -2.9465 | 0.0444513 |
| HbA1c at baseline | 0.5184 | 0.4521958 |

After this initial reduction in HbA1c the longitudinal trajectory of HbA1c is estimated using the UKPDS outcomes model (15) rather than the Whitehall II statistical analysis. The UKPDS dataset is made up of a newly diagnosed diabetic population. As part of the UKPDS Outcomes model, longitudinal trial data were analysed using a random effects model, which means that unobservable differences between individuals are accounted for in the analysis. The model can be used to predict HbA1c over time from the point of diagnosis. The coefficients of the model are reported in Table 16.

Table 16: Coefficient estimates for HbA1c estimated from UKPDS data

| | Mean Coefficient | Coefficient standard error |
|--|------------------|----------------------------|
| Intercept | -0.024 | 0.017 |
| Log transformation of year since diagnosis | 0.144 | 0.009 |
| Binary variable for year after diagnosis | -0.333 | 0.05 |
| HbA1c score in last period | 0.759 | 0.004 |
| HbA1c score at diagnosis | 0.085 | 0.004 |

It was important to maintain heterogeneity in the individual glycaemic trajectories before and after diagnosis. Therefore, the random error terms used to determine individual trajectories in glycaemia before diagnosis were used to induce random noise in the trajectory after diagnosis. We sampled the

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2
3 expected random error term for each individual after diagnosis conditional on pre-diagnosis slope,
4 assuming a 0.8 correlation between these values.
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8 The epidemiological literature for many of the health outcomes included in the model treats diabetes
9 diagnosis as a discrete health state, rather than a continuous risk function conditional on HbA1c. This
10 poses two methodological challenges in type 2 diabetes modelling. Firstly, diabetes diagnosis is
11 complex with several tests and a high proportion of undetected diagnoses. Therefore, it is not
12 necessarily an appropriate indicator of risk in the model. Secondly, we would prefer to model the
13 relationship on a continuous scale to avoid artificial steps in risk; however the evidence is not always
14 available to describe risk on a continuous scale. We took two main steps to reduce the impact of this
15 on our model. Firstly, we used the HbA1c threshold of 6.5% to indicate type-2 diabetes regardless of
16 detection, and to ensure consistency in natural history across interventions and counterfactuals.
17 Secondly, the QRISK2 model was adapted to incorporate continuous risk by HbA1c.
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27 **METABOLIC RISK FACTOR SCREENING, DIAGNOSIS AND TREATMENT**

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29
30 It is assumed that individuals eligible for anti-hypertensive treatment or statins will be identified
31 through opportunistic screening if they meet certain criteria and attend the GP for at least one visit in
32 the simulation period.
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- 35 1. Individuals with a history of cardiovascular disease;
- 36 2. Individuals with a major microvascular event (foot ulcer, blindness, renal failure or
37 amputation);
- 38 3. Individuals with diagnosed diabetes;
- 39 4. Individuals with systolic blood pressure greater than 160mmHg.
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45 Individuals may also be detected with diabetes through opportunistic screening if the following
46 criteria are met.
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- 49 1. Individuals with a history of cardiovascular disease;
- 50 2. Individuals with a major microvascular event (foot ulcer, blindness, renal failure or
51 amputation);
- 52 3. At baseline individuals are assigned an HbA1c threshold above which diabetes is detected
53 opportunistically, individuals with an HbA1c above their individual threshold will attend the
54 GP to be diagnosed with diabetes. The threshold is sampled from the distribution of HbA1c
55 tests in a cohort of recently diagnosed patients in clinical practice (16).
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3 The base case has been designed to represent a health system with moderate levels of screening for
4 hypertension, diabetes, and dyslipidaemia.
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8 It is assumed that there are three, non-mutually exclusive outcomes from the vascular checks or
9 opportunistic screening. Firstly, that the patient receives statins to reduce cardiovascular risk.
10 Secondly, that the patient has high blood pressure and should be treated with anti-hypertensive
11 medication. Thirdly, the model evaluates whether the blood glucose test indicates a diagnosis with
12 type 2 diabetes. The following threshold estimates were used to determine these outcomes.
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14

- 15
16 1. Statins are initiated if the individual has greater than or equal to 20% 10 year CVD risk
17 estimated from the QRISK2 2012 algorithm (17).
- 18
19 2. Anti-hypertensive treatment is initiated if systolic blood pressure is greater than 160. If the
20 individual has a history of CVD, diabetes or a CVD risk >20%, the threshold for systolic
21 blood pressure is 140 (18).
- 22
23 3. Type 2 diabetes is diagnosed if the individual has an HbA1c test greater than 6.5. In the base
24 case it is assumed that FPG and 2-hr glucose are not used for diabetes diagnosis. However,
25 future adaptations of the model could use these tests for diagnosis.
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31 It is assumed within the model that if initiated, statins are effective in reducing an individual's total
32 cholesterol, and so an average effect is applied to all patients being prescribed them. A recent HTA
33 reviewed the literature on the effectiveness and cost-effectiveness of statins in individuals with acute
34 coronary syndrome (20). This report estimated the change in LDL cholesterol for four statin
35 treatments and doses compared with placebo from a Bayesian meta-analysis. The analysis estimated a
36 reduction in LDL cholesterol of -1.45 for simvastatin. This estimate was used to describe the effect of
37 statins in reducing total cholesterol. It was assumed that the effect was instantaneous upon receiving
38 statins and maintained as long as the individual receives statins. It was also assumed that individuals
39 receiving statins no longer experienced annual changes in cholesterol. HDL cholesterol was assumed
40 constant over time if patients received statins.
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48 Non-adherence to statin treatment is a common problem. Two recent HTAs reviewed the literature on
49 continuation and compliance with statin treatment. They both concluded that there was a lack of
50 adequate reporting, but that the proportion of patients fully compliant with treatment appears to
51 decrease with time, particularly in the first 12 months after initiating treatment, and can fall below
52 60% after five years (20;21). Although a certain amount of non-compliance is included within trial
53 data, clinical trials are not considered to be representative of continuation and compliance in general
54 practice. A yearly reduction in statin compliance used in the HTA analysis is reported in Table 17. It
55 is based on the published estimate of compliance for the first five years of statin treatment for primary
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prevention in general clinical practice (21). Compliance declines to a minimum of 65% after five years of treatment. It is assumed that there is no further drop after five years.

Table 17: Proportion of patients assumed to be compliant with statin treatment, derived from Table 62 in (20)

| Year after statin initiation | 1 | 2 | 3 | 4 | 5 |
|------------------------------|-----|-----|------|------|------|
| Proportion compliant | 0.8 | 0.7 | 0.68 | 0.65 | 0.65 |

In the simulation, it is assumed in the base case that only 65% of individuals initiate statins when they are deemed eligible. However those that initiate statins remain on statins for their lifetime. Those who refuse statins may be prescribed them again at a later date.

The change in systolic blood pressure following antihypertensive treatment was obtained from a meta-analysis of anti-hypertensive treatments (22). This study identified an average change in systolic blood pressure of -8.4 mmHg for monotherapy with calcium channel blockers. It is assumed that this reduction in systolic blood pressure is maintained for as long as the individual receives anti-hypertensive treatment. For simplicity we do not assume that the individual switches between anti-hypertensive treatments over time. Once an individual is receiving anti-hypertensive treatment it is assumed that their systolic blood pressure is stable and does not change over time. Non-adherence and discontinuation are not modelled for anti-hypertensives.

COMORBID OUTCOMES AND MORTALITY

In every model cycle individuals within the model are evaluated to determine whether they have a clinical event, including mortality, within the cycle period. In each case the simulation estimates the probability that an individual has the event and uses a random number draw to determine whether the event occurred.

CARDIOVASCULAR DISEASE

First Cardiovascular event

Several statistical models for cardiovascular events were identified in a review of economic evaluations for diabetes prevention (4). The UKPDS outcomes model (23), Framingham risk equation (24) and QRISK2 (25) have all been used in previous models to estimate cardiovascular events. The Framingham risk equation was not adopted because, unlike the QRISK2 model, it is not estimated from a UK population. The UKPDS outcomes model would be ideally suited to estimate the risk of cardiovascular disease in a population diagnosed with type 2 diabetes. Whilst this is an important outcome of the cost-effectiveness model, there was concern that it would not be representative of individuals with normal glucose tolerance or impaired glucose regulation. It was important that

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reductions in cardiovascular disease risk in these populations were represented to capture the population-wide benefits of public health interventions. The QRISK2 model was selected for use in the cost-effectiveness model because it is a validated model of cardiovascular risk in a UK population that could be used to generate probabilities for diabetic and non-diabetic populations. We considered using the UKPDS outcomes model specifically to estimate cardiovascular risk in patients with type 2 diabetes. However, it would not be possible to control for shifts in absolute risk generated by the different risk scores due to different baselines and covariates. This would lead to some individuals experiencing counterintuitive and favourable shifts in risk after onset of type 2 diabetes. Therefore, we decided to use diabetes as a covariate adjustment to the QRISK2 model to ensure that the change in individual status was consistent across individuals.

We accessed the 2012 version of the QRISK from the website (26). The QRISK2 equation estimates the probability of a cardiovascular event in the next year conditional on ethnicity, smoking status, age, BMI, ratio of total/HDL cholesterol, Townsend score, atrial fibrillation, rheumatoid arthritis, renal disease, hypertension, diabetes, and family history of cardiovascular disease. Data on all these variables was available from the HSE 2011. Table 18 reports the coefficient estimates for the QRISK2 algorithm. The standard errors were not reported within the open source code. Where possible, standard errors were imputed from a previous publication of the risk equation (27). Coefficients that were not reported in this publication were assumed to have standard errors of 20%.

Table 18: Coefficients from the 2012 QRISK2 risk equation and estimate standard errors

| Covariates | Estimated coefficients adjusting for individual characteristics | | | | | | | | |
|------------------------|---|----------------|-----------|--------|-------------------------|---------|----------------|---------|----------------|
| | Women | | Men | | Interaction terms | Women | | Men | |
| | Mean | Standard error | Mean | Mean | | Mean | Standard error | Mean | Standard error |
| White | 0.0000 | 0.0000 | 0.0000 | 0.0000 | Age1*former smoker | 0.1774 | 0.035 | -3.881 | 0.776 |
| Indian | 0.2163 | 0.0537 | 0.3163 | 0.0425 | Age1*light smoker | -0.3277 | 0.066 | -16.703 | 3.341 |
| Pakistani | 0.6905 | 0.0698 | 0.6092 | 0.0547 | Age1*moderate smoker | -1.1533 | 0.231 | -15.374 | 3.075 |
| Bangladeshi | 0.3423 | 0.1073 | 0.5958 | 0.0727 | Age1*Heavy smoker | -1.5397 | 0.308 | -17.645 | 3.529 |
| Other Asian | 0.0731 | 0.1071 | 0.1142 | 0.0845 | Age1*AF | -4.6084 | 0.922 | -7.028 | 1.406 |
| Caribbean | -0.0989 | 0.0619 | -0.3489 | 0.0641 | Age1*renal disease | -2.6401 | 0.528 | -17.015 | 3.403 |
| Black African | -0.2352 | 0.1275 | -0.3604 | 0.1094 | Age1*hypertension | -2.2480 | 0.450 | 33.963 | 6.793 |
| Chinese | -0.2956 | 0.1721 | -0.2666 | 0.1538 | Age1*Diabetes | -1.8452 | 0.369 | 12.789 | 2.558 |
| Other | -0.1010 | 0.0793 | -0.1208 | 0.0734 | Age1*BMI | -3.0851 | 0.617 | 3.268 | 0.654 |
| Non-smoker | 0.0000 | 0.0000 | 0.0000 | 0.0000 | Age1*family history CVD | -0.2481 | 0.050 | -17.922 | 3.584 |
| Former smoker | 0.2033 | 0.0152 | 0.2684 | 0.0108 | Age1*SBP | -0.0132 | 0.003 | -0.151 | 0.030 |
| Light smoker | 0.4820 | 0.0220 | 0.5005 | 0.0166 | Age1*Townsend | -0.0369 | 0.007 | -2.550 | 0.510 |
| Moderate smoker | 0.6126 | 0.0178 | 0.6375 | 0.0148 | Age2*former smoker | -0.0051 | 0.001 | 7.971 | 1.594 |
| Heavy smoker | 0.7481 | 0.0194 | 0.7424 | 0.0143 | Age2*light smoker | -0.0005 | 0.000 | 23.686 | 4.737 |
| Age 1* | 5.0327 | | 47.3164 | | Age2*moderate smoker | 0.0105 | 0.002 | 23.137 | 4.627 |
| Age 2* | -0.0108 | | -101.2362 | | Age2*Heavy smoker | 0.0155 | 0.003 | 26.867 | 5.373 |
| BMI* | -0.4724 | 0.0423 | 0.5425 | 0.0299 | Age2*AF | 0.0507 | 0.010 | 14.452 | 2.890 |
| Ratio Total / HDL chol | 0.1326 | 0.0044 | 0.1443 | 0.0022 | Age2*renal disease | 0.0343 | 0.007 | 28.270 | 5.654 |
| SBP | 0.0106 | 0.0045 | 0.0081 | 0.0046 | Age2*hypertension | 0.0258 | 0.005 | -18.817 | 3.763 |
| Townsend | 0.0597 | 0.0068 | 0.0365 | 0.0048 | Age2*Diabetes | 0.0180 | 0.004 | 0.963 | 0.193 |
| AF | 1.3261 | 0.0310 | 0.7547 | 0.1018 | Age2*BMI | 0.0345 | 0.007 | 10.551 | 2.110 |

| | | | | | | | | | |
|--|--------|--------|--------|--------|----------------------------|---------|-------|--------|-------|
| Rheumatoid arthritis | 0.3626 | 0.0319 | 0.3089 | 0.0445 | Age2*family history CVD | -0.0062 | 0.001 | 26.605 | 5.321 |
| Renal disease | 0.7636 | 0.0639 | 0.7441 | 0.0702 | Age2*SBP | 0.0000 | 0.000 | 0.291 | 0.058 |
| Hypertension | 0.5421 | 0.0115 | 0.4978 | 0.0112 | Age2*Townsend | -0.0011 | 0.000 | 3.007 | 0.601 |
| Diabetes | 0.8940 | 0.0199 | 0.7776 | 0.0175 | | | | | |
| Family history of CVD | 0.5997 | 0.0122 | 0.6965 | 0.0111 | | | | | |
| AF Atrial Fibrillation CVD Cardiovascular disease SBP systolic blood pressure * covariates transformed with fractional polynomials | | | | | | | | | |

The QRISK2 risk equation can be used to calculate the probability of a cardiovascular event including coronary heart disease (angina or myocardial infarction), stroke, transient ischaemic attacks and fatality due to cardiovascular disease. The equation estimates the probability of a cardiovascular event in the next period conditional on the coefficients listed in Table 18. The equation for the probability of an event in the next period is calculated as

$$p(Y = 1) = 1 - S(1)^\theta$$

$$\theta = \sum \beta X$$

The probability of an event is calculated from the survival function at 1 year raised to the power of θ , where θ is the sum product of the coefficients reported in Table 18 multiplied by the individual's characteristics. Underlying survival curves for men and women were extracted from the QRISK2 open source file. Mean estimates for the continuous variables were also reported in the open source files.

We modified the QRISK assumptions regarding the relationship between IGR, diabetes and cardiovascular disease. Firstly, we assumed that individuals with HbA1c > 6.5 have an increased risk of cardiovascular disease even if they have not received a formal diagnosis. Secondly, risk of cardiovascular disease was assumed to increase with HbA1c for test results greater than 6.5 to reflect observations from the UKPDS that HbA1c increases the risk of MI and Stroke (23). Thirdly, prior to type 2 diabetes (HbA1c > 6.5) HbA1c is linearly associated with cardiovascular disease. A study from the EPIC Cohort has found that a unit increase in HbA1c increases the risk of coronary heart disease by a hazard ratio of 1.25, after adjustment for other risk factors (28). Individuals with an HbA1c greater than the mean HbA1c observed in the HSE 2011 cohort were at greater risk of CVD than those with an HbA1c lower than the HSE mean.

The QRISK algorithm identifies which individuals experience a cardiovascular event but does not specify the nature of the event. The nature of the cardiovascular event was determined independently. A targeted search of recent Health Technology appraisals of cardiovascular disease was performed to identify a model for the progression of cardiovascular disease following a first event. All QRISK events are assigned to a specific diagnosis according to age and sex specific distributions of

cardiovascular events used in a previous Health Technology Assessment (HTA) (21). Table 19 reports the probability of cardiovascular outcomes by age and gender.

Table 19: The probability distribution of cardiovascular events by age and gender

| | Age | Stable angina | Unstable angina | MI rate | Fatal CHD | TIA | Stroke | Fatal CVD |
|-------|-------|---------------|-----------------|---------|-----------|-------|--------|-----------|
| Men | 45-54 | 0.307 | 0.107 | 0.295 | 0.071 | 0.060 | 0.129 | 0.030 |
| | 55-64 | 0.328 | 0.071 | 0.172 | 0.086 | 0.089 | 0.206 | 0.048 |
| | 65-74 | 0.214 | 0.083 | 0.173 | 0.097 | 0.100 | 0.270 | 0.063 |
| | 75-84 | 0.191 | 0.081 | 0.161 | 0.063 | 0.080 | 0.343 | 0.080 |
| | 85+ | 0.214 | 0.096 | 0.186 | 0.055 | 0.016 | 0.351 | 0.082 |
| Women | 45-54 | 0.325 | 0.117 | 0.080 | 0.037 | 0.160 | 0.229 | 0.054 |
| | 55-64 | 0.346 | 0.073 | 0.092 | 0.039 | 0.095 | 0.288 | 0.067 |
| | 65-74 | 0.202 | 0.052 | 0.121 | 0.081 | 0.073 | 0.382 | 0.090 |
| | 75-84 | 0.149 | 0.034 | 0.102 | 0.043 | 0.098 | 0.464 | 0.109 |
| | 85+ | 0.136 | 0.029 | 0.100 | 0.030 | 0.087 | 0.501 | 0.117 |

Subsequent Cardiovascular events

After an individual has experienced a cardiovascular event, it is not possible to predict the transition to subsequent cardiovascular events using QRISK2. Instead, as with assigning first CVD events, the probability of subsequent events was estimated from the HTA evaluating statins (21). This study reported the probability of future events, conditional on the nature of the previous event. Table 20 to Table 24 report the probabilities within a year of transitioning from stable angina, unstable angina, myocardial infarction (MI), transient ischemic attack (TIA) or stroke for individuals in different age groups. The tables suggests that, for example 99.46% of individuals with stable angina will remain in the stable angina state, but 0.13%, 0.32% and 0.01% will progress to unstable angina, MI or death from coronary heart disease (CHD) respectively.

Table 20: Probability of cardiovascular event conditional on age and status of previous event (age 45-54)

| Age 45-54 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9946 | 0.0013 | 0 | 0.0032 | 0 | 0 | 0 | 0 | 0.0009 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.9127 | 0.0495 | 0 | 0 | 0 | 0 | 0.0362 | 0.0016 |
| | Unstable angina (subsequent) | 0 | 0 | 0.9729 | 0.0186 | 0 | 0 | 0 | 0 | 0.0081 | 0.0004 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.128 | 0.8531 | 0 | 0.0015 | 0 | 0.0167 | 0.0007 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0162 | 0.978 | 0 | 0.0004 | 0 | 0.0052 | 0.0002 |
| | TIA | 0 | 0 | 0 | 0.0016 | 0 | 0.9912 | 0.0035 | 0 | 0.0024 | 0.0013 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0016 | 0 | 0 | 0.0431 | 0.9461 | 0.0046 | 0.0046 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0016 | 0 | 0 | 0.0144 | 0.9798 | 0.0021 | 0.0021 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Table 21: Probability of cardiovascular event conditional on age and status of previous event (age 55-64)

| Age 55-64 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9880 | 0.0033 | 0 | 0.0057 | 0 | 0 | 0 | 0 | 0.0030 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.8670 | 0.0494 | 0 | 0 | 0 | 0 | 0.0800 | 0.0036 |
| | Unstable angina (subsequent) | 0 | 0 | 0.9415 | 0.0471 | 0 | 0 | 0 | 0 | 0.0109 | 0.0005 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.1087 | 0.8409 | 0 | 0.0047 | 0 | 0.0439 | 0.0019 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0183 | 0.9678 | 0 | 0.0015 | 0 | 0.0119 | 0.0005 |
| | TIA | 0 | 0 | 0 | 0.0029 | 0 | 0.9666 | 0.0159 | 0 | 0.0079 | 0.0068 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0029 | 0 | 0 | 0.0471 | 0.9159 | 0.0171 | 0.0171 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0029 | 0 | 0 | 0.0205 | 0.9622 | 0.0072 | 0.0072 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Table 22: Probability of cardiovascular event conditional on age and status of previous event (age 65-74)

| Age 65-74 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9760 | 0.0060 | 0 | 0.0110 | 0 | 0 | 0 | 0 | 0.0070 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.8144 | 0.0479 | 0 | 0 | 0 | 0 | 0.1319 | 0.0059 |
| | Unstable angina (subsequent) | 0 | 0 | 0.9021 | 0.0844 | 0 | 0 | 0 | 0 | 0.0129 | 0.0006 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.0948 | 0.8106 | 0 | 0.0098 | 0 | 0.0811 | 0.0036 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0183 | 0.9585 | 0 | 0.0032 | 0 | 0.0191 | 0.0008 |
| | TIA | 0 | 0 | 0 | 0.0055 | 0 | 0.9174 | 0.0423 | 0 | 0.0185 | 0.0163 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0055 | 0 | 0 | 0.0485 | 0.8673 | 0.0393 | 0.0393 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0055 | 0 | 0 | 0.0237 | 0.9412 | 0.0148 | 0.0148 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Table 23: Probability of cardiovascular event conditional on age and status of previous event (age 75-84)

| Age 75-84 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9680 | 0.0087 | 0 | 0.0163 | 0 | 0 | 0 | 0 | 0.0070 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.7366 | 0.0448 | 0 | 0 | 0 | 0 | 0.2093 | 0.0093 |
| | Unstable angina (subsequent) | 0 | 0 | 0.8360 | 0.1484 | 0 | 0 | 0 | 0 | 0.0149 | 0.0007 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.0794 | 0.7502 | 0 | 0.0200 | 0 | 0.1440 | 0.0064 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0171 | 0.9466 | 0 | 0.0066 | 0 | 0.0286 | 0.0013 |
| | TIA | 0 | 0 | 0 | 0.0082 | 0 | 0.8514 | 0.0878 | 0 | 0.0185 | 0.0342 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0082 | 0 | 0 | 0.0471 | 0.7736 | 0.0856 | 0.0856 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0082 | 0 | 0 | 0.0251 | 0.9107 | 0.0280 | 0.0280 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Table 24: Probability of cardiovascular event conditional on age and status of previous event (age 85-94)

| Age 85-94 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9600 | 0.0114 | 0 | 0.0216 | 0 | 0 | 0 | 0 | 0.0070 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.6315 | 0.0396 | 0 | 0 | 0 | 0 | 0.3149 | 0.0140 |
| | Unstable angina (subsequent) | 0 | 0 | 0.7255 | 0.2568 | 0 | 0 | 0 | 0 | 0.0170 | 0.0008 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.0623 | 0.6498 | 0 | 0.0380 | 0 | 0.2393 | 0.0106 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0148 | 0.9311 | 0 | 0.0124 | 0 | 0.0399 | 0.0018 |
| | TIA | 0 | 0 | 0 | 0.0108 | 0 | 0.7967 | 0.1286 | 0 | 0.0185 | 0.0453 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0108 | 0 | 0 | 0.0409 | 0.6153 | 0.1665 | 0.1665 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0108 | 0 | 0 | 0.0248 | 0.8655 | 0.0494 | 0.0494 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Congestive Heart Failure

The review of previous economic evaluations of diabetes prevention cost-effectiveness studies found that only a small number of models had included congestive heart failure as a separate outcome. Discussion with the stakeholder group identified that the UKPDS Outcomes model would be an appropriate risk model for congestive heart failure in type 2 diabetes patients. However, it was suggested that this would not be an appropriate risk equation for individuals with normal glucose tolerance or impaired glucose tolerance. The Framingham risk equation was suggested as an alternative. The main limitation of this equation is that it is quite old and is based on a non-UK population. However, a citation search of this article did not identify a more recent or UK based alternative.

Congestive heart failure was included as a separate cardiovascular event because it was not included as an outcome of the QRISK2. The Framingham Heart Study has reported logistic regressions to estimate the 4 year probability of congestive heart failure for men and women (29). The equations included age, diabetes diagnosis (either formal diagnosis or HbA1c>6.5), BMI and systolic blood pressure to adjust risk based on individual characteristics. We used this risk equation to estimate the probability of congestive heart failure in the SPHR diabetes prevention model. Table 25 describes the covariates for the logit models to estimate the probability of congestive heart failure in men and women.

Table 25: Logistic regression coefficients to estimate the 4-year probability of congestive heart failure from the Framingham study

| Variables | Units | Regression Coefficient | OR (95% CI) | P |
|---|-------------------|------------------------|------------------|-------|
| Men | | | | |
| Intercept | | -9.2087 | | |
| Age | 10 y | 0.0412 | 1.51 (1.31-1.74) | <.001 |
| Left ventricular hypertrophy | Yes/no | 0.9026 | 2.47 (1.31-3.77) | <.001 |
| Heart rate | 10 bpm | 0.0166 | 1.18 (1.08-1.29) | <.001 |
| Systolic blood pressure | 20 mm Hg | 0.00804 | 1.17 (1.04-1.32) | 0.007 |
| Congenital heart disease | Yes/no | 1.6079 | 4.99 (3.80-6.55) | <.001 |
| Valve disease | Yes/no | 0.9714 | 2.64 (1.89-3.69) | <.001 |
| Diabetes | Yes/no | 0.2244 | 1.25 (0.89-1.76) | 0.2 |
| Women | | | | |
| Intercept | | -10.7988 | | |
| Age | 10 y | 0.0503 | 1.65 (1.42-1.93) | <.001 |
| left ventricular hypertrophy | Yes/no | 1.3402 | 3.82 (2.50-5.83) | <.001 |
| Heart rate | 100 cL | 0.0105 | 1.11 (1.01-1.23) | 0.03 |
| Systolic blood pressure | 10 bpm | 0.00337 | 1.07 (0.96-1.20) | 0.24 |
| congenital heart disease | 20 mm Hg | 1.5549 | 4.74 (3.49-6.42) | <.001 |
| Valve disease | Yes/no | 1.3929 | 4.03 (2.86-5.67) | <.001 |
| Diabetes | Yes/no | 1.3857 | 4.00 (2.78-5.74) | <.001 |
| BMI | kg/m ² | 0.0578 | 1.06 (1.03-1.09) | <.001 |
| Valve disease and diabetes | Yes/no | -0.986 | 0.37 (0.18-0.78) | 0.009 |
| *OR indicates odds ratio; CI, confidence interval; LVH, left ventricular hypertrophy; CHD, congenital heart disease; and BMI, body mass index. Predicted probability of heart failure can be calculated as: $p = 1/(1+\exp(-x\beta))$, where $x\beta = \text{Intercept} + \text{Sum (of regression coefficient*value of risk factor)}$ | | | | |

Many of the risk factors included in this risk equation were not simulated in the diabetes model. We adjusted the baseline odds of CHD to reflect the expected prevalence of these symptoms in a UK population.

The proportion of the UK population with left ventricular hypertrophy was assumed to be 5% in line with previous analyses of the Whitehall II cohort (30). The heart rate for men was assumed to be 63.0bpm and for women 65.6bpm based on data from previous Whitehall II cohort analyses (31). The prevalence of congenital heart disease was estimated from an epidemiology study in the North of England. The study reports the prevalence of congenital heart disease among live births which was used to estimate the adult prevalence (32). This may over-estimate the prevalence, because the life expectancy of births with congenital heart disease is reduced compared with the general population. However, given the low prevalence it is unlikely to impact on the results. The prevalence of valve disease was estimated from the Echocardiographic Heart of England Screening study (33).

1
2
3 Using the estimated population values, the intercept values were adjusted to account for the
4 population risk in men and women. This resulted in a risk equation with age, systolic blood pressure,
5 diabetes and BMI in women to describe the risk of congestive heart failure.
6
7

8 9 MICROVASCULAR COMPLICATIONS

10
11 The review of previous economic evaluations identified that the UKPDS data was commonly used to
12 estimate the incidence of microvascular complications (4). This data has the advantage of being
13 estimated from a UK diabetic population. Given that the events described in the UKPDS outcomes
14 model are indicative of late stage microvascular complications, we did not believe it was necessary to
15 seek an alternative model that would be representative of an impaired glucose tolerance population.
16
17

18
19 We adopted a simple approach to modelling microvascular complications. We used both versions of
20 the UKPDS Outcomes model to estimate the occurrence of major events relating to these
21 complications, including renal failure, amputation, foot ulcer, and blindness (15;23). These have the
22 greatest cost and utility impact compared with earlier stages of microvascular complications, so are
23 more likely to have an impact on the SPHR diabetes prevention outcomes. As a consequence, we
24 assumed that microvascular complications only occur in individuals with HbA1c>6.5. Whilst some
25 individuals with hyperglycaemia (HbA1c>6.0) may be at risk of developing microvascular
26 complications, it is unlikely that they will progress to renal failure, amputation or blindness before a
27 diagnosis of diabetes. Importantly, we did not assume that only individuals who have a formal
28 diagnosis of diabetes are at risk of these complications. This allows us to incorporate the costs of
29 undetected diabetes into the simulation.
30
31

32
33 The UKPDS includes four statistical models to predict foot ulcers, amputation with no prior ulcer,
34 amputation with prior ulcer and a second amputation (23). In order to simplify the simulation of
35 neuropathy outcomes we consolidated the models for first amputation with and without prior ulcer
36 into a single equation. The parametric survival models were used to generate estimates of the
37 cumulative hazard in the current and previous period. From which the probability of organ damage
38 being diagnosed was estimated.
39
40

$$41 \quad p(\text{Death}) = 1 - \exp(H(t) - H(t - 1))$$

42
43 The functional form for the microvascular models included exponential and Weibull. The logistic
44 model was also used to estimate the probability of an event over the annual time interval.
45
46

47 48 **Retinopathy**

49
50 We used the UKPDS outcomes model v2 to estimate the incidence of blindness in individuals with
51 HbA1c>6.5. The exponential model assumes a baseline hazard λ , which can be calculated from the
52 model coefficients reported in Table 26 and the individual characteristics for \mathbf{X} .
53
54
55
56
57
58
59
60

$$\lambda = \exp(\beta_0 + X\beta_k)$$

Table 26: Parameters of the UKPDS2 Exponential Blindness survival model

| | Mean coefficient | Standard error | Modified mean coefficient |
|-------------------|------------------|----------------|---------------------------|
| Lambda | -11.607 | 0.759 | -10.967 |
| Age at diagnosis | 0.047 | 0.009 | 0.047 |
| HbA1c | 0.171 | 0.032 | 0.171 |
| Heart rate | 0.080 | 0.039 | |
| SBP | 0.068 | 0.032 | 0.068 |
| White Blood Count | 0.052 | 0.019 | |
| CHF History | 0.841 | 0.287 | 0.841 |
| IHD History | 0.0610 | 0.208 | 0.061 |

The age at diagnosis coefficient was multiplied by age in the current year if the individual had not been diagnosed with diabetes or by the age at diagnosis if the individual had received a diagnosis. The expected values for the risk factors not included in the SPHR model (heart rate and white blood count) were taken from Figure 3 of the UKPDS publication in which these are described (23). Assuming these mean values, it was possible to modify the baseline risk without simulating heart rate and white blood cell count.

Neuropathy

We used the UKPDS outcomes model v2 to estimate the incidence of ulcer and amputation in individuals with HbA1c>6.5. The parameters of the ulcer and first amputation models are reported in Table 27.

Table 27: Parameters of the UKPDS2 Exponential model for Ulcer, Weibull model for first amputation with no prior ulcer and exponential model for 1st amputation with prior ulcer

| | Ulcer | | 1 st Amputation no prior ulcer | | 1 st Amputation prior ulcer | | 2 nd Amputation | |
|---------------------|----------|----------------|---|----------------|--|----------------|----------------------------|----------------|
| | Logistic | | Weibull | | Exponential | | Exponential | |
| | Mean | Standard error | Mean | Standard error | Mean | Standard error | Mean | Standard error |
| lambda | -11.295 | 1.130 | -14.844 | 1.205 | -0.881 | 1.39 | -3.455 | 0.565 |
| Rho | | | 2.067 | 0.193 | | | | |
| Age at diagnosis | 0.043 | 0.014 | 0.023 | 0.011 | -0.065 | 0.027 | | |
| Female | -0.962 | 0.255 | -0.0445 | 0.189 | | | | |
| Atrial fibrillation | | | 1.088 | 0.398 | | | | |
| BMI | 0.053 | 0.019 | | | | | | |
| HbA1c | 0.160 | 0.056 | 0.248 | 0.042 | | | 0.127 | 0.06 |
| HDL | | | -0.059 | 0.032 | | | | |
| Heart rate | | | 0.098 | 0.050 | | | | |
| MMALB | | | 0.602 | 0.180 | | | | |
| PVD | 0.968 | 0.258 | 1.010 | 0.189 | 1.769 | 0.449 | | |
| SBP | | | 0.086 | 0.043 | | | | |
| WBC | | | 0.040 | 0.017 | | | | |
| Stroke History | | | 1.299 | 0.245 | | | | |

The exponential model assumes a baseline hazard λ , which can be calculated from the model coefficients reported in Table 27 and the individual characteristics for \mathbf{X} .

$$\lambda = \exp(\beta_0 + \mathbf{X}\boldsymbol{\beta})$$

The Weibull model for amputation assumes a baseline hazard:

$$h(t) = \rho t^{\rho-1} \exp(\lambda)$$

where λ is also conditional on the coefficients and individual characteristics at time t . The logistic model for ulcer is described below.

$$\Pr(y = 1|\mathbf{X}) = \frac{\exp(\mathbf{X}\boldsymbol{\beta})}{1 + \exp(\mathbf{X}\boldsymbol{\beta})}$$

The ulcer and amputation models include a number of covariates that were not included in the simulation. As such it was necessary to adjust the statistical models to account for these measures. We estimated a value for the missing covariates and added the value multiplied by the coefficient to the baseline hazard.

The expected values for the risk factors not included in the SPHR diabetes prevention model (heart rate, white blood count, micro-/macroalbuminuria, peripheral vascular disease and atrial fibrillation)

were taken from Figure 3 of the UKPDS publication in which these are described (23). In the ulcer model we assumed that 2% of the population had peripheral vascular disease.

The amputation risk model with a history of ulcer was not included in the simulation, but was used to estimate an additional log hazard ratio to append onto the amputation model without a history of ulcer. The log hazard was estimated for each model assuming the same values for other covariates. The difference in the log hazard between the two models was used to approximate the log hazard ratio for a history of ulcer in the amputation model (10.241). The final model specifications are reported in Table 28.

Table 28: Coefficients estimates for Ulcer and 1st Amputation

| | Ulcer | | 1 st Amputation | | 2 nd Amputation | |
|------------------|----------|----------------|----------------------------|----------------|----------------------------|----------------|
| | Logistic | | Weibull | | Exponential | |
| | Mean | Standard error | Mean | Standard error | Mean | Standard error |
| Lambda | -11.276 | 1.13 | -13.954 | 1.205 | -3.455 | 0.565 |
| Rho | | | 2.067 | 0.193 | | |
| Age at Diagnosis | 0.043 | 0.014 | 0.023 | 0.011 | | |
| Female | -0.962 | 0.255 | -0.445 | 0.189 | | |
| BMI | 0.053 | 0.019 | | | | |
| HbA1c | 0.160 | 0.056 | 0.248 | 0.042 | 0.127 | 0.06 |
| HDL | | | -0.059 | 0.032 | | |
| Stroke | | | 1.299 | 0.245 | | |
| Foot Ulcer | | | 10.241 | | | |

Nephropathy

We used the UKPDS outcomes model v1 to estimate the incidence of renal failure in individuals with HbA1c>6.5. Early validation analyses identified that the UKPDS v2 model implements in the SPHR model substantially overestimated the incidence of renal failure. The Weibull model for renal failure assumes a baseline hazard:

$$h(t) = \rho t^{\rho-1} \exp(\lambda)$$

where λ is also conditional on the coefficients and individual characteristics at time t . The parameters of the renal failure risk model are reported in Table 29.

Table 29: Parameters of the UKPDS2 Weibull renal failure survival model

| | Mean | Standard error |
|-----------------|---------|----------------|
| Lambda | -10.016 | 0.939 |
| Shape parameter | 1.865 | 0.387 |
| SBP | 0.404 | 0.106 |
| BLIND History | 2.082 | 0.551 |

CANCER

The conceptual model identified breast cancer and colorectal cancer risk as being related to BMI. However, these outcomes were not frequently included in previous cost-effectiveness models for diabetes prevention. Discussion with stakeholders identified the EPIC Norfolk epidemiology cohort study as a key source of information about cancer risk in a UK population. Therefore, we searched publications from this cohort to identify studies reporting the incidence of these risks. In order to obtain the best quality evidence for the relationship between BMI and cancer risk we searched for a recent systematic review and meta-analysis using key terms 'Body Mass Index' and 'Cancer', filtering for meta-analysis studies.

Breast cancer

Incidence rates for breast cancer in the UK were estimated from the European Prospective Investigation of Cancer (EPIC) cohort. This is a large multi-centre cohort study looking at diet and cancer. In 2004 the UK incidence of breast cancer by menopausal status was reported in a paper from this study investigating the relationship between body size and breast cancer (34). The estimates of the breast cancer incidence in the UK are reported in Table 30.

Table 30: UK breast cancer incidence

| | Number of Cases | Person Years | Mean BMI | Incidence Rate of per person-year | Reference |
|-------------------|-----------------|--------------|----------|-----------------------------------|-----------|
| UK pre-menopause | 102 | 103114.6 | 24 | 0.00099 | (34) |
| UK post-menopause | 238 | 84214.6 | 24 | 0.00283 | (34) |

A large meta-analysis that included 221 prospective observational studies has reported relative risks of cancers per unit increase in BMI, including breast cancer by menopausal status (35). We included a risk adjustment in the model so that individuals with higher BMI have a higher probability of pre-and post-menopausal breast cancer (35). In the simulation we adjusted the incidence of breast cancer by multiplying the linear relative risk by the difference in the individual's BMI and the average BMI reported in the EPIC cohort. The relative risk and confidence intervals per 5mg/m² increase in BMI are reported in Table 31.

Table 31: Relative risk of Breast cancer by BMI

| | Mean Relative risk | 2.5 th Confidence Interval | 97.5 th Confidence Interval | Reference |
|-------------------|--------------------|---------------------------------------|--|-----------|
| UK pre-menopause | 0.89 | 0.84 | 0.94 | (35) |
| UK post-menopause | 1.09 | 1.04 | 1.14 | (35) |

Colorectal cancer

Incidence rates for colorectal cancer in the UK were reported from the European Prospective Investigation of Cancer (EPIC) cohort. The UK incidence of colorectal cancer is reported by gender in a paper from this study investigating the relationship between body size and colon and rectal cancer (34). The estimates of the colorectal cancer incidence are reported in Table 32.

Table 32: UK colorectal cancer incidence

| | Number of Cases | Person Years | Mean Age | Mean BMI | Incidence Rate of per person-year | Reference |
|--------|-----------------|--------------|----------|----------|-----------------------------------|-----------|
| Male | 125 | 118468 | 53.1 | 25.4 | 0.00106 | (36) |
| Female | 145 | 277133 | 47.7 | 24.5 | 0.00052 | (36) |

The risk of colorectal cancer has been linked to obesity. We included a risk adjustment in the model to reflect observations that the incidence of breast cancer is increased in individuals with higher BMI. A large meta-analysis that included 221 prospective observational studies has reported relative risks of BMI and cancers, including colon cancer by gender (35). We selected linear relative risk estimates estimated from pooled European and Australian populations. In the simulation we adjusted the incidence of colorectal cancer by multiplying the relative risk by the difference in the individual's BMI and the average BMI reported in the EPIC cohort. The relative risk and confidence intervals per 5mg/m² increase in BMI are reported in Table 33.

Table 33: Relative risk of colon cancer by BMI

| | Mean Relative risk | 2.5 th Confidence Interval | 97.5 th Confidence Interval | Reference |
|-------------------|--------------------|---------------------------------------|--|-----------|
| UK pre-menopause | 1.21 | 1.18 | 1.24 | (35) |
| UK post-menopause | 1.04 | 1 | 1.07 | (35) |

OSTEOARTHRITIS

The stakeholder group requested that BMI and diabetes be included as independent risk factors for osteoarthritis based on recent evidence (37). Osteoarthritis had not been included as a health state in previous cost-effectiveness models. A search for studies using key words 'Diabetes', 'Osteoarthritis' and 'Cohort Studies' did not identify a UK based study with diabetes and BMI included as independent covariates in the risk model. The Bruneck cohort, a longitudinal study of inhabitants of a town in Italy reported diabetes and BMI as independent risk factors for osteoarthritis (37). The cohort may not be representative of the UK. However, the individuals are from a European country, the study has a large sample size and has estimated the independent effects of BMI and diabetes on the risk of osteoarthritis. No UK based studies identified in our searches met these requirements. The data used to estimate the incidence of osteoarthritis is reported in Table 34.

Table 34: Incidence of osteoarthritis and estimated risk factors

| | No cases | Person years | Mean BMI | Incidence rate | Reference |
|-------------|--------------|--------------|----------|----------------|-----------------------------|
| No diabetes | 73 | 13835 | 24.8 | 0.0053 | (37) |
| | Hazard ratio | 2.5th | 97.5th | | Reference |
| HR Diabetes | 2.06 | 1.11 | 3.84 | | (37) |
| HR BMI | 1.076 | 1.023 | 1.133 | | (37) Personal communication |

DEPRESSION

Depression was not included as a health state in previous cost-effectiveness models for diabetes prevention. However, a member of the stakeholder group identified that a relationship between diabetes and depression was included in the CORE diabetes treatment model (38). With this in mind, we decided to include depression as a health state in the model, but not to model its severity.

Some individuals enter the simulation with depression at baseline according to individual responses in the Health Survey for England 2011 questionnaire. Depression is described as a chronic state from which individuals do not completely remit. We did not estimate the effect of depression on the longitudinal changes for BMI, glycaemia, systolic blood pressure and cholesterol. As a consequence it was not possible to relate the impact of depression to the incidence of diabetes and CVD risk.

In the simulation, individuals can develop depression in any cycle of the model. The baseline incidence of depression among all individuals without a history of depression was estimated from a study examining the bidirectional association between depressive symptoms and type 2 diabetes (39). Although the study was not from a UK population, the US cohort included ethnically diverse men and women aged 45 to 84 years. We assumed that diagnosis of diabetes and/or cardiovascular disease increases the incidence of depression in individuals who do not have depression at baseline. We identified a method for inflating risk of depression for individuals with diabetes from the US cohort study described above (39). The risk of depression in individuals who have had a stroke was also inflated according to a US cohort study (40). Odds of depression and odds ratios for inflated risk of depression due to diabetes or stroke are presented in Table 35.

Table 35: Baseline incidence of depression

| Baseline Risk of depression | Mean | 2.5 th CI | 97.5th |
|------------------------------|--------|----------------------|--------|
| Depression cases in NGT | 336 | | |
| Person years | 9139 | | |
| Odds of depression | 0.0382 | | |
| Log odds of depression | -3.266 | | |
| Inflated risk for Diabetes | | | |
| Odds ratio of diabetes | 1.52 | 1.09 | 2.12 |
| Log odds ratio of diabetes | 0.419 | | |
| Inflate risk of stroke | | | |
| Odds ratio of stroke | 6.3 | 1.7 | 23.2 |
| Log odds ratio stroke | 1.8406 | | |
| NGT Normal Glucose Tolerance | | | |

MORTALITY

Cardiovascular Mortality

Cardiovascular mortality is included as an event within the QRISK2 and the probability of subsequent cardiovascular events obtained from an HTA assessing statins (21) as described in the cardiovascular disease section above.

Cancer Mortality

Cancer mortality rates were obtained from the Office of National statistics (41). The ONS report one and five year net survival rates for various cancer types, by age group and gender. Net survival was an estimate of the probability of survival from the cancer alone. It can be interpreted as the survival of cancer patients after taking into account the background mortality that the patients would have experienced if they had not had cancer.

The age-adjusted 5-year survival rate for breast cancer and colorectal cancer were used to estimate an annual risk of mortality assuming a constant rate of mortality. We assume that the mortality rate does not increase due to cancer beyond 5 years after cancer diagnosis. The five year survival rate for breast cancer is 84.3%, which translated into a 3.37% annual probability of death from breast cancer. The five year survival rate for persons with colorectal cancer is 55.3%, which translated into an 11.16% annual probability of death from colorectal cancer.

Other cause Mortality (including diabetes risk)

Other cause mortality describes the risk of death from any cause except cardiovascular disease and cancer. All-cause mortality rates by age and sex were extracted from the Office of National Statistics (42). The mortality statistics report the number of deaths by ICD codes for 5-year age groups. We subtracted the number of cardiovascular disease, breast and colorectal cancer related deaths from the all-cause mortality total to estimate other cause mortality rates by age and sex (Table 33).

Table 36: All cause and derived other cause mortality from the Office of National statistics

| | All cause | All cause | Other cause | Other cause | | All cause | All cause | Other cause | Other cause |
|----|-----------|-----------|-------------|-------------|-----|-----------|-----------|-------------|-------------|
| | Men | Women | Men | Women | | Men | Women | Men | Women |
| 1 | 0.0004 | 0.0003 | 0.0003 | 0.0003 | 51 | 0.0034 | 0.0024 | 0.0025 | 0.0017 |
| 2 | 0.0002 | 0.0002 | 0.0002 | 0.0002 | 52 | 0.0039 | 0.0026 | 0.0029 | 0.0019 |
| 3 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 53 | 0.0044 | 0.0028 | 0.0032 | 0.0020 |
| 4 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 54 | 0.0045 | 0.0032 | 0.0034 | 0.0022 |
| 5 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 55 | 0.0051 | 0.0033 | 0.0037 | 0.0024 |
| 6 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 56 | 0.0057 | 0.0037 | 0.0041 | 0.0027 |
| 7 | 0.0001 | 0.0001 | 0.0001 | 0.0000 | 57 | 0.0061 | 0.0041 | 0.0044 | 0.0030 |
| 8 | 0.0001 | 0.0001 | 0.0001 | 0.0000 | 58 | 0.0069 | 0.0041 | 0.0050 | 0.0030 |
| 9 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 59 | 0.0071 | 0.0050 | 0.0052 | 0.0036 |
| 10 | 0.0001 | 0.0000 | 0.0001 | 0.0000 | 60 | 0.0081 | 0.0054 | 0.0059 | 0.0040 |
| 11 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 61 | 0.0086 | 0.0057 | 0.0063 | 0.0042 |
| 12 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 62 | 0.0096 | 0.0062 | 0.0070 | 0.0046 |
| 13 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 63 | 0.0104 | 0.0067 | 0.0076 | 0.0050 |
| 14 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 64 | 0.0108 | 0.0072 | 0.0079 | 0.0053 |
| 15 | 0.0002 | 0.0001 | 0.0002 | 0.0001 | 65 | 0.0125 | 0.0082 | 0.0091 | 0.0061 |
| 16 | 0.0002 | 0.0001 | 0.0002 | 0.0001 | 66 | 0.0141 | 0.0090 | 0.0103 | 0.0067 |
| 17 | 0.0003 | 0.0002 | 0.0003 | 0.0002 | 67 | 0.0148 | 0.0097 | 0.0108 | 0.0072 |
| 18 | 0.0004 | 0.0002 | 0.0004 | 0.0002 | 68 | 0.0162 | 0.0107 | 0.0118 | 0.0079 |
| 19 | 0.0004 | 0.0002 | 0.0004 | 0.0002 | 69 | 0.0181 | 0.0118 | 0.0132 | 0.0087 |
| 20 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 70 | 0.0218 | 0.0138 | 0.0157 | 0.0101 |
| 21 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 71 | 0.0234 | 0.0145 | 0.0168 | 0.0106 |
| 22 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 72 | 0.0252 | 0.0167 | 0.0182 | 0.0122 |
| 23 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 73 | 0.0269 | 0.0173 | 0.0193 | 0.0127 |
| 24 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 74 | 0.0310 | 0.0200 | 0.0223 | 0.0147 |
| 25 | 0.0006 | 0.0003 | 0.0006 | 0.0002 | 75 | 0.0327 | 0.0222 | 0.0233 | 0.0157 |
| 26 | 0.0006 | 0.0003 | 0.0005 | 0.0002 | 76 | 0.0375 | 0.0249 | 0.0267 | 0.0176 |
| 27 | 0.0006 | 0.0004 | 0.0005 | 0.0003 | 77 | 0.0411 | 0.0284 | 0.0293 | 0.0202 |
| 28 | 0.0007 | 0.0003 | 0.0006 | 0.0003 | 78 | 0.0458 | 0.0321 | 0.0326 | 0.0228 |
| 29 | 0.0007 | 0.0003 | 0.0006 | 0.0003 | 79 | 0.0523 | 0.0358 | 0.0372 | 0.0254 |
| 30 | 0.0007 | 0.0004 | 0.0006 | 0.0003 | 80 | 0.0585 | 0.0411 | 0.0418 | 0.0289 |
| 31 | 0.0008 | 0.0004 | 0.0007 | 0.0004 | 81 | 0.0652 | 0.0456 | 0.0465 | 0.0321 |
| 32 | 0.0007 | 0.0005 | 0.0007 | 0.0004 | 82 | 0.0745 | 0.0530 | 0.0531 | 0.0372 |
| 33 | 0.0008 | 0.0005 | 0.0007 | 0.0004 | 83 | 0.0833 | 0.0606 | 0.0594 | 0.0426 |
| 34 | 0.0009 | 0.0005 | 0.0008 | 0.0004 | 84 | 0.0931 | 0.0678 | 0.0664 | 0.0476 |
| 35 | 0.0010 | 0.0006 | 0.0008 | 0.0005 | 85 | 0.1040 | 0.0760 | 0.0738 | 0.0537 |
| 36 | 0.0011 | 0.0006 | 0.0010 | 0.0005 | 86 | 0.1147 | 0.0872 | 0.0814 | 0.0617 |
| 37 | 0.0013 | 0.0006 | 0.0011 | 0.0005 | 87 | 0.1300 | 0.0977 | 0.0923 | 0.0692 |
| 38 | 0.0013 | 0.0007 | 0.0011 | 0.0006 | 88 | 0.1468 | 0.1106 | 0.1042 | 0.0782 |
| 39 | 0.0013 | 0.0007 | 0.0011 | 0.0006 | 89 | 0.1643 | 0.1242 | 0.1166 | 0.0879 |
| 40 | 0.0015 | 0.0009 | 0.0012 | 0.0006 | 90 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 41 | 0.0016 | 0.0010 | 0.0013 | 0.0007 | 91 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 42 | 0.0018 | 0.0010 | 0.0015 | 0.0008 | 92 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 43 | 0.0018 | 0.0012 | 0.0015 | 0.0009 | 93 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 44 | 0.0020 | 0.0012 | 0.0017 | 0.0009 | 94 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 45 | 0.0022 | 0.0014 | 0.0017 | 0.0010 | 95 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 46 | 0.0023 | 0.0016 | 0.0018 | 0.0011 | 96 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 47 | 0.0023 | 0.0015 | 0.0018 | 0.0011 | 97 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 48 | 0.0027 | 0.0017 | 0.0021 | 0.0012 | 98 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 49 | 0.0028 | 0.0019 | 0.0022 | 0.0014 | 99 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 50 | 0.0030 | 0.0021 | 0.0023 | 0.0015 | 100 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |

The rate of other cause mortality by age and sex was treated as the baseline hazard. Following input from stakeholders, an increased risk of mortality was assigned to individuals with diabetes using data

1
2
3 from a published meta-analysis (43). This study used data from 820,900 people from 97 prospective
4 studies to calculate hazard ratios for cause-specific death, according to baseline diabetes status (43).
5 Cause of death was separated into vascular disease, cancer and other cause mortality. From this study
6 we estimated that individuals with a diagnosis of diabetes have a fixed increased risk of other cause
7 mortality (Hazard ratio 1.8 (95% CI 1.71-1.9)). The estimates reported in the meta-analysis include
8 increased risk of death from renal disease, therefore mortality from renal disease was not simulated
9 separately to avoid double counting of benefits.
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15 16 **UTILITIES**

17 18 **Baseline Utility**

19
20 Baseline utilities for all individuals in the cohort were extracted from the HSE 2011. The tariffs for
21 the responses to the 3 level EQ-5D were derived from a UK population study (44). Baseline utility
22 was assumed to decline due to ageing. In the simulation, utility declines by an absolute decrement of
23 0.004 per year. This estimate is based on previous HTA modelling in cardiovascular disease (21).
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28 29 **Utility Decrements**

30
31 The utility decrements for long term chronic conditions were applied to the age and BMI adjusted
32 EQ-5D score. It was assumed that a diagnosis of diabetes was not associated with a reduction in EQ-
33 5D independent of the utility decrements associated with complications, comorbidities or depression.
34 Cardiovascular disease, renal failure, amputation, foot ulcers, blindness, cancer, osteoarthritis and
35 depression were all assumed to result in utility decrements. The utility decrements are measured as a
36 factor which is applied to the individual's age and BMI adjusted baseline. If individuals have multiple
37 chronic conditions the utility decrements are multiplied together to give the individual's overall utility
38 decrement from comorbidities and complications, in line with current NICE guidelines for combining
39 comorbidities (45).
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45
46 Due to the number of health states it was not practical to conduct a systematic review to identify
47 utility decrements for all health states. A pragmatic approach was taken to search for health states
48 within existing health technology assessments for the relevant disease area or by considering studies
49 used in previous economic models for diabetes prevention. Discussions with experts in health
50 economic modelling were also used to identify prominent sources of data for health state utilities.
51
52
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55
56 Two sources of data were identified for diabetes related complications. A recent study from the
57 UKPDS estimated the impact of changes in health states from a longitudinal cohort (46). They
58 estimated the impact of myocardial infarction, ischaemic heart disease, stroke, heart failure,
59 amputation and blindness on quality of life using seven rounds of EQ-5D questionnaires administered
60 between 1997 and 2007. This data was used to estimate the utility decrement for amputation and

1
2
3 congestive heart failure. The absolute decrement for amputation was converted into utility decrement
4 factors that could be multiplied by the individuals' current EQ-5D to estimate the relative effect of the
5 complication.
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9 Utility decrements for renal failure and foot ulcers were not available from the UKPDS study
10 described above. A study by Coffey et al. (2000) was used to estimate utility decrements for renal
11 failure and foot ulcers (47). In this study, 2,048 subjects with type 1 and type 2 diabetes were
12 recruited from specialty clinics. The Self-Administered Quality of Well Being index (QWB-SA) was
13 used to calculate a health utility score.
14
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17
18 Utility decrements for cardiovascular events were taken from an HTA assessing statins to reflect the
19 utility decrements in all patients (21) rather than using the UKPDS, which is only representative of a
20 diabetic population. The study conducted a literature review to identify appropriate utility multipliers
21 for stable angina, unstable angina, myocardial infarction and stroke. We used these estimates in the
22 model and assume that transient ischaemic attack is not associated with a utility decrement in line
23 with this HTA.
24
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28
29 A systematic review of breast cancer utility studies was identified following consultation with
30 colleagues with experience in this area. The review highlighted a single burden of illness study with a
31 broad utility decrement for cancer (48), rather than utilities by cancer type or disease status. This
32 study was most compatible with the structure of the cost-effectiveness structure. Within this study
33 1823 cancer survivors and 5469 age-, sex-, and educational attainment-matched control subjects
34 completed EQ-5D questionnaires to estimate utility with and without cancer.
35
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39 The utility decrement for osteoarthritis was taken from a Health Technology Assessment that assessed
40 the clinical effectiveness and cost-effectiveness of glucosamine sulphate/hydrochloride and
41 chondroitin sulphate in modifying the progression of osteoarthritis of the knee (49).
42
43
44

45 A review of cost-effectiveness studies highlights the scarcity of studies of health-related quality of life
46 in depression (50). The utility studies identified in the review described depression states by severity
47 and did not adjust for comorbid conditions. Furthermore, the valuations were variable between studies
48 suggesting poor consistency in the estimations. Therefore, it was difficult to apply these in the model.
49 We decided to use a study which had used the EQ-5D in an RCT, for consistency with our utility
50 measure (51). They report an average post treatment utility of 0.67, from which we estimated the
51 utility decrement compared with the average utility reported in the HSE dataset. The decrement was
52 then converted into a relative utility reduction.
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58
59 Table 37 reports the multiplicative utility factors that are used in the model to describe health utility
60 decrements from comorbid complications. The mean absolute decrement estimated in each study is

reported alongside the baseline utility for each study. The utility factor was estimated by dividing the implied health utility with the comorbidity by the baseline utility.

Table 37: Utility decrement factors

| | Mean Absolute decrement | St. error absolute decrement | Baseline Utility | Multiplicative Utility Factor | Source |
|---|-------------------------|------------------------------|------------------|-------------------------------|----------------|
| Foot ulcer | -0.099 | 0.013 | 0.689 | 0.856 | Coffey (47) |
| Amputation | -0.172 | 0.045 | 0.807 | 0.787 | UKPDS (52) |
| Blind | 0.033 | 0.027 | 0.807 | 1.041 | UKPDS (52) |
| Renal failure | -0.078 | 0.026 | 0.689 | 0.887 | Coffey (47) |
| Stable Angina | | | | 0.801 | Ward HTA (21) |
| Unstable Angina y1 | | | | 0.770 | Ward HTA (21) |
| Unstable Angina y2 | | | | 0.770 | Ward HTA (21) |
| Myocardial Infarction y1 | | | | 0.760 | Ward HTA (21) |
| Myocardial Infarction y2 | | | | 0.760 | Ward HTA (21) |
| Transient Ischaemic Attack | | | | 1.000 | Ward HTA (21) |
| Stroke y1 | | | | 0.629 | Ward HTA (21) |
| Stroke y2 | | | | 0.629 | Ward HTA (21) |
| Breast Cancer | -0.060 | | 0.800 | 0.913 | Yabroff (48) |
| Colorectal Cancer | -0.060 | | 0.800 | 0.913 | Yabroff (48) |
| Osteoarthritis | -0.101 | | | | Black HTA (49) |
| Depression | -0.116 | | 0.7905 | 0.875 | Benedict (51) |
| Congestive Heart Failure | -0.101 | 0.032 | | 0.875 | UKPDS (52) |
| UKPDS baseline utility 0.807; HSE baseline 0.7905 | | | | | |

COSTS

At any given time period of the model individuals can have multiple health complications that incur direct healthcare costs. Some of the health states are mutually exclusive; however an individual can accrue multiple complications within the model. Each health state is associated with an average cost, which is accrued by all individuals for every time period for which the state is indicated. Resource use for each comorbidity is added together and no savings are assumed to be made from the use of the same resources for two or more comorbidities for an individual. An exception to this is an assumed adjustment to the utilisation of GP services for individuals with chronic diseases. In the majority of cases it is assumed that the unit costs of healthcare for someone with ID would be the same as the unit costs for an individual in the general population. The exception was cost for a GP appointment, which was expected to be 40% higher than in the general population due to increased length of consultation. All costs were inflated to 2014/15 values using the retail price index where necessary, from the Personal Social Services Research Unit (PSSRU) sources of information (53). Table 38 shows a summary of all the unit costs used in the model and their sources.

Table 38: Summary of all drug, treatment, care and resource costs included in the model

| Drug, Treatment, Care and Resource Costs of | | Cost per year/ incident in 2014/15 prices (* 2006 prices) | Source |
|--|---|--|------------|
| Screening and Intervention costs | | | |
| | Intervention per person | £270 | PHE |
| First line diabetes treatment - low cost diabetes monotherapy | | | |
| | Ongoing costs of diabetes monotherapy – made up of... | £79.06 | |
| | Metformin 500 mg <i>bid</i> standard (85% of patients) or modified release (15%) tablets | £18.83 | BNF (54) |
| | Nurse at GP (consultation) | £25.52 | PSSRU (53) |
| | Health care assistant (10 mins) | £3.40 | PSSRU (53) |
| | Urine sample | £1.00 | (55) |
| | Eye screening | £24.31 | (56) |
| | Lab tests – made up of... | £6.00 | |
| | <i>HbA1c test</i> | £3.00 | (55) |
| | <i>Lipids test</i> | £1.00 | (55) |
| | <i>Liver function test</i> | £1.00 | (55) |
| | <i>B12 test</i> | £1.00 | (55) |
| | Additional first year costs of diabetes monotherapy – made up of... | £103 | |
| | Nurse at GP (2 x consultations) | £51.03 | PSSRU (53) |
| | Health care assistant (2 x 10 mins) | £6.80 | PSSRU (53) |
| | Urine sample (x2) | £2.00 | (55) |
| | Lab tests as above (x2) | £12.00 | (55) |
| | Smoking cessation (central estimate of cost of nicotine replacement therapy) taken up by 50% of the assumed 20% of population who smoke | £30.90 | PSSRU (53) |
| | Second line diabetes treatment - Metformin and Gliptins– made up of... | £529 | |
| | Sitagliptin 100 mg daily | £434 | BNF (54) |
| | Metformin 500 mg <i>bid</i> standard (85% of patients) or modified release (15%) tablets | £85 | BNF (54) |
| | Self-monitoring strips (82 per annum) (57) | £16.36 | BNF (54) |
| | Nurse at GP (consultation) | £25.52 | (53) |
| | Health care assistant (10 mins) | £3.40 | (53) |
| | Urine sample | £1.00 | (55) |
| | Eye screening | £24.31 | (56) |
| | Lab tests as for first line treatment | £6.00 | (55) |
| | Third line diabetes treatment - Insulin and oral anti-diabetics – made up of... | £1,503 | |
| | Nurse at GP (3 x consultations) | £76.55 | PSSRU (53) |
| | Health care assistant (3 x 10 mins) | £10.21 | PSSRU (53) |
| | Urine sample (x3) | £3.00 | (55) |
| | Eye screening | £24.31 | (56) |
| | Lab tests as for first line treatment (x3) | £18.00 | (55) |
| | Insulin treatment costs – made up of... | £1,376 | |
| | <i>Glargine</i> | £830.83 | (58) |
| | <i>Oral anti-diabetics</i> | £57.75 | (58) |
| | <i>Reagent test strips</i> | £292.74 | (58) |
| | <i>Hypoglycaemic rescue</i> | £30.98 | (58) |
| | <i>Pen delivery devices</i> | £72.44 | (58) |
| | <i>Sharps</i> | £90.98 | (58) |

| | | | |
|--|--|---------|------------|
| Other primary care costs | | | |
| | GP visit (17 minutes) | £46.95 | PSSRU (53) |
| | Diagnosis of hypertension (including ambulatory blood pressure monitoring) | £56.51 | (19) |
| | Annual treatment with statins (simvastatin 20 mg <i>bid</i>) | £26.59 | BNF (54) |
| | Annual treatment with anti-hypertensives | £195.94 | (59) |
| Cardiovascular disease costs | | | |
| | Unstable Angina year 1: <i>Secondary care costs: 100% hospitalisation, 50% revascularisation procedure, three outpatient appointments.</i> <i>Primary care costs (three GP visits) and medications</i> | £4,674 | (20) |
| | Myocardial infarction year 1 <i>Secondary care costs: 100% hospitalisation, 50% revascularisation procedure, three outpatient appointments.</i> <i>Primary care costs (three GP visits) and medications.</i> | £4,813 | (20) |
| | Subsequent ACS care costs <i>Secondary care costs (one outpatient appointment).</i> <i>Primary care costs (three GP visits) and medications.</i> | £410 | (20) |
| | Stroke year 1 (NHS costs) <i>Costs of acute events reported in Youman et al. (60) weighted by the distribution of severity of stroke (21).</i> | £9,716 | (60) |
| | Social care costs of stroke in subsequent years <i>The costs of ongoing care at home or in an institution weighted by the distribution of severity of stroke and discharge locations.</i> | £2,730 | (20) |
| | Fatal coronary heart disease <i>Assumed that 50% of fatalities incurred cost.</i> | £713 | (61) |
| | Fatal non cardiac vascular event <i>Assumed that 50% of fatalities incurred cost.</i> | £4,443 | (60) |
| | Congestive heart failure | £3,091 | UKPDS (62) |
| Other complications of diabetes costs | | | |
| | Renal failure – weighted composite of... | £25,046 | |
| | <i>Haemodialysis with overheads</i> | £42,049 | (63) |
| | <i>Automated peritoneal dialysis</i> | £27,217 | (63) |
| | <i>Continuous ambulatory peritoneal dialysis</i> | £19,742 | (63) |
| | <i>Transplant (year 1)</i> | £23,660 | (64) |
| | <i>Immunosuppressant (10 years)</i> | £6,959 | (64) |
| | Foot ulcers | £216 | (65) |
| | Amputation first year | £10,101 | UKPDS (66) |
| | Amputation subsequent years | £1,896 | UKPDS (66) |
| | Blindness first year | £1,434 | UKPDS (66) |
| | Blindness subsequent years | £479 | UKPDS (66) |
| | Breast cancer | £13,818 | (67) |
| | Colorectal cancer | £18,729 | (68) |
| | Osteoarthritis | £962 | (69) |
| | Depression - made up of... | £137 | (70) |
| | <i>Practice nurse at surgery</i> | £13.70 | |
| | <i>Practice nurse at home visit</i> | £0.54 | |
| | <i>Practice nurse telephone</i> | £0.99 | |
| | <i>Health visitor</i> | £1.94 | |
| | <i>District nurse</i> | £0.38 | |
| | <i>Other nurse</i> | £1.17 | |
| | <i>HCA phlebotomist</i> | £1.05 | |

| | | | | |
|--|--|-------------------------------|-------|--|
| | | <i>Other primary care</i> | £4.85 | |
| | | <i>Out of hours</i> | £6.18 | |
| | | <i>NHS direct</i> | £2.28 | |
| | | <i>Walk-in centre</i> | £8.15 | |
| | | <i>Prescribed medications</i> | £74 | |
| | | <i>Secondary care</i> | £21 | |
| Assumed 20% smoking prevalence and 50% uptake of smoking cessation services SANG Stable angina; UANG unstable angina; MI myocardial infarction; TIA transient ischemic attack; CHD congestive heart failure; ACS acute Coronary Syndrome; UKPDS United Kingdom prospective Diabetes Study. Assume | | | | |

Opportunistic screening

Recent guidelines for hypertension have recommended that hypertension be confirmed with ambulatory blood pressure monitoring (ABPM) (18). The cost of ABPM assessment is included in the cost of diagnosis (£53.40) (19), however, we assume that the test does not alter the initial diagnosis.

A cost of diabetes diagnosis is included in the model based on the cost of an HbA1c test.

The cost of screening for high cardiovascular risk was not included as a cost associated with initiation with statins because most GP practices in the UK routinely commission and use cardiovascular risk scores that are easy to access within a normal consultation.

Diabetes

A three stage diabetes treatment regimen is applied in the model as a trade-off between model simplicity and capturing key cost differences between the interventions. At diagnosis all patients are prescribed low cost treatments, represented by Metformin (weighted average of standard and modified release) to describe the average cost of these medications. If HbA1c increases above 7.4% the individual is prescribed the more expensive Gliptins in addition to Metformin, based on a recent HTA (71). For costing purposes the second drug to be added to Metformin was assumed to be Sitagliptin. The individual continues to receive Metformin plus Gliptins for a period of time until they require insulin. Within the model the individual is switched to insulin in the first annual cycle at which HbA1c exceeds 8.5% (71). The insulin Glargine was chosen to represent insulin treatment in the UK. The cost of diabetes in the year of diagnosis is assumed to be greater than subsequent years because the individual will receive more contact time whilst their diabetes is being controlled.

Other Primary Care Costs

Individuals who are prescribed statins receive a daily dose of 40mg of generic Simvastatin. The individual remains on statins for the rest of their life. A unit cost of anti-hypertensives was obtained from a 2004 study (59) and inflated to 2014/15 prices. Due to the number of different anti-hypertensive treatments available and possibilities for combination therapies, using the cost from this study of prescriptions was preferred to using costs directly from the BNF. The stakeholder group

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3 advised that attendance at visits to monitor cardiovascular risk on statins and anti-hypertensives are
4 not perfect. Therefore, the costs of GP attendance to monitor blood pressure and cardiovascular risk
5 are assumed to be accounted for within the model for GP attendance.
6
7

8 9 **Cardiovascular costs**

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11 Costs for cardiovascular disease were obtained from a 2009 HTA for high dose lipid-lowering therapy
12 (20). Table 38 shows the details of included costs. The costs of fatal stroke and MI were obtained
13 from two separate studies (60;61), and it was assumed that 50% of individuals would incur these costs.
14 The costs of congestive heart failure were estimated from the UKPDS costing study for complications
15 related to diabetes (62).
16
17

18 19 **Microvascular costs**

20
21 The cost of renal failure was estimated from three studies reporting the costs of dialysis type (63), the
22 costs of transplantation (64) and the prevalence of dialysis and transplant (72). The overall cost was
23 estimated as a weighted average of the treatment outcomes.
24
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26
27 The cost of foot ulcers was estimated from a US Cost of Illness study (65). A search of the literature
28 did not identify any UK based studies. The costs were converted from dollars to pounds using
29 Purchasing Power Parities reported by the OECD (73).
30
31

32
33 The costs of amputation and blindness in the first year of surgery and in subsequent years were
34 reported in a recent UKPDS costing study (66).
35
36

37 38 **Costs of Other Comorbidities**

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40 Disease progression for breast cancer and colorectal cancer was not included in the model. Therefore,
41 a lifetime cost of cancer care was imposed at diagnosis in the model. Costs for breast and colon cancer
42 were taken from two screening appraisals (67;68). Breast cancer costs were estimated as a weighted
43 average depending on the prognosis at diagnosis, whereas colon cancer costs were estimated as a
44 weighted average depending on the Dukes tumour stage.
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47
48 The annual cost of osteoarthritis was estimated in a costing study (69). In this report the authors
49 estimated the expected cost of osteoarthritis from three previous costing studies. The costs include GP
50 attendance, nurse consultations, replacement surgery, help at home and prescription medications.
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54 A recent trial to prevent secondary depressive episodes collected comprehensive cost data from a
55 sample of individuals with depression (70). The resource uses identified in the control arm were
56 extracted to estimate the costs of depression. The costs from this data were not implemented directly
57 into the model; this would have over-estimated the number of GP visits as the model already accounts
58 for GP attendance due to depression. Therefore, a revised estimate of the cost of depression,
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3 excluding GP consultation was estimated using updated unit costs. Given that this cost captures the
4 costs of depression following the first acute episode we assumed that this cost adequately described
5 the ongoing healthcare costs for individuals with a history of depression. It is possible that this will
6 overestimate costs for patients who successfully remit and avoid future depression. However, there is
7 evidence from the literature to suggest that individuals with a history of depression have a high
8 utilisation of healthcare resources to support this assumption (74).
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13 **INTERVENTION**

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17 The subgroup analysis estimates the per person cost savings and health outcomes of delivering the
18 DPP lifestyle intervention in the 22 chosen subgroups. Interventions will be commissioned from a
19 handful of national providers and will include a mixture of dietary educational advice and physical
20 activity, with the aim of reducing both weight and diabetes risk.
21
22
23

24 The SPHR Diabetes Prevention Model does not explicitly model changes in diet or physical activity.
25 Instead interventions are assumed to impact directly upon individual risk factors such as BMI, blood
26 pressure, cholesterol and HbA1c. In the model these changes then impact upon incidence rates of type
27 2 diabetes and related diseases. This section of the technical appendix describes the assumptions
28 around the intervention that are used as default settings in the model.
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33 **Intervention Uptake**

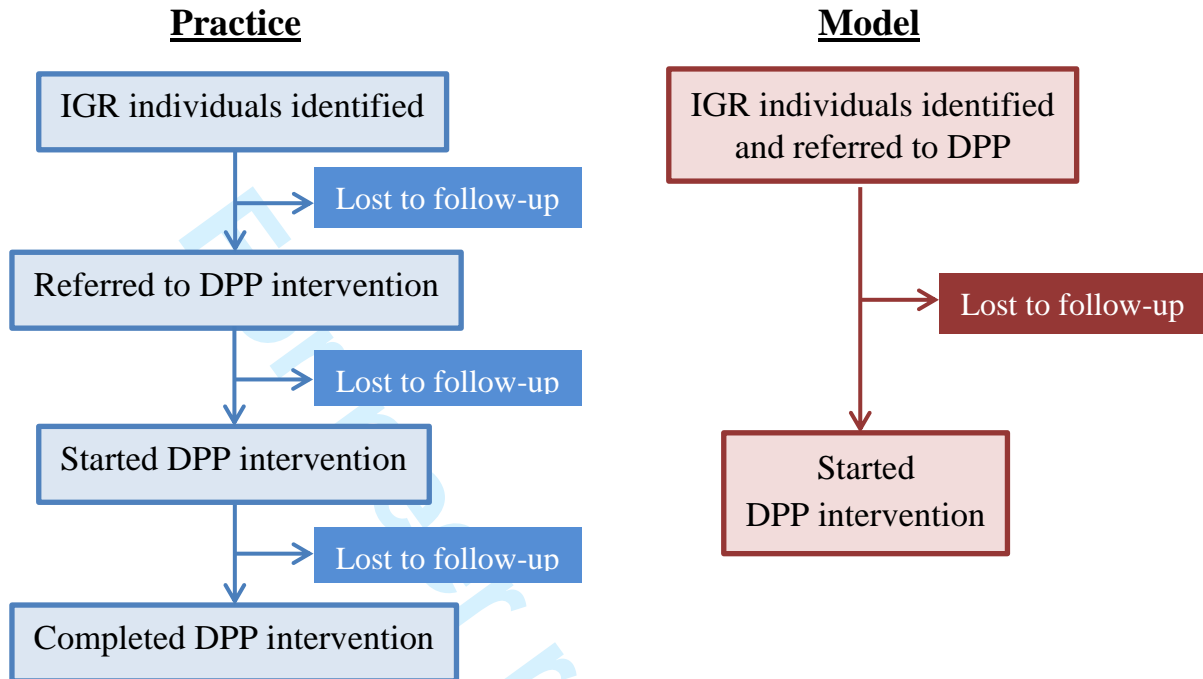
34
35 In practice, of the IGR individuals identified through HbA1c testing, only a proportion will receive
36 the intervention. Some individuals may not be referred for intervention. Of those referred, some will
37 choose not to take up the intervention, and of those that do attend the first intervention session, some
38 will not complete the intervention (Figure 2).
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43 Referral rates are not directly modelled, and instead it is assumed that all individuals are identified
44 and referred for intervention prior to the model start. This is partly because of lack of data around
45 referral rates and partly because referral rates are a function of the number of available intervention
46 places.
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50 Intervention uptake is defined as the proportion of those referred to the intervention who decide to
51 take up the intervention. The original aim of the analysis was to include data around differential
52 uptake of interventions in different population subgroups. However, good quality data could not be
53 identified and instead a uniform uptake rate of 32% has been used. It is assumed that those who
54 decided not to take up the intervention incur no costs and no benefits of intervention. No costs of
55 identifying or referring individuals to intervention are modelled. In practice, some individuals who
56 start the intervention will not complete it and therefore not gain full benefit. However, non-
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completion is partially accounted for in the estimate of effectiveness used in the model (74), so has not been explicitly built in. This is discussed further below.

Figure 2: Schematic showing intervention uptake and completion in practice and in the model



Intervention Effectiveness

The effectiveness data used in the model comes from a PHE evidence review of pragmatic lifestyle interventions for prevention of type 2 diabetes (75). This updates a previous review by Dunkley and others (76). Both reviews incorporate meta-analyses of a wide range of different lifestyle interventions aimed at reducing type-2 diabetes, and report a variety of outcomes including type-2 diabetes incidence rate and weight loss. The PHE evidence review also includes some analysis of differential effectiveness in population subgroups and for different intervention characteristics.

PHE, NHS England and Diabetes UK have specified that they wish the commissioned DPP intervention to fulfil 9-12 NICE guidelines as recommended in PH38 (3). NICE guidelines include using particular strategies that are associated with increased effectiveness, specifying the minimum amount of contact time and follow-up sessions, and delivering the programme through qualified practitioners. Both the PHE evidence review and the Dunkley meta-analysis indicate that interventions have increased effectiveness if they fulfil a greater number of NICE guidelines (75;76). In line with this, the model uses the results from the subgroup analysis of interventions fulfilling 9-12 NICE guidelines as the mean effectiveness (weight loss of 3.24kg – Table 12 in the PHE Evidence Review (75)).

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3 Unlike the Dunkley meta-analysis, the PHE evidence review does not report differences in HbA1c,
4 systolic blood pressure (SBP) or cholesterol for this subgroup of interventions. However, it is clear
5 from the Dunkley analysis that there will be concurrent reductions in these other metabolic factors,
6 and that the effectiveness of the intervention would be underestimated in the model if they were not
7 included. To incorporate these changes, the differences in HbA1c, SBP and cholesterol were
8 extrapolated from the Dunkley analysis to reflect the updated weight loss used from the PHE evidence
9 review. This assumes that relationships between changes in metabolic factors are linear. The
10 intervention effectiveness for each metabolic factor used in the model is reported in Table 39.
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17 **Table 39: Mean intervention effectiveness used in the model**

| | Mean values from Dunkley et al supplementary Table 7 (76) | Used in the DPP analysis: Default Mean weight loss from Table 12 of PHE evidence review for 9-12 NICE guidelines (75) | Used in the DPP analysis: Sensitivity analysis - 25% Lower |
|--------------------------------|---|---|--|
| Weight (kg) | -2.12 | -3.24 | -2.43 |
| BMI (kg/m ²) | -0.96 | -1.47 | -1.10 |
| HbA1c (%) | -0.13 | -0.20 | -0.15 |
| Systolic Blood Pressure (mmHg) | -4.3 | -6.57 | -4.93 |
| Total Cholesterol (mmol/l) | -0.18 | -0.28 | -0.21 |

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35 There is good evidence from the PHE evidence review and other studies that intervention
36 effectiveness is unlikely to be uniform across the population, and in particular varies according to the
37 baseline BMI of individuals, those with higher baseline BMI reporting increased weight loss and
38 diabetes risk reduction than those with lower baseline BMI (75;77-79). A differential intervention
39 effect by baseline BMI was therefore implemented in the model. Again this was taken from the PHE
40 evidence review as shown in Table 40 (75).
41
42
43
44

45 **Table 40: Weight change results per unit baseline BMI from the PHE Evidence Review (75)**

| Subgroup | Weight change | Unit | Study Median |
|----------|--------------------------|-------------------------------------|------------------------|
| BMI | -0.23 kg (-0.53 to 0.07) | Per unit increase in mean study BMI | 31.5 kg/m ² |

46
47
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52 Personalised intervention effects for each individual, dependent upon their baseline BMI were
53 calculated using the following equation:
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$$\text{Personalised Intervention Effect} = \text{Mean Intervention Effect} + \text{BMI Effect} * (\text{Individual BMI} - \text{Median BMI})$$

| | |
|--------|--|
| Where: | Mean Intervention Effect = -3.24 kg |
| | BMI Effect = -0.23 kg |
| | Individual BMI = the baseline BMI of each individual in the population |
| | Median BMI = 31.5 kg/m ² (the median of the mean BMI from each study included in the PHE meta-analysis) |

For example, for an individual with baseline BMI of 30, the personalised intervention effect would correspond to a weight loss of 2.895kg (smaller than the mean intervention effect), whereas for an individual with baseline BMI of 35, the personalised intervention effect would correspond to a weight loss of 4.045kg (larger than the mean intervention effect). Note that in individuals with BMI < 17.5, the effect of the intervention would be to actually increase weight. However, there are very few such IGR individuals in the model and an intervention focussing on weight loss may not in any case be the best option for individuals who are already underweight.

From this personalised change in weight due to the intervention, individualised changes in BMI, HbA1c, SBP and cholesterol were derived. Individuals in the intervention arm of the model who take up the intervention were assumed to receive this reduction in their metabolic factors instantaneously at the start of the model.

In practice, some individuals who start the intervention will not complete it. The PHE evidence review contains a mixture of studies that have used either intention to treat or complete case analysis (75). Intention to treat analysis takes non-completion into account, whereas complete case analysis does not. However, it is unclear which studies have been used to derive the estimate of effectiveness for 9-12 NICE guidelines. It is likely therefore that the effectiveness estimate used in the model only partially accounts for non-completion and therefore may be higher than is realistic in practice.

The Whitehall II BMI trajectory model estimates an indirect relationship between BMI change and changes in metabolic risk factors. The changes to HbA1c, systolic blood pressure and cholesterol were adjusted to avoid double counting of the indirect effects through BMI and direct effects of the intervention.

Intervention Costs

The actual intervention cost of the DPP will be determined through the DPP procurement process in early 2016. As this was still undergoing at the time of this analysis, PHE suggested that the mid average cost from their impact assessment of £270 per participant should be used as the default cost. This incorporates expected retention rates of participants, but does not include any local costs of identifying or referring individuals for intervention.

Duration of Intervention Effect

There is very little published information about how long the effectiveness of intensive lifestyle interventions is likely to endure in participants before weight is regained. In the model, default intervention effectiveness is assumed to decline linearly from its peak at the start of the model until individuals reach the BMI/SBP/HbA1c/cholesterol level that they would have been without intervention. It has been assumed for the analysis that this process takes five years.

MODEL PARAMETERS

All parameters used in the model, their distributions for PSA and their sources are documented here.

GP Attendance in the General Population

GP attendance is estimated from statistical analysis of the Yorkshire Health Study (11). In the PSA, the parameters are sampled from a multivariate normal distribution, using the mean estimates described in Table 41 and covariance matrix in Table 42.

Table 41: GP attendance reported in the Yorkshire Health Study (N= 18,437) ⁽¹¹⁾

| | Mean | Standard error | Uncertainty Distribution |
|-----------------------|---------|----------------|--------------------------|
| Age | 0.0076 | 0.0005 | MULTIVARIATE NORMAL |
| Male | -0.1495 | 0.0159 | MULTIVARIATE NORMAL |
| BMI | 0.0110 | 0.0015 | MULTIVARIATE NORMAL |
| Ethnicity (Non-white) | 0.2620 | 0.0375 | MULTIVARIATE NORMAL |
| Heart Disease | 0.2533 | 0.0289 | MULTIVARIATE NORMAL |
| Depression | 0.6127 | 0.0224 | MULTIVARIATE NORMAL |
| Osteoarthritis | 0.2641 | 0.0238 | MULTIVARIATE NORMAL |
| Diabetes | 0.2702 | 0.0278 | MULTIVARIATE NORMAL |
| Stroke | 0.1659 | 0.0474 | MULTIVARIATE NORMAL |
| Cancer | 0.2672 | 0.0414 | MULTIVARIATE NORMAL |
| Intercept | -0.5014 | 0.0468 | MULTIVARIATE NORMAL |
| Alpha | 0.3423 | 0.0108 | MULTIVARIATE NORMAL |

Table 42: Variance-covariance matrix for GP attendance regression

| | Age | Male | BMI | Ethnicity (Non-white) | Heart Disease | Depression | Osteoarthritis | Diabetes | Stroke | Cancer | Intercept | Alpha |
|-----------------------|--------|--------|--------|-----------------------|---------------|------------|----------------|----------|---------|--------|-----------|-------|
| Age | 0.0000 | | | | | | | | | | | |
| Male | 0.0000 | 0.0003 | | | | | | | | | | |
| BMI | 0.0000 | 0.0000 | 0.0000 | | | | | | | | | |
| Ethnicity (Non-white) | 0.0000 | 0.0000 | 0.0000 | 0.0014 | | | | | | | | |
| Heart Disease | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0008 | | | | | | | |
| Depression | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0005 | | | | | | |
| Osteoarthritis | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0006 | | | | | |
| Diabetes | 0.0000 | 0.0000 | 0.0000 | 0.0000 | -0.0001 | 0.0000 | 0.0000 | 0.0008 | | | | |
| Stroke | 0.0000 | 0.0000 | 0.0000 | 0.0000 | -0.0002 | -0.0001 | 0.0000 | -0.0001 | 0.0022 | | | |
| Cancer | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | -0.0001 | 0.0017 | | |

| | | | | | | | | | | | | |
|-----------|--------|--------|---------|---------|--------|--------|--------|--------|--------|--------|--------|--------|
| Intercept | 0.0000 | 0.0000 | -0.0001 | -0.0002 | 0.0002 | 0.0000 | 0.0002 | 0.0003 | 0.0000 | 0.0001 | 0.0022 | |
| Alpha | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0010 |

Whitehall II Statistical Model of Metabolic Trajectories

The metabolic trajectories used in the model are derived from statistical analysis of the longitudinal Whitehall II cohort (13). The parameters derived from this model are described in the following tables.

Table 43: Coefficient estimates for metabolic risk factor parallel growth models

| | Parameter Description | Estimated Mean | Standard error | p-value |
|-----------------------------|---|----------------|----------------|---------|
| BMI Intercept | | | | |
| α_{10} | Population mean BMI intercept | 2.2521 | 0.045 | <0.001 |
| γ_{10} | Age at baseline coefficient for BMI intercept | 0.0056 | 0.001 | <0.001 |
| | Sex coefficient for BMI intercept | -0.0311 | 0.012 | 0.009 |
| | Family history of CVD coefficient for BMI intercept | -0.0079 | 0.012 | 0.515 |
| ν_{10} | Random error term for BMI intercept | 0.1165 | 0.003 | <0.001 |
| BMI linear slope | | | | |
| α_{11} | Population mean BMI linear slope | 0.6409 | 0.042 | <0.001 |
| γ_{11} | Age at baseline coefficient for BMI linear slope | -0.0084 | 0.001 | <0.001 |
| | Sex coefficient for BMI linear slope | -0.0285 | 0.011 | 0.009 |
| | Family history of CVD coefficient for BMI linear slope | -0.0155 | 0.010 | 0.117 |
| ν_{11} | Random error term for BMI linear slope | 0.0222 | <0.001 | <0.001 |
| BMI quadratic slope | | | | |
| α_{12} | Population mean BMI quadratic slope | -0.2007 | 0.023 | <0.001 |
| γ_{12} | Age at baseline coefficient for quadratic slope | 0.0026 | <0.001 | <0.001 |
| | Sex coefficient for quadratic slope | 0.0089 | 0.006 | 0.147 |
| | Family history of CVD coefficient for quadratic slope | 0.0104 | 0.006 | 0.061 |
| ϵ_1 | Random error term for BMI | 0.0104 | <0.001 | <0.001 |
| Glyc Intercept | | | | |
| α_{20} | Population mean glyc intercept | 0 | NA | NA |
| γ_{20} | Smoker coefficient for glyc intercept | -0.1388 | 0.029 | <0.001 |
| τ_{20} | Association between BMI intercept and glyc intercept | 0.2620 | 0.024 | <0.001 |
| ν_{20} | Random error term for glyc intercept | 0.0851 | 0.008 | <0.001 |
| Glyc linear slope | | | | |
| α_{21} | Population mean glyc linear slope | -0.4255 | 0.071 | <0.001 |
| γ_{21} | Sex coefficient for glyc linear slope | 0.1486 | 0.045 | 0.001 |
| | Ethnicity coefficient for glyc linear slope | -0.0218 | 0.081 | 0.786 |
| | Family history of T2DM coefficient for glyc linear slope | -0.0512 | 0.054 | 0.345 |
| | Smoker coefficient for glyc linear slope | 0.1796 | 0.066 | 0.007 |
| τ_{21} | Association between BMI intercept and glyc linear slope | 0.0821 | 0.024 | 0.001 |
| τ_{22} | Association between BMI linear slope and glyc linear slope | 0.1984 | 0.073 | 0.007 |
| ν_{21} | Random error term for glyc linear slope | 0.0222 | 0.011 | 0.053 |
| Glyc quadratic slope | | | | |
| α_{22} | Population mean glyc quadratic slope | 0.1094 | 0.025 | <0.001 |
| γ_{22} | Sex coefficient for glyc quadratic slope | -0.0855 | 0.027 | 0.002 |
| | Ethnicity coefficient for glyc quadratic slope | 0.0899 | 0.049 | 0.067 |
| | Family history of T2DM coefficient for glyc quadratic slope | 0.0633 | 0.033 | 0.052 |
| | Smoker coefficient for glyc quadratic slope | -0.0390 | 0.040 | 0.330 |
| ν_{22} | Random error term for glyc quadratic slope | 0.0107 | 0.003 | 0.002 |
| ϵ_2 | Glyc measurement error | 0.0707 | 0.005 | <0.001 |
| SBP Intercept | | | | |
| α_{30} | Population mean SBP intercept | 0.6934 | 0.021 | <0.001 |
| γ_{30} | Age at baseline coefficient for SBP intercept | 0.0043 | <0.001 | <0.001 |

| | | | | |
|------------------|---|---------|--------|--------|
| | Sex coefficient for SBP intercept | 0.0380 | 0.004 | <0.001 |
| | Smoking coefficient for SBP intercept | -0.0243 | 0.006 | <0.001 |
| | Ethnicity coefficient for SBP intercept | 0.0078 | 0.007 | 0.300 |
| | Family history of CVD coefficient for SBP intercept | 0.0061 | 0.004 | 0.160 |
| τ_{31} | Association between BMI intercept and SBP intercept | 0.1080 | 0.006 | <0.001 |
| v_{30} | Random error term for SBP intercept | 0.0085 | 0.00 | <0.001 |
| SBP linear slope | | | | |
| α_{31} | Population mean SBP linear slope | -0.0227 | 0.021 | 0.278 |
| γ_{31} | Age at baseline coefficient for SBP linear slope | 0.0024 | <0.001 | <0.001 |
| | Sex coefficient for SBP linear slope | -0.0004 | 0.004 | 0.927 |
| | Smoking coefficient for SBP linear slope | 0.0205 | 0.005 | <0.001 |
| | Ethnicity coefficient for SBP linear slope | 0.0224 | 0.007 | 0.001 |
| | Family history of CVD coefficient for SBP linear slope | -0.0013 | 0.004 | 0.748 |
| τ_{31} | Association between BMI intercept and SBP linear slope | -0.0396 | 0.006 | <0.001 |
| | Association between BMI linear slope and SBP linear slope | 0.2325 | 0.019 | <0.001 |
| v_{31} | Random error term for SBP linear slope | 0.0024 | <0.001 | <0.001 |
| ϵ_3 | SBP measurement error variance | 0.0093 | <0.001 | <0.001 |
| TC Intercept | | | | |
| α_{40} | Population mean TC intercept | 2.9956 | 0.176 | <0.001 |
| γ_{40} | Age at baseline coefficient for TC intercept | 0.0456 | 0.003 | <0.001 |
| | Sex coefficient for TC intercept | 0.0660 | 0.036 | 0.070 |
| τ_{40} | Association between BMI intercept and TC intercept | 0.4459 | 0.049 | <0.001 |
| v_{40} | Random error term for TC intercept | 0.8960 | 0.025 | <0.001 |
| TC linear slope | | | | |
| α_{41} | Population mean TC linear slope | 2.1216 | 0.128 | <0.001 |
| γ_{41} | Age at baseline coefficient for TC linear slope | -0.0316 | 0.002 | <0.001 |
| | Sex coefficient for TC linear slope | -0.2677 | 0.026 | <0.001 |
| τ_{41} | Association between BMI intercept and TC linear slope | -0.4808 | 0.035 | <0.001 |
| τ_{42} | Association between BMI linear slope and TC linear slope | 0.9802 | 0.108 | <0.001 |
| v_{41} | Random error term for TC linear slope | 0.1583 | 0.011 | <0.001 |
| ϵ_4 | TC measurement error variance | 0.3426 | 0.006 | <0.001 |
| HDL Intercept | | | | |
| α_{50} | Population mean HDL intercept | 2.4124 | 0.054 | <0.001 |
| γ_{50} | Age at baseline coefficient for HDL intercept | 0.0032 | 0.011 | <0.001 |
| | Sex coefficient for HDL intercept | -0.3710 | 0.001 | <0.001 |
| τ_{51} | Association between BMI intercept and HDL intercept | -0.3514 | 0.015 | <0.001 |
| v_{50} | Random error term for HDL intercept | 0.0827 | -0.040 | <0.001 |
| HDL linear slope | | | | |
| α_{51} | Population mean HDL linear slope | 0.1241 | 0.034 | <0.001 |
| γ_{51} | Age at baseline coefficient for HDL linear slope | 0.0020 | 0.001 | <0.001 |
| | Sex coefficient for HDL linear slope | 0.0041 | 0.007 | 0.558 |
| τ_{51} | Association between BMI intercept and HDL linear slope | -0.0400 | 0.010 | <0.001 |
| v_{51} | Random error term for HDL linear slope | 0.0090 | 0.001 | <0.001 |
| ϵ_5 | HDL measurement error variance | 0.0333 | 0.001 | <0.001 |

Table 44: Coefficient estimates for latent glycaemic measurement model

| | Parameter Description | Estimated Mean | Standard error | p-value |
|---------------|-----------------------------------|----------------|----------------|---------|
| μ_0 | FPG intercept | 4.2903 | 0.089 | <0.001 |
| θ_{01} | Glycaemic factor to FPG | 1 | NA | NA |
| θ_{02} | Age to FPG | 0.0031 | 0.001 | 0.022 |
| θ_{03} | Sex to FPG | 0.2129 | 0.021 | <0.001 |
| θ_{04} | Ethnicity to FPG | 0.0100 | 0.037 | 0.786 |
| θ_{05} | Family history of diabetes to FPG | 0.1168 | 0.025 | <0.001 |
| ϵ_0 | FPG measurement error variance | 0.1649 | 0.007 | <0.001 |
| μ_1 | 2-hr Glucose intercept | 0.5707 | 0.223 | 0.011 |
| θ_{11} | Glycaemic factor to 2-hr glucose | 2.4384 | 0.078 | <0.001 |
| θ_{12} | Age to 2-hr glucose | 0.0716 | 0.003 | <0.001 |

| | | | | |
|-----------------|--|---------|-------|--------|
| θ_{13} | Sex to 2-hr glucose | -0.1411 | 0.058 | 0.014 |
| θ_{14} | Ethnicity to 2-hr glucose | 0.3047 | 0.100 | 0.002 |
| θ_{15} | Family history of diabetes to 2-hr glucose | 0.3496 | 0.068 | <0.001 |
| ε_1 | 2-hr measurement error variance | 2.3679 | 0.054 | <0.001 |
| μ_2 | HbA1c intercept | 4.4769 | 0.073 | <0.001 |
| θ_{21} | Glycaemic factor to HBA1c | 0.5074 | 0.016 | <0.001 |
| θ_{22} | Age to HBA1c | 0.0101 | 0.001 | <0.001 |
| θ_{23} | Sex to HBA1c | -0.0457 | 0.001 | <0.001 |
| θ_{24} | Ethnicity to HBA1c | 0.1854 | 0.030 | <0.001 |
| θ_{25} | Family history of diabetes to HBA1c | 0.0563 | 0.020 | 0.004 |
| ε_2 | HbA1c measurement error variance | 0.1166 | 0.003 | <0.001 |

Table 45: Covariance matrix Ω for individual random error

| | | | | | | | | | | | |
|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| | u_{10} | u_{11} | u_{20} | u_{21} | u_{22} | u_{30} | u_{31} | u_{40} | u_{41} | u_{50} | u_{51} |
| u_{10} | 0.1165 | | | | | | | | | | |
| u_{11} | 0.0095 | 0.0131 | | | | | | | | | |
| u_{20} | <0.0010 | <0.0010 | 0.0851 | | | | | | | | |
| u_{21} | <0.0010 | <0.0010 | 0.0222 | 0.0209 | | | | | | | |
| u_{22} | <0.0010 | <0.0010 | <0.0010 | <0.0010 | 0.0107 | | | | | | |
| u_{30} | <0.0010 | <0.0010 | 0.0080 | <0.0010 | <0.0010 | 0.0085 | | | | | |
| u_{31} | <0.0010 | <0.0010 | <0.0010 | 0.0018 | <0.0010 | <0.0017 | 0.0024 | | | | |
| u_{40} | <0.0010 | <0.0010 | 0.0324 | <0.0010 | <0.0010 | 0.0031 | <0.0010 | 0.8960 | | | |
| u_{41} | <0.0010 | <0.0010 | <0.0010 | <0.0012 | <0.0010 | <0.0010 | 0.0066 | -0.2229 | 0.1583 | | |
| u_{50} | <0.0010 | <0.0010 | -0.0118 | <0.0010 | <0.0010 | 0.0010 | <0.0010 | 0.0273 | <0.0010 | 0.0827 | |
| u_{51} | <0.0010 | <0.0010 | <0.0010 | -0.0059 | <0.0010 | <0.0010 | 0.0020 | <0.0010 | 0.0159 | 0.0061 | 0.0090 |

HbA1c trajectory in individuals diagnosed with type 2 diabetes

The input parameters for the initial reduction in HbA1c and long term trend in HbA1c following diagnosis, derived from analysis of the UKPDS outcomes model (15), are reported in Table 46 and Table 47 respectively.

Table 46: Estimated change in HbA1c in first year following diabetes diagnosis

| | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|---------------------------|--------------|-------------|-------------|------------------|
| Change in HbA1c Intercept | NORMAL | -2.9465 | 0.0444513 | -2.9465 |
| HbA1c at baseline | NORMAL | 0.5184 | 0.4521958 | 0.5184 |

Table 47: Estimated change in HbA1c following diabetes diagnosis over long term

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|---|--------------|-------------|-------------|------------------|
| Longitudinal HbA1c for diabetes intercept | NORMAL | -0.024 | 0.017 | -0.024 |
| Longitudinal HbA1c for diabetes log(time since diagnosis) | NORMAL | 0.144 | 0.009 | 0.144 |
| Longitudinal HbA1c for diabetes Second year | NORMAL | -0.333 | 0.05 | -0.333 |
| Longitudinal HbA1c for diabetes lag HbA1c | NORMAL | 0.759 | 0.004 | 0.759 |
| Longitudinal HbA1c for diabetes HbA1c at diagnosis | NORMAL | 0.085 | 0.004 | 0.0896 |

Systolic blood pressure and cholesterol trajectory following treatment

The changes in systolic blood pressure and total cholesterol following treatment with anti-hypertensives or statins, and statin uptake are reported in Table 48.

Table 48: Treatment effects following treatment

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|------------------------------------|--------------|-------------|-------------|------------------|--------|
| Simvastatin treatment effects | NORMAL | -1.45 | 0.11 | -1.45 | (20) |
| Anti-hypertensive treatment effect | NORMAL | -8.4 | 0.638 | -8.4 | (22) |
| Statin Uptake | UNIFORM | 0.65 | (0.4-0.9) | 0.65 | (21) |

Metabolic Risk Factor screening

The distribution for the HbA1c threshold at which opportunistic screening for type 2 Diabetes is initiated even if the individual does not have a history of cardiovascular disease, microvascular disease or identified impaired glucose regulation is reported in Table 49.

Table 49: Threshold for HbA1c opportunistic diagnosis

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|-----------------------|--------------|-------------|-------------|------------------|--------|
| HbA1c at diagnosis | NORMAL | 8.1 | 0.073 | 8.1 | (16) |

COMORBID OUTCOMES AND MORTALITY

Cardiovascular Disease

Cardiovascular risk is estimated using the QRISK2 model (25). Parameter distributions for men and women are reported in Table 50.

Table 50: Input parameters of the QRISK2 risk model

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|--------------------------|--------------|-------------|-------------|------------------|
| QRISK female ethnicity 2 | NORMAL | 0.2163 | 0.0537 | 0.2163 |
| QRISK female ethnicity 3 | NORMAL | 0.6905 | 0.069 | 0.6905 |
| QRISK female ethnicity 4 | NORMAL | 0.3423 | 0.1073 | 0.3423 |
| QRISK female ethnicity 5 | NORMAL | 0.0731 | 0.1071 | 0.0731 |
| QRISK female ethnicity 6 | NORMAL | -0.0989 | 0.0619 | -0.0989 |
| QRISK female ethnicity 7 | NORMAL | -0.2352 | 0.1275 | -0.2352 |
| QRISK female ethnicity 8 | NORMAL | -0.2956 | 0.1721 | -0.2956 |
| QRISK female ethnicity 9 | NORMAL | -0.1010 | 0.0793 | -0.1010 |
| QRISK female smoke 2 | NORMAL | 0.2033 | 0.0152 | 0.2033 |
| QRISK female smoke 3 | NORMAL | 0.48200 | 0.0220 | 0.4820 |
| QRISK female smoke 4 | NORMAL | 0.6126 | 0.0178 | 0.6126 |
| QRISK female smoke 5 | NORMAL | 0.7481 | 0.0194 | 0.7481 |
| QRISK female age 1 | NORMAL | 5.0373 | 1.0065 | 5.0327 |
| QRISK female age 2 | NORMAL | -0.0108 | 0.0022 | -0.0108 |
| QRISK female bmi | NORMAL | 0.4724 | 0.0423 | 0.4724 |
| QRISK female cholesterol | NORMAL | 0.6375 | 0.0143 | 0.6375 |

| | | | | | |
|----|--|----------|-----------|----------|-----------|
| 1 | QRISK female sbp | NORMAL | 0.0106 | 0.0045 | 0.0106 |
| 2 | QRISK female townsend | NORMAL | 0.060 | 0.0068 | 0.060 |
| 3 | QRISK female fibrillation | NORMAL | 1.3261 | 0.0310 | 1.3261 |
| 4 | QRISK female RA | NORMAL | 0.3626 | 0.0319 | 0.3626 |
| 5 | QRISK female Renal | NORMAL | 0.7636 | 0.0639 | 0.7636 |
| 6 | QRISK female Hypertension | NORMAL | 0.5421 | 0.0115 | 0.5421 |
| 7 | QRISK female diabetes | NORMAL | 0.8940 | 0.0199 | 0.8940 |
| 8 | QRISK female family history cvd | NORMAL | 0.5997 | 0.0122 | 0.5997 |
| 9 | QRISK female age 1 * smoke 1 | NORMAL | 0.1774 | 0.0355 | 0.1774 |
| 10 | QRISK female age 1 * smoke 2 | NORMAL | -0.3277 | 0.0655 | -0.3277 |
| 11 | QRISK age1 * smoke 3 | NORMAL | -1.1533 | 0.2307 | -1.1533 |
| 12 | QRISK female age 1 * smoke 4 | NORMAL | -1.5397 | 0.3079 | -1.5397 |
| 13 | QRISK female age 1 * atrial fibrillation | NORMAL | -4.6084 | 0.922 | -4.6084 |
| 14 | QRISK female age 1 * renal | NORMAL | -2.6401 | 0.5280 | -2.6401 |
| 15 | QRISK female age 1 * hypertension | NORMAL | -2.2480 | 0.4496 | -2.2480 |
| 16 | QRISK female age 1 * diabetes | NORMAL | -1.8452 | 0.3690 | -1.8452 |
| 17 | QRISK female age 1 * bmi | NORMAL | -3.0851 | 0.6170 | -3.0851 |
| 18 | QRISK female age 1 * family history cvd | NORMAL | -0.2481 | 0.0496 | -0.2481 |
| 19 | QRISK female age 1 * sbp | NORMAL | -0.0132 | 0.0026 | -0.0132 |
| 20 | QRISK female age 1 * town | NORMAL | -0.0369 | 0.0074 | -0.0369 |
| 21 | QRISK female age 2 * smoke 1 | NORMAL | -0.0053 | 0.0001 | -0.0053 |
| 22 | QRISK female age 2 * smoke 2 | NORMAL | -0.0005 | 0.0001 | -0.0005 |
| 23 | QRISK female age 2 * smoke 3 | NORMAL | -0.0105 | 0.0021 | -0.0105 |
| 24 | QRISK female age 2 * smoke 4 | NORMAL | -0.0155 | 0.0031 | -0.0155 |
| 25 | QRISK female age 2 * fibrillation | NORMAL | -0.0507 | 0.0101 | -0.0507 |
| 26 | QRISK female age 2 * renal | NORMAL | 0.0343 | 0.0069 | 0.0343 |
| 27 | QRISK female age 2 * hypertension | NORMAL | 0.0258 | 0.0051 | 0.0258 |
| 28 | QRISK female age 2 * diabetes | NORMAL | 0.0180 | 0.0036 | 0.0180 |
| 29 | QRISK female age 2 * bmi | NORMAL | 0.0345 | 0.0069 | 0.0345 |
| 30 | QRISK female age 2 * family history cardiovascular | NORMAL | -0.0062 | 0.0012 | -0.0062 |
| 31 | QRISK female age 2 * sbp | NORMAL | -0.000029 | 0.000006 | -0.000029 |
| 32 | QRISK female age 2 * townsend | NORMAL | -0.0011 | 0.0002 | -0.0011 |
| 33 | QRISK female 1 year survival | CONSTANT | 0.9983 | NA | NA |
| 34 | QRISK male ethnicity 2 | NORMAL | 0.3163 | 0.0425 | 0.3163 |
| 35 | QRISK male ethnicity 3 | NORMAL | 0.6092 | 0.0547 | 0.6092 |
| 36 | QRISK male ethnicity 4 | NORMAL | 0.5958 | 0.0727 | 0.5958 |
| 37 | QRISK male ethnicity 5 | NORMAL | 0.1142 | 0.0845 | 0.1142 |
| 38 | QRISK male ethnicity 6 | NORMAL | -0.3489 | 0.0641 | -0.3489 |
| 39 | QRISK male ethnicity 7 | NORMAL | -0.3604 | 0.1094 | -0.3604 |
| 40 | QRISK male ethnicity 8 | NORMAL | -0.2666 | 0.1538 | -0.2666 |
| 41 | QRISK male ethnicity 9 | NORMAL | -0.1208 | 0.0734 | -0.1208 |
| 42 | QRISK male SMOKE 2 | NORMAL | 0.2033 | 0.0152 | 0.2033 |
| 43 | QRISK male SMOKE 3 | NORMAL | 0.4820 | 0.0220 | 0.4820 |
| 44 | QRISK male SMOKE 4 | NORMAL | 0.6126 | 0.0178 | 0.6126 |
| 45 | QRISK male SMOKE 5 | NORMAL | 0.7481 | 0.0194 | 0.7481 |
| 46 | QRISK male age 1 | NORMAL | 47.316 | 9.4630 | 47.316 |
| 47 | QRISK male age 2 | NORMAL | -101.236 | 20.247 | -101.236 |
| 48 | QRISK male bmi | NORMAL | 0.5425 | 0.0299 | 0.5425 |
| 49 | QRISK male cholesterol | NORMAL | 0.14425 | 0.0022 | 0.14425 |
| 50 | QRISK male sbp | NORMAL | 0.0081 | 0.0046 | 0.0081 |
| 51 | QRISK male townsend | NORMAL | 0.0365 | 0.0048 | 0.0365 |
| 52 | QRISK male fibrillation | NORMAL | 0.7547 | 0.1018 | 0.7547 |
| 53 | QRISK male RA | NORMAL | 0.3089 | 0.0445 | 0.3089 |
| 54 | QRISK male renal | NORMAL | 0.7441 | 0.0702 | 0.7441 |
| 55 | QRISK male hypertension | NORMAL | 0.6965 | 0.011 | 0.6965 |
| 56 | QRISK male age 1 smoke 1 | NORMAL | -3.8805 | 0.7761 | -3.8805 |
| 57 | QRISK male age 1 smoke 2 | NORMAL | -16.703 | 3.3406 | -16.703 |
| 58 | QRISK male age 1 smoke 3 | NORMAL | -15.3738 | 3.5291 | -15.3738 |
| 59 | QRISK male age 1 smoke 4 | NORMAL | -17.6453 | 3.5291 | -17.6453 |

| | | | | |
|-------------------------------|----------|----------|--------|----------|
| QRISK male age 1 fibrillation | NORMAL | -7.0146 | 1.4056 | -7.0282 |
| QRISK male age 1 renal | NORMAL | -17.015 | 3.4029 | -17.015 |
| QRISK male age 1 hypertension | NORMAL | 33.9625 | 6.7925 | 33.9625 |
| QRISK male age 1 diabetes | NORMAL | 12.7886 | 2.5577 | 12.7886 |
| QRISK male age 1 bmi | NORMAL | 3.2680 | 0.6536 | 3.2680 |
| QRISK male age 1 fxcd | NORMAL | -17.9219 | 3.5844 | -17.9219 |
| QRISK male age 1 sbp | NORMAL | -0.1511 | 0.030 | -0.1511 |
| QRISK male age 1 town | NORMAL | -2.5502 | 0.5100 | -2.5502 |
| QRISK male age 2 SMOKE 1 | NORMAL | 7.9709 | 1.5942 | 7.9709 |
| QRISK male age 2 SMOKE 2 | NORMAL | 23.6859 | 4.7372 | 23.6859 |
| QRISK male age 2 SMOKE 3 | NORMAL | 23.1371 | 4.6274 | 23.1371 |
| QRISK male age 2 SMOKE 4 | NORMAL | 26.8674 | 5.3735 | 26.8674 |
| QRISK male age 2 Fibrillation | NORMAL | 14.4518 | 2.8904 | 14.4518 |
| QRISK male age 2 renal | NORMAL | 28.2702 | 5.654 | 28.2702 |
| QRISK male age 2 hypertension | NORMAL | -18.8167 | 3.7633 | -18.8167 |
| QRISK male age 2 diabetes | NORMAL | 0.9630 | 0.1926 | 0.963 |
| QRISK male age 2 bmi | NORMAL | 10.5517 | 2.1103 | 10.5517 |
| QRISK male age 2 FXCD | NORMAL | 26.6047 | 5.3209 | 26.6047 |
| QRISK male age 2 sbp | NORMAL | 0.2911 | 0.0582 | 0.2911 |
| QRISK male age 2 town | NORMAL | 3.007 | 0.6014 | 3.007 |
| QRISK2 male 1 year survival | CONSTANT | 0.997 | NA | NA |

The QRISK2 model was modified to allow a linear relationship between HbA1c and the risk of cardiovascular disease for individuals with IGR and type 2 Diabetes (HbA1c>42 mmol/mol). The parameter distributions for these additional inputs are reported in Table 51.

Table 51: Additional parameters for linear relationship between HbA1c and cardiovascular disease

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|---|--------------|-------------|-------------|------------------|--------|
| Female RR of MI due to HbA1c in diabetics | LOGNORMAL | 0.078 | 0.030 | 1.08 | (25) |
| Male RR of MI due to HbA1c in diabetics | LOGNORMAL | 0.108 | 0.023 | 1.11 | (25) |
| RR of stroke due to HbA1c in diabetics | LOGNORMAL | 0.092 | 0.026 | 1.096 | (25) |
| Log(RR) of cvd due to IGR | NORMAL | 0.223 | 0.043 | 1.25 | (28) |

Congestive Heart Failure

The parameter distributions for congestive heart failure based on the Framingham Heart Study (29) are reported in Table 52.

Table 52: Input parameters for Congestive Heart Failure Risk model for men and women

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|--|--------------|-------------|-------------|------------------|
| Male Heart failure baseline hazard | NORMAL | -9.2087 | 0.9209 | -9.2087 |
| Male Heart failure Age | NORMAL | 0.0412 | 0.0278 | 0.0412 |
| Male Heart failure LVH | NORMAL | 0.9026 | 1.0359 | 0.9026 |
| Male Heart failure Heart rate | NORMAL | 0.0166 | 0.0174 | 0.0166 |
| Male Heart failure Systolic blood pressure | NORMAL | 0.00804 | 0.0117 | 0.00804 |
| Male Heart failure CHD | NORMAL | 1.6079 | 0.5336 | 1.6079 |
| Male Heart failure Valve disease | NORMAL | 0.9714 | 0.6557 | 0.9714 |
| Male Heart failure Diabetes | NORMAL | 0.2244 | 0.6682 | 0.2244 |
| Female Heart failure baseline hazard | NORMAL | -10.7988 | 1.0799 | -10.7988 |

| | | | | |
|---|--------|---------|--------|---------|
| Female Heart failure Age | NORMAL | 0.0503 | 0.0301 | 0.0503 |
| Female Heart failure LVH | NORMAL | 1.3402 | 0.8298 | 1.3402 |
| Female Heart failure Heart rate | NORMAL | 0.0105 | 0.0193 | 0.0105 |
| Female Heart failure Systolic blood pressure | NORMAL | 0.00337 | 0.0109 | 0.00337 |
| Female Heart failure CHD | NORMAL | 1.5549 | 0.5973 | 1.5549 |
| Female Heart failure Valve disease | NORMAL | 1.3929 | 0.6707 | 1.3929 |
| Female Heart failure Diabetes | NORMAL | 1.3857 | 0.7105 | 1.3857 |
| Female Heart failure BMI | NORMAL | 0.0578 | 0.0555 | 0.0578 |
| Female Heart failure Valve disease & Diabetes | NORMAL | -0.986 | 1.4370 | -0.986 |

Microvascular Complications

The parameter distributions for the risk models for foot ulcer, blindness, renal failure, first amputation and second amputation are reported in Table 53. Parameters for renal failure were based on the UKPDS Outcomes Model 1 (15), whereas parameters for other microvascular complications were based on the UKPDS Outcomes Model 2 (23).

Table 53: Input parameters for microvascular complications

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|--|--------------|-------------|-------------|------------------|
| Renal failure baseline hazard | NORMAL | -10.016 | 0.939 | -10.016 |
| Renal failure Weibull shape | NORMAL | 1.865 | 1.4352 | 1.865 |
| Renal failure systolic blood pressure | NORMAL | 0.404 | 0.106 | 0.404 |
| Renal failure blindness | NORMAL | 2.082 | 0.551 | 2.082 |
| Foot ulcer baseline hazard | NORMAL | -11.295 | 1.13 | -11.295 |
| Foot ulcer age at diagnosis | NORMAL | 0.043 | 0.014 | 0.043 |
| Foot ulcer female | NORMAL | -0.962 | 0.255 | -0.962 |
| Foot ulcer BMI | NORMAL | 0.053 | 0.019 | 0.053 |
| Foot ulcer HbA1c | NORMAL | 0.16 | 0.056 | 0.16 |
| Foot ulcer PVD | NORMAL | 0.968 | 0.258 | 0.968 |
| Amputation baseline hazard | NORMAL | -14.844 | 1.205 | -14.844 |
| Amputation age at diagnosis | NORMAL | 0.023 | 0.011 | 0.023 |
| Amputation female | NORMAL | -0.445 | 0.189 | -0.445 |
| Amputation atrial fibrillation | NORMAL | 1.088 | 0.398 | 1.088 |
| Amputation HbA1c | NORMAL | 0.248 | 0.042 | 0.248 |
| Amputation HDL | NORMAL | -0.059 | 0.032 | -0.059 |
| Amputation heart rate | NORMAL | 0.098 | 0.05 | 0.098 |
| Amputation MMALB | NORMAL | 0.602 | 0.18 | 0.602 |
| Amputation peripheral vascular disease | NORMAL | 1.01 | 0.189 | 1.01 |
| Amputation white blood count | NORMAL | 0.04 | 0.017 | 0.04 |
| Amputation Stroke | NORMAL | 1.299 | 0.245 | 1.299 |
| Amputation shape | NORMAL | 2.067 | 0.193 | 2.067 |
| Amputation with Ulcer lambda | NORMAL | -0.881 | 0.139 | -0.881 |
| Amputation with Ulcer age at diagnosis | NORMAL | -0.065 | 0.027 | -0.065 |
| Amputation with Ulcer PVD | NORMAL | 1.769 | 0.449 | 1.769 |
| Second Amputation baseline hazard | NORMAL | -3.455 | 0.565 | -3.455 |
| Second Amputation HbA1c | NORMAL | 0.127 | 0.06 | 0.127 |
| Blindness baseline hazard | NORMAL | -10.6774 | 0.759 | -10.6774 |
| Blindness age at diagnosis | NORMAL | 0.047 | 0.009 | 0.047 |
| Blindness HbA1c | NORMAL | 0.171 | 0.032 | 0.171 |
| Blindness heart rate | NORMAL | 0.08 | 0.039 | 0.08 |
| Blindness systolic blood pressure | NORMAL | 0.068 | 0.032 | 0.068 |
| Blindness white blood cells | NORMAL | 0.052 | 0.019 | 0.052 |

| | | | | |
|---------------|--------|-------|-------|-------|
| Blindness CHF | NORMAL | 0.841 | 0.287 | 0.841 |
| Blindness IHD | NORMAL | 0.61 | 0.208 | 0.61 |

Cancer

The parameter distributions for the incidence and hazard ratios for breast cancer and colorectal cancer are reported in Table 54.

Table 54: Input parameters for breast cancer and colorectal cancer risk models

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|--|--------------|-------------|-------------|------------------|-----------------|
| Colorectal cancer men | NORMAL | 0.0011 | 0.0001 | 0.0011 | ⁽³⁶⁾ |
| Colorectal cancer women | NORMAL | 0.0005 | 0.0000 | 0.0005 | ⁽³⁶⁾ |
| Breast cancer pre-menopause | NORMAL | 0.0010 | 0.0001 | 0.0010 | ⁽³⁴⁾ |
| Breast cancer post-menopause | NORMAL | 0.0028 | 0.0002 | 0.0028 | ⁽³⁴⁾ |
| Colorectal cancer BMI relative risk for men | LOGNORMAL | 0.1906 | 0.0111 | 1.21 | ⁽³⁵⁾ |
| Colorectal cancer BMI relative risk for women | LOGNORMAL | 0.0392 | 0.0151 | 1.04 | ⁽³⁵⁾ |
| Breast cancer BMI relative risk for pre-menopause | LOGNORMAL | -0.1165 | 0.0251 | 0.89 | ⁽³⁵⁾ |
| Breast cancer BMI relative risk for post-menopause | LOGNORMAL | 0.0862 | 0.0205 | 1.09 | ⁽³⁵⁾ |

The parameter distributions for breast and colorectal cancer mortality are reported in Table 55.

Table 55: Input parameters for breast cancer and colorectal cancer mortality (41)

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|-----------------------------------|--------------|-------------|-------------|------------------|
| Breast cancer 5 year survival | BETA | 439.69 | 2354.44 | 0.157 |
| Colorectal cancer 5 year survival | BETA | 1457.56 | 1806.35 | 0.447 |

Osteoarthritis

The parameter distributions for the incidence and hazard ratios for osteoarthritis are reported below.

Table 56: Input parameters for the osteoarthritis risk model (37)

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|-------------------------------|--------------|-------------|-------------|------------------|
| Osteoarthritis incidence | NORMAL | 0.0053 | 0.0000004 | 0.0053 |
| Osteoarthritis RR of diabetes | LOGNORMAL | 0.723 | 0.317 | 2.06 |
| Osteoarthritis RR of BMI | LOGNORMAL | 0.073 | 0.026 | 1.076 |

Depression

The parameter distributions for the incidence and hazard ratios for depression are reported below.

Table 57: Input parameters for the depression risk model

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|-------------------------|--------------|-------------|-------------|------------------|--------|
| Odds of depression | BETA | 336 | 8803 | 0.0397 | (39) |
| Odds ratio for diabetes | LOGNORMAL | 0.4187 | 0.1483 | 1.52 | (39) |
| Odds ratio for stroke | LOGNORMAL | 1.8406 | 0.5826 | 6.3 | (40) |

UTILITIES

The parameter distributions used to estimate health state utilities in the model are reported below.

Table 58: Utility input parameters

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|---|--------------|-------------|-------------|------------------|--------|
| Renal/ulcer baseline utility | NORMAL | 0.689 | 0.014 | 0.689 | (47) |
| Renal dialysis | NORMAL | -0.078 | 0.026 | -0.078 | (47) |
| Foot ulcer | NORMAL | -0.099 | 0.013 | -0.099 | (47) |
| Amputation/heart failure baseline utility | NORMAL | 0.807 | 0.005 | 0.807 | (23) |
| Heart failure | NORMAL | -0.101 | 0.032 | -0.101 | (23) |
| Amputation | NORMAL | -0.172 | 0.045 | -0.172 | (23) |
| Stable angina multiplicative factor decrement | NORMAL | 0.801 | 0.038 | 0.801 | (21) |
| Unstable angina multiplicative factor decrement | NORMAL | 0.77 | 0.038 | 0.77 | (21) |
| MI multiplicative factor decrement | NORMAL | 0.76 | 0.018 | 0.76 | (21) |
| Stroke multiplicative factor decrement | NORMAL | 0.629 | 0.04 | 0.629 | (21) |
| Cancer baseline utility | NORMAL | 0.8 | 0.0026 | 0.8 | (48) |
| Cancer decrement | NORMAL | -0.06 | 0.008 | -0.06 | (48) |
| Osteoarthritis utility | NORMAL | 0.69 | 0.069 | 0.69 | (49) |
| Depression baseline utility | NORMAL | 0.48 | 0.048 | 0.48 | (51) |
| Depression remitters | NORMAL | 0.31 | 0.031 | 0.31 | (51) |
| Depression responders | NORMAL | 0.20 | 0.020 | 0.20 | (51) |
| Depression non-responders | NORMAL | 0.070 | 0.007 | 0.070 | (51) |
| Depression drop-outs | NORMAL | 0.050 | 0.005 | 0.050 | (51) |
| Age utility decrement | NORMAL | -0.004 | 0.0001 | -0.004 | (21) |

UNIT HEALTH CARE COSTS

The parameter distributions used to estimate health state utilities in the model are reported below.

Table 59: Cost input parameters

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|---------------------------|--------------|-------------|-------------|------------------|--------|
| DPP Intervention | GAMMA | | | £270 | PHE |
| DIABETES COSTS | | | | | |
| Insulin (annual cost) | GAMMA | 3.367 | 408.6 | £1375.72 | (58) |
| Metformin (annual cost) | CONSTANT | NA | NA | £18.83 | (54) |
| Sitagliptin (annual cost) | CONSTANT | NA | NA | £433.77 | (54) |

| | | | | | |
|---------------------------------------|----------|----------|----------|-----------|------|
| Nurse appointment (Advanced) | GAMMA | 100 | 0.26 | £25.52 | (53) |
| Health care assistant appointment | GAMMA | 100 | 0.03 | £3.40 | (53) |
| Eye screening | GAMMA | 15.3664 | 1.58219 | £24.31 | (56) |
| HbA1c test | GAMMA | 100 | 0.03 | £3.00 | (55) |
| Lipids test | GAMMA | 100 | 0.01 | £1.00 | (55) |
| LfT test | GAMMA | 100 | 0.01 | £1.00 | (55) |
| B12 test | GAMMA | 100 | 0.01 | £1.00 | (55) |
| Urine test | GAMMA | 100 | 0.01 | £1.00 | (55) |
| Nicotine replacement therapy | GAMMA | 100 | 1.03 | £103.00 | (53) |
| CVD COSTS | | | | | |
| Unstable Angina hospital admission | GAMMA | 100 | 12.75591 | £1275.59 | (20) |
| Revascularisation in hospital | GAMMA | 100 | 60.36846 | £6036.85 | (20) |
| MI Hospital admission | GAMMA | 100 | 15.54896 | £1554.90 | (20) |
| First Outpatient appointment | GAMMA | 100 | 1.653571 | £165.36 | (20) |
| Subsequent outpatient appointments | GAMMA | 100 | 1.100574 | £110.06 | (20) |
| Fatal CHD | GAMMA | 100 | 7.125001 | £712.50 | (38) |
| Fatal Stroke | GAMMA | 100 | 44.42562 | £4442.56 | (60) |
| First year stroke | GAMMA | 100 | 97.15908 | £9715.91 | (60) |
| Subsequent year stroke | GAMMA | 100 | 27.29644 | £2729.64 | (20) |
| Glytrin Spray | CONSTANT | NA | NA | £12.61 | (20) |
| Isosorbide mononitrate | CONSTANT | NA | NA | £13.54 | (20) |
| Verapamil | CONSTANT | NA | NA | £50.57 | (20) |
| Atenolol | CONSTANT | NA | NA | £36.42 | (20) |
| Aspirin | CONSTANT | NA | NA | £8.01 | (20) |
| Ramipril | CONSTANT | NA | NA | £90.45 | (20) |
| ARB | CONSTANT | NA | NA | £253.28 | (20) |
| Clopidogrel | CONSTANT | NA | NA | £554.41 | (20) |
| Congestive Heart Failure | GAMMA | 67.20788 | 45.99274 | £3091.07 | (62) |
| MICROVASCULAR COSTS | | | | | |
| Blindness year 1 | GAMMA | 10.26317 | 139.7079 | £1433.85 | (66) |
| Blindness subsequent years | GAMMA | 11.31099 | 42.37999 | £479.36 | (66) |
| Amputation year 1 | GAMMA | 19.37193 | 521.4492 | £10101.48 | (66) |
| Amputation subsequent years | GAMMA | 4.597909 | 412.4212 | £1896.28 | (66) |
| Renal Haemodialysis | GAMMA | 100 | 420.49 | £42049.00 | (63) |
| Renal Automated Peritoneal dialysis | GAMMA | 100 | 272.1714 | £27217.14 | (63) |
| Renal Ambulatory peritoneal dialysis | GAMMA | 100 | 197.4225 | £19742.25 | (63) |
| Renal transplant | GAMMA | 100 | 236.5973 | £23659.73 | (64) |
| Immunosuppressants | GAMMA | 100 | 69.58745 | £6958.75 | (64) |
| Foot ulcer not infected | GAMMA | 100 | 1.677526 | £167.75 | (65) |
| Foot ulcer with cellulitis | GAMMA | 100 | 4.431003 | £443.10 | (65) |
| Foot ulcer with osteomyelitis | GAMMA | 100 | 8.215817 | £821.58 | (65) |
| OTHER DISEASE COSTS | | | | | |
| Breast Cancer | GAMMA | 100 | 138.1811 | £13818.11 | (67) |
| Colorectal cancer Dukes A | GAMMA | 100 | 100.9135 | £10091.35 | (68) |
| Colorectal cancer Dukes B | GAMMA | 100 | 173.1532 | £17315.32 | (68) |
| Colorectal cancer Dukes C | GAMMA | 100 | 265.5026 | £26550.26 | (68) |
| Colorectal cancer Dukes D | GAMMA | 100 | 166.2553 | £16625.53 | (68) |
| Osteoarthritis | GAMMA | 100 | 9.616886 | £961.69 | (69) |
| Depression – Practice nurse surgery | GAMMA | 100 | 0.090154 | £9.02 | (70) |
| Depression – Practice nurse home | GAMMA | 100 | 0.270463 | 27.05 | (70) |
| Depression – Practice nurse telephone | GAMMA | 100 | 0.090154 | 9.02 | (70) |
| Depression – Health visitor | GAMMA | 100 | 0.387834 | 38.78 | (70) |
| Depression – District nurse | GAMMA | 100 | 0.377628 | 37.76 | (70) |
| Depression – Other nurse | GAMMA | 100 | 0.090154 | 9.02 | (70) |
| Depression – HCA phlebotomist | GAMMA | 100 | 0.034021 | 3.40 | (70) |
| Depression – Other primary care | GAMMA | 100 | 0.255154 | 25.52 | (70) |
| Depression – Out of Hours | GAMMA | 100 | 0.268661 | 26.87 | (70) |
| Depression – NHS Direct | GAMMA | 100 | 0.25295 | 25.30 | (70) |
| Depression – Walk-in Centre | GAMMA | 100 | 0.388316 | 38.83 | (70) |
| Depression – Prescribed medicines | GAMMA | 100 | 0.096144 | 9.61 | (70) |

| | | | | | |
|-----------------------------|----------|-----|------|---------|------|
| Depression – Secondary Care | GAMMA | 100 | 0.81 | 81.00 | (70) |
| DIAGNOSIS AND OTHER COSTS | | | | | |
| GP appointment | GAMMA | 100 | 0.47 | £46.95 | (53) |
| Diabetes diagnosis | GAMMA | 100 | 0.12 | £14.81 | (55) |
| Hypertension diagnosis | GAMMA | 100 | 0.57 | £56.51 | (19) |
| Anti-hypertensives | GAMMA | 100 | 1.96 | £195.94 | (59) |
| Simvastatin | CONSTANT | NA | NA | £26.59 | (54) |

QUALITY ASSURANCE

Within ScHARR, research is conducted within a framework of standards and systems that ensure high quality science and governance. This includes ensuring staff receive appropriate training and operate within a culture of high quality research, building sufficient time into each project for quality assurance (including error checking and validation), internal and external review of models and ideally external peer review through publication in academic journals.

The SPHR Diabetes Prevention Model has undergone an extensive process of quality assurance and error checking, both during its development and during the adaptations required for this analysis. Face validity around the model structure and assumptions was provided during model development by means of regular input from a group of stakeholders, including clinicians, diabetes researchers, patients and public health commissioners, and during model adaptation by a group of stakeholders representing the seven DPP demonstrator sites.

A guide to checking, avoiding and identifying errors in health economic models has recently been developed within ScHARR (81). Where possible, the suggested black box verification tests were carried out as part of model development. A more complex set of internal validations were also carried out to ensure that the model was behaving as planned (e.g. that metabolic trajectories and risk equations work in the intended way). The model has also undergone a series of validations against external data (82), and the structure and model assumptions have undergone formal peer review for a publications associated with the model (12). Finally, in addition to ScHARR's own process of model quality assurance and error checking, the model code was externally reviewed and refactored as part of the PHE project adaptation by Dr Mat Hall, a software engineer from the Department of Computer Science at the University of Sheffield.

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The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been endorsed and co-published by the following journals:

- BJOG: An International Journal of Obstetrics and Gynaecology
- [BMC Medicine 2013; 11:80](#)
- [BMJ 2013;346:f1049](#)
- [Clinical Therapeutics 27 March 2013 \(Article in Press DOI: 10.1016/j.clinthera.2013.03.003\)](#)
- [Cost Effectiveness and Resource Allocation 2013 11:6.](#)
- [The European Journal of Health Economics 2013 Mar 26. \[Epub ahead of print\]](#)
- International Journal of Technology Assessment in Health Care
- [Journal of Medical Economics 2013 Mar 25. \[Epub ahead of print\]](#)
- [Pharmacoeconomics 2013 Mar 26. \[Epub ahead of print\]](#)
- [Value in Health 2013 March - April;16\(2\):e1-e5](#)

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

| Section/item | Item No | Recommendation | Reported on page No/ line No |
|---------------------------------|---------|---|--|
| Title and abstract | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared. | <u>Page 1 Line 1</u> |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | <u>Pages 5 & 6</u> |
| Introduction | | | |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions. | <u>Page 8 paragraph 1</u> <u>Page 8 Lines 22-26</u> |
| Methods | | | |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | <u>Page 9 Lines 10-14 & Page 11 Lines 18-26</u> |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | <u>Page 8 Lines 22-23</u> |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | <u>Page 9 Lines 23-24</u> |
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | <u>Pages 10-11</u> |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | <u>Page 12 Lines 2-4</u> |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and | <u>Page 12 Lines 6-7</u> |



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|----|-------------------------|-----|---|--------------------|
| 1 | | | outcomes and say why appropriate. | Page 12 Lines 6-7 |
| 2 | | | | |
| 3 | Choice of health | 10 | Describe what outcomes were used as the measure(s) of | |
| 4 | outcomes | | benefit in the evaluation and their relevance for the type of | |
| 5 | | | analysis performed. | Page 12 Lines 2-3 |
| 6 | | | | |
| 7 | Measurement of | 11a | <i>Single study-based estimates:</i> Describe fully the design | |
| 8 | effectiveness | | features of the single effectiveness study and why the single | |
| 9 | | | study was a sufficient source of clinical effectiveness data. | Page 10 Lines 9-13 |
| 10 | | | | |
| 11 | | 11b | <i>Synthesis-based estimates:</i> Describe fully the methods used for | |
| 12 | | | identification of included studies and synthesis of clinical | |
| 13 | | | effectiveness data. | N/A |
| 14 | Measurement and | 12 | If applicable, describe the population and methods used to | |
| 15 | valuation of preference | | elicit preferences for outcomes. | |
| 16 | based outcomes | | | N/A |
| 17 | | | | |
| 18 | Estimating resources | 13a | <i>Single study-based economic evaluation:</i> Describe approaches | |
| 19 | and costs | | used to estimate resource use associated with the alternative | |
| 20 | | | interventions. Describe primary or secondary research methods | |
| 21 | | | for valuing each resource item in terms of its unit cost. | |
| 22 | | | Describe any adjustments made to approximate to opportunity | |
| 23 | | | costs. | N/A |
| 24 | | | | |
| 25 | | | | |
| 26 | | 13b | <i>Model-based economic evaluation:</i> Describe approaches and | |
| 27 | | | data sources used to estimate resource use associated with | |
| 28 | | | model health states. Describe primary or secondary research | |
| 29 | | | methods for valuing each resource item in terms of its unit | Page 11 Lines 4-10 |
| 30 | | | cost. Describe any adjustments made to approximate to | & Supplementary |
| 31 | | | opportunity costs. | Appendix |
| 32 | | | | Pages 44-49 |
| 33 | | | | |
| 34 | Currency, price date, | 14 | Report the dates of the estimated resource quantities and unit | |
| 35 | and conversion | | costs. Describe methods for adjusting estimated unit costs to | |
| 36 | | | the year of reported costs if necessary. Describe methods for | Page 9 Line 23 |
| 37 | | | converting costs into a common currency base and the | & Supplementary |
| 38 | | | exchange rate. | Appendix |
| 39 | | | | Pages 44-49 |
| 40 | Choice of model | 15 | Describe and give reasons for the specific type of decision- | Page 9 Line 8 & |
| 41 | | | analytical model used. Providing a figure to show model | Figure S1 in |
| 42 | | | structure is strongly recommended. | Supplementary |
| 43 | | | | Appendix |
| 44 | Assumptions | 16 | Describe all structural or other assumptions underpinning the | Supplementary |
| 45 | | | decision-analytical model. | Appendix |
| 46 | | | | Pages 10-70 |
| 47 | Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This | |
| 48 | | | could include methods for dealing with skewed, missing, or | |
| 49 | | | censored data; extrapolation methods; methods for pooling | |
| 50 | | | data; approaches to validate or make adjustments (such as half | |
| 51 | | | cycle corrections) to a model; and methods for handling | Supplementary |
| 52 | | | population heterogeneity and uncertainty. | Appendix |
| 53 | | | | Pages 10-70 |
| 54 | | | | |
| 55 | Results | | | |
| 56 | Study parameters | 18 | Report the values, ranges, references, and, if used, probability | |
| 57 | | | distributions for all parameters. Report reasons or sources for | |
| 58 | | | distributions used to represent uncertainty where appropriate. | |
| 59 | | | Providing a table to show the input values is strongly | Supplementary |
| 60 | | | recommended. | Appendix |
| | | | | Pages 53-70 |

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|---|---|-----|---|--|
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 | Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | Page 13 Table 1 |
| 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 | Characterising uncertainty | 20a | <i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). | N/A |
| | | 20b | <i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | Pages 15-16 Figure 3 Tables S3 & S4 |
| 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 | Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | Pages 14-15 Figures 1,2,4,S3 & S4 Table S4 |
| 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 | Discussion Study findings, limitations, generalisability, and current knowledge | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | Pages 17-19 |
| 31 32 33 34 35 36 37 38 39 40 41 | Other Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | Page 3 Lines 5-9 |
| 36 37 38 39 40 41 | Conflicts of interest | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | Page 2 Lines 19-23 |

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The CHEERS Statement may be accessed by the publication links above.

The ISPOR CHEERS Task Force Report provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

The citation for the CHEERS Task Force Report is:

Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. *Value Health* 2013;16:231-50.



BMJ Open

Assessing the Potential Return on Investment of the Proposed UK NHS Diabetes Prevention Programme in Different Population Subgroups: An Economic Evaluation

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2016-014953.R2 |
| Article Type: | Research |
| Date Submitted by the Author: | 17-May-2017 |
| Complete List of Authors: | Thomas, Chloe; University of Sheffield, School of Health and Related Research Sadler, Susannah; University of Sheffield Breeze, Penny; University of Sheffield, Squires, Hazel; University of Sheffield, School of Health and Related Research Gillett, Michael; UNIVERSITY OF SHEFFIELD, SCHOOL OF HEALTH AND RELATED RESEARCH Brennan, Alan; University of Sheffield, School of Health and Related Research (SchARR) |
| Primary Subject Heading: | Health economics |
| Secondary Subject Heading: | Diabetes and endocrinology, Public health |
| Keywords: | PUBLIC HEALTH, DIABETES & ENDOCRINOLOGY, HEALTH ECONOMICS |
| | |

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3 1 Assessing the Potential Return on Investment of the Proposed UK NHS Diabetes Prevention
4 2 Programme in Different Population Subgroups: An Economic Evaluation
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11 Contributors

12 CT contributed to planning the project, carried out the model adaptation and wrote the manuscript.
13 She is guarantor. SS contributed to planning the project, adapting the model and writing the
14 manuscript. PB developed the model and revised the draft paper. HS contributed to the conceptual
15 development of the model adaptation and revised the draft paper. MG provided specialist knowledge
16 around model inputs and revised the draft paper. AB was principle investigator for the project and
17 contributed to the analysis and manuscript.

18 Competing Interests

19 All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf
20 and declare that the only support for the submitted work was from the funders mentioned below. The
21 authors have no financial relationships with any organisations that might have an interest in the
22 submitted work in the previous three years other than Public Health England and NHS England and
23 no other relationships or activities that could appear to have influenced the submitted work.

1 **Ethical Approval**

2 Ethical approval was not needed for this study because the model is based on publicly available data
3 and analysis of secondary data.

4 **Funding**

5 This abstract presents independent research commissioned and funded by Public Health England
6 (PHE) with support from NHS England, Diabetes UK and the Department of Health. Model
7 development was funded by the National Institute for Health Research (NIHR)'s School for Public
8 Health Research (SPHR). The views expressed are those of the authors and not necessarily those of
9 PHE, NHS England, Diabetes UK, the NIHR or the Department of Health.

10 **Role of the Sponser**

11 Public Health England commissioned the work with the following objective: 'To model the potential
12 cost-effectiveness of the NHS DPP for different sub-groups of the population (for example by gender,
13 BME groups, age profile, working age/retired, level of deprivation)'. PHE also specified the nature of
14 the intervention including its expected cost, uptake and its proposed adherence to NICE guidelines.
15 However, PHE did not have any influence over the findings of the analysis. The decision to submit
16 the article for publication was made entirely independently of the funders.

17 **Acknowledgements**

18 We would like to thank the PHE steering group and stakeholders from the DPP demonstrator sites for
19 advice about model parameters relating to the DPP intervention and useful outputs. Many thanks also
20 to Maxine Johnson, Kelly Mackenzie, Tom Sanders and Elizabeth Goyder for their involvement in
21 stakeholder workshops and advice about other aspects of the project. We are also extremely grateful
22 to Pete Dodd and Mat Hall for their excellent quality assurance work with the SPHR Diabetes
23 Prevention Model. Finally, this work could not have been carried out without the SPHR Diabetes
24 Prevention Model, which was funded by the National Institute for Health Research's School for
25 Public Health Research.

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3 **1 Transparency**
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6 2 The lead author (CT) affirms that the manuscript is an honest, accurate, and transparent account of the
7
8 3 study being reported; that no important aspects of the study have been omitted; and that any
9
10 4 discrepancies from the study as planned have been explained.
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13 **5 Patient Involvement**
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16 6 Patients were not involved in this study.
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19 **7 Data Sharing Agreement**
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22 8 Detailed results for each subgroup analysed in the model are available on request by email from the
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24 9 corresponding author.
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3 **1 ABSTRACT**

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6 **2 Objectives**

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To evaluate potential return on investment of the NHS Diabetes Prevention Programme (DPP) in England, and estimate which population subgroups are likely to benefit most in terms of cost-effectiveness, cost-savings and health benefits.

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Economic Analysis using the School for Public Health Research Diabetes Prevention Model

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Adults aged 16 or over with high risk of type 2 diabetes (HbA1c 6-6.4%). Population subgroups defined by age, sex, ethnicity, socioeconomic deprivation, baseline BMI, baseline HbA1c and working status.

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14 Interventions

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The proposed NHS DPP: An intensive lifestyle intervention focussing on dietary advice, physical activity and weight loss. Comparator: No diabetes prevention intervention.

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17 Main outcome measures

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Incremental costs, savings and return on investment, quality adjusted life years (QALYs), diabetes cases, cardiovascular cases and net monetary benefit from an NHS perspective.

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Intervention costs will be recouped through NHS savings within 12 years, with net NHS saving of £1.28 over 20 years for each £1 invested. Per 100,000 DPP interventions given, 3,552 QALYs are

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3 1 gained. The DPP is most cost-effective and cost-saving in obese individuals, those with baseline
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5 2 HbA1c 6.2-6.4% and those aged 40-74. QALY gains are lower in minority ethnic and low
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7 3 socioeconomic status subgroups. Probabilistic sensitivity analysis suggests that there is 97%
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9 4 probability that the DPP will be cost-effective within 20 years. NHS savings are highly sensitive to
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11 5 intervention cost, effectiveness and duration of effect.
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13 14 **Conclusions**

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17 7 The DPP is likely to be cost-effective and cost-saving under current assumptions. Prioritising obese
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19 8 individuals could create the most value for money and obtain the greatest health benefits per
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21 9 individual targeted. Low socioeconomic status or ethnic minority groups may gain fewer QALYs per
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23 10 intervention, so targeting strategies should ensure the DPP does not contribute to widening health
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25 11 inequalities. Further evidence is needed around the differential responsiveness of population
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27 12 subgroups to the DPP.
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3 **1 ARTICLE SUMMARY**
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6 **2 Strengths and Limitations of this Study:**
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- Strength: The study uses the SPHR Diabetes Prevention Model, which synthesises a broad range of evidence from published data about type 2 diabetes risk factors and the complex disease progression pathways that lead from a diabetes diagnosis.
 - Strength: The individual patient level model structure allows the heterogeneity present within the population to be modelled, enabling detailed subgroup analysis.
 - Limitation: The NHS DPP has recently begun national implementation and direct data collection on its effectiveness in practice in England has not yet been obtained, therefore the analysis assumes that effectiveness will be similar to that obtained in pragmatic trials of intensive lifestyle interventions aimed at preventing type 2 diabetes, whilst also undertaking sensitivity analysis around this assumption.
 - Limitation: The analysis uses a comparator of “no NHS DPP intervention”, which does not fully represent the current situation where some localities do have programmes for high risk individuals. These were not modelled due to limited evidence and heterogeneity of intervention implementation between localities.
 - Limitation: Data about the long-term effectiveness of lifestyle interventions and the differential response of population subgroups to such interventions is limited. Further research is required to inform these parameters.

1 INTRODUCTION

2 Type-2 diabetes is a major public health priority in the UK. Currently there are over 2.9 million
3 people with diabetes in England ¹, and estimated to be a further 5 million at high risk of developing
4 the disease ². Diabetes is estimated to directly cost the NHS in England about £5.6 billion per year ³,
5 of which most contributes to treating complications of the disease such as amputation, blindness,
6 kidney failure and cardiovascular disease (CVD). To help tackle this problem, Public Health England
7 (PHE), NHS England and Diabetes UK are together implementing the NHS Diabetes Prevention
8 Programme (DPP) ⁴. The NHS DPP consists of intensive lifestyle management programmes aimed at
9 those at high risk of diabetes due to impaired glucose regulation (IGR), defined as HbA1c 6-6.4%
10 (42-47 mmol/mol) or fasting plasma glucose of 5.5-6.9 mmol/l. It is expected that IGR individuals
11 will be identified through a mixture of NHS Health Checks and opportunistic or targeted screening
12 processes, and that 100,000 individuals will be referred to the DPP each year once the programme is
13 running.

14 Previous economic evaluations indicate that lifestyle interventions such as that planned for the NHS
15 DPP can be cost-effective ⁵⁻⁸. However, there is evidence that diabetes prevention interventions may
16 be differentially effective in different population subgroups ⁹⁻¹³, thereby potentially leading to
17 differential cost-effectiveness. Given the limited number of available interventions, analysis of
18 potential disparities in cost-effectiveness of the DPP between different subgroups is important not
19 only to maximise potential health benefits and cost-savings, but also to ensure that health benefits are
20 distributed in the population in a fair and equitable manner, which is an important consideration for
21 public health interventions.

22 This study aims to (a) model the potential cost-effectiveness of the proposed NHS DPP in the English
23 population using an adaptation of the National Institute for Health Research (NIHR) School for Public
24 Health Research (SPHR) Diabetes Prevention Model ^{7,14}, and (b) investigate in which subgroups,
25 defined by age, gender, ethnicity, socioeconomic deprivation, baseline BMI, baseline HbA1c and

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3 1 working status the DPP is likely to have the most benefit in terms of cost-effectiveness, cost-savings
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5 2 and health benefits.
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8 **METHODS**

9 10 **Model Structure**

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14 5 The SPHR Diabetes Prevention Model was developed to forecast long-term health and health care
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16 6 costs under alternative scenarios for diabetes prevention. A detailed description of the methodology
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18 7 and assumptions used in the model can be found in the supplementary appendix.

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21 8 The model is an individual patient simulation model based upon the evolution of personalised
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23 9 trajectories for metabolic factors including body mass index (BMI), systolic blood pressure (SBP),
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25 10 cholesterol and measures of blood glucose (including HbA1c)¹⁵. The baseline population consists of a
26
27 11 representative sample of the English population obtained from the Health Survey for England (HSE)
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29 12 ¹⁶. HSE 2011 was chosen to inform the baseline population in the model due to its focus on diabetes
30
31 13 and cardiovascular disease, meaning it incorporates information about relevant metabolic factors.
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33 14 Individuals aged below 16 were excluded from the analysis.
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36 15 The model runs in annual cycles (see schematic in Figure S1 of the supplementary material). For each
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38 16 person, their BMI, cholesterol, SBP and HbA1c progress from year to year. Every year in the model,
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40 17 an individual may visit their GP or undergo a health check, and be diagnosed with and treated for
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42 18 hypertension, high cardiovascular risk, diabetes, microvascular complications of diabetes,
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44 19 cardiovascular disease (CVD), congestive heart failure, osteoarthritis, depression and breast or colon
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46 20 cancer, or may die. Utility of each individual in each year of the model is dependent upon their age,
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48 21 gender and medical conditions. Each condition is associated with a utility (health related quality of
49
50 22 life) decrement and a healthcare cost. Details of how all utilities and costs were modelled can be
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52 23 found in the supplementary appendix. Total costs and QALYs are aggregated over all individuals in
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54 24 the model. Costs are at 2014 values in English pounds. The model perspective is that of the NHS in
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56 25 England.
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1 **Intervention**

2 The NHS DPP is an intensive lifestyle intervention focussing on dietary advice, physical activity and
3 weight loss, aimed at individuals in England at high risk of diabetes. The model begins at the point
4 where individuals eligible for the DPP (HbA1c 6-6.4%/42-47 mmol/mol; aged ≥ 16) have been
5 identified and does not incorporate any local costs or utility change associated with identification or
6 referral. Table S1 of the supplementary material details baseline characteristics for the 1,492 high risk
7 individuals in the HSE 2011.

8 An intervention uptake rate of 32% was assumed in consultation with Public Health England. It was
9 assumed that those who did not take up the intervention incurred no extra costs or benefits.

10 Effectiveness evidence came from a recent PHE commissioned evidence review and meta-analysis of
11 pragmatic diabetes prevention interventions, carried out specifically to inform the likely effectiveness
12 of the NHS DPP⁹. PHE, NHS England and Diabetes UK have specified that in order to maximise
13 intervention effectiveness, they wish the commissioned DPP to fulfil at least 9-12 guidelines as
14 recommended in NICE guidance for diabetes prevention (PH38)¹⁷. NICE guidelines include using
15 particular strategies associated with increased effectiveness, specifying the minimum amount of
16 contact time and follow-up sessions, and delivering the programme through qualified practitioners. In
17 line with this, a mean weight loss of 3.24kg was assumed, taken from the meta-analysis of
18 interventions fulfilling 9-12 NICE guidelines⁹. Data about concomitant reduction in systolic blood
19 pressure, total cholesterol and HbA1c was not available from the PHE evidence review and so was
20 linearly extrapolated from an earlier review and meta-analysis¹⁸ (see Table S2 and supplementary
21 methods for details). Current evidence indicates that whilst there may potentially be a small number
22 of adverse musculoskeletal events associated with intensive lifestyle intervention compared with
23 control, these are not significant so were not incorporated into the analysis¹¹.

24 There is some evidence to indicate that effectiveness of lifestyle interventions to prevent type 2
25 diabetes differs between population subgroups, although study quality varies⁹⁻¹³. Stratification of
26 intervention effectiveness by baseline BMI was implemented into the model, again using data from

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2
3 1 the PHE meta-analysis⁹. There was insufficient evidence around differential effectiveness for other
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5 2 subgroups to incorporate into the model. In practice, some individuals who start the intervention will
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7 3 not complete it. Most of the studies used to derive the estimate of effectiveness in the PHE meta-
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9 4 analysis used intention to treat analysis, but two have not (personal communication from N. Ashra). It
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11 5 is likely therefore that the effectiveness estimate used in the model only partially accounts for non-
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13 6 completion and therefore may be higher than is realistic in practice. Sensitivity analysis was carried
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15 7 out to account for this possibility. A linear rate of weight regain (plus reduction in the intervention
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17 8 effects on HbA1c, SBP and cholesterol) was assumed over the first five years in line with the
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19 9 assumptions used to produce the NICE guidelines for diabetes prevention (PH38)¹⁹. This meant that
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21 10 individuals' metabolic trajectories returned to where they would have been without intervention,
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23 11 within five years of intervention implementation.

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26 12 The cost of the NHS DPP was determined through the DPP procurement process in 2016. As this was
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28 13 still undergoing at the time of this analysis, the average cost from the NHS England impact
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30 14 assessment of £270 per participant was used²⁰. This is the price that the NHS is willing to pay per
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32 15 person starting the intervention and incorporates expected retention rates of participants. Due to the
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34 16 NHS perspective taken, potential out of pocket costs for intervention attendees were not included. In
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36 17 the control simulation, it was assumed that IGR individuals would not receive any intervention and
37
38 18 would therefore not incur any extra costs or changes to their metabolic trajectories.

19 **Subgroups**

20 Population subgroups were selected for analysis due to the potential influence of different
21 characteristics on diabetes risk and for equity implications. The following subgroups were chosen:

- 22 • 4 Age groups (Age 16-40; Age 40-59; Age 60-74; Age \geq 75)
- 23 • 2 Gender groups (Male; Female)
- 24 • 2 Ethnicity groups (White; BME)
- 25 • 5 Deprivation groups (IMD quintiles 1-5)
- 26 • 3 Working status groups (Working; Retired; Other)

- 1 • 4 BMI groups (BMI < 25 kg/m²; BMI 25-29.9 kg/m²; BMI 30-34.9 kg/m²; BMI ≥ 35 kg/m²)
- 2 • 2 HbA1c groups (HbA1c 6-6.19%; HbA1c 6.2-6.49%)

3 The analysis models a single year of NHS DPP intervention and all the downstream cost savings and
4 health benefits (including life years, QALYs, and reduction in diabetes and CVD cases) that this
5 produces over the subsequent 20 years. 1000 model runs were performed for each of the 1,492 HSE
6 2011 individuals in the deterministic analysis and model outcomes for each subgroup extracted from
7 the total results. All costs were discounted by 3.5% and QALYs by 1.5%, as per Department of Health
8 guidelines²¹.

9 **Sensitivity Analysis**

10 Four deterministic one-way sensitivity analyses were performed to investigate the sensitivity of the
11 results to a more conservative set of intervention parameters. The assumptions around intervention
12 specification for each of these scenarios are shown in Table S2 of the supplementary materials.

- 13 1. Uniform intervention effectiveness (no stratification by BMI)
- 14 2. 25% lower mean effectiveness
- 15 3. Three year duration of intervention effect (instead of five years)
- 16 4. Higher intervention cost of £350 (instead of £270).

17 A fifth sensitivity analysis was also carried out in which a series of combinatorial subgroups were
18 modelled, defined by both BMI and age, or BMI and HbA1c, in order to observe the interaction
19 between characteristics.

20 Probabilistic sensitivity analysis (PSA) was carried out to describe the uncertainty in parameter inputs
21 of the model and how this translates into uncertainty in the outcomes of the model. A suitable
22 distribution was selected for each parameter, based upon its mean and standard error. Random
23 sampling simultaneously across all input parameter distributions allowed parameter uncertainty to be
24 quantified. 5000 different random samples of parameter values were selected, and each was applied to

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1 the 1,492 individuals in the simulation. A list of model parameters, their distribution for PSA and their
2 source is provided in Tables 42-60 in the supplementary appendix.

For peer review only

1 RESULTS

2 Population Results

3 Model results suggest that a year of DPP implementation in the English IGR population is likely to
4 reduce healthcare costs from the first year of implementation, recoup intervention costs within 12
5 years (by the end of 2027/28) and be cost-effective compared with no DPP intervention (at a
6 willingness to pay threshold of £20,000 per QALY gained) within 6 years (by the end of 2021/22)
7 (Figure 1). For every 100,000 interventions given, the DPP is expected to prevent or delay 4,147 cases
8 of diabetes and 413 cases of CVD (Table 1).

9 The subdivision of NHS costs/savings by disease area is shown in Table 1. This indicates that most
10 cost-savings arise due to reductions in the cost of treating diabetes or CVD, with high savings also
11 accrued through a reduction in other primary care costs including GP visits and prescription of statins
12 and anti-hypertensives. The timing of cost-savings varies depending upon disease area, with cost-
13 savings in CVD care, diagnostics and other primary care accumulating in the short-term, whilst cost-
14 savings in diabetes treatment, microvascular disease and other complications accumulate more slowly.
15 This indicates that one year of the DPP implemented now is likely to continue saving money in the
16 NHS for many years in the future despite a fairly transient (diminishing over five years) effect on
17 metabolic risk factors, due to knock-on delays in progression to more complex diabetes (requiring
18 insulin) and to expensive microvascular complications of diabetes.

19 Return on investment is calculated by dividing total savings or monetised benefit (excluding
20 intervention costs) by the cost of the intervention to work out the gain obtained for each £1 invested in
21 the DPP. The model estimates that at 20 years following intervention implementation, for every £1
22 invested in the DPP, £1.28 of NHS savings and £9.21 worth of total net monetary benefit (calculated
23 using £60,000 as the value of a QALY) will be produced (Figure 1 & Table 1).

24 25 Subgroup Results

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3 1 Across the subgroup dimensions examined, the biggest differentials in cost-effectiveness are seen in
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5 2 the subgroups defined by baseline BMI (Figure 1). The NHS DPP is estimated to be most cost-
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7 3 effective in individuals with BMI ≥ 35 kg/m² (12% of the eligible population). For this subgroup,
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9 4 NHS savings outweigh initial investment within five years and rise to a net value of £520 per person
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11 5 within 20 years (Figure 2). QALYs gained over 20 years are also highest (6,377 per 100,000
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13 6 individuals), and there are the largest reductions in diabetes and CVD cases (maximum reduction of
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15 7 diabetes cases = 5,484 at year 6, and maximum reduction of CVD cases = 846 at year 7 – see Figure
16
17 8 S2 of the supplementary materials). The 20 year return on investment is estimated to be £2.93 per £1
18
19 9 spent on intervention (Figure 1) and over £17 per £1 spent if monetised health benefits are included at
20
21 10 £60,000 per QALY. The second most cost-saving group is those who have BMI 30-34 kg/m². In
22
23 11 contrast, the non-obese subgroups have substantially worse estimated return on investment, with the
24
25 12 BMI < 25 kg/m² subgroup not recouping intervention costs within the 20 year modelled period.

26
27
28 13 Across the other dimensions for defining subgroups, IMD deprivation quintile makes a relatively
29
30 14 small difference to return on investment. Age makes a much larger difference with the middle age
31
32 15 groups (40-59, and 60-74) showing better return on investment than the younger (<40) and older (\geq
33
34 16 75) groups. Estimated return on investment is marginally better for females than males, marginally
35
36 17 different between working, retired and other, and marginally better for a white versus BME subgroup.
37
38 18 The other large subgroup difference is between those above or below 6.2% HbA1c at baseline, with
39
40 19 the higher HbA1c subgroup showing a larger return on investment than the lower HbA1c subgroup.

41
42
43 20 There are three subgroups to which net mean cost-savings do not accrue within the 20 years following
44
45 21 intervention implementation. These include the oldest age group (≥ 75), individuals who are normal
46
47 22 weight or underweight (BMI <25) and individuals with HbA1c 6-6.19. Note that subgroup
48
49 23 characteristics are not mutually exclusive, so although on average the intervention is not cost-saving
50
51 24 in people of normal weight, it may be cost-saving in certain individuals with other characteristics
52
53 25 which correlate with cost-savings, such as high HbA1c.

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2
3 1 In general, subgroups that obtain the highest cost-savings also obtain the highest QALY gains and are
4
5 2 the most cost-effective, as cost savings relate to preventing disease progression. However, the DPP
6
7 3 also reduces mortality of older individuals, resulting in higher QALYs than might otherwise be
8
9 4 expected in subgroups containing higher numbers of older people. Equally subgroups containing
10
11 5 younger individuals (including the BME group and the most socioeconomically deprived group) gain
12
13 6 fewer incremental QALYs and life years; their disease and mortality risk is reduced due to their lower
14
15 7 age so the NHS DPP is less effective, suggesting that the health benefits of the DPP may not be
16
17 8 equitably distributed (Figure S2 and S3 in the supplementary appendix).

19
20 9 In all subgroups, numbers of incremental diabetes/CVD cases drop in the short-term whilst the
21
22 10 intervention effect is operating and then rise again at the point when weight has been fully regained.
23
24 11 This indicates that most cases of diabetes/CVD are likely to be delayed rather than prevented entirely
25
26 12 based upon current assumptions about long term effectiveness of the interventions.

27 28 29 13 **Sensitivity Analyses**

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32 14 The PSA estimation of mean incremental total cost savings per person is £131 and of mean
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34 15 incremental QALYs is 0.0388 at 20 years following intervention implementation in England (Table
35
36 16 S3 of the supplementary materials). This is higher for both cost-savings and QALY gains than found
37
38 17 during deterministic analysis; the difference is due to non-linearity in the model, which is likely to be
39
40 18 particularly important around the BMI stratified estimation of intervention effect. The probability that
41
42 19 the NHS DPP will be cost-effective in 20 years compared with no DPP intervention, at a willingness
43
44 20 to pay threshold of £20,000 per QALY is 97% (see Figure 3), and the probability that the DPP will be
45
46 21 cost-saving for the NHS 20 years after intervention implementation is 70%. As in the deterministic
47
48 22 analysis, BMI is the most important criteria for determining cost-effectiveness, with the two highest
49
50 23 BMI subgroups being more cost-saving and cost-effective than other population subgroups (Table S3
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52 24 of the supplementary materials and Figure 3).

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54
55 25 One-way sensitivity analysis indicates that under conservative scenarios of higher intervention cost
56
57 26 (£350 instead of £270), 25% lower intervention effectiveness or lower duration of intervention effect

1 (three year decline instead of five year) the NHS DPP would take longer than 20 years to recoup
2 initial intervention costs in the majority of subgroups (Table S4 of the supplementary materials). The
3 intervention is still likely to be cost-effective (at a threshold of £20,000 per QALY) within a 10 year
4 time horizon in all but the least cost-effective subgroups. Of these scenarios, reducing duration of
5 intervention effect has the most significant impact on outcomes, with only the BMI \geq 35 subgroup
6 remaining cost-saving. However, in all three scenarios, the relative cost-effectiveness of subgroups
7 remains unchanged compared with the basecase analysis.

8 If intervention effect is no longer stratified by BMI, the difference between subgroups of a particular
9 population characteristic is reduced compared with the base case scenario. Whilst for some subgroups,
10 such as those defined by BMI, a clear gradient is still apparent, for other groups such as those defined
11 by IMD quintile or ethnicity the difference in outcomes is minimal, suggesting that stratification of
12 intervention effectiveness by BMI is a key driver of differential cost-effectiveness in those groups in
13 the base case analysis.

14 Combinatorial analysis indicates that the high return on investment in the BMI 35+ subgroup is
15 mitigated in individuals who are also aged 75+ and reduced to only £1.54 per £1 spent, whereas in
16 individuals aged 40-59 it is improved even further to £3.20 (Figure 4). An even higher return on
17 investment of £3.52 could potentially be obtained if individuals who have both BMI 35+ and HbA1c
18 6.2-6.4% are selected for the NHS DPP intervention. This suggests that subgroups with high benefits
19 can be combined to potentially increase the return on investment even further.

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1 DISCUSSION

2 It is essential with large-scale and expensive national programmes such as the NHS DPP that a cost-
3 effectiveness analysis using the best currently available data is carried out prior to implementation:
4 firstly, to determine whether the intervention should be carried out at all; secondly, to enable effective
5 budgeting; and thirdly, where interventions are limited, to estimate who is likely to benefit most and
6 therefore should be prioritised. This analysis suggests that the NHS DPP is highly likely to be cost-
7 effective and cost-saving over the medium to long-term using current assumptions around
8 intervention cost, effectiveness and duration of effect, and should start to save costs for the NHS from
9 the first year of implementation, recouping the initial investment in the intervention by year 12. The
10 number of potential individuals at high risk of type 2 diabetes in England (estimated to be about 5
11 million ²) far exceeds the 100,000 interventions that NHS England plans to offer each year ³. This
12 analysis indicates that prioritising obese individuals in particular (BMI \geq 30 kg/m²), combined with
13 those with the highest baseline HbA1c and focussing on those aged between 40 and 74 (the ages
14 covered in any case by the NHS Health Check) is likely to create the most value for money in the
15 programme by obtaining both the greatest cost-savings for the NHS and the highest health benefits per
16 individual targeted.

17 This study does suggest that care may have to be taken when implementing the NHS DPP to ensure
18 that it does not lead to greater health inequalities in some groups at high risk of type 2 diabetes and its
19 complications, including individuals from minority ethnic or socioeconomically deprived
20 backgrounds. The analysis shows a tendency for the NHS DPP to provide fewer QALYs to these
21 subgroups than to individuals from more socioeconomically advantaged or white ethnic backgrounds.

22 Given that the model does not incorporate (nor is there any clear evidence for) differential
23 effectiveness of the NHS DPP by socioeconomic status or ethnicity, these differences are likely to
24 occur for two main reasons. Firstly; disease risk is influenced by subgroup - for example, both
25 ethnicity and socioeconomic status are parameters in the QRISK equations that are used in the model
26 to determine CVD risk ²². This means that even if a given individual reduces their metabolic risk
27 factors through the DPP, they may still be at high risk of disease due to environmental or genetic

1 factors outside the scope of the intervention. Secondly, subgroups differ in key personal
2 characteristics associated with intervention efficacy – for example, mean age is lower than average in
3 the BME subgroup and in the most socioeconomically deprived quintile. Low mean age results in
4 lower health benefits and return on investment from the NHS DPP than high age due to the lower
5 absolute risks of disease and mortality in such individuals and therefore lower ability to benefit .
6 Given that BME and low socioeconomic status subgroups also tend to suffer from low uptake of
7 lifestyle interventions ^{23;24}, it is important that NHS DPP providers make particular efforts to engage
8 individuals from these groups if exacerbation of health inequalities is to be avoided.

9 A major strength of this analysis is the synthesis of a broad range of evidence using the SPHR
10 Diabetes Prevention Model ^{7;14}. This is an individual patient simulation model that incorporates a
11 large amount of evidence from published data about type 2 diabetes risk factors and the complex
12 disease progression pathways that lead from a diabetes diagnosis, and is able to represent the
13 heterogeneity present within the English population and thereby model population subgroups.
14 However, the model only takes healthcare costs into account, meaning that wider societal costs and
15 benefits cannot be calculated, and even within healthcare does not incorporate diseases such as
16 dementia that may impact upon long-term healthcare costs. A more important limitation is that the
17 comparator of “no NHS DPP intervention” used for this analysis does not fully represent the current
18 situation where some localities do have programmes for high risk individuals. These were not
19 modelled due to limited evidence and heterogeneity of intervention implementation between
20 localities. Subgroup analysis has also been limited by the relatively small number of IGR individuals
21 in the HSE data, meaning that smaller subgroups (such as individual minority ethnic groups) or a
22 larger variety of subgroup combinations, both of which would provide useful information for those
23 implementing the NHS DPP, cannot be accurately modelled.

24 Whilst this study is not based on actual clinical data from the NHS DPP, because such data does not
25 yet exist as the national programme implementation is just beginning, it does use the most recently
26 published estimates of intervention effectiveness from a PHE evidence review designed specifically to
27 inform the development of the NHS DPP ⁹, and therefore is likely to provide a more accurate estimate

1 of NHS DPP cost-effectiveness than previous economic analyses of diabetes prevention interventions.
2 However, data about the long-term effectiveness of lifestyle interventions and the differential
3 response of population subgroups to such interventions is limited and represents the most important
4 limitation of this study. Deterministic sensitivity analysis indicates that the cost-effectiveness of the
5 NHS DPP is substantially influenced by parameters such as intervention effectiveness and duration of
6 intervention effect, which could also impact on the ordering of subgroups. Future research should
7 therefore focus primarily on improving estimates of subgroup effectiveness, and gathering evidence
8 about initial weight loss and weight regain rates due to the NHS DPP, which could be added to the
9 model. The biggest challenges in performing good quality subgroup analysis are sufficiently powering
10 the clinical studies to account for subgroups that may only comprise a small proportion of the
11 population, and taking into account potential interaction between personal characteristics that could
12 lead to confounding across subgroups in intervention uptake rates or effectiveness. The National
13 Institute for Health Research (NIHR) is commissioning a formal evaluation of the NHS DPP which
14 will include cost-effectiveness analysis. Careful statistical design of this analysis and long-term
15 follow-up of participants should enable these challenges to be overcome successfully and provide
16 high quality data for updating and improving the accuracy of model predictions.

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Table 1: Mean cumulative incremental outcomes per person given the intervention in England. Costs and cost-ineffective returns are shown in red whereas savings and cost-effective returns are shown in black. Costs are discounted at 3.5% whereas QALYs are discounted at 1.5%.

| | Year 1 2016/17 | Year 2 2017/18 | Year 3 2018/19 | Year 4 2019/20 | Year 5 2020/21 | Year 10 2025/26 | Year 15 2030/31 | Year 20 2035/36 |
|---|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|--------------------|--------------------|
| TOTAL COSTS | £240 | £218 | £195 | £173 | £150 | £23 | -£43 | -£75 |
| DPP Costs | £270 | £270 | £270 | £270 | £270 | £270 | £270 | £270 |
| NHS Costs | -£30 | -£52 | -£75 | -£97 | -£120 | -£247 | -£313 | -£345 |
| <i>Diabetes Treatment</i> | -£1 | -£3 | -£6 | -£9 | -£17 | -£79 | -£106 | -£115 |
| <i>CVD Treatment</i> | -£11 | -£18 | -£25 | -£32 | -£37 | -£56 | -£65 | -£69 |
| <i>Microvascular Complications¹</i> | -£1 | -£3 | -£5 | -£7 | -£10 | -£27 | -£46 | -£60 |
| <i>Other Complications²</i> | -£2 | -£5 | -£8 | -£12 | -£15 | -£30 | -£40 | -£45 |
| <i>Diagnostics³</i> | -£4 | -£4 | -£5 | -£5 | -£4 | -£3 | -£2 | -£2 |
| <i>Other Primary Care⁴</i> | -£11 | -£19 | -£26 | -£32 | -£37 | -£52 | -£54 | -£54 |
| Life Years ⁵ | 6 | 41 | 130 | 281 | 486 | 1,795 | 2,838 | 3,487 |
| QALYs ⁵ | 50 | 133 | 269 | 457 | 686 | 1,986 | 2,966 | 3,552 |
| Diabetes Cases ⁵ | -1043 | -1995 | -3000 | -3788 | -4147 | -1812 | -766 | -654 |
| CVD Cases ⁵ | -183 | -273 | -344 | -396 | -413 | -394 | -325 | -282 |
| ICER (£/QALY) | £475,625 | £163,636 | £72,715 | £37,870 | £21,860 | £1,162 | -£1,446 | -£2,120 |
| Net Monetary Benefit ⁶ | -£209 | -£138 | -£34 | £101 | £262 | £1,169 | £1,822 | £2,207 |
| RoI: Total Savings ⁷ | £0.11 | £0.19 | £0.28 | £0.36 | £0.44 | £0.91 | £1.16 | £1.28 |
| RoI: NMB ⁷ | £0.22 | £0.49 | £0.87 | £1.37 | £1.97 | £5.33 | £7.75 | £9.17 |
| DPP Diabetes Prevention Programme; NHS National Health Service; QALY Quality Adjusted Life Year; CVD Cardiovascular Disease; ICER Incremental Cost-Effectiveness Ratio; RoI Return on Investment; NMB Net Monetary Benefit. | | | | | | | | |
| ¹ Includes costs of nephropathy, ulcer, amputation and retinopathy | | | | | | | | |
| ² Includes costs of osteoarthritis, depression, breast and colon cancer | | | | | | | | |
| ³ Diagnosis of diabetes, high CVD risk and hypertension | | | | | | | | |
| ⁴ Includes costs of GP visits and prescription of statins and anti-hypertensives | | | | | | | | |
| ⁵ Per 100,000 individuals given the DPP intervention | | | | | | | | |
| ⁶ Value of a QALY assumed to be £60,000 for net monetary benefit analysis ¹⁷ | | | | | | | | |
| ⁷ Return on Investment per £1 invested in the DPP | | | | | | | | |

1 **FIGURE LEGENDS**

2 Figure 1: Bar charts showing: A) the year that the NHS DPP becomes cost-saving (recoups
3 intervention costs); B) the year that the NHS DPP becomes cost-effective; C) the total NHS return on
4 investment within 20 years per £1 spent on the NHSDPP for each of the population subgroups.
5 Vertical arrows indicate that the DPP is not cost-saving within the 20 year period modelled.

6 Figure 2: Graphs showing cumulative incremental (net) costs per person given the intervention over a
7 20 year time horizon for each subgroup and for the total population. Annual incremental costs per
8 person are shown as a dotted line on the total population graph. Costs are discounted at 3.5%

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21 Figure 3: PSA Results. A) Cost-effectiveness acceptability curve showing the probability that the DPP
22 or no intervention will be cost-effective over a range of different willingness to pay thresholds. B)
23 Distribution of PSA results for i) the total population and ii) BMI subgroups on the cost-effectiveness
24 plane. Error bars represent 95% confidence intervals for incremental total costs and incremental
25 QALYs. The cost-effectiveness (CE) threshold is £20,000/QALY. Note that the size of the 95%
26 confidence intervals and therefore the probability that the intervention will be cost-effective or cost-
27 saving is partially related to the size of each subgroup within the total IGR population of England, in
28 addition to being related to the distribution of results on the cost-effectiveness plane.
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38 Figure 4: Graphs showing the interaction between BMI and: A) age; B) HbA1c. Return on investment
39 in combinatorial subgroups defined using two personal characteristics.
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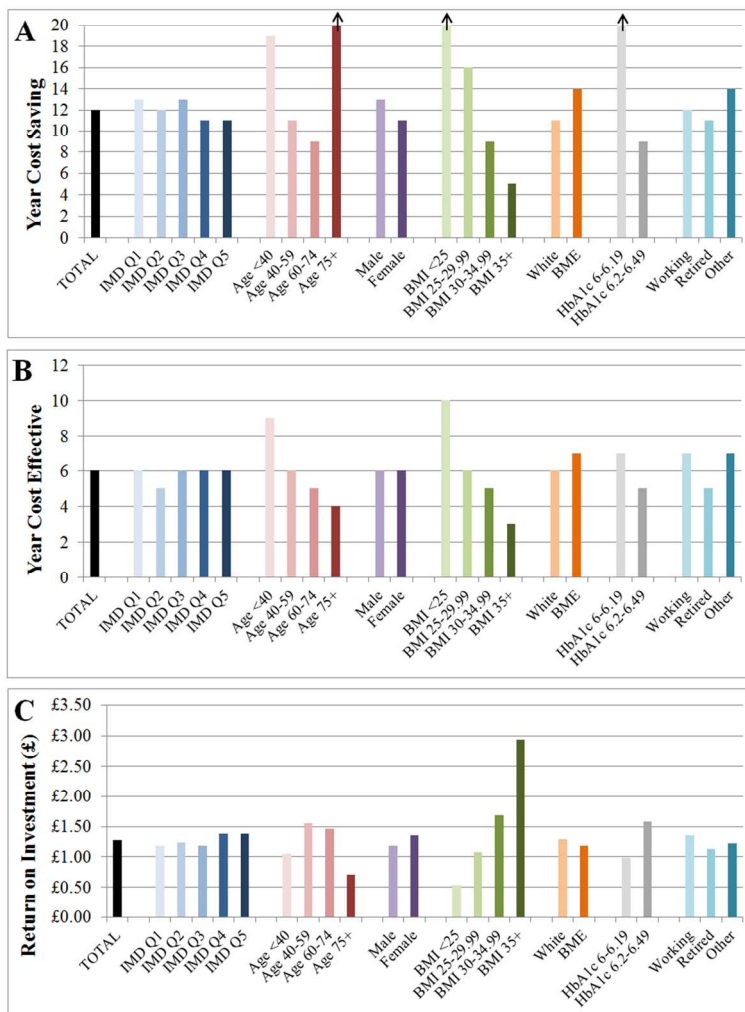


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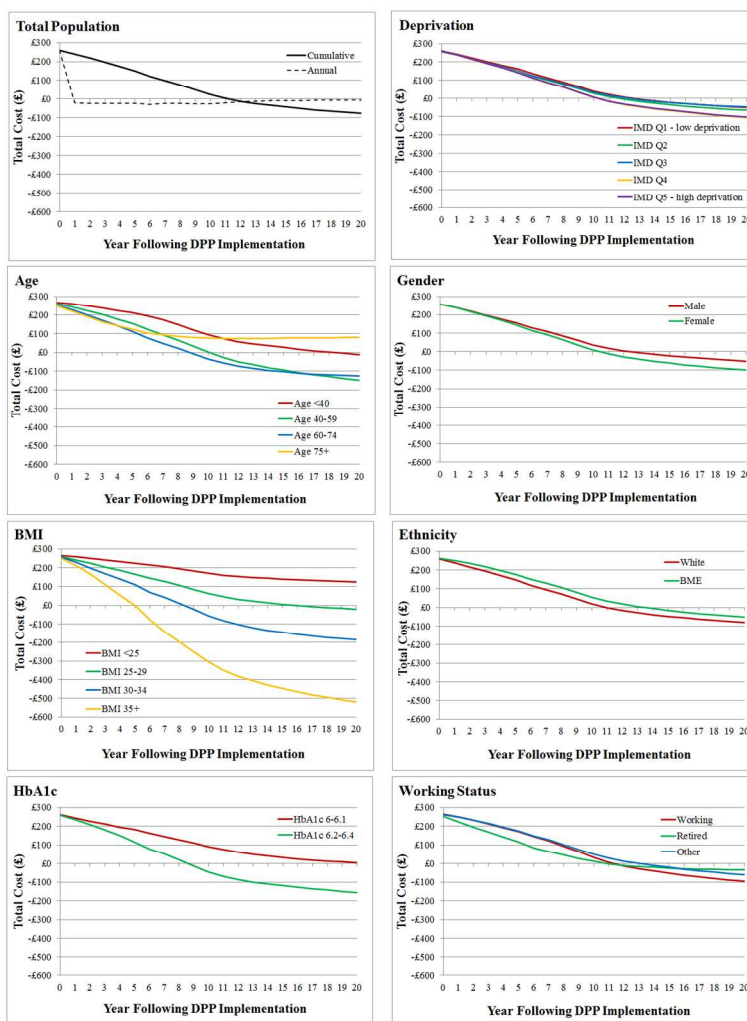


Figure 2: Graphs showing cumulative incremental (net) costs per person given the intervention over a 20 year time horizon for each subgroup and for the total population. Annual incremental costs per person are shown as a dotted line on the total population graph. Costs are discounted at 3.5%.

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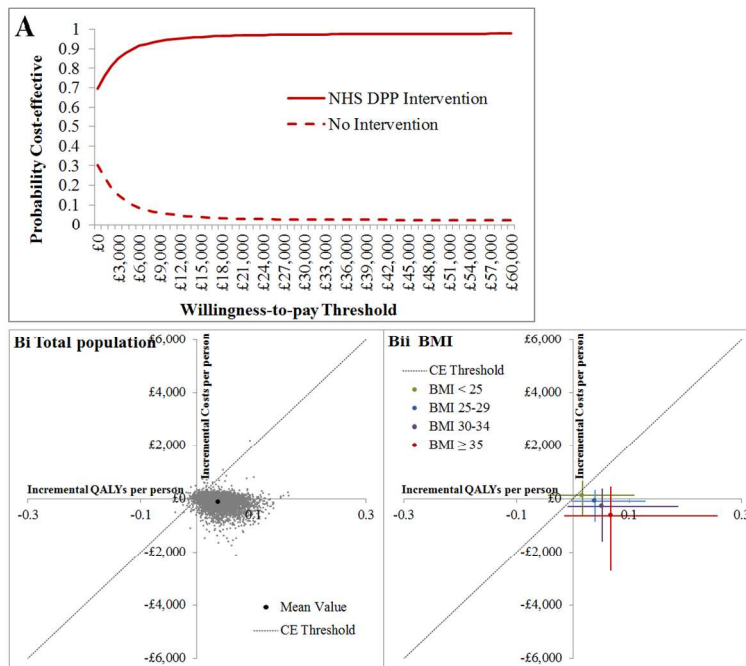


Figure 3: PSA Results. A) Cost-effectiveness acceptability curve showing the probability that the DPP or no intervention will be cost-effective over a range of different willingness to pay thresholds. B) Distribution of PSA results for i) the total population and ii) BMI subgroups on the cost-effectiveness plane. Error bars represent 95% confidence intervals for incremental total costs and incremental QALYs. The cost-effectiveness (CE) threshold is £20,000/QALY. Note that the size of the 95% confidence intervals and therefore the probability that the intervention will be cost-effective or cost-saving is partially related to the size of each subgroup within the total IGR population of England, in addition to being related to the distribution of results on the cost-effectiveness plane.

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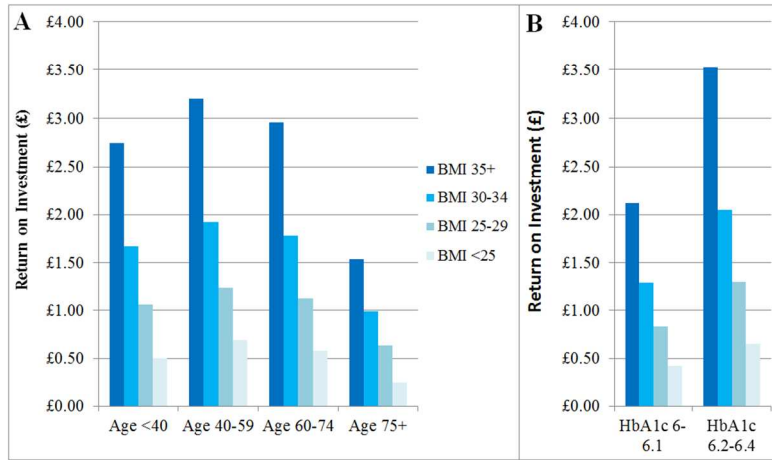


Figure 4: Graphs showing the interaction between BMI and: A) age; B) HbA1c. Return on investment in combinatorial subgroups defined using two personal characteristics.

190x254mm (300 x 300 DPI)

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3 ONLINE ONLY SUPPLEMENTAL MATERIAL
4

5 Full Title: Assessing the Potential Return on Investment of the Proposed NHS Diabetes
6 Prevention Programme in Different Population Subgroups: An Economic Evaluation
7

8
9 Running Title: Return on Investment of the NHS DPP
10

11 Chloe Thomas, Susi Sadler, Penny Breeze, Hazel Squires, Michael Gillett, Alan Brennan
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13

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A) SUPPLEMENTARY TABLES & FIGURES

| CHARACTERISTIC | NUMBER | PERCENTAGE | |
|---|--------|--------------------|--------|
| Male | 644 | 43.2% | |
| Female | 848 | 56.8% | |
| White | 1332 | 89.3% | |
| BME | 160 | 10.7% | |
| <i>Indian</i> | 46 | 3.1% | |
| <i>Pakistani</i> | 23 | 1.5% | |
| <i>Bangladeshi</i> | 5 | 0.3% | |
| <i>Other Asian</i> | 19 | 1.3% | |
| <i>Caribbean</i> | 16 | 1.1% | |
| <i>African</i> | 28 | 1.9% | |
| <i>Chinese</i> | 4 | 0.3% | |
| <i>Other</i> | 19 | 1.3% | |
| Age1 < 40 | 279 | 18.7% | |
| Age2 40-59 | 482 | 32.3% | |
| Age3 60-74 | 453 | 30.4% | |
| Age4 75+ | 278 | 18.6% | |
| IMD 1 (least deprived) | 339 | 22.7% | |
| IMD 2 | 436 | 29.2% | |
| IMD 3 | 177 | 11.9% | |
| IMD 4 | 297 | 19.9% | |
| IMD 5 (most deprived) | 243 | 16.3% | |
| Working | 679 | 45.5% | |
| Retired | 584 | 39.1% | |
| Other | 229 | 15.3% | |
| BMI1 < 25 kg/m ² | 409 | 27.4% | |
| BMI2 25-29 kg/m ² | 586 | 39.3% | |
| BMI3 30-34 kg/m ² | 324 | 21.7% | |
| BMI4 ≥ 35 kg/m ² | 173 | 11.6% | |
| HbA1c 6-6.1 % (42-44 mmol/mol) | 763 | 51.1% | |
| HbA1c 6.2-6.4 % (45-47 mmol/mol) | 729 | 48.9% | |
| | MEAN | STANDARD DEVIATION | MEDIAN |
| Age (years) | 57.1 | 17.8 | 58.0 |
| BMI (kg/m ²) | 28.4 | 5.7 | 27.8 |
| Total Cholesterol (mmol/l) | 5.7 | 1.0 | 5.7 |
| HDL Cholesterol (mmol/l) | 1.5 | 0.4 | 1.5 |
| HbA1c (%) | 6.19 | 0.14 | 6.19 |
| Systolic Blood Pressure (mm Hg) | 129.7 | 17.2 | 128.5 |
| EQ-5D (TTO) | 0.739 | 0.307 | 0.796 |
| BME Black and Minority Ethnic; BMI Body Mass Index; IMD Index of Multiple Deprivation; CVD Cardiovascular Disease; IGR Impaired Glucose Regulation; HDL High Density Lipoprotein; EQ-5D 5 dimensions Euroqol (health related quality of life index); TTO Time Trade-Off | | | |

Table S1: Baseline characteristics of the IGR individuals from HSE 2011, following imputation of missing metabolic data (N=1,492).

| SPECIFICATION | BASE-CASE | SA 1 | SA 2 | SA 3 | SA 4 |
|---|-----------|-------------|--------------|----------------|-------------|
| Intervention Uptake* | 32% | 32% | 32% | 32% | 32% |
| Intervention Effectiveness ^{6,15} : | | | | | |
| <i>Mean weight change (kg)</i> | -3.24 | -3.24 | -2.43 | -3.24 | -3.24 |
| <i>Mean BMI change (kg/m²)</i> | -1.47 | -1.47 | -1.10 | -1.47 | -1.47 |
| <i>Mean SBP change (mmHg)</i> | -6.57 | -6.57 | -0.15 | -6.57 | -6.57 |
| <i>Mean cholesterol change (mmol/l)</i> | -0.28 | -0.28 | -4.93 | -0.28 | -0.28 |
| <i>Mean HbA1c change (%)</i> | -0.20 | -0.20 | -0.21 | -0.20 | -0.20 |
| Stratification of Intervention Effectiveness (kg) ^{6 **} | -0.23 | None | -0.23 | -0.23 | -0.23 |
| Intervention Cost* | £270 | £270 | £270 | £270 | £350 |
| Time to Weight Regain* | 5 years | 5 years | 5 years | 3 years | 5 years |
| * PHE estimates of expected values | | | | | |
| ** extra weight loss per unit increase in baseline BMI above 31.5 kg/m ² , or weight gain per unit decrease in baseline BMI below 31.5 kg/m ² | | | | | |

Table S2: Key intervention specification parameters in the basecase and one-way sensitivity analysis (SA) scenarios. Values in bold indicate differences from basecase.

| | TOTAL COST | QALYS | NET MONETARY BENEFIT* | PROBABILITY COST-EFFECTIVE** | PROBABILITY COST-SAVING |
|--|------------|-------|-----------------------|------------------------------|-------------------------|
| Total Population | -£131 | 0.038 | -£3,376 | 97% | 70% |
| <i>IMD Q1: low deprivation</i> | -£110 | 0.041 | -£2,638 | 83% | 57% |
| <i>IMD Q2</i> | -£121 | 0.039 | -£3,034 | 87% | 60% |
| <i>IMD Q3</i> | -£141 | 0.039 | -£3,608 | 71% | 53% |
| <i>IMD Q4</i> | -£138 | 0.039 | -£3,543 | 83% | 58% |
| <i>IMD Q5: high deprivation</i> | -£159 | 0.033 | -£4,760 | 78% | 60% |
| <i>Age <40</i> | -£35 | 0.019 | -£1,811 | 64% | 46% |
| <i>Age 40-59</i> | -£215 | 0.036 | -£5,909 | 89% | 72% |
| <i>Age 60-74</i> | -£194 | 0.054 | -£3,591 | 91% | 66% |
| <i>Age 75+</i> | £24 | 0.043 | £563 | 81% | 40% |
| <i>Male</i> | -£105 | 0.041 | -£2,529 | 91% | 59% |
| <i>Female</i> | -£156 | 0.036 | -£4,303 | 94% | 68% |
| <i>BMI <25</i> | £123 | 0.016 | £7,396 | 51% | 26% |
| <i>BMI 25-29</i> | -£83 | 0.039 | -£2,130 | 89% | 55% |
| <i>BMI 30-34</i> | -£277 | 0.051 | -£5,360 | 92% | 74% |
| <i>BMI 35+</i> | -£627 | 0.067 | -£9,286 | 93% | 83% |
| <i>White</i> | -£132 | 0.039 | -£3,311 | 97% | 70% |
| <i>BME</i> | -£121 | 0.030 | -£4,045 | 61% | 51% |
| <i>HbA1c 6-6.1</i> | -£39 | 0.029 | -£1,305 | 87% | 49% |
| <i>HbA1c 6.2-6.4</i> | -£226 | 0.048 | -£4,706 | 96% | 76% |
| <i>Working</i> | -£150 | 0.036 | -£4,090 | 91% | 68% |
| <i>Retired</i> | -£102 | 0.048 | -£2,088 | 93% | 58% |
| <i>Other</i> | -£101 | 0.025 | -£3,915 | 68% | 52% |
| *Value of a QALY assumed to be £60,000 for net monetary benefit analysis ¹⁷ | | | | | |
| **At a willingness to pay threshold of £20,000 per QALY | | | | | |

Table S3: Summary table showing incremental PSA results for each subgroup compared with no DPP intervention. All results are reported per person given the intervention at 20 years following intervention implementation. Costs are discounted at 3.5% and QALYs at 1.5%. Higher cost savings, QALY gains and net monetary benefit are shown in deeper shades of red, whereas lowest cost savings, QALY gains and net monetary benefit are shown in blue.

| | BASECASE* | | SA1 | | SA2 | | SA3 | | SA4 | |
|----------------------|-----------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| | Year CS | Year CE | Year CS | Year CE | Year CS | Year CE | Year CS | Year CE | Year CS | Year CE |
| Total Population | 12 | 6 | 10 | 5 | 20 | 7 | NCS | 8 | NCS | 7 |
| <i>IMD Q1</i> | 13 | 6 | 10 | 5 | NCS | 7 | NCS | 8 | NCS | 7 |
| <i>IMD Q2</i> | 12 | 5 | 10 | 5 | NCS | 6 | NCS | 7 | NCS | 6 |
| <i>IMD Q3</i> | 13 | 6 | 10 | 5 | NCS | 7 | NCS | 8 | NCS | 7 |
| <i>IMD Q4</i> | 11 | 6 | 10 | 5 | 16 | 6 | NCS | 8 | 17 | 7 |
| <i>IMD Q5</i> | 11 | 6 | 9 | 5 | 16 | 7 | NCS | 9 | 17 | 7 |
| <i>Age <40</i> | 19 | 9 | 11 | 8 | NCS | 11 | NCS | 17 | NCS | 11 |
| <i>Age 40-59</i> | 11 | 6 | 9 | 6 | 14 | 7 | NCS | 9 | 14 | 7 |
| <i>Age 60-74</i> | 9 | 5 | 8 | 4 | 12 | 6 | NCS | 6 | 13 | 6 |
| <i>Age 75+</i> | NCS | 4 | NCS | 4 | NCS | 5 | NCS | 5 | NCS | 5 |
| <i>Male</i> | 13 | 6 | 10 | 5 | NCS | 6 | NCS | 8 | NCS | 7 |
| <i>Female</i> | 11 | 6 | 10 | 5 | 16 | 7 | NCS | 8 | 18 | 7 |
| <i>BMI <25</i> | NCS | 10 | 11 | 6 | NCS | 13 | NCS | NCE | NCS | 13 |
| <i>BMI 25-29</i> | 16 | 6 | 10 | 5 | NCS | 7 | NCS | 8 | NCS | 7 |
| <i>BMI 30-34</i> | 9 | 5 | 9 | 5 | 11 | 6 | NCS | 6 | 11 | 6 |
| <i>BMI 35+</i> | 5 | 3 | 7 | 4 | 6 | 4 | 8 | 4 | 7 | 4 |
| <i>White</i> | 11 | 6 | 10 | 5 | 19 | 6 | NCS | 7 | NCS | 6 |
| <i>BME</i> | 14 | 7 | 10 | 6 | NCS | 9 | NCS | 11 | NCS | 9 |
| <i>HbA1c 6-6.1</i> | NCS | 7 | 14 | 6 | NCS | 8 | NCS | 10 | NCS | 9 |
| <i>HbA1c 6.2-6.4</i> | 9 | 5 | 8 | 4 | 12 | 6 | NCS | 6 | 12 | 6 |
| <i>Working</i> | 12 | 7 | 10 | 6 | 17 | 8 | NCS | 9 | 19 | 8 |
| <i>Retired</i> | 11 | 5 | 9 | 4 | NCS | 5 | NCS | 6 | NCS | 5 |
| <i>Other</i> | 14 | 7 | 10 | 6 | NCS | 8 | NCS | 11 | NCS | 9 |

CS Cost-Saving; CE Cost-Effective; NCS Not Cost-Saving within 20 years; NCE Not Cost-Effective within 20 years
 *Stratified intervention effect by BMI, 5 year duration of intervention effect, intervention cost £270.

Table S4: Comparison of the year that the intervention becomes cost-saving and cost-effective (using a threshold of £20,000 per QALY) between different population subgroups for each deterministic sensitivity analysis. Depth of shading represents how early cost-savings/cost-effectiveness occur, with darker grey representing earlier years.

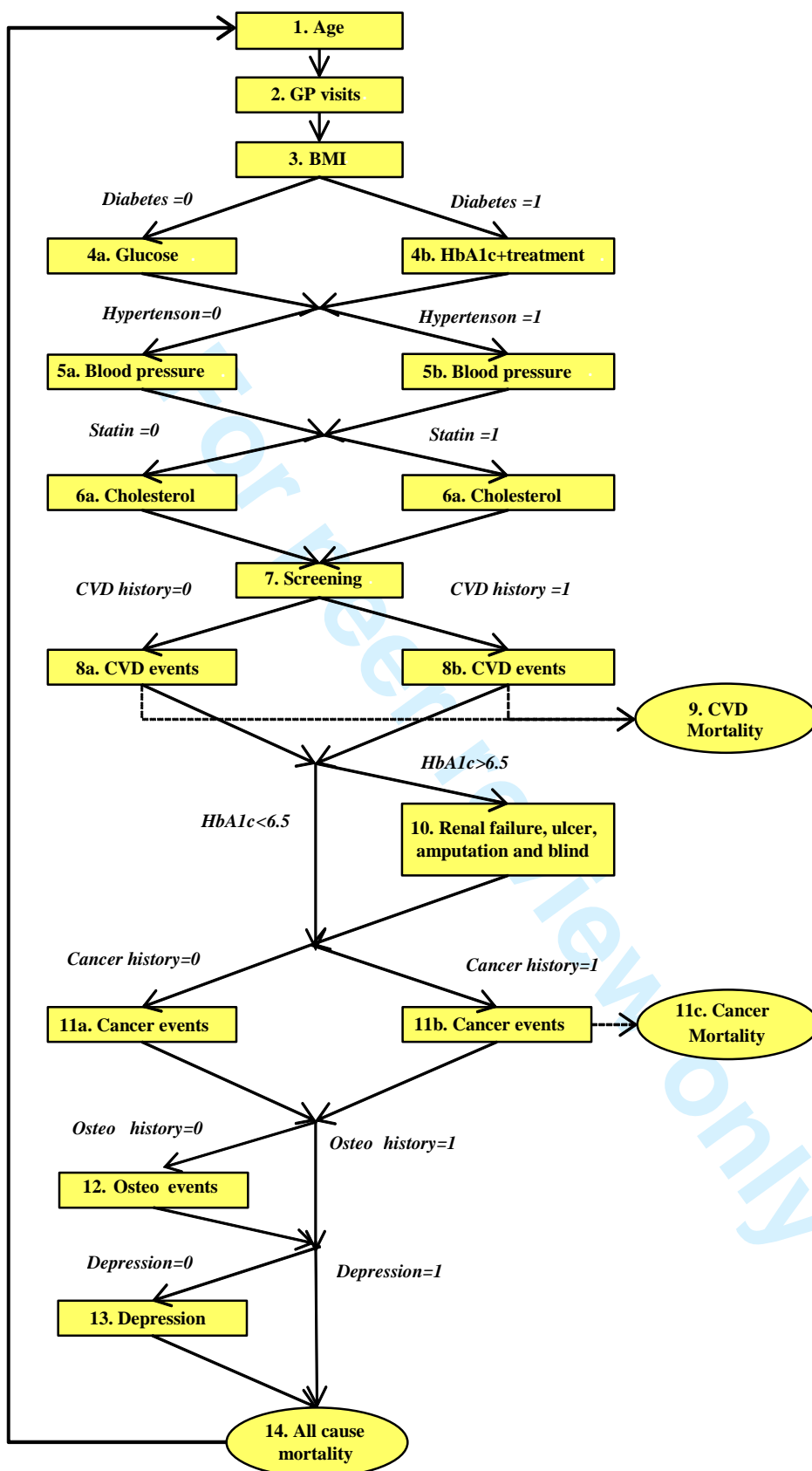


Figure S1: Model schematic showing what happens in each yearly cycle.

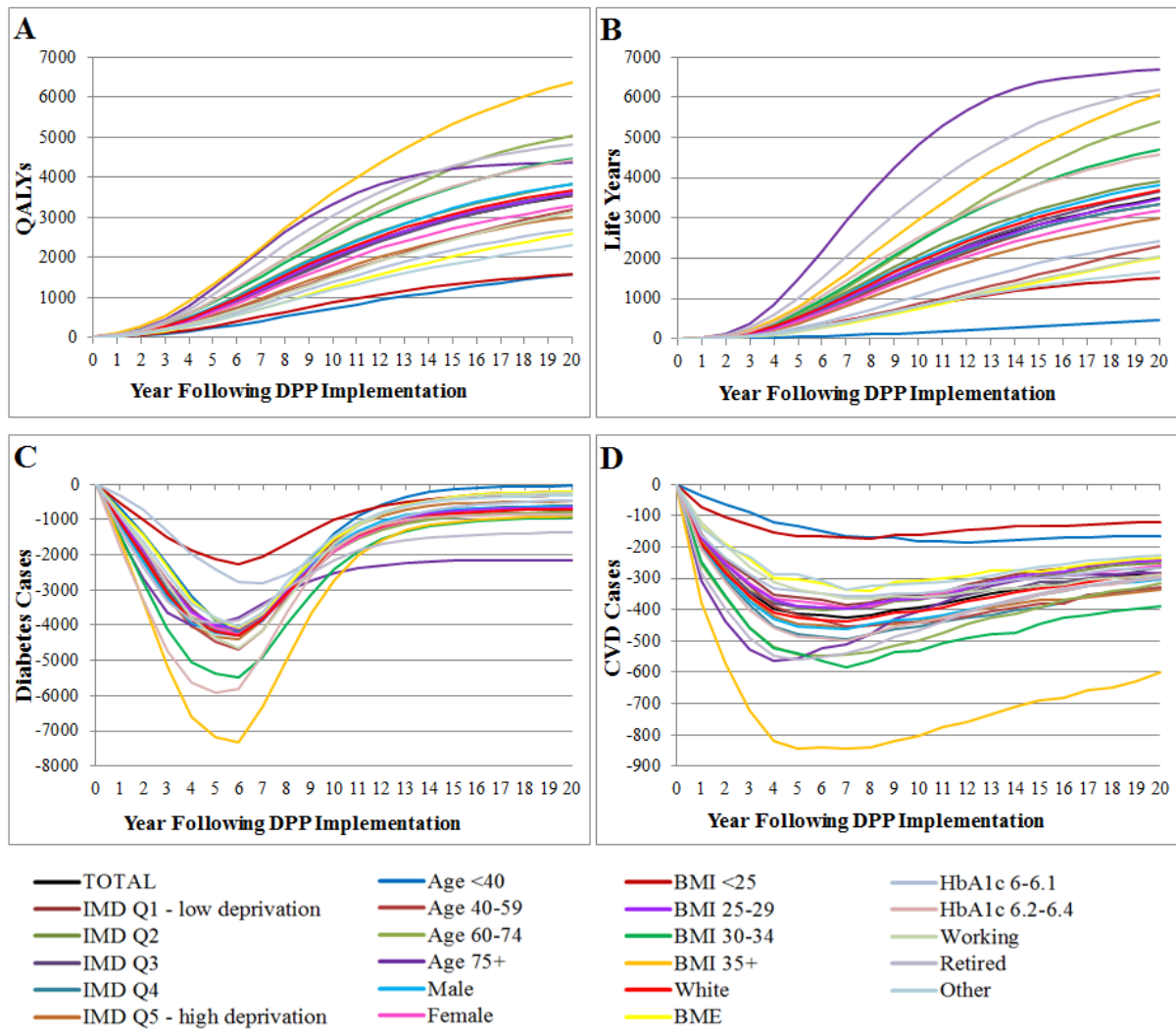


Figure S2: Graphs showing cumulative gain of A) QALYs and B) life years; and reduction in C) incremental diabetes cases and D) incremental CVD cases, per 100,000 individuals across all subgroups over 20 years.

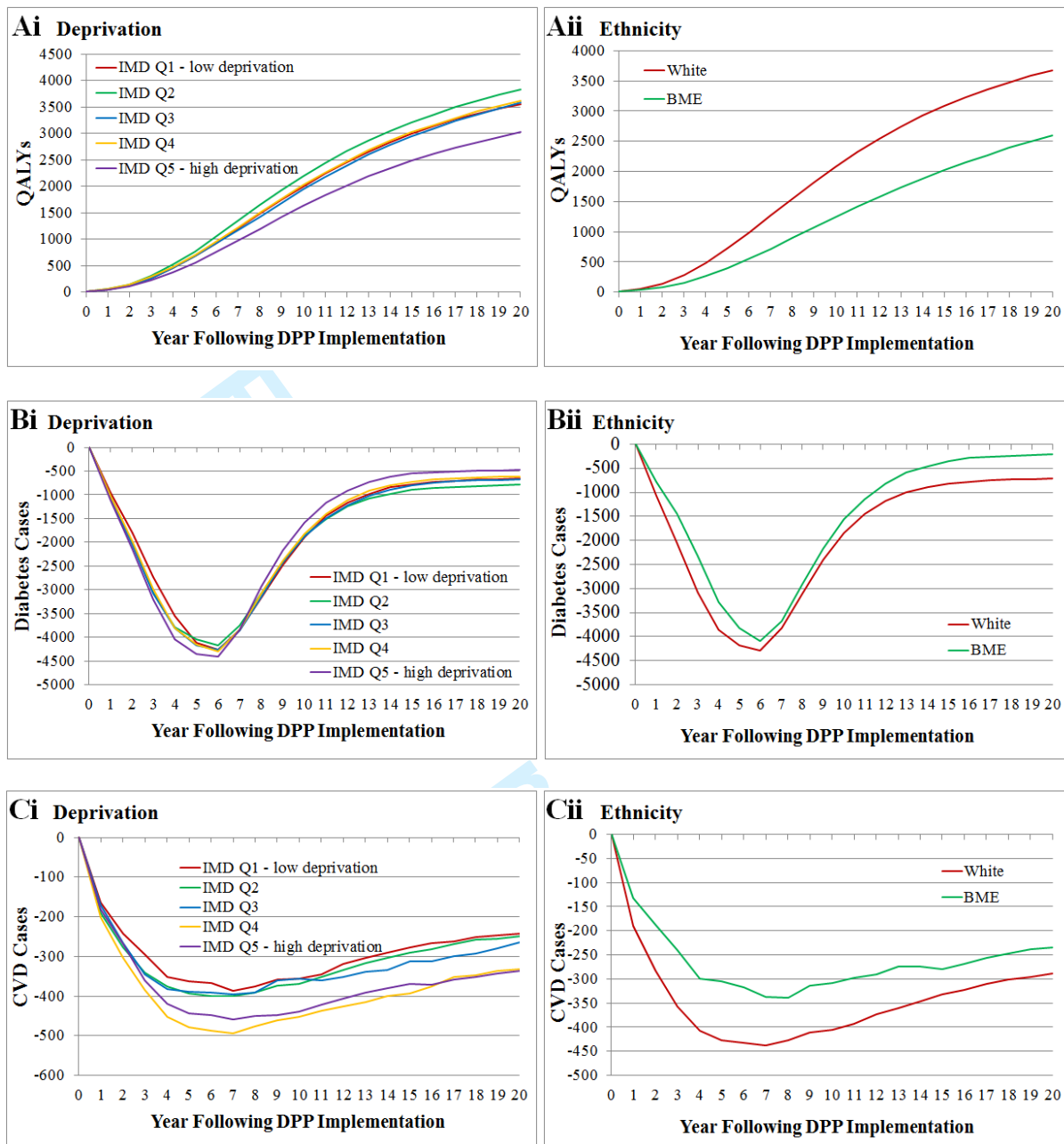


Figure S3: Graphs showing: A) cumulative incremental QALY gain; B) incremental reduction in diabetes cases and C) incremental reduction in CVD cases per 100,000 individuals in different deprivation quintiles (i) and ethnic groups (ii)

B) SUPPLEMENTARY METHODS

CONCEPTUAL MODELLING

A conceptual model of the problem and a model-based conceptual model were developed according to a new conceptual modelling framework for complex public health models (1). In line with this framework the conceptual models were developed in collaboration with a project stakeholder group comprising health economists, public health specialists, research collaborators from other SPHR groups, diabetologists, local commissioners and lay members. The conceptual model of the problem mapped out all relevant factors associated with diabetes based upon iterative literature searches. Key initial sources were reports of two existing diabetes prevention models used for National Institute for Health and Care Excellence public health guidance (2;3). This conceptual model of the problem was presented at a Stakeholder Workshop. Discussion at the workshop led to modifications of the model, identifying additional outcomes such as depression and helping to identify a suitable conceptual model boundary for the cost-effectiveness model structure.

MODEL STRUCTURE

The model is based upon individual longitudinal trajectories of metabolic risk factors (BMI, systolic blood pressure [SBP], cholesterol and HbA1c [measure of blood glucose]). For each individual, yearly changes in these risk factors occur, dependent upon the individuals' baseline characteristics. Figure 1 in the main article illustrates the sequence of updating clinical characteristics and clinical events that are estimated within a cycle of the model. This sequence is repeated for every annual cycle of the model. The first stage of the sequence updates the age of the individual. The second stage estimates how many times the individual attends the GP. The third stage estimates the change in BMI of the individual from the previous period. In the fourth stage, if the individual has not been diagnosed as diabetic (Diabetes_Dx=0) their change in glycaemia is estimated using the Whitehall II model. If they are diabetic (Diabetes_Dx=1), it is estimated using the UKPDS model. In stages five and six the individual's blood pressure and cholesterol are updated using the Whitehall II model if the individual is not identified as hypertensive or receiving statins. In stage seven, the individual may undergo assessment for diabetes, hypertension and dyslipidaemia during a GP consultation. From stage eight onwards the individual may experience cardiovascular outcomes, diabetes related complications, cancer, osteoarthritis or depression. If the individual has a history of cardiovascular disease (CVD history=1), they follow a different pathway in stage eight to those without a history of cardiovascular disease (CVD history=0). Individuals with HbA1c greater than 6.5 are assumed to be at risk of diabetes related complications. Individuals who do not have a history of cancer (Cancer history=0) are

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3 at risk of cancer diagnosis, whereas those with a diagnosis of cancer (Cancer history=1) are at risk of
4 mortality due to cancer. Individuals without a history of osteoarthritis or depression may develop
5 these conditions in stages 12 and 13. Finally, all individuals are at risk of dying due to causes other
6 than cardiovascular or cancer mortality. Death from renal disease is included in the estimate of other-
7 cause mortality.
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11 12 13 14 15 **DATA SELECTION**

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18 Having developed and agreed the model structure and boundary with the stakeholder group the
19 project team sought suitable sources of data for the baseline population, GP attendance, metabolic risk
20 trajectories, treatment algorithms, and risk models for long term health outcomes, health care and
21 health related. Given the complexity of the model it was not possible to use systematic review
22 methods to identify all sources of data for these model inputs. As a consequence we used a series of
23 methods to identify the most appropriate sources of data within the time constraints of the project.
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29 Firstly, we discussed data sources with the stakeholder groups and identified key studies in the UK
30 that have been used to investigate diabetes and its complications and comorbidities. The stakeholder
31 group included experts in the epidemiology of non-communicable disease who provided useful
32 insight into the strengths and limitations of prominent cohort studies and trials that have studied the
33 risks of long term health outcomes included in the model. The stakeholder group also included
34 diabetes prevention cost-effectiveness modellers, whose understanding of studies that could be used to
35 inform risk parameters, costs and health related quality of life estimates. Secondly, we used a review
36 of economic evaluations of diabetes prevention and weight management cost-effectiveness studies to
37 identify sources of data used in similar economic evaluations (4). Thirdly, we conducted targeted
38 literature searches where data could not be identified from large scale studies of a UK population, or
39 could be arguably described as representative of a UK population through processes described above.
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50 **BASELINE POPULATION**

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52 The model required demographic, anthropometric and metabolic characteristics that would be
53 representative of the UK general population. The Health Survey for England (HSE) was suggested by
54 the stakeholder group because it collects up-to-date cross-sectional data on the characteristics of all
55 ages of the English population. It also benefits from being a reasonably good representation of the
56 socioeconomic profile of England. A major advantage of this dataset is that includes important
57 clinical risk factors such as HbA1c, SBP, and cholesterol. The characteristics of individuals included
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3 in the cost-effectiveness model were based sampled from the HSE 2011 dataset (5). The HSE 2011
4 focused on CVD and associated risk factors. The whole dataset was obtained from the UK Data
5 Service. The total sample size of the HSE 2011 is 10,617 but individuals aged under 16 were excluded
6 resulting in 8,610 in total.
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10 Only a subset of variables reported in the HSE 2011 cohort was needed to inform the baseline
11 characteristics in the economic model. A list of model baseline characteristics and the corresponding
12 variable name and description from the HSE 2011 are listed below in Table 1. Two questions for
13 smoking were combined to describe smoking status according to the QRISK2 algorithm in which
14 former smokers and the intensity of smoking are recorded within one measure. The number of
15 missing data for each observation in the HSE data is detailed in Table 1 and summary statistics for the
16 data extracted from the HSE2011 dataset are reported in Table 2.
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Table 1: HSE variable names and missing data summary

| Model requirements | HSE 2011 variable name | HSE 2011 variable description | No. Missing data entries |
|-----------------------------------|------------------------|--|--------------------------|
| Age | Age | Age last birthday | 0 |
| Sex | Sex | Sex | 0 |
| Ethnicity | Origin | Ethnic origin of individual | 36 |
| Deprivation (Townsend) | qimd | Quintile of IMD SCORE | 0 |
| Weight | wtval | Valid weight (Kg) inc. estimated>130kg | 1284 |
| Height | htval | Valid height (cm) | 1207 |
| BMI | bmival | Valid BMI | 1431 |
| Waist circumference | wstval | Valid Mean Waist (cm) | 2871 |
| Waist-Hip ratio | whval | Valid Mean Waist/Hip ratio | 2882 |
| Total Cholesterol | cholval | Valid Total Cholesterol Result | 4760 |
| HDL cholesterol | hdlval | Valid HDL Cholesterol Result | 4760 |
| HbA1c | glyhbval | Valid Glycated HB Result | 4360 |
| FPG | | | N/A |
| 2-hr glucose | | | N/A |
| Systolic Blood pressure | omsysval | Omron Valid Mean Systolic BP | 3593 |
| Hypertension treatment | medcinbp | Currently taking any medicines, tablets or pills for high BP | 6050 |
| Gestational diabetes | pregdi | Whether pregnant when told had diabetes | 8008 |
| Anxiety/depression | Anxiety | Anxiety/Depression | 930 |
| Smoking | cigsta3 | Cigarette Smoking Status: Current/Ex-Reg/Never-Reg | 75 |
| | cigst2 | Cigarette Smoking Status - Banded current smokers | 74 |
| Statins | lipid | Lipid lowering (Cholesterol/Fibrinogen) - prescribed | 5804 |
| Rheumatoid Arthritis | compm12 | XIII Musculoskeletal system | 5 |
| Atrial Fibrillation | murmur1 | Doctor diagnosed heart murmur (excluding pregnant) | 2008 |
| Family history diabetes | | | N/A |
| History of Cardiovascular disease | cvdis2 | Had CVD (Angina, Heart Attack or Stroke) | 3 |
| Economic Activity | econact | Economic status | 37 |

Table 2: Characteristics of final sample from HSE 2011 (N=8610)

| Characteristic | Number | Percentage | |
|---|-------------|---------------------------------------|---------------|
| Male | 3822 | 44.4% | |
| White | 7719 | 89.7% | |
| Indian | 206 | 2.4% | |
| Pakistani | 141 | 1.6% | |
| Bangladeshi | 46 | 0.5% | |
| Other Asian | 97 | 1.1% | |
| Caribbean | 78 | 0.9% | |
| African | 120 | 1.4% | |
| Chinese | 35 | 0.4% | |
| Other | 168 | 2.0% | |
| IMD 1 (least deprived) | 1774 | 20.6% | |
| IMD 2 | 1823 | 21.2% | |
| IMD 3 | 1830 | 21.3% | |
| IMD 4 | 1597 | 18.5% | |
| IMD 5 (most deprived) | 1586 | 18.4% | |
| Non-smoker | 4550 | 52.8% | |
| Past smoker | 2353 | 27.3% | |
| Current smoker | 1707 | 19.8% | |
| Anti-hypertensive treatment | 1544 | 17.9% | |
| Statins | 929 | 10.8% | |
| Pre-existing CVD | 639 | 7.4% | |
| Diagnosed diabetes | 572 | 6.6% | |
| Missing HbA1c data | 4706 | 54.7% | |
| Undiagnosed diabetes (HbA1c \geq 6.5) before imputation HbA1c | 98 | 1.1% (2.5% those with HbA1c data) | |
| Undiagnosed diabetes (HbA1c \geq 6.5) after imputation HbA1c | 761 | 8.8% | |
| IGR (HbA1c 6-6.4%) before imputation HbA1c | 529 | 6.1% (13.6% those with HbA1c data) | |
| IGR (HbA1c 6-6.4%) after imputation HbA1c | 1492 | 17.3% | |
| | Mean | Standard deviation | Median |
| Age (years) | 49.6 | 18.7 | 49.0 |
| BMI (kg/m ²) | 27.4 | 5.4 | 26.6 |
| Total Cholesterol (mmol/l) | 5.4 | 1.1 | 5.4 |
| HDL Cholesterol (mmol/l) | 1.5 | 0.4 | 1.5 |
| HbA1c (%) | 5.7 | 0.8 | 5.6 |
| Systolic Blood Pressure (mm Hg) | 126.3 | 17.0 | 124.5 |
| EQ-5D (TTO) | 0.825 | 0.244 | 0.848 |
| BMI Body Mass Index; IMD Index of Multiple Deprivation; CVD Cardiovascular Disease; IGR Impaired Glucose Regulation; HDL High Density Lipoprotein; EQ-5D 5 dimensions EuroQol (health related quality of life index) ; TTO Time Trade-Off | | | |

A complete dataset was required for all individuals at baseline. However, no measurements for Fasting Plasma Glucose (FPG) or 2 hour glucose were obtained for the HSE 2011 cohort. In addition,

the questionnaire did not collect information about individual family history of diabetes or family history of Cardiovascular Disease (CVD). These variables were imputed from other datasets.

Many individuals were lacking responses to some questions but had data for others. One way of dealing with this is to exclude all individuals with incomplete data from the sample. However, this would have reduced the sample size dramatically, which would have been detrimental to the analysis. It was decided that it would be better to make use of all the data available to represent a broad range of individuals within the UK population. With this in mind, we decided to use assumptions and imputation models to estimate missing data.

MISSING DATA IMPUTATION

Ethnicity

Only a small number of individuals had missing data for ethnicity. In the QRISK2 algorithm the indicator for white includes individuals for whom ethnicity is not recorded. In order to be consistent with the QRISK2 algorithm we assumed that individuals with missing ethnicity data were white.

Anthropometric data

A large proportion of anthropometric data was missing in the cohort. Table 3 reports the number of individuals with two or more anthropometric records missing. This illustrates that only 758 individuals had no anthropometric data at all. Imputation models for anthropometric data were developed utilising observations from other measures to help improve their accuracy.

Table 3: Multi-way assessment of missing data

| Conditions | Number of individuals |
|--------------------------------------|-----------------------|
| No weight and no height | 1060 |
| No weight and no waist circumference | 907 |
| No weight and no hip circumference | 906 |
| No height and no waist circumference | 818 |
| No height and no hip circumference | 817 |
| No hip and no waist | 2865 |
| No anthropometric data | 758 |

Two imputation models were generated for each of the following anthropometric measures: weight, height, waist circumference and hip circumference. The first imputation method included an alternative anthropometric measure to improve precision. The second included only age and/or sex, to be used if the alternative measure was also missing. Simple ordinary least squares (OLS) regression models were used to predict missing data. Summary data for each measure confirmed that the data were approximately normally distributed. Covariate selection was made by selecting the

anthropometric measure that maximised the Adjusted R-squared statistic, and age and sex were included if the coefficients were statistically significant ($P < 0.1$).

The imputation models for weight are reported in Table 4. Individuals' sex and age were included in both models. A quadratic relationship between age and weight was identified. Waist circumference had a positive and significant relationship with weight. The R^2 for model 1 suggested that 80% of the variation in weight is described by the model. The R^2 for model 2 was much lower as only 18% of the variation in weight was described by age and sex. The residual standard error is reported for both models.

Table 4: Imputation model for weight

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | -17.76 | 50.249 |
| Sex | 2.614 | 13.036 |
| Age | 0.064 | 0.903 |
| Age*Age | -0.0027 | -0.0086 |
| Waist circumference | 1.060 | |
| R-squared | 0.7981 | 0.1831 |
| Residual standard error | 7.483 | 15.31 |

The imputation models for height are reported in Table 5. Individuals' sex and age were included in both models. A quadratic relationship between age and height was identified. Waist circumference had a positive and significant relationship with height. The R^2 for model 1 suggested that 53% of the variation in height is described by the model suggesting a fairly good fit. The R^2 for model 2 was slightly lower in which 52% of the variation in height was described by age and sex. The residual standard error is reported for both models.

Table 5: Imputation model for height

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | 157.4 | 162.1 |
| Sex | 12.82 | 13.43 |
| Age | 0.081 | 0.1291 |
| Age*Age | -0.0021 | -0.0025 |
| Waist circumference | 0.071 | |
| R-squared | 0.532 | 0.5244 |
| Residual standard error | 6.617 | 6.682 |

The imputation models for waist circumference are reported in Table 6. Individuals' sex and age were included in both models. A quadratic relationship between age and waist circumference fit to the data better than a linear relationship. Weight had a positive and significant relationship with waist circumference. The R^2 for model 1 suggested that 81% of the variation in waist circumference is described by the model suggesting a very good fit. The R^2 for model 2 was much lower in which only

22% of the variation in waist circumference was described by age and sex which is a moderately poor fit. The residual standard error is reported for both models.

Table 6: Imputation model for waist

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | 28.73 | 65.327 |
| Sex | 0.5754 | 9.569 |
| Age | 0.1404 | 0.7617 |
| Age*Age | 0.0007 | -0.0053 |
| Weight | 0.7098 | |
| R-squared | 0.8096 | 0.2196 |
| Residual standard error | 6.122 | 12.44 |

The imputation models for hip circumference are reported in Table 7. Individuals' sex and age were included in both models. A quadratic relationship between age and hip circumference fit to the data better than a linear relationship. Weight had a positive and significant relationship with hip circumference. The R^2 for model 1 suggested that 80% of the variation in hip circumference is described by the model suggesting a very good fit. The R^2 for model 2 was much lower in which only 2% of the variation in hip circumference was described by age and sex which is a very poor fit. The residual standard error is reported for both models.

Table 7: Imputation model for hip

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | 66.9145 | 96.891 |
| Sex | -8.3709 | -0.9783 |
| Age | -0.1714 | 0.3528 |
| Age*Age | 0.0021 | -0.0029 |
| Weight | 0.5866 | |
| R-squared | 0.7949 | 0.023 |
| Residual standard error | 4.539 | 10.1 |

Metabolic data

A large proportion of metabolic data was missing in the cohort, ranging from 2997-4309 observations for each metabolic measurement. Table 8 reports the number of individuals with two or more metabolic records missing. This illustrates that 2987 individuals have no metabolic data. Imputation models for metabolic data were developed utilising observations from other measures to help improve their accuracy.

Table 8: Multi-way assessment of missing data

| Conditions | Number of individuals |
|--------------------------------------|-----------------------|
| No HbA1c and no cholesterol | 4309 |
| No HbA1c and no blood pressure | 2997 |
| No cholesterol and no blood pressure | 3050 |
| No metabolic data | 2987 |

Two imputation models were generated for each of the following metabolic measures: total cholesterol, high density lipoprotein (HDL) cholesterol, HbA1c and systolic blood pressure (SBP) and. The first imputation method included an alternative metabolic measure to improve precision. The second included only age and/or sex, to be used if the alternative measure was also missing. Simple ordinary least squares (OLS) regression models were used to predict missing data. Summary data for each measure confirmed that the data were approximately normally distributed. Covariate selection was made by selecting the metabolic measure that maximised the adjusted R-squared statistic, and age and sex were included if the coefficients were statistically significant ($P < 0.1$).

These imputation models were developed to estimate metabolic data from information collected in the HSE. An alternative approach would have been to use estimates of these measures from the natural history statistical models. At the time of the analysis it was uncertain what form and design the natural history models would take, therefore the HSE imputation models were developed for use until a better alternative was found.

The imputation models for total cholesterol are reported in Table 9. Individuals' age was included in both models. A quadratic relationship between age and weight was identified. Diastolic blood pressure had a positive and significant relationship with total cholesterol. The R^2 for model 1 suggested that 20% of the variation in total cholesterol is described by the model. The R^2 for model 2 was lower in which only 18% of the variation in total cholesterol was described by age. The residual standard error is reported for both models.

Table 9: Imputation model for total cholesterol

| Coefficient | Model 1 | Model 2 |
|--------------------------|---------|---------|
| Intercept | 1.973 | 2.821 |
| Age | 0.0774 | 0.0904 |
| Age*Age | -0.0006 | -0.0007 |
| Diastolic blood pressure | 0.0159 | |
| R-squared | 0.2035 | 0.1792 |
| Residual standard error | 0.9526 | 0.9741 |

The imputation models for HDL cholesterol are reported in Table 10. Individuals' sex and age were included in both models. A quadratic relationship between age and height was identified. Diastolic blood pressure had a negative and significant relationship with HDL cholesterol. The R^2 for model 1

suggested that only 13% of the variation in HDL cholesterol is described by the model suggesting a relatively poor fit. The R^2 for model 2 suggested that 12% of the variation in HDL cholesterol was described by age and sex. The residual standard error is reported for both models.

Table 10: Imputation model for HDL Cholesterol

| Coefficient | Model 1 | Model 2 |
|--------------------------|---------|----------|
| Intercept | 1.501 | 1.383 |
| Sex | -0.279 | -0.274 |
| Age | 0.0086 | 0.0075 |
| Age*Age | -0.0001 | -0.00004 |
| Diastolic blood pressure | -0.0018 | |
| R-squared | 0.1198 | 0.1157 |
| Residual standard error | 0.4122 | 0.417 |

The imputation models for HbA1c are reported in Table 11. Individuals' age was included in both models. A quadratic relationship between age and HbA1c fit to the data better than a linear relationship. SBP had a positive and significant relationship with HbA1c. The R^2 for model 1 suggested that only 19% of the variation in HbA1c is described by the model, suggesting a modest fit. The R^2 for model 2 described 18% of the variation in HbA1c by age alone. The residual standard error is reported for both models.

Table 11: Imputation model for HbA1c

| Coefficient | Model 1 | Model 2 |
|-------------------------|----------|----------|
| Intercept | 4.732 | 4.962 |
| Age | 0.0141 | 1.422 |
| Age*Age | -0.00003 | -0.00003 |
| Systolic blood pressure | 0.002 | |
| R-squared | 0.1941 | 0.1835 |
| Residual standard error | 0.4243 | 0.4228 |

The imputation models for SBP are reported in Table 12. Individuals' sex and age were included in both models. A linear relationship between age and SBP fit to the data better than a quadratic relationship. Total cholesterol and HbA1c had a positive and significant relationship with SBP, whereas HDL cholesterol had a negative significant relationship with SBP. The R^2 for model 1 suggested that 22% of the variation in SBP is described by the model suggesting a modest fit. The R^2 for model 2 was similar in which only 20% of the variation in SBP was described by age and sex. The residual standard error is reported for both models.

Table 12: Imputation model for Systolic Blood Pressure

| Coefficient | Model 1 | Model 2 |
|-------------------------|---------|---------|
| Intercept | 84.983 | 104.132 |
| Sex | 6.982 | 6.396 |
| Age | 0.330 | 0.380 |
| Total cholesterol | 2.093 | |
| HDL cholesterol | -0.746 | |
| HbA1c | 1.986 | |
| R-squared | 0.2235 | 0.2047 |
| Residual standard error | 14.59 | 15.1 |

Treatment for Hypertension and Statins

A large proportion of individuals had missing data for questions relating to whether they received treatment for hypertension or high cholesterol. The majority of non-responses to these questions were coded to suggest that the question was not applicable to the individual. As a consequence it was assumed that individuals with missing treatment data were not taking these medications.

Gestational Diabetes

Only 30 respondents without current diabetes reported that they had been diagnosed with diabetes during a pregnancy in the past. Most individuals had missing data for this question due to it not being applicable. The missing data was assumed to indicate that individuals had not had gestational diabetes.

Anxiety/Depression

Most individuals who had missing data for anxiety and depression did so because the question was not applicable. A small sample N=69 refused to answer the question. We assumed that individuals with missing data for anxiety and depression did not have severe anxiety/depression.

Smoking

Individuals with missing data for smoking status were assumed to be non-smokers, without a history of smoking.

Rheumatoid Arthritis and Atrial Fibrillation

A very small sample of individuals had missing data for musculoskeletal illness (N=5) and atrial fibrillation (N=1). These individuals were assumed to not suffer from these illnesses.

Family history of diabetes

No questions in the HSE referred to the individual having a family history of diabetes, so this data had to be imputed. It was important that data was correlated with other risk factors for diabetes, such as HbA1c and ethnicity. We analysed a cross-section of the Whitehall II dataset to generate a logistic

1
2
3 regression to describe the probability that an individual has a history of diabetes conditional on their
4 HbA1c and ethnic origin. The model is described in Table 13.
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6

7 **Table 13: Imputation model for history of diabetes**
8

| | Coefficient |
|-----------------|-------------------|
| Intercept | -3.29077 (0.4430) |
| HbA1c | 0.28960 (0.0840) |
| HDL Cholesterol | 0.81940 (0.13878) |

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16 **Economic Activity**

17 Individuals without information about their employment status were assumed to be retired if aged 65
18 or over and in employment if under 65.
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24 **POPULATION SELECTION**

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27 The DPP is only eligible to individuals with impaired glucose regulation (IGR), defined as HbA1c 6-
28 6.4% in the model. The process of identifying eligible individuals or referring them to the DPP was
29 not explicitly modelled. Instead, all individuals from the HSE 2011 with actual or imputed HbA1c
30 levels between 6-6.4% are assumed to have been previously identified by a variety of means, and only
31 these IGR individuals are included in the simulation. This means that the costs of identifying IGR
32 individuals or referring them to the DPP intervention are not included.
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40 **GP ATTENDANCE IN THE GENERAL POPULATION**

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43 Frequency of GP visits (separate from NHS health checks) was simulated in the dataset for two
44 reasons; firstly, to estimate the healthcare utilisation for the ID population without diabetes and
45 cardiovascular disease and secondly, to predict the likelihood that individuals participate in
46 opportunistic screening for diabetes and vascular risks. It was assumed that GP attendance in the ID
47 population occurs at the same frequency as in the general population. However, for cost purposes,
48 consultations were assumed to take 40% longer than the general population average (see Costs
49 section).
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55 GP attendance conditional on age, sex, BMI, ethnicity, and health outcomes was derived from
56 analysis of wave 1 of the Yorkshire Health Study (11). The analysis used a negative binomial
57 regression model to estimate self-reported rate of GP attendance per 3 months (Table 14). The
58 estimated number of GP visits was multiplied by 4 to reflect the annual number of visits per year.
59
60

Table 14: GP attendance reported in the Yorkshire Health Study (N= 18,437)

| | Model 1 | | Model 2 | |
|-----------------------|---------|----------------|---------|----------------|
| | Mean | Standard error | Mean | Standard error |
| Age | 0.0057 | 0.0005 | 0.0076 | 0.0005 |
| Male | -0.1502 | 0.0155 | -0.1495 | 0.0159 |
| BMI | 0.0020 | 0.0015 | 0.0110 | 0.0015 |
| IMD score 2010 | 0.0043 | 0.0005 | | |
| Ethnicity (Non-white) | 0.1814 | 0.0370 | 0.2620 | 0.0375 |
| Heart Disease | 0.1588 | 0.0281 | 0.2533 | 0.0289 |
| Depression | 0.2390 | 0.0240 | 0.6127 | 0.0224 |
| Osteoarthritis | 0.0313 | 0.0240 | 0.2641 | 0.0238 |
| Diabetes | 0.2023 | 0.0270 | 0.2702 | 0.0278 |
| Stroke | 0.0069 | 0.0460 | 0.1659 | 0.0474 |
| Cancer | 0.1908 | 0.0400 | 0.2672 | 0.0414 |
| Intercept | 0.6275 | 0.0590 | -0.5014 | 0.0468 |
| Alpha | 0.3328 | 0.0097 | 0.3423 | 0.0108 |

LONGITUDINAL TRAJECTORIES OF METABOLIC RISK FACTORS

A detailed description of the statistical analysis behind the personalised metabolic risk factor trajectories that underlie disease risk in the SPHR Diabetes Prevention model has previously been published (12), so this report provides only a brief summary.

A statistical analysis of the Whitehall II cohort study (13) was developed to describe correlated longitudinal changes in metabolic risk factors including BMI, latent blood glucose (an underlying, unobservable propensity for diabetes), total cholesterol, HDL cholesterol and systolic blood pressure. Parallel latent growth modelling was used to estimate the unobservable latent glycaemia and from this identify associations with test results for HbA1c, FPG, and 2-hour glucose. The growth factors (longitudinal changes) for BMI, glycaemia, systolic blood pressure, total and HDL cholesterol could then be estimated through statistical analysis. These growth factors are conditional on several individual characteristics including age, sex, ethnicity, smoking, family history of CVD, and family history of type 2 diabetes. Deprivation was excluded from the final analysis because it was not associated with the growth models, and it estimated counter-intuitive coefficients.

Unobservable heterogeneity between individual growth factors not explained by patient characteristics was incorporated into the growth models as random error terms. Correlation between the random error terms for glycaemia, total cholesterol, HDL cholesterol and systolic blood pressure was estimated from the Whitehall II cohort. This means that in the simulation, an individual with a higher growth rate for glycaemia is more likely to have a higher growth rate of total cholesterol and systolic blood pressure.

The baseline observations for BMI, HbA1c, systolic blood pressure, cholesterol and HDL cholesterol were extracted from the Health Survey for England 2011 in order to simulate a representative sample. The predicted intercept for these metabolic risk factors was estimated using the Whitehall II analysis to give population estimates of the individuals' starting values, conditional on their characteristics. The difference between the simulated and observed baseline risk factors was taken to estimate the individuals' random deviation from the population expectation. The individual random error in the slope trajectory was sampled from a conditional multivariate normal distribution to allow correlation between the intercept and slope random errors.

Following a diagnosis of diabetes in the simulation all individuals experience an initial fall in HbA1c due to changes in diet and lifestyle as observed in the UKPDS trial (14). The expected change in HbA1c conditional on HbA1c at diagnosis was estimated by fitting a simple linear regression to three aggregate outcomes reported in the study. These showed that the change in HbA1c increases for higher HbA1c scores at diagnosis. The regression parameters to estimate change in HbA1c are reported in Table 15.

Table 15: Estimated change in HbA1c following diabetes diagnosis

| | Mean | Standard error |
|---------------------------|---------|----------------|
| Change in HbA1c Intercept | -2.9465 | 0.0444513 |
| HbA1c at baseline | 0.5184 | 0.4521958 |

After this initial reduction in HbA1c the longitudinal trajectory of HbA1c is estimated using the UKPDS outcomes model (15) rather than the Whitehall II statistical analysis. The UKPDS dataset is made up of a newly diagnosed diabetic population. As part of the UKPDS Outcomes model, longitudinal trial data were analysed using a random effects model, which means that unobservable differences between individuals are accounted for in the analysis. The model can be used to predict HbA1c over time from the point of diagnosis. The coefficients of the model are reported in Table 16.

Table 16: Coefficient estimates for HbA1c estimated from UKPDS data

| | Mean Coefficient | Coefficient standard error |
|--|------------------|----------------------------|
| Intercept | -0.024 | 0.017 |
| Log transformation of year since diagnosis | 0.144 | 0.009 |
| Binary variable for year after diagnosis | -0.333 | 0.05 |
| HbA1c score in last period | 0.759 | 0.004 |
| HbA1c score at diagnosis | 0.085 | 0.004 |

It was important to maintain heterogeneity in the individual glycaemic trajectories before and after diagnosis. Therefore, the random error terms used to determine individual trajectories in glycaemia before diagnosis were used to induce random noise in the trajectory after diagnosis. We sampled the

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3 expected random error term for each individual after diagnosis conditional on pre-diagnosis slope,
4 assuming a 0.8 correlation between these values.
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8 The epidemiological literature for many of the health outcomes included in the model treats diabetes
9 diagnosis as a discrete health state, rather than a continuous risk function conditional on HbA1c. This
10 poses two methodological challenges in type 2 diabetes modelling. Firstly, diabetes diagnosis is
11 complex with several tests and a high proportion of undetected diagnoses. Therefore, it is not
12 necessarily an appropriate indicator of risk in the model. Secondly, we would prefer to model the
13 relationship on a continuous scale to avoid artificial steps in risk; however the evidence is not always
14 available to describe risk on a continuous scale. We took two main steps to reduce the impact of this
15 on our model. Firstly, we used the HbA1c threshold of 6.5% to indicate type-2 diabetes regardless of
16 detection, and to ensure consistency in natural history across interventions and counterfactuals.
17 Secondly, the QRISK2 model was adapted to incorporate continuous risk by HbA1c.
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27 **METABOLIC RISK FACTOR SCREENING, DIAGNOSIS AND TREATMENT**

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29
30 It is assumed that individuals eligible for anti-hypertensive treatment or statins will be identified
31 through opportunistic screening if they meet certain criteria and attend the GP for at least one visit in
32 the simulation period.
33

- 34
35 1. Individuals with a history of cardiovascular disease;
- 36
37 2. Individuals with a major microvascular event (foot ulcer, blindness, renal failure or
38 amputation);
- 39
40 3. Individuals with diagnosed diabetes;
- 41
42 4. Individuals with systolic blood pressure greater than 160mmHg.

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44
45 Individuals may also be detected with diabetes through opportunistic screening if the following
46 criteria are met.
47

- 48
49 1. Individuals with a history of cardiovascular disease;
- 50
51 2. Individuals with a major microvascular event (foot ulcer, blindness, renal failure or
52 amputation);
- 53
54 3. At baseline individuals are assigned an HbA1c threshold above which diabetes is detected
55 opportunistically, individuals with an HbA1c above their individual threshold will attend the
56 GP to be diagnosed with diabetes. The threshold is sampled from the distribution of HbA1c
57 tests in a cohort of recently diagnosed patients in clinical practice (16).
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3 The base case has been designed to represent a health system with moderate levels of screening for
4 hypertension, diabetes, and dyslipidaemia.
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8 It is assumed that there are three, non-mutually exclusive outcomes from the vascular checks or
9 opportunistic screening. Firstly, that the patient receives statins to reduce cardiovascular risk.
10 Secondly, that the patient has high blood pressure and should be treated with anti-hypertensive
11 medication. Thirdly, the model evaluates whether the blood glucose test indicates a diagnosis with
12 type 2 diabetes. The following threshold estimates were used to determine these outcomes.
13
14

- 15
16 1. Statins are initiated if the individual has greater than or equal to 20% 10 year CVD risk
17 estimated from the QRISK2 2012 algorithm (17).
- 18
19 2. Anti-hypertensive treatment is initiated if systolic blood pressure is greater than 160. If the
20 individual has a history of CVD, diabetes or a CVD risk >20%, the threshold for systolic
21 blood pressure is 140 (18).
- 22
23 3. Type 2 diabetes is diagnosed if the individual has an HbA1c test greater than 6.5. In the base
24 case it is assumed that FPG and 2-hr glucose are not used for diabetes diagnosis. However,
25 future adaptations of the model could use these tests for diagnosis.
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31 It is assumed within the model that if initiated, statins are effective in reducing an individual's total
32 cholesterol, and so an average effect is applied to all patients being prescribed them. A recent HTA
33 reviewed the literature on the effectiveness and cost-effectiveness of statins in individuals with acute
34 coronary syndrome (20). This report estimated the change in LDL cholesterol for four statin
35 treatments and doses compared with placebo from a Bayesian meta-analysis. The analysis estimated a
36 reduction in LDL cholesterol of -1.45 for simvastatin. This estimate was used to describe the effect of
37 statins in reducing total cholesterol. It was assumed that the effect was instantaneous upon receiving
38 statins and maintained as long as the individual receives statins. It was also assumed that individuals
39 receiving statins no longer experienced annual changes in cholesterol. HDL cholesterol was assumed
40 constant over time if patients received statins.
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48 Non-adherence to statin treatment is a common problem. Two recent HTAs reviewed the literature on
49 continuation and compliance with statin treatment. They both concluded that there was a lack of
50 adequate reporting, but that the proportion of patients fully compliant with treatment appears to
51 decrease with time, particularly in the first 12 months after initiating treatment, and can fall below
52 60% after five years (20;21). Although a certain amount of non-compliance is included within trial
53 data, clinical trials are not considered to be representative of continuation and compliance in general
54 practice. A yearly reduction in statin compliance used in the HTA analysis is reported in Table 17. It
55 is based on the published estimate of compliance for the first five years of statin treatment for primary
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prevention in general clinical practice (21). Compliance declines to a minimum of 65% after five years of treatment. It is assumed that there is no further drop after five years.

Table 17: Proportion of patients assumed to be compliant with statin treatment, derived from Table 62 in (20)

| Year after statin initiation | 1 | 2 | 3 | 4 | 5 |
|------------------------------|-----|-----|------|------|------|
| Proportion compliant | 0.8 | 0.7 | 0.68 | 0.65 | 0.65 |

In the simulation, it is assumed in the base case that only 65% of individuals initiate statins when they are deemed eligible. However those that initiate statins remain on statins for their lifetime. Those who refuse statins may be prescribed them again at a later date.

The change in systolic blood pressure following antihypertensive treatment was obtained from a meta-analysis of anti-hypertensive treatments (22). This study identified an average change in systolic blood pressure of -8.4 mmHg for monotherapy with calcium channel blockers. It is assumed that this reduction in systolic blood pressure is maintained for as long as the individual receives anti-hypertensive treatment. For simplicity we do not assume that the individual switches between anti-hypertensive treatments over time. Once an individual is receiving anti-hypertensive treatment it is assumed that their systolic blood pressure is stable and does not change over time. Non-adherence and discontinuation are not modelled for anti-hypertensives.

COMORBID OUTCOMES AND MORTALITY

In every model cycle individuals within the model are evaluated to determine whether they have a clinical event, including mortality, within the cycle period. In each case the simulation estimates the probability that an individual has the event and uses a random number draw to determine whether the event occurred.

CARDIOVASCULAR DISEASE

First Cardiovascular event

Several statistical models for cardiovascular events were identified in a review of economic evaluations for diabetes prevention (4). The UKPDS outcomes model (23), Framingham risk equation (24) and QRISK2 (25) have all been used in previous models to estimate cardiovascular events. The Framingham risk equation was not adopted because, unlike the QRISK2 model, it is not estimated from a UK population. The UKPDS outcomes model would be ideally suited to estimate the risk of cardiovascular disease in a population diagnosed with type 2 diabetes. Whilst this is an important outcome of the cost-effectiveness model, there was concern that it would not be representative of individuals with normal glucose tolerance or impaired glucose regulation. It was important that

reductions in cardiovascular disease risk in these populations were represented to capture the population-wide benefits of public health interventions. The QRISK2 model was selected for use in the cost-effectiveness model because it is a validated model of cardiovascular risk in a UK population that could be used to generate probabilities for diabetic and non-diabetic populations. We considered using the UKPDS outcomes model specifically to estimate cardiovascular risk in patients with type 2 diabetes. However, it would not be possible to control for shifts in absolute risk generated by the different risk scores due to different baselines and covariates. This would lead to some individuals experiencing counterintuitive and favourable shifts in risk after onset of type 2 diabetes. Therefore, we decided to use diabetes as a covariate adjustment to the QRISK2 model to ensure that the change in individual status was consistent across individuals.

We accessed the 2012 version of the QRISK from the website (26). The QRISK2 equation estimates the probability of a cardiovascular event in the next year conditional on ethnicity, smoking status, age, BMI, ratio of total/HDL cholesterol, Townsend score, atrial fibrillation, rheumatoid arthritis, renal disease, hypertension, diabetes, and family history of cardiovascular disease. Data on all these variables was available from the HSE 2011. Table 18 reports the coefficient estimates for the QRISK2 algorithm. The standard errors were not reported within the open source code. Where possible, standard errors were imputed from a previous publication of the risk equation (27). Coefficients that were not reported in this publication were assumed to have standard errors of 20%.

Table 18: Coefficients from the 2012 QRISK2 risk equation and estimate standard errors

| Covariates | Estimated coefficients adjusting for individual characteristics | | | | | | | | |
|------------------------|---|----------------|-----------|----------------|-------------------------|---------|----------------|---------|----------------|
| | Women | | Men | | Interaction terms | Women | | Men | |
| | Mean | Standard error | Mean | Standard error | | Mean | Standard error | Mean | Standard error |
| White | 0.0000 | 0.0000 | 0.0000 | 0.0000 | Age1*former smoker | 0.1774 | 0.035 | -3.881 | 0.776 |
| Indian | 0.2163 | 0.0537 | 0.3163 | 0.0425 | Age1*light smoker | -0.3277 | 0.066 | -16.703 | 3.341 |
| Pakistani | 0.6905 | 0.0698 | 0.6092 | 0.0547 | Age1*moderate smoker | -1.1533 | 0.231 | -15.374 | 3.075 |
| Bangladeshi | 0.3423 | 0.1073 | 0.5958 | 0.0727 | Age1*Heavy smoker | -1.5397 | 0.308 | -17.645 | 3.529 |
| Other Asian | 0.0731 | 0.1071 | 0.1142 | 0.0845 | Age1*AF | -4.6084 | 0.922 | -7.028 | 1.406 |
| Caribbean | -0.0989 | 0.0619 | -0.3489 | 0.0641 | Age1*renal disease | -2.6401 | 0.528 | -17.015 | 3.403 |
| Black African | -0.2352 | 0.1275 | -0.3604 | 0.1094 | Age1*hypertension | -2.2480 | 0.450 | 33.963 | 6.793 |
| Chinese | -0.2956 | 0.1721 | -0.2666 | 0.1538 | Age1*Diabetes | -1.8452 | 0.369 | 12.789 | 2.558 |
| Other | -0.1010 | 0.0793 | -0.1208 | 0.0734 | Age1*BMI | -3.0851 | 0.617 | 3.268 | 0.654 |
| Non-smoker | 0.0000 | 0.0000 | 0.0000 | 0.0000 | Age1*family history CVD | -0.2481 | 0.050 | -17.922 | 3.584 |
| Former smoker | 0.2033 | 0.0152 | 0.2684 | 0.0108 | Age1*SBP | -0.0132 | 0.003 | -0.151 | 0.030 |
| Light smoker | 0.4820 | 0.0220 | 0.5005 | 0.0166 | Age1*Townsend | -0.0369 | 0.007 | -2.550 | 0.510 |
| Moderate smoker | 0.6126 | 0.0178 | 0.6375 | 0.0148 | Age2*former smoker | -0.0051 | 0.001 | 7.971 | 1.594 |
| Heavy smoker | 0.7481 | 0.0194 | 0.7424 | 0.0143 | Age2*light smoker | -0.0005 | 0.000 | 23.686 | 4.737 |
| Age 1* | 5.0327 | | 47.3164 | | Age2*moderate smoker | 0.0105 | 0.002 | 23.137 | 4.627 |
| Age 2* | -0.0108 | | -101.2362 | | Age2*Heavy smoker | 0.0155 | 0.003 | 26.867 | 5.373 |
| BMI* | -0.4724 | 0.0423 | 0.5425 | 0.0299 | Age2*AF | 0.0507 | 0.010 | 14.452 | 2.890 |
| Ratio Total / HDL chol | 0.1326 | 0.0044 | 0.1443 | 0.0022 | Age2*renal disease | 0.0343 | 0.007 | 28.270 | 5.654 |
| SBP | 0.0106 | 0.0045 | 0.0081 | 0.0046 | Age2*hypertension | 0.0258 | 0.005 | -18.817 | 3.763 |
| Townsend | 0.0597 | 0.0068 | 0.0365 | 0.0048 | Age2*Diabetes | 0.0180 | 0.004 | 0.963 | 0.193 |
| AF | 1.3261 | 0.0310 | 0.7547 | 0.1018 | Age2*BMI | 0.0345 | 0.007 | 10.551 | 2.110 |

| | | | | | | | | | |
|--|--------|--------|--------|--------|----------------------------|---------|-------|--------|-------|
| Rheumatoid arthritis | 0.3626 | 0.0319 | 0.3089 | 0.0445 | Age2*family history CVD | -0.0062 | 0.001 | 26.605 | 5.321 |
| Renal disease | 0.7636 | 0.0639 | 0.7441 | 0.0702 | Age2*SBP | 0.0000 | 0.000 | 0.291 | 0.058 |
| Hypertension | 0.5421 | 0.0115 | 0.4978 | 0.0112 | Age2*Townsend | -0.0011 | 0.000 | 3.007 | 0.601 |
| Diabetes | 0.8940 | 0.0199 | 0.7776 | 0.0175 | | | | | |
| Family history of CVD | 0.5997 | 0.0122 | 0.6965 | 0.0111 | | | | | |
| AF Atrial Fibrillation CVD Cardiovascular disease SBP systolic blood pressure * covariates transformed with fractional polynomials | | | | | | | | | |

The QRISK2 risk equation can be used to calculate the probability of a cardiovascular event including coronary heart disease (angina or myocardial infarction), stroke, transient ischaemic attacks and fatality due to cardiovascular disease. The equation estimates the probability of a cardiovascular event in the next period conditional on the coefficients listed in Table 18. The equation for the probability of an event in the next period is calculated as

$$p(Y = 1) = 1 - S(1)^\theta$$

$$\theta = \sum \beta X$$

The probability of an event is calculated from the survival function at 1 year raised to the power of θ , where θ is the sum product of the coefficients reported in Table 18 multiplied by the individual's characteristics. Underlying survival curves for men and women were extracted from the QRISK2 open source file. Mean estimates for the continuous variables were also reported in the open source files.

We modified the QRISK assumptions regarding the relationship between IGR, diabetes and cardiovascular disease. Firstly, we assumed that individuals with HbA1c > 6.5 have an increased risk of cardiovascular disease even if they have not received a formal diagnosis. Secondly, risk of cardiovascular disease was assumed to increase with HbA1c for test results greater than 6.5 to reflect observations from the UKPDS that HbA1c increases the risk of MI and Stroke (23). Thirdly, prior to type 2 diabetes (HbA1c > 6.5) HbA1c is linearly associated with cardiovascular disease. A study from the EPIC Cohort has found that a unit increase in HbA1c increases the risk of coronary heart disease by a hazard ratio of 1.25, after adjustment for other risk factors (28). Individuals with an HbA1c greater than the mean HbA1c observed in the HSE 2011 cohort were at greater risk of CVD than those with an HbA1c lower than the HSE mean.

The QRISK algorithm identifies which individuals experience a cardiovascular event but does not specify the nature of the event. The nature of the cardiovascular event was determined independently. A targeted search of recent Health Technology appraisals of cardiovascular disease was performed to identify a model for the progression of cardiovascular disease following a first event. All QRISK events are assigned to a specific diagnosis according to age and sex specific distributions of

cardiovascular events used in a previous Health Technology Assessment (HTA) (21). Table 19 reports the probability of cardiovascular outcomes by age and gender.

Table 19: The probability distribution of cardiovascular events by age and gender

| | Age | Stable angina | Unstable angina | MI rate | Fatal CHD | TIA | Stroke | Fatal CVD |
|-------|-------|---------------|-----------------|---------|-----------|-------|--------|-----------|
| Men | 45-54 | 0.307 | 0.107 | 0.295 | 0.071 | 0.060 | 0.129 | 0.030 |
| | 55-64 | 0.328 | 0.071 | 0.172 | 0.086 | 0.089 | 0.206 | 0.048 |
| | 65-74 | 0.214 | 0.083 | 0.173 | 0.097 | 0.100 | 0.270 | 0.063 |
| | 75-84 | 0.191 | 0.081 | 0.161 | 0.063 | 0.080 | 0.343 | 0.080 |
| | 85+ | 0.214 | 0.096 | 0.186 | 0.055 | 0.016 | 0.351 | 0.082 |
| Women | 45-54 | 0.325 | 0.117 | 0.080 | 0.037 | 0.160 | 0.229 | 0.054 |
| | 55-64 | 0.346 | 0.073 | 0.092 | 0.039 | 0.095 | 0.288 | 0.067 |
| | 65-74 | 0.202 | 0.052 | 0.121 | 0.081 | 0.073 | 0.382 | 0.090 |
| | 75-84 | 0.149 | 0.034 | 0.102 | 0.043 | 0.098 | 0.464 | 0.109 |
| | 85+ | 0.136 | 0.029 | 0.100 | 0.030 | 0.087 | 0.501 | 0.117 |

Subsequent Cardiovascular events

After an individual has experienced a cardiovascular event, it is not possible to predict the transition to subsequent cardiovascular events using QRISK2. Instead, as with assigning first CVD events, the probability of subsequent events was estimated from the HTA evaluating statins (21). This study reported the probability of future events, conditional on the nature of the previous event. Table 20 to Table 24 report the probabilities within a year of transitioning from stable angina, unstable angina, myocardial infarction (MI), transient ischemic attack (TIA) or stroke for individuals in different age groups. The tables suggests that, for example 99.46% of individuals with stable angina will remain in the stable angina state, but 0.13%, 0.32% and 0.01% will progress to unstable angina, MI or death from coronary heart disease (CHD) respectively.

Table 20: Probability of cardiovascular event conditional on age and status of previous event (age 45-54)

| Age 45-54 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9946 | 0.0013 | 0 | 0.0032 | 0 | 0 | 0 | 0 | 0.0009 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.9127 | 0.0495 | 0 | 0 | 0 | 0 | 0.0362 | 0.0016 |
| | Unstable angina (subsequent) | 0 | 0 | 0.9729 | 0.0186 | 0 | 0 | 0 | 0 | 0.0081 | 0.0004 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.128 | 0.8531 | 0 | 0.0015 | 0 | 0.0167 | 0.0007 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0162 | 0.978 | 0 | 0.0004 | 0 | 0.0052 | 0.0002 |
| | TIA | 0 | 0 | 0 | 0.0016 | 0 | 0.9912 | 0.0035 | 0 | 0.0024 | 0.0013 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0016 | 0 | 0 | 0.0431 | 0.9461 | 0.0046 | 0.0046 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0016 | 0 | 0 | 0.0144 | 0.9798 | 0.0021 | 0.0021 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Table 21: Probability of cardiovascular event conditional on age and status of previous event (age 55-64)

| Age 55-64 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9880 | 0.0033 | 0 | 0.0057 | 0 | 0 | 0 | 0 | 0.0030 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.8670 | 0.0494 | 0 | 0 | 0 | 0 | 0.0800 | 0.0036 |
| | Unstable angina (subsequent) | 0 | 0 | 0.9415 | 0.0471 | 0 | 0 | 0 | 0 | 0.0109 | 0.0005 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.1087 | 0.8409 | 0 | 0.0047 | 0 | 0.0439 | 0.0019 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0183 | 0.9678 | 0 | 0.0015 | 0 | 0.0119 | 0.0005 |
| | TIA | 0 | 0 | 0 | 0.0029 | 0 | 0.9666 | 0.0159 | 0 | 0.0079 | 0.0068 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0029 | 0 | 0 | 0.0471 | 0.9159 | 0.0171 | 0.0171 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0029 | 0 | 0 | 0.0205 | 0.9622 | 0.0072 | 0.0072 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Table 22: Probability of cardiovascular event conditional on age and status of previous event (age 65-74)

| Age 65-74 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9760 | 0.0060 | 0 | 0.0110 | 0 | 0 | 0 | 0 | 0.0070 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.8144 | 0.0479 | 0 | 0 | 0 | 0 | 0.1319 | 0.0059 |
| | Unstable angina (subsequent) | 0 | 0 | 0.9021 | 0.0844 | 0 | 0 | 0 | 0 | 0.0129 | 0.0006 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.0948 | 0.8106 | 0 | 0.0098 | 0 | 0.0811 | 0.0036 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0183 | 0.9585 | 0 | 0.0032 | 0 | 0.0191 | 0.0008 |
| | TIA | 0 | 0 | 0 | 0.0055 | 0 | 0.9174 | 0.0423 | 0 | 0.0185 | 0.0163 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0055 | 0 | 0 | 0.0485 | 0.8673 | 0.0393 | 0.0393 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0055 | 0 | 0 | 0.0237 | 0.9412 | 0.0148 | 0.0148 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Table 23: Probability of cardiovascular event conditional on age and status of previous event (age 75-84)

| Age 75-84 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9680 | 0.0087 | 0 | 0.0163 | 0 | 0 | 0 | 0 | 0.0070 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.7366 | 0.0448 | 0 | 0 | 0 | 0 | 0.2093 | 0.0093 |
| | Unstable angina (subsequent) | 0 | 0 | 0.8360 | 0.1484 | 0 | 0 | 0 | 0 | 0.0149 | 0.0007 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.0794 | 0.7502 | 0 | 0.0200 | 0 | 0.1440 | 0.0064 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0171 | 0.9466 | 0 | 0.0066 | 0 | 0.0286 | 0.0013 |
| | TIA | 0 | 0 | 0 | 0.0082 | 0 | 0.8514 | 0.0878 | 0 | 0.0185 | 0.0342 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0082 | 0 | 0 | 0.0471 | 0.7736 | 0.0856 | 0.0856 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0082 | 0 | 0 | 0.0251 | 0.9107 | 0.0280 | 0.0280 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Table 24: Probability of cardiovascular event conditional on age and status of previous event (age 85-94)

| Age 85-94 | | To | | | | | | | | | |
|-----------|--------------------------------------|---------------|-------------------|-------------------|--------|--------|--------|----------|----------|-----------|-----------|
| | | Stable angina | Unstable angina 1 | Unstable angina 2 | MI 1 | MI 2 | TIA | Stroke 1 | Stroke 2 | CHD death | CVD death |
| From | Stable angina | 0.9600 | 0.0114 | 0 | 0.0216 | 0 | 0 | 0 | 0 | 0.0070 | 0 |
| | Unstable angina (1 st yr) | 0 | 0 | 0.6315 | 0.0396 | 0 | 0 | 0 | 0 | 0.3149 | 0.0140 |
| | Unstable angina (subsequent) | 0 | 0 | 0.7255 | 0.2568 | 0 | 0 | 0 | 0 | 0.0170 | 0.0008 |
| | MI (1 st yr) | 0 | 0 | 0 | 0.0623 | 0.6498 | 0 | 0.0380 | 0 | 0.2393 | 0.0106 |
| | MI (subsequent) | 0 | 0 | 0 | 0.0148 | 0.9311 | 0 | 0.0124 | 0 | 0.0399 | 0.0018 |
| | TIA | 0 | 0 | 0 | 0.0108 | 0 | 0.7967 | 0.1286 | 0 | 0.0185 | 0.0453 |
| | Stroke (1 st yr) | 0 | 0 | 0 | 0.0108 | 0 | 0 | 0.0409 | 0.6153 | 0.1665 | 0.1665 |
| | Stroke (subsequent) | 0 | 0 | 0 | 0.0108 | 0 | 0 | 0.0248 | 0.8655 | 0.0494 | 0.0494 |

MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease

Congestive Heart Failure

The review of previous economic evaluations of diabetes prevention cost-effectiveness studies found that only a small number of models had included congestive heart failure as a separate outcome. Discussion with the stakeholder group identified that the UKPDS Outcomes model would be an appropriate risk model for congestive heart failure in type 2 diabetes patients. However, it was suggested that this would not be an appropriate risk equation for individuals with normal glucose tolerance or impaired glucose tolerance. The Framingham risk equation was suggested as an alternative. The main limitation of this equation is that it is quite old and is based on a non-UK population. However, a citation search of this article did not identify a more recent or UK based alternative.

Congestive heart failure was included as a separate cardiovascular event because it was not included as an outcome of the QRISK2. The Framingham Heart Study has reported logistic regressions to estimate the 4 year probability of congestive heart failure for men and women (29). The equations included age, diabetes diagnosis (either formal diagnosis or HbA1c>6.5), BMI and systolic blood pressure to adjust risk based on individual characteristics. We used this risk equation to estimate the probability of congestive heart failure in the SPHR diabetes prevention model. Table 25 describes the covariates for the logit models to estimate the probability of congestive heart failure in men and women.

Table 25: Logistic regression coefficients to estimate the 4-year probability of congestive heart failure from the Framingham study

| Variables | Units | Regression Coefficient | OR (95% CI) | P |
|---|-------------------|------------------------|------------------|-------|
| Men | | | | |
| Intercept | | -9.2087 | | |
| Age | 10 y | 0.0412 | 1.51 (1.31-1.74) | <.001 |
| Left ventricular hypertrophy | Yes/no | 0.9026 | 2.47 (1.31-3.77) | <.001 |
| Heart rate | 10 bpm | 0.0166 | 1.18 (1.08-1.29) | <.001 |
| Systolic blood pressure | 20 mm Hg | 0.00804 | 1.17 (1.04-1.32) | 0.007 |
| Congenital heart disease | Yes/no | 1.6079 | 4.99 (3.80-6.55) | <.001 |
| Valve disease | Yes/no | 0.9714 | 2.64 (1.89-3.69) | <.001 |
| Diabetes | Yes/no | 0.2244 | 1.25 (0.89-1.76) | 0.2 |
| Women | | | | |
| Intercept | | -10.7988 | | |
| Age | 10 y | 0.0503 | 1.65 (1.42-1.93) | <.001 |
| left ventricular hypertrophy | Yes/no | 1.3402 | 3.82 (2.50-5.83) | <.001 |
| Heart rate | 100 cL | 0.0105 | 1.11 (1.01-1.23) | 0.03 |
| Systolic blood pressure | 10 bpm | 0.00337 | 1.07 (0.96-1.20) | 0.24 |
| congenital heart disease | 20 mm Hg | 1.5549 | 4.74 (3.49-6.42) | <.001 |
| Valve disease | Yes/no | 1.3929 | 4.03 (2.86-5.67) | <.001 |
| Diabetes | Yes/no | 1.3857 | 4.00 (2.78-5.74) | <.001 |
| BMI | kg/m ² | 0.0578 | 1.06 (1.03-1.09) | <.001 |
| Valve disease and diabetes | Yes/no | -0.986 | 0.37 (0.18-0.78) | 0.009 |
| *OR indicates odds ratio; CI, confidence interval; LVH, left ventricular hypertrophy; CHD, congenital heart disease; and BMI, body mass index. Predicted probability of heart failure can be calculated as: $p = 1/(1+\exp(-x\beta))$, where $x\beta = \text{Intercept} + \text{Sum (of regression coefficient*value of risk factor)}$ | | | | |

Many of the risk factors included in this risk equation were not simulated in the diabetes model. We adjusted the baseline odds of CHD to reflect the expected prevalence of these symptoms in a UK population.

The proportion of the UK population with left ventricular hypertrophy was assumed to be 5% in line with previous analyses of the Whitehall II cohort (30). The heart rate for men was assumed to be 63.0bpm and for women 65.6bpm based on data from previous Whitehall II cohort analyses (31). The prevalence of congenital heart disease was estimated from an epidemiology study in the North of England. The study reports the prevalence of congenital heart disease among live births which was used to estimate the adult prevalence (32). This may over-estimate the prevalence, because the life expectancy of births with congenital heart disease is reduced compared with the general population. However, given the low prevalence it is unlikely to impact on the results. The prevalence of valve disease was estimated from the Echocardiographic Heart of England Screening study (33).

1
2
3 Using the estimated population values, the intercept values were adjusted to account for the
4 population risk in men and women. This resulted in a risk equation with age, systolic blood pressure,
5 diabetes and BMI in women to describe the risk of congestive heart failure.
6
7

8 9 MICROVASCULAR COMPLICATIONS

10
11 The review of previous economic evaluations identified that the UKPDS data was commonly used to
12 estimate the incidence of microvascular complications (4). This data has the advantage of being
13 estimated from a UK diabetic population. Given that the events described in the UKPDS outcomes
14 model are indicative of late stage microvascular complications, we did not believe it was necessary to
15 seek an alternative model that would be representative of an impaired glucose tolerance population.
16
17

18
19 We adopted a simple approach to modelling microvascular complications. We used both versions of
20 the UKPDS Outcomes model to estimate the occurrence of major events relating to these
21 complications, including renal failure, amputation, foot ulcer, and blindness (15;23). These have the
22 greatest cost and utility impact compared with earlier stages of microvascular complications, so are
23 more likely to have an impact on the SPHR diabetes prevention outcomes. As a consequence, we
24 assumed that microvascular complications only occur in individuals with HbA1c>6.5. Whilst some
25 individuals with hyperglycaemia (HbA1c>6.0) may be at risk of developing microvascular
26 complications, it is unlikely that they will progress to renal failure, amputation or blindness before a
27 diagnosis of diabetes. Importantly, we did not assume that only individuals who have a formal
28 diagnosis of diabetes are at risk of these complications. This allows us to incorporate the costs of
29 undetected diabetes into the simulation.
30
31

32
33 The UKPDS includes four statistical models to predict foot ulcers, amputation with no prior ulcer,
34 amputation with prior ulcer and a second amputation (23). In order to simplify the simulation of
35 neuropathy outcomes we consolidated the models for first amputation with and without prior ulcer
36 into a single equation. The parametric survival models were used to generate estimates of the
37 cumulative hazard in the current and previous period. From which the probability of organ damage
38 being diagnosed was estimated.
39
40

$$41 \quad p(\text{Death}) = 1 - \exp(H(t) - H(t - 1))$$

42
43 The functional form for the microvascular models included exponential and Weibull. The logistic
44 model was also used to estimate the probability of an event over the annual time interval.
45
46

47 48 **Retinopathy**

49
50 We used the UKPDS outcomes model v2 to estimate the incidence of blindness in individuals with
51 HbA1c>6.5. The exponential model assumes a baseline hazard λ , which can be calculated from the
52 model coefficients reported in Table 26 and the individual characteristics for \mathbf{X} .
53
54
55
56
57
58
59
60

$$\lambda = \exp(\beta_0 + X\beta_k)$$

Table 26: Parameters of the UKPDS2 Exponential Blindness survival model

| | Mean coefficient | Standard error | Modified mean coefficient |
|-------------------|------------------|----------------|---------------------------|
| Lambda | -11.607 | 0.759 | -10.967 |
| Age at diagnosis | 0.047 | 0.009 | 0.047 |
| HbA1c | 0.171 | 0.032 | 0.171 |
| Heart rate | 0.080 | 0.039 | |
| SBP | 0.068 | 0.032 | 0.068 |
| White Blood Count | 0.052 | 0.019 | |
| CHF History | 0.841 | 0.287 | 0.841 |
| IHD History | 0.0610 | 0.208 | 0.061 |

The age at diagnosis coefficient was multiplied by age in the current year if the individual had not been diagnosed with diabetes or by the age at diagnosis if the individual had received a diagnosis. The expected values for the risk factors not included in the SPHR model (heart rate and white blood count) were taken from Figure 3 of the UKPDS publication in which these are described (23). Assuming these mean values, it was possible to modify the baseline risk without simulating heart rate and white blood cell count.

Neuropathy

We used the UKPDS outcomes model v2 to estimate the incidence of ulcer and amputation in individuals with HbA1c>6.5. The parameters of the ulcer and first amputation models are reported in Table 27.

Table 27: Parameters of the UKPDS2 Exponential model for Ulcer, Weibull model for first amputation with no prior ulcer and exponential model for 1st amputation with prior ulcer

| | Ulcer | | 1 st Amputation no prior ulcer | | 1 st Amputation prior ulcer | | 2 nd Amputation | |
|---------------------|----------|----------------|---|----------------|--|----------------|----------------------------|----------------|
| | Logistic | | Weibull | | Exponential | | Exponential | |
| | Mean | Standard error | Mean | Standard error | Mean | Standard error | Mean | Standard error |
| lambda | -11.295 | 1.130 | -14.844 | 1.205 | -0.881 | 1.39 | -3.455 | 0.565 |
| Rho | | | 2.067 | 0.193 | | | | |
| Age at diagnosis | 0.043 | 0.014 | 0.023 | 0.011 | -0.065 | 0.027 | | |
| Female | -0.962 | 0.255 | -0.0445 | 0.189 | | | | |
| Atrial fibrillation | | | 1.088 | 0.398 | | | | |
| BMI | 0.053 | 0.019 | | | | | | |
| HbA1c | 0.160 | 0.056 | 0.248 | 0.042 | | | 0.127 | 0.06 |
| HDL | | | -0.059 | 0.032 | | | | |
| Heart rate | | | 0.098 | 0.050 | | | | |
| MMALB | | | 0.602 | 0.180 | | | | |
| PVD | 0.968 | 0.258 | 1.010 | 0.189 | 1.769 | 0.449 | | |
| SBP | | | 0.086 | 0.043 | | | | |
| WBC | | | 0.040 | 0.017 | | | | |
| Stroke History | | | 1.299 | 0.245 | | | | |

The exponential model assumes a baseline hazard λ , which can be calculated from the model coefficients reported in Table 27 and the individual characteristics for \mathbf{X} .

$$\lambda = \exp(\beta_0 + \mathbf{X}\boldsymbol{\beta})$$

The Weibull model for amputation assumes a baseline hazard:

$$h(t) = \rho t^{\rho-1} \exp(\lambda)$$

where λ is also conditional on the coefficients and individual characteristics at time t . The logistic model for ulcer is described below.

$$\Pr(y = 1|\mathbf{X}) = \frac{\exp(\mathbf{X}\boldsymbol{\beta})}{1 + \exp(\mathbf{X}\boldsymbol{\beta})}$$

The ulcer and amputation models include a number of covariates that were not included in the simulation. As such it was necessary to adjust the statistical models to account for these measures. We estimated a value for the missing covariates and added the value multiplied by the coefficient to the baseline hazard.

The expected values for the risk factors not included in the SPHR diabetes prevention model (heart rate, white blood count, micro-/macroalbuminuria, peripheral vascular disease and atrial fibrillation)

were taken from Figure 3 of the UKPDS publication in which these are described (23). In the ulcer model we assumed that 2% of the population had peripheral vascular disease.

The amputation risk model with a history of ulcer was not included in the simulation, but was used to estimate an additional log hazard ratio to append onto the amputation model without a history of ulcer. The log hazard was estimated for each model assuming the same values for other covariates. The difference in the log hazard between the two models was used to approximate the log hazard ratio for a history of ulcer in the amputation model (10.241). The final model specifications are reported in Table 28.

Table 28: Coefficients estimates for Ulcer and 1st Amputation

| | Ulcer | | 1 st Amputation | | 2 nd Amputation | |
|------------------|----------|----------------|----------------------------|----------------|----------------------------|----------------|
| | Logistic | | Weibull | | Exponential | |
| | Mean | Standard error | Mean | Standard error | Mean | Standard error |
| Lambda | -11.276 | 1.13 | -13.954 | 1.205 | -3.455 | 0.565 |
| Rho | | | 2.067 | 0.193 | | |
| Age at Diagnosis | 0.043 | 0.014 | 0.023 | 0.011 | | |
| Female | -0.962 | 0.255 | -0.445 | 0.189 | | |
| BMI | 0.053 | 0.019 | | | | |
| HbA1c | 0.160 | 0.056 | 0.248 | 0.042 | 0.127 | 0.06 |
| HDL | | | -0.059 | 0.032 | | |
| Stroke | | | 1.299 | 0.245 | | |
| Foot Ulcer | | | 10.241 | | | |

Nephropathy

We used the UKPDS outcomes model v1 to estimate the incidence of renal failure in individuals with HbA1c>6.5. Early validation analyses identified that the UKPDS v2 model implements in the SPHR model substantially overestimated the incidence of renal failure. The Weibull model for renal failure assumes a baseline hazard:

$$h(t) = \rho t^{\rho-1} \exp(\lambda)$$

where λ is also conditional on the coefficients and individual characteristics at time t . The parameters of the renal failure risk model are reported in Table 29.

Table 29: Parameters of the UKPDS2 Weibull renal failure survival model

| | Mean | Standard error |
|-----------------|---------|----------------|
| Lambda | -10.016 | 0.939 |
| Shape parameter | 1.865 | 0.387 |
| SBP | 0.404 | 0.106 |
| BLIND History | 2.082 | 0.551 |

CANCER

The conceptual model identified breast cancer and colorectal cancer risk as being related to BMI. However, these outcomes were not frequently included in previous cost-effectiveness models for diabetes prevention. Discussion with stakeholders identified the EPIC Norfolk epidemiology cohort study as a key source of information about cancer risk in a UK population. Therefore, we searched publications from this cohort to identify studies reporting the incidence of these risks. In order to obtain the best quality evidence for the relationship between BMI and cancer risk we searched for a recent systematic review and meta-analysis using key terms 'Body Mass Index' and 'Cancer', filtering for meta-analysis studies.

Breast cancer

Incidence rates for breast cancer in the UK were estimated from the European Prospective Investigation of Cancer (EPIC) cohort. This is a large multi-centre cohort study looking at diet and cancer. In 2004 the UK incidence of breast cancer by menopausal status was reported in a paper from this study investigating the relationship between body size and breast cancer (34). The estimates of the breast cancer incidence in the UK are reported in Table 30.

Table 30: UK breast cancer incidence

| | Number of Cases | Person Years | Mean BMI | Incidence Rate of per person-year | Reference |
|-------------------|-----------------|--------------|----------|-----------------------------------|-----------|
| UK pre-menopause | 102 | 103114.6 | 24 | 0.00099 | (34) |
| UK post-menopause | 238 | 84214.6 | 24 | 0.00283 | (34) |

A large meta-analysis that included 221 prospective observational studies has reported relative risks of cancers per unit increase in BMI, including breast cancer by menopausal status (35). We included a risk adjustment in the model so that individuals with higher BMI have a higher probability of pre-and post-menopausal breast cancer (35). In the simulation we adjusted the incidence of breast cancer by multiplying the linear relative risk by the difference in the individual's BMI and the average BMI reported in the EPIC cohort. The relative risk and confidence intervals per 5mg/m² increase in BMI are reported in Table 31.

Table 31: Relative risk of Breast cancer by BMI

| | Mean Relative risk | 2.5 th Confidence Interval | 97.5 th Confidence Interval | Reference |
|-------------------|--------------------|---------------------------------------|--|-----------|
| UK pre-menopause | 0.89 | 0.84 | 0.94 | (35) |
| UK post-menopause | 1.09 | 1.04 | 1.14 | (35) |

Colorectal cancer

Incidence rates for colorectal cancer in the UK were reported from the European Prospective Investigation of Cancer (EPIC) cohort. The UK incidence of colorectal cancer is reported by gender in a paper from this study investigating the relationship between body size and colon and rectal cancer (34). The estimates of the colorectal cancer incidence are reported in Table 32.

Table 32: UK colorectal cancer incidence

| | Number of Cases | Person Years | Mean Age | Mean BMI | Incidence Rate of per person-year | Reference |
|--------|-----------------|--------------|----------|----------|-----------------------------------|-----------|
| Male | 125 | 118468 | 53.1 | 25.4 | 0.00106 | (36) |
| Female | 145 | 277133 | 47.7 | 24.5 | 0.00052 | (36) |

The risk of colorectal cancer has been linked to obesity. We included a risk adjustment in the model to reflect observations that the incidence of breast cancer is increased in individuals with higher BMI. A large meta-analysis that included 221 prospective observational studies has reported relative risks of BMI and cancers, including colon cancer by gender (35). We selected linear relative risk estimates estimated from pooled European and Australian populations. In the simulation we adjusted the incidence of colorectal cancer by multiplying the relative risk by the difference in the individual's BMI and the average BMI reported in the EPIC cohort. The relative risk and confidence intervals per 5mg/m² increase in BMI are reported in Table 33.

Table 33: Relative risk of colon cancer by BMI

| | Mean Relative risk | 2.5 th Confidence Interval | 97.5 th Confidence Interval | Reference |
|-------------------|--------------------|---------------------------------------|--|-----------|
| UK pre-menopause | 1.21 | 1.18 | 1.24 | (35) |
| UK post-menopause | 1.04 | 1 | 1.07 | (35) |

OSTEOARTHRITIS

The stakeholder group requested that BMI and diabetes be included as independent risk factors for osteoarthritis based on recent evidence (37). Osteoarthritis had not been included as a health state in previous cost-effectiveness models. A search for studies using key words 'Diabetes', 'Osteoarthritis' and 'Cohort Studies' did not identify a UK based study with diabetes and BMI included as independent covariates in the risk model. The Bruneck cohort, a longitudinal study of inhabitants of a town in Italy reported diabetes and BMI as independent risk factors for osteoarthritis (37). The cohort may not be representative of the UK. However, the individuals are from a European country, the study has a large sample size and has estimated the independent effects of BMI and diabetes on the risk of osteoarthritis. No UK based studies identified in our searches met these requirements. The data used to estimate the incidence of osteoarthritis is reported in Table 34.

Table 34: Incidence of osteoarthritis and estimated risk factors

| | No cases | Person years | Mean BMI | Incidence rate | Reference |
|-------------|--------------|--------------|----------|----------------|-----------------------------|
| No diabetes | 73 | 13835 | 24.8 | 0.0053 | (37) |
| | Hazard ratio | 2.5th | 97.5th | | Reference |
| HR Diabetes | 2.06 | 1.11 | 3.84 | | (37) |
| HR BMI | 1.076 | 1.023 | 1.133 | | (37) Personal communication |

DEPRESSION

Depression was not included as a health state in previous cost-effectiveness models for diabetes prevention. However, a member of the stakeholder group identified that a relationship between diabetes and depression was included in the CORE diabetes treatment model (38). With this in mind, we decided to include depression as a health state in the model, but not to model its severity.

Some individuals enter the simulation with depression at baseline according to individual responses in the Health Survey for England 2011 questionnaire. Depression is described as a chronic state from which individuals do not completely remit. We did not estimate the effect of depression on the longitudinal changes for BMI, glycaemia, systolic blood pressure and cholesterol. As a consequence it was not possible to relate the impact of depression to the incidence of diabetes and CVD risk.

In the simulation, individuals can develop depression in any cycle of the model. The baseline incidence of depression among all individuals without a history of depression was estimated from a study examining the bidirectional association between depressive symptoms and type 2 diabetes (39). Although the study was not from a UK population, the US cohort included ethnically diverse men and women aged 45 to 84 years. We assumed that diagnosis of diabetes and/or cardiovascular disease increases the incidence of depression in individuals who do not have depression at baseline. We identified a method for inflating risk of depression for individuals with diabetes from the US cohort study described above (39). The risk of depression in individuals who have had a stroke was also inflated according to a US cohort study (40). Odds of depression and odds ratios for inflated risk of depression due to diabetes or stroke are presented in Table 35.

Table 35: Baseline incidence of depression

| Baseline Risk of depression | Mean | 2.5 th CI | 97.5th |
|------------------------------|--------|----------------------|--------|
| Depression cases in NGT | 336 | | |
| Person years | 9139 | | |
| Odds of depression | 0.0382 | | |
| Log odds of depression | -3.266 | | |
| Inflated risk for Diabetes | | | |
| Odds ratio of diabetes | 1.52 | 1.09 | 2.12 |
| Log odds ratio of diabetes | 0.419 | | |
| Inflate risk of stroke | | | |
| Odds ratio of stroke | 6.3 | 1.7 | 23.2 |
| Log odds ratio stroke | 1.8406 | | |
| NGT Normal Glucose Tolerance | | | |

MORTALITY

Cardiovascular Mortality

Cardiovascular mortality is included as an event within the QRISK2 and the probability of subsequent cardiovascular events obtained from an HTA assessing statins (21) as described in the cardiovascular disease section above.

Cancer Mortality

Cancer mortality rates were obtained from the Office of National statistics (41). The ONS report one and five year net survival rates for various cancer types, by age group and gender. Net survival was an estimate of the probability of survival from the cancer alone. It can be interpreted as the survival of cancer patients after taking into account the background mortality that the patients would have experienced if they had not had cancer.

The age-adjusted 5-year survival rate for breast cancer and colorectal cancer were used to estimate an annual risk of mortality assuming a constant rate of mortality. We assume that the mortality rate does not increase due to cancer beyond 5 years after cancer diagnosis. The five year survival rate for breast cancer is 84.3%, which translated into a 3.37% annual probability of death from breast cancer. The five year survival rate for persons with colorectal cancer is 55.3%, which translated into an 11.16% annual probability of death from colorectal cancer.

Other cause Mortality (including diabetes risk)

Other cause mortality describes the risk of death from any cause except cardiovascular disease and cancer. All-cause mortality rates by age and sex were extracted from the Office of National Statistics (42). The mortality statistics report the number of deaths by ICD codes for 5-year age groups. We subtracted the number of cardiovascular disease, breast and colorectal cancer related deaths from the all-cause mortality total to estimate other cause mortality rates by age and sex (Table 33).

Table 36: All cause and derived other cause mortality from the Office of National statistics

| | All cause | All cause | Other cause | Other cause | | All cause | All cause | Other cause | Other cause |
|----|-----------|-----------|-------------|-------------|-----|-----------|-----------|-------------|-------------|
| | Men | Women | Men | Women | | Men | Women | Men | Women |
| 1 | 0.0004 | 0.0003 | 0.0003 | 0.0003 | 51 | 0.0034 | 0.0024 | 0.0025 | 0.0017 |
| 2 | 0.0002 | 0.0002 | 0.0002 | 0.0002 | 52 | 0.0039 | 0.0026 | 0.0029 | 0.0019 |
| 3 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 53 | 0.0044 | 0.0028 | 0.0032 | 0.0020 |
| 4 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 54 | 0.0045 | 0.0032 | 0.0034 | 0.0022 |
| 5 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 55 | 0.0051 | 0.0033 | 0.0037 | 0.0024 |
| 6 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 56 | 0.0057 | 0.0037 | 0.0041 | 0.0027 |
| 7 | 0.0001 | 0.0001 | 0.0001 | 0.0000 | 57 | 0.0061 | 0.0041 | 0.0044 | 0.0030 |
| 8 | 0.0001 | 0.0001 | 0.0001 | 0.0000 | 58 | 0.0069 | 0.0041 | 0.0050 | 0.0030 |
| 9 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 59 | 0.0071 | 0.0050 | 0.0052 | 0.0036 |
| 10 | 0.0001 | 0.0000 | 0.0001 | 0.0000 | 60 | 0.0081 | 0.0054 | 0.0059 | 0.0040 |
| 11 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 61 | 0.0086 | 0.0057 | 0.0063 | 0.0042 |
| 12 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 62 | 0.0096 | 0.0062 | 0.0070 | 0.0046 |
| 13 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 63 | 0.0104 | 0.0067 | 0.0076 | 0.0050 |
| 14 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 64 | 0.0108 | 0.0072 | 0.0079 | 0.0053 |
| 15 | 0.0002 | 0.0001 | 0.0002 | 0.0001 | 65 | 0.0125 | 0.0082 | 0.0091 | 0.0061 |
| 16 | 0.0002 | 0.0001 | 0.0002 | 0.0001 | 66 | 0.0141 | 0.0090 | 0.0103 | 0.0067 |
| 17 | 0.0003 | 0.0002 | 0.0003 | 0.0002 | 67 | 0.0148 | 0.0097 | 0.0108 | 0.0072 |
| 18 | 0.0004 | 0.0002 | 0.0004 | 0.0002 | 68 | 0.0162 | 0.0107 | 0.0118 | 0.0079 |
| 19 | 0.0004 | 0.0002 | 0.0004 | 0.0002 | 69 | 0.0181 | 0.0118 | 0.0132 | 0.0087 |
| 20 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 70 | 0.0218 | 0.0138 | 0.0157 | 0.0101 |
| 21 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 71 | 0.0234 | 0.0145 | 0.0168 | 0.0106 |
| 22 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 72 | 0.0252 | 0.0167 | 0.0182 | 0.0122 |
| 23 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 73 | 0.0269 | 0.0173 | 0.0193 | 0.0127 |
| 24 | 0.0005 | 0.0002 | 0.0005 | 0.0002 | 74 | 0.0310 | 0.0200 | 0.0223 | 0.0147 |
| 25 | 0.0006 | 0.0003 | 0.0006 | 0.0002 | 75 | 0.0327 | 0.0222 | 0.0233 | 0.0157 |
| 26 | 0.0006 | 0.0003 | 0.0005 | 0.0002 | 76 | 0.0375 | 0.0249 | 0.0267 | 0.0176 |
| 27 | 0.0006 | 0.0004 | 0.0005 | 0.0003 | 77 | 0.0411 | 0.0284 | 0.0293 | 0.0202 |
| 28 | 0.0007 | 0.0003 | 0.0006 | 0.0003 | 78 | 0.0458 | 0.0321 | 0.0326 | 0.0228 |
| 29 | 0.0007 | 0.0003 | 0.0006 | 0.0003 | 79 | 0.0523 | 0.0358 | 0.0372 | 0.0254 |
| 30 | 0.0007 | 0.0004 | 0.0006 | 0.0003 | 80 | 0.0585 | 0.0411 | 0.0418 | 0.0289 |
| 31 | 0.0008 | 0.0004 | 0.0007 | 0.0004 | 81 | 0.0652 | 0.0456 | 0.0465 | 0.0321 |
| 32 | 0.0007 | 0.0005 | 0.0007 | 0.0004 | 82 | 0.0745 | 0.0530 | 0.0531 | 0.0372 |
| 33 | 0.0008 | 0.0005 | 0.0007 | 0.0004 | 83 | 0.0833 | 0.0606 | 0.0594 | 0.0426 |
| 34 | 0.0009 | 0.0005 | 0.0008 | 0.0004 | 84 | 0.0931 | 0.0678 | 0.0664 | 0.0476 |
| 35 | 0.0010 | 0.0006 | 0.0008 | 0.0005 | 85 | 0.1040 | 0.0760 | 0.0738 | 0.0537 |
| 36 | 0.0011 | 0.0006 | 0.0010 | 0.0005 | 86 | 0.1147 | 0.0872 | 0.0814 | 0.0617 |
| 37 | 0.0013 | 0.0006 | 0.0011 | 0.0005 | 87 | 0.1300 | 0.0977 | 0.0923 | 0.0692 |
| 38 | 0.0013 | 0.0007 | 0.0011 | 0.0006 | 88 | 0.1468 | 0.1106 | 0.1042 | 0.0782 |
| 39 | 0.0013 | 0.0007 | 0.0011 | 0.0006 | 89 | 0.1643 | 0.1242 | 0.1166 | 0.0879 |
| 40 | 0.0015 | 0.0009 | 0.0012 | 0.0006 | 90 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 41 | 0.0016 | 0.0010 | 0.0013 | 0.0007 | 91 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 42 | 0.0018 | 0.0010 | 0.0015 | 0.0008 | 92 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 43 | 0.0018 | 0.0012 | 0.0015 | 0.0009 | 93 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 44 | 0.0020 | 0.0012 | 0.0017 | 0.0009 | 94 | 0.2285 | 0.1982 | 0.1660 | 0.1425 |
| 45 | 0.0022 | 0.0014 | 0.0017 | 0.0010 | 95 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 46 | 0.0023 | 0.0016 | 0.0018 | 0.0011 | 96 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 47 | 0.0023 | 0.0015 | 0.0018 | 0.0011 | 97 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 48 | 0.0027 | 0.0017 | 0.0021 | 0.0012 | 98 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 49 | 0.0028 | 0.0019 | 0.0022 | 0.0014 | 99 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |
| 50 | 0.0030 | 0.0021 | 0.0023 | 0.0015 | 100 | 0.2285 | 0.1982 | 0.1751 | 0.1509 |

The rate of other cause mortality by age and sex was treated as the baseline hazard. Following input from stakeholders, an increased risk of mortality was assigned to individuals with diabetes using data

1
2
3 from a published meta-analysis (43). This study used data from 820,900 people from 97 prospective
4 studies to calculate hazard ratios for cause-specific death, according to baseline diabetes status (43).
5 Cause of death was separated into vascular disease, cancer and other cause mortality. From this study
6 we estimated that individuals with a diagnosis of diabetes have a fixed increased risk of other cause
7 mortality (Hazard ratio 1.8 (95% CI 1.71-1.9)). The estimates reported in the meta-analysis include
8 increased risk of death from renal disease, therefore mortality from renal disease was not simulated
9 separately to avoid double counting of benefits.
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15 16 UTILITIES

17 18 19 **Baseline Utility**

20
21 Baseline utilities for all individuals in the cohort were extracted from the HSE 2011. The tariffs for
22 the responses to the 3 level EQ-5D were derived from a UK population study (44). Baseline utility
23 was assumed to decline due to ageing. In the simulation, utility declines by an absolute decrement of
24 0.004 per year. This estimate is based on previous HTA modelling in cardiovascular disease (21).
25
26
27

28 29 **Utility Decrements**

30
31 The utility decrements for long term chronic conditions were applied to the age and BMI adjusted
32 EQ-5D score. It was assumed that a diagnosis of diabetes was not associated with a reduction in EQ-
33 5D independent of the utility decrements associated with complications, comorbidities or depression.
34 Cardiovascular disease, renal failure, amputation, foot ulcers, blindness, cancer, osteoarthritis and
35 depression were all assumed to result in utility decrements. The utility decrements are measured as a
36 factor which is applied to the individual's age and BMI adjusted baseline. If individuals have multiple
37 chronic conditions the utility decrements are multiplied together to give the individual's overall utility
38 decrement from comorbidities and complications, in line with current NICE guidelines for combining
39 comorbidities (45).
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45
46 Due to the number of health states it was not practical to conduct a systematic review to identify
47 utility decrements for all health states. A pragmatic approach was taken to search for health states
48 within existing health technology assessments for the relevant disease area or by considering studies
49 used in previous economic models for diabetes prevention. Discussions with experts in health
50 economic modelling were also used to identify prominent sources of data for health state utilities.
51
52
53

54
55 Two sources of data were identified for diabetes related complications. A recent study from the
56 UKPDS estimated the impact of changes in health states from a longitudinal cohort (46). They
57 estimated the impact of myocardial infarction, ischaemic heart disease, stroke, heart failure,
58 amputation and blindness on quality of life using seven rounds of EQ-5D questionnaires administered
59 between 1997 and 2007. This data was used to estimate the utility decrement for amputation and
60

1
2
3 congestive heart failure. The absolute decrement for amputation was converted into utility decrement
4 factors that could be multiplied by the individuals' current EQ-5D to estimate the relative effect of the
5 complication.
6
7

8
9 Utility decrements for renal failure and foot ulcers were not available from the UKPDS study
10 described above. A study by Coffey et al. (2000) was used to estimate utility decrements for renal
11 failure and foot ulcers (47). In this study, 2,048 subjects with type 1 and type 2 diabetes were
12 recruited from specialty clinics. The Self-Administered Quality of Well Being index (QWB-SA) was
13 used to calculate a health utility score.
14
15
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17
18 Utility decrements for cardiovascular events were taken from an HTA assessing statins to reflect the
19 utility decrements in all patients (21) rather than using the UKPDS, which is only representative of a
20 diabetic population. The study conducted a literature review to identify appropriate utility multipliers
21 for stable angina, unstable angina, myocardial infarction and stroke. We used these estimates in the
22 model and assume that transient ischaemic attack is not associated with a utility decrement in line
23 with this HTA.
24
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28
29 A systematic review of breast cancer utility studies was identified following consultation with
30 colleagues with experience in this area. The review highlighted a single burden of illness study with a
31 broad utility decrement for cancer (48), rather than utilities by cancer type or disease status. This
32 study was most compatible with the structure of the cost-effectiveness structure. Within this study
33 1823 cancer survivors and 5469 age-, sex-, and educational attainment-matched control subjects
34 completed EQ-5D questionnaires to estimate utility with and without cancer.
35
36
37
38

39 The utility decrement for osteoarthritis was taken from a Health Technology Assessment that assessed
40 the clinical effectiveness and cost-effectiveness of glucosamine sulphate/hydrochloride and
41 chondroitin sulphate in modifying the progression of osteoarthritis of the knee (49).
42
43
44

45 A review of cost-effectiveness studies highlights the scarcity of studies of health-related quality of life
46 in depression (50). The utility studies identified in the review described depression states by severity
47 and did not adjust for comorbid conditions. Furthermore, the valuations were variable between studies
48 suggesting poor consistency in the estimations. Therefore, it was difficult to apply these in the model.
49 We decided to use a study which had used the EQ-5D in an RCT, for consistency with our utility
50 measure (51). They report an average post treatment utility of 0.67, from which we estimated the
51 utility decrement compared with the average utility reported in the HSE dataset. The decrement was
52 then converted into a relative utility reduction.
53
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58
59 Table 37 reports the multiplicative utility factors that are used in the model to describe health utility
60 decrements from comorbid complications. The mean absolute decrement estimated in each study is

reported alongside the baseline utility for each study. The utility factor was estimated by dividing the implied health utility with the comorbidity by the baseline utility.

Table 37: Utility decrement factors

| | Mean Absolute decrement | St. error absolute decrement | Baseline Utility | Multiplicative Utility Factor | Source |
|---|-------------------------|------------------------------|------------------|-------------------------------|----------------|
| Foot ulcer | -0.099 | 0.013 | 0.689 | 0.856 | Coffey (47) |
| Amputation | -0.172 | 0.045 | 0.807 | 0.787 | UKPDS (52) |
| Blind | 0.033 | 0.027 | 0.807 | 1.041 | UKPDS (52) |
| Renal failure | -0.078 | 0.026 | 0.689 | 0.887 | Coffey (47) |
| Stable Angina | | | | 0.801 | Ward HTA (21) |
| Unstable Angina y1 | | | | 0.770 | Ward HTA (21) |
| Unstable Angina y2 | | | | 0.770 | Ward HTA (21) |
| Myocardial Infarction y1 | | | | 0.760 | Ward HTA (21) |
| Myocardial Infarction y2 | | | | 0.760 | Ward HTA (21) |
| Transient Ischaemic Attack | | | | 1.000 | Ward HTA (21) |
| Stroke y1 | | | | 0.629 | Ward HTA (21) |
| Stroke y2 | | | | 0.629 | Ward HTA (21) |
| Breast Cancer | -0.060 | | 0.800 | 0.913 | Yabroff (48) |
| Colorectal Cancer | -0.060 | | 0.800 | 0.913 | Yabroff (48) |
| Osteoarthritis | -0.101 | | | | Black HTA (49) |
| Depression | -0.116 | | 0.7905 | 0.875 | Benedict (51) |
| Congestive Heart Failure | -0.101 | 0.032 | | 0.875 | UKPDS (52) |
| UKPDS baseline utility 0.807; HSE baseline 0.7905 | | | | | |

COSTS

At any given time period of the model individuals can have multiple health complications that incur direct healthcare costs. Some of the health states are mutually exclusive; however an individual can accrue multiple complications within the model. Each health state is associated with an average cost, which is accrued by all individuals for every time period for which the state is indicated. Resource use for each comorbidity is added together and no savings are assumed to be made from the use of the same resources for two or more comorbidities for an individual. An exception to this is an assumed adjustment to the utilisation of GP services for individuals with chronic diseases. In the majority of cases it is assumed that the unit costs of healthcare for someone with ID would be the same as the unit costs for an individual in the general population. The exception was cost for a GP appointment, which was expected to be 40% higher than in the general population due to increased length of consultation. All costs were inflated to 2014/15 values using the retail price index where necessary, from the Personal Social Services Research Unit (PSSRU) sources of information (53). Table 38 shows a summary of all the unit costs used in the model and their sources.

Table 38: Summary of all drug, treatment, care and resource costs included in the model

| Drug, Treatment, Care and Resource Costs of | | Cost per year/ incident in 2014/15 prices (* 2006 prices) | Source |
|--|---|--|------------|
| Screening and Intervention costs | | | |
| | Intervention per person | £270 | PHE |
| First line diabetes treatment - low cost diabetes monotherapy | | | |
| | Ongoing costs of diabetes monotherapy – made up of... | £79.06 | |
| | Metformin 500 mg <i>bid</i> standard (85% of patients) or modified release (15%) tablets | £18.83 | BNF (54) |
| | Nurse at GP (consultation) | £25.52 | PSSRU (53) |
| | Health care assistant (10 mins) | £3.40 | PSSRU (53) |
| | Urine sample | £1.00 | (55) |
| | Eye screening | £24.31 | (56) |
| | Lab tests – made up of... | £6.00 | |
| | <i>HbA1c test</i> | £3.00 | (55) |
| | <i>Lipids test</i> | £1.00 | (55) |
| | <i>Liver function test</i> | £1.00 | (55) |
| | <i>B12 test</i> | £1.00 | (55) |
| | Additional first year costs of diabetes monotherapy – made up of... | £103 | |
| | Nurse at GP (2 x consultations) | £51.03 | PSSRU (53) |
| | Health care assistant (2 x 10 mins) | £6.80 | PSSRU (53) |
| | Urine sample (x2) | £2.00 | (55) |
| | Lab tests as above (x2) | £12.00 | (55) |
| | Smoking cessation (central estimate of cost of nicotine replacement therapy) taken up by 50% of the assumed 20% of population who smoke | £30.90 | PSSRU (53) |
| | Second line diabetes treatment - Metformin and Gliptins– made up of... | £529 | |
| | Sitagliptin 100 mg daily | £434 | BNF (54) |
| | Metformin 500 mg <i>bid</i> standard (85% of patients) or modified release (15%) tablets | £85 | BNF (54) |
| | Self-monitoring strips (82 per annum) (57) | £16.36 | BNF (54) |
| | Nurse at GP (consultation) | £25.52 | (53) |
| | Health care assistant (10 mins) | £3.40 | (53) |
| | Urine sample | £1.00 | (55) |
| | Eye screening | £24.31 | (56) |
| | Lab tests as for first line treatment | £6.00 | (55) |
| | Third line diabetes treatment - Insulin and oral anti-diabetics – made up of... | £1,503 | |
| | Nurse at GP (3 x consultations) | £76.55 | PSSRU (53) |
| | Health care assistant (3 x 10 mins) | £10.21 | PSSRU (53) |
| | Urine sample (x3) | £3.00 | (55) |
| | Eye screening | £24.31 | (56) |
| | Lab tests as for first line treatment (x3) | £18.00 | (55) |
| | Insulin treatment costs – made up of... | £1,376 | |
| | <i>Glargine</i> | £830.83 | (58) |
| | <i>Oral anti-diabetics</i> | £57.75 | (58) |
| | <i>Reagent test strips</i> | £292.74 | (58) |
| | <i>Hypoglycaemic rescue</i> | £30.98 | (58) |
| | <i>Pen delivery devices</i> | £72.44 | (58) |
| | <i>Sharps</i> | £90.98 | (58) |

| | | | |
|--|---|---------|------------|
| Other primary care costs | | | |
| | GP visit (17 minutes) | £46.95 | PSSRU (53) |
| | Diagnosis of hypertension (including ambulatory blood pressure monitoring) | £56.51 | (19) |
| | Annual treatment with statins (simvastatin 20 mg <i>bid</i>) | £26.59 | BNF (54) |
| | Annual treatment with anti-hypertensives | £195.94 | (59) |
| Cardiovascular disease costs | | | |
| | Unstable Angina year 1: <i>Secondary care costs: 100% hospitalisation, 50% revascularisation procedure, three outpatient appointments.</i> <i>Primary care costs (three GP visits) and medications</i> | £4,674 | (20) |
| | Myocardial infarction year 1 <i>Secondary care costs: 100% hospitalisation, 50% revascularisation procedure, three outpatient appointments</i> <i>Primary care costs (three GP visits) and medications.</i> | £4,813 | (20) |
| | Subsequent ACS care costs <i>Secondary care costs (one outpatient appointment).</i> <i>Primary care costs (three GP visits) and medications.</i> | £410 | (20) |
| | Stroke year 1 (NHS costs) <i>Costs of acute events reported in Youman et al. (60) weighted by the distribution of severity of stroke (21).</i> | £9,716 | (60) |
| | Social care costs of stroke in subsequent years <i>The costs of ongoing care at home or in an institution weighted by the distribution of severity of stroke and discharge locations.</i> | £2,730 | (20) |
| | Fatal coronary heart disease <i>Assumed that 50% of fatalities incurred cost.</i> | £713 | (61) |
| | Fatal non cardiac vascular event <i>Assumed that 50% of fatalities incurred cost.</i> | £4,443 | (60) |
| | Congestive heart failure | £3,091 | UKPDS (62) |
| Other complications of diabetes costs | | | |
| | Renal failure – weighted composite of... | £25,046 | |
| | <i>Haemodialysis with overheads</i> | £42,049 | (63) |
| | <i>Automated peritoneal dialysis</i> | £27,217 | (63) |
| | <i>Continuous ambulatory peritoneal dialysis</i> | £19,742 | (63) |
| | <i>Transplant (year 1)</i> | £23,660 | (64) |
| | <i>Immunosuppressant (10 years)</i> | £6,959 | (64) |
| | Foot ulcers | £216 | (65) |
| | Amputation first year | £10,101 | UKPDS (66) |
| | Amputation subsequent years | £1,896 | UKPDS (66) |
| | Blindness first year | £1,434 | UKPDS (66) |
| | Blindness subsequent years | £479 | UKPDS (66) |
| | Breast cancer | £13,818 | (67) |
| | Colorectal cancer | £18,729 | (68) |
| | Osteoarthritis | £962 | (69) |
| | Depression - made up of... | £137 | (70) |
| | <i>Practice nurse at surgery</i> | £13.70 | |
| | <i>Practice nurse at home visit</i> | £0.54 | |
| | <i>Practice nurse telephone</i> | £0.99 | |
| | <i>Health visitor</i> | £1.94 | |
| | <i>District nurse</i> | £0.38 | |
| | <i>Other nurse</i> | £1.17 | |
| | <i>HCA phlebotomist</i> | £1.05 | |

| | | | | |
|--|--|-------------------------------|-------|--|
| | | <i>Other primary care</i> | £4.85 | |
| | | <i>Out of hours</i> | £6.18 | |
| | | <i>NHS direct</i> | £2.28 | |
| | | <i>Walk-in centre</i> | £8.15 | |
| | | <i>Prescribed medications</i> | £74 | |
| | | <i>Secondary care</i> | £21 | |
| Assumed 20% smoking prevalence and 50% uptake of smoking cessation services SANG Stable angina; UANG unstable angina; MI myocardial infarction; TIA transient ischemic attack; CHD congestive heart failure; ACS acute Coronary Syndrome; UKPDS United Kingdom prospective Diabetes Study. Assume | | | | |

Opportunistic screening

Recent guidelines for hypertension have recommended that hypertension be confirmed with ambulatory blood pressure monitoring (ABPM) (18). The cost of ABPM assessment is included in the cost of diagnosis (£53.40) (19), however, we assume that the test does not alter the initial diagnosis.

A cost of diabetes diagnosis is included in the model based on the cost of an HbA1c test.

The cost of screening for high cardiovascular risk was not included as a cost associated with initiation with statins because most GP practices in the UK routinely commission and use cardiovascular risk scores that are easy to access within a normal consultation.

Diabetes

A three stage diabetes treatment regimen is applied in the model as a trade-off between model simplicity and capturing key cost differences between the interventions. At diagnosis all patients are prescribed low cost treatments, represented by Metformin (weighted average of standard and modified release) to describe the average cost of these medications. If HbA1c increases above 7.4% the individual is prescribed the more expensive Gliptins in addition to Metformin, based on a recent HTA (71). For costing purposes the second drug to be added to Metformin was assumed to be Sitagliptin. The individual continues to receive Metformin plus Gliptins for a period of time until they require insulin. Within the model the individual is switched to insulin in the first annual cycle at which HbA1c exceeds 8.5% (71). The insulin Glargine was chosen to represent insulin treatment in the UK. The cost of diabetes in the year of diagnosis is assumed to be greater than subsequent years because the individual will receive more contact time whilst their diabetes is being controlled.

Other Primary Care Costs

Individuals who are prescribed statins receive a daily dose of 40mg of generic Simvastatin. The individual remains on statins for the rest of their life. A unit cost of anti-hypertensives was obtained from a 2004 study (59) and inflated to 2014/15 prices. Due to the number of different anti-hypertensive treatments available and possibilities for combination therapies, using the cost from this study of prescriptions was preferred to using costs directly from the BNF. The stakeholder group

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3 advised that attendance at visits to monitor cardiovascular risk on statins and anti-hypertensives are
4 not perfect. Therefore, the costs of GP attendance to monitor blood pressure and cardiovascular risk
5 are assumed to be accounted for within the model for GP attendance.
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8 9 **Cardiovascular costs**

10 Costs for cardiovascular disease were obtained from a 2009 HTA for high dose lipid-lowering therapy
11 (20). Table 38 shows the details of included costs. The costs of fatal stroke and MI were obtained
12 from two separate studies (60;61), and it was assumed that 50% of individuals would incur these costs.
13 The costs of congestive heart failure were estimated from the UKPDS costing study for complications
14 related to diabetes (62).
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17 18 19 **Microvascular costs**

20 The cost of renal failure was estimated from three studies reporting the costs of dialysis type (63), the
21 costs of transplantation (64) and the prevalence of dialysis and transplant (72). The overall cost was
22 estimated as a weighted average of the treatment outcomes.
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25 The cost of foot ulcers was estimated from a US Cost of Illness study (65). A search of the literature
26 did not identify any UK based studies. The costs were converted from dollars to pounds using
27 Purchasing Power Parities reported by the OECD (73).
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30 The costs of amputation and blindness in the first year of surgery and in subsequent years were
31 reported in a recent UKPDS costing study (66).
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34 35 36 **Costs of Other Comorbidities**

37 Disease progression for breast cancer and colorectal cancer was not included in the model. Therefore,
38 a lifetime cost of cancer care was imposed at diagnosis in the model. Costs for breast and colon cancer
39 were taken from two screening appraisals (67;68). Breast cancer costs were estimated as a weighted
40 average depending on the prognosis at diagnosis, whereas colon cancer costs were estimated as a
41 weighted average depending on the Dukes tumour stage.
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44 The annual cost of osteoarthritis was estimated in a costing study (69). In this report the authors
45 estimated the expected cost of osteoarthritis from three previous costing studies. The costs include GP
46 attendance, nurse consultations, replacement surgery, help at home and prescription medications.
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49 A recent trial to prevent secondary depressive episodes collected comprehensive cost data from a
50 sample of individuals with depression (70). The resource uses identified in the control arm were
51 extracted to estimate the costs of depression. The costs from this data were not implemented directly
52 into the model; this would have over-estimated the number of GP visits as the model already accounts
53 for GP attendance due to depression. Therefore, a revised estimate of the cost of depression,
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3 excluding GP consultation was estimated using updated unit costs. Given that this cost captures the
4 costs of depression following the first acute episode we assumed that this cost adequately described
5 the ongoing healthcare costs for individuals with a history of depression. It is possible that this will
6 overestimate costs for patients who successfully remit and avoid future depression. However, there is
7 evidence from the literature to suggest that individuals with a history of depression have a high
8 utilisation of healthcare resources to support this assumption (74).
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13 **INTERVENTION**

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17 The subgroup analysis estimates the per person cost savings and health outcomes of delivering the
18 DPP lifestyle intervention in the 22 chosen subgroups. Interventions will be commissioned from a
19 handful of national providers and will include a mixture of dietary educational advice and physical
20 activity, with the aim of reducing both weight and diabetes risk.
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24 The SPHR Diabetes Prevention Model does not explicitly model changes in diet or physical activity.
25 Instead interventions are assumed to impact directly upon individual risk factors such as BMI, blood
26 pressure, cholesterol and HbA1c. In the model these changes then impact upon incidence rates of type
27 2 diabetes and related diseases. This section of the technical appendix describes the assumptions
28 around the intervention that are used as default settings in the model.
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33 **Intervention Uptake**

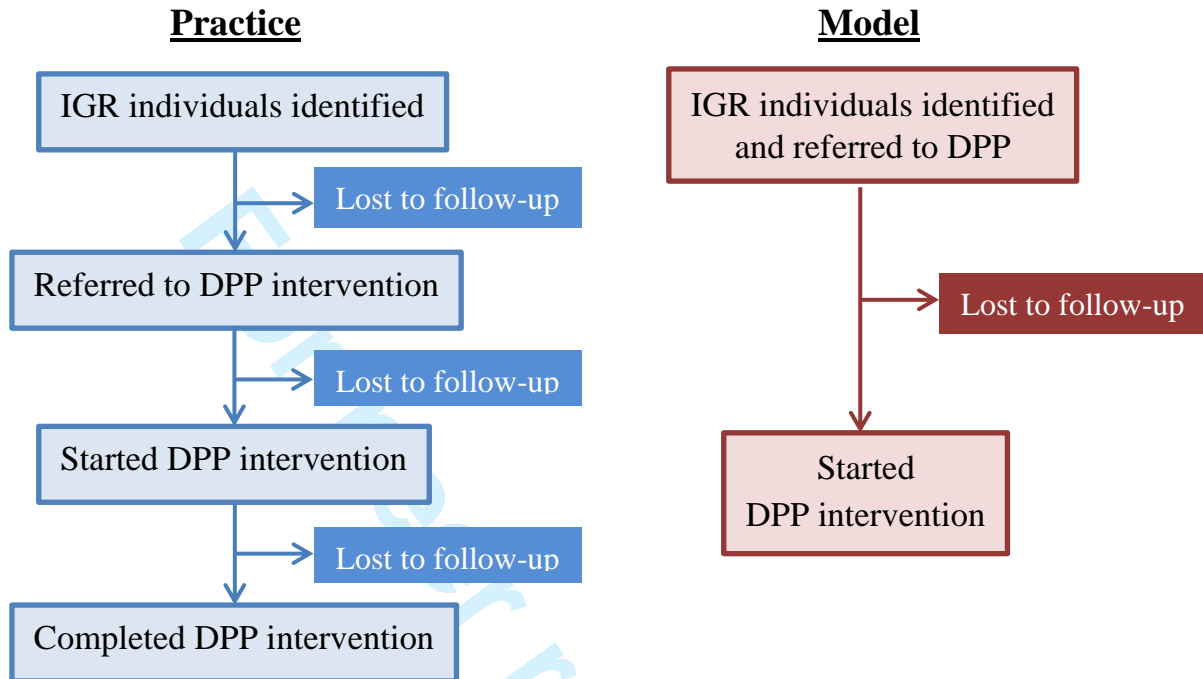
34
35 In practice, of the IGR individuals identified through HbA1c testing, only a proportion will receive
36 the intervention. Some individuals may not be referred for intervention. Of those referred, some will
37 choose not to take up the intervention, and of those that do attend the first intervention session, some
38 will not complete the intervention (Figure 2).
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43 Referral rates are not directly modelled, and instead it is assumed that all individuals are identified
44 and referred for intervention prior to the model start. This is partly because of lack of data around
45 referral rates and partly because referral rates are a function of the number of available intervention
46 places.
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50 Intervention uptake is defined as the proportion of those referred to the intervention who decide to
51 take up the intervention. The original aim of the analysis was to include data around differential
52 uptake of interventions in different population subgroups. However, good quality data could not be
53 identified and instead a uniform uptake rate of 32% has been used. It is assumed that those who
54 decided not to take up the intervention incur no costs and no benefits of intervention. No costs of
55 identifying or referring individuals to intervention are modelled. In practice, some individuals who
56 start the intervention will not complete it and therefore not gain full benefit. However, non-
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completion is partially accounted for in the estimate of effectiveness used in the model (74), so has not been explicitly built in. This is discussed further below.

Figure 2: Schematic showing intervention uptake and completion in practice and in the model



Intervention Effectiveness

The effectiveness data used in the model comes from a PHE evidence review of pragmatic lifestyle interventions for prevention of type 2 diabetes (75). This updates a previous review by Dunkley and others (76). Both reviews incorporate meta-analyses of a wide range of different lifestyle interventions aimed at reducing type-2 diabetes, and report a variety of outcomes including type-2 diabetes incidence rate and weight loss. The PHE evidence review also includes some analysis of differential effectiveness in population subgroups and for different intervention characteristics.

PHE, NHS England and Diabetes UK have specified that they wish the commissioned DPP intervention to fulfil 9-12 NICE guidelines as recommended in PH38 (3). NICE guidelines include using particular strategies that are associated with increased effectiveness, specifying the minimum amount of contact time and follow-up sessions, and delivering the programme through qualified practitioners. Both the PHE evidence review and the Dunkley meta-analysis indicate that interventions have increased effectiveness if they fulfil a greater number of NICE guidelines (75;76). In line with this, the model uses the results from the subgroup analysis of interventions fulfilling 9-12 NICE guidelines as the mean effectiveness (weight loss of 3.24kg – Table 12 in the PHE Evidence Review (75)).

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3 Unlike the Dunkley meta-analysis, the PHE evidence review does not report differences in HbA1c,
4 systolic blood pressure (SBP) or cholesterol for this subgroup of interventions. However, it is clear
5 from the Dunkley analysis that there will be concurrent reductions in these other metabolic factors,
6 and that the effectiveness of the intervention would be underestimated in the model if they were not
7 included. To incorporate these changes, the differences in HbA1c, SBP and cholesterol were
8 extrapolated from the Dunkley analysis to reflect the updated weight loss used from the PHE evidence
9 review. This assumes that relationships between changes in metabolic factors are linear. The
10 intervention effectiveness for each metabolic factor used in the model is reported in Table 39.
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17 **Table 39: Mean intervention effectiveness used in the model**

| | Mean values from Dunkley et al supplementary Table 7 (76) | Used in the DPP analysis: Default Mean weight loss from Table 12 of PHE evidence review for 9-12 NICE guidelines (75) | Used in the DPP analysis: Sensitivity analysis - 25% Lower |
|--------------------------------|---|---|--|
| Weight (kg) | -2.12 | -3.24 | -2.43 |
| BMI (kg/m ²) | -0.96 | -1.47 | -1.10 |
| HbA1c (%) | -0.13 | -0.20 | -0.15 |
| Systolic Blood Pressure (mmHg) | -4.3 | -6.57 | -4.93 |
| Total Cholesterol (mmol/l) | -0.18 | -0.28 | -0.21 |

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35 There is good evidence from the PHE evidence review and other studies that intervention
36 effectiveness is unlikely to be uniform across the population, and in particular varies according to the
37 baseline BMI of individuals, those with higher baseline BMI reporting increased weight loss and
38 diabetes risk reduction than those with lower baseline BMI (75;77-79). A differential intervention
39 effect by baseline BMI was therefore implemented in the model. Again this was taken from the PHE
40 evidence review as shown in Table 40 (75).
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45 **Table 40: Weight change results per unit baseline BMI from the PHE Evidence Review (75)**

| Subgroup | Weight change | Unit | Study Median |
|----------|--------------------------|-------------------------------------|------------------------|
| BMI | -0.23 kg (-0.53 to 0.07) | Per unit increase in mean study BMI | 31.5 kg/m ² |

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52 Personalised intervention effects for each individual, dependent upon their baseline BMI were
53 calculated using the following equation:
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$$\text{Personalised Intervention Effect} = \text{Mean Intervention Effect} \\ + \text{BMI Effect} * (\text{Individual BMI} - \text{Median BMI})$$

| | |
|--------|--|
| Where: | Mean Intervention Effect = -3.24 kg |
| | BMI Effect = -0.23 kg |
| | Individual BMI = the baseline BMI of each individual in the population |
| | Median BMI = 31.5 kg/m ² (the median of the mean BMI from each study included in the PHE meta-analysis) |

For example, for an individual with baseline BMI of 30, the personalised intervention effect would correspond to a weight loss of 2.895kg (smaller than the mean intervention effect), whereas for an individual with baseline BMI of 35, the personalised intervention effect would correspond to a weight loss of 4.045kg (larger than the mean intervention effect). Note that in individuals with BMI < 17.5, the effect of the intervention would be to actually increase weight. However, there are very few such IGR individuals in the model and an intervention focussing on weight loss may not in any case be the best option for individuals who are already underweight.

From this personalised change in weight due to the intervention, individualised changes in BMI, HbA1c, SBP and cholesterol were derived. Individuals in the intervention arm of the model who take up the intervention were assumed to receive this reduction in their metabolic factors instantaneously at the start of the model.

In practice, some individuals who start the intervention will not complete it. The PHE evidence review contains a mixture of studies that have used either intention to treat or complete case analysis (75). Intention to treat analysis takes non-completion into account, whereas complete case analysis does not. However, it is unclear which studies have been used to derive the estimate of effectiveness for 9-12 NICE guidelines. It is likely therefore that the effectiveness estimate used in the model only partially accounts for non-completion and therefore may be higher than is realistic in practice.

The Whitehall II BMI trajectory model estimates an indirect relationship between BMI change and changes in metabolic risk factors. The changes to HbA1c, systolic blood pressure and cholesterol were adjusted to avoid double counting of the indirect effects through BMI and direct effects of the intervention.

Intervention Costs

The actual intervention cost of the DPP will be determined through the DPP procurement process in early 2016. As this was still undergoing at the time of this analysis, PHE suggested that the mid average cost from their impact assessment of £270 per participant should be used as the default cost. This incorporates expected retention rates of participants, but does not include any local costs of identifying or referring individuals for intervention.

Duration of Intervention Effect

There is very little published information about how long the effectiveness of intensive lifestyle interventions is likely to endure in participants before weight is regained. In the model, default intervention effectiveness is assumed to decline linearly from its peak at the start of the model until individuals reach the BMI/SBP/HbA1c/cholesterol level that they would have been without intervention. It has been assumed for the analysis that this process takes five years.

MODEL PARAMETERS

All parameters used in the model, their distributions for PSA and their sources are documented here.

GP Attendance in the General Population

GP attendance is estimated from statistical analysis of the Yorkshire Health Study (11). In the PSA, the parameters are sampled from a multivariate normal distribution, using the mean estimates described in Table 41 and covariance matrix in Table 42.

Table 41: GP attendance reported in the Yorkshire Health Study (N= 18,437) ⁽¹¹⁾

| | Mean | Standard error | Uncertainty Distribution |
|-----------------------|---------|----------------|--------------------------|
| Age | 0.0076 | 0.0005 | MULTIVARIATE NORMAL |
| Male | -0.1495 | 0.0159 | MULTIVARIATE NORMAL |
| BMI | 0.0110 | 0.0015 | MULTIVARIATE NORMAL |
| Ethnicity (Non-white) | 0.2620 | 0.0375 | MULTIVARIATE NORMAL |
| Heart Disease | 0.2533 | 0.0289 | MULTIVARIATE NORMAL |
| Depression | 0.6127 | 0.0224 | MULTIVARIATE NORMAL |
| Osteoarthritis | 0.2641 | 0.0238 | MULTIVARIATE NORMAL |
| Diabetes | 0.2702 | 0.0278 | MULTIVARIATE NORMAL |
| Stroke | 0.1659 | 0.0474 | MULTIVARIATE NORMAL |
| Cancer | 0.2672 | 0.0414 | MULTIVARIATE NORMAL |
| Intercept | -0.5014 | 0.0468 | MULTIVARIATE NORMAL |
| Alpha | 0.3423 | 0.0108 | MULTIVARIATE NORMAL |

Table 42: Variance-covariance matrix for GP attendance regression

| | Age | Male | BMI | Ethnicity (Non-white) | Heart Disease | Depression | Osteoarthritis | Diabetes | Stroke | Cancer | Intercept | Alpha |
|-----------------------|--------|--------|--------|-----------------------|---------------|------------|----------------|----------|---------|--------|-----------|-------|
| Age | 0.0000 | | | | | | | | | | | |
| Male | 0.0000 | 0.0003 | | | | | | | | | | |
| BMI | 0.0000 | 0.0000 | 0.0000 | | | | | | | | | |
| Ethnicity (Non-white) | 0.0000 | 0.0000 | 0.0000 | 0.0014 | | | | | | | | |
| Heart Disease | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0008 | | | | | | | |
| Depression | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0005 | | | | | | |
| Osteoarthritis | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0006 | | | | | |
| Diabetes | 0.0000 | 0.0000 | 0.0000 | 0.0000 | -0.0001 | 0.0000 | 0.0000 | 0.0008 | | | | |
| Stroke | 0.0000 | 0.0000 | 0.0000 | 0.0000 | -0.0002 | -0.0001 | 0.0000 | -0.0001 | 0.0022 | | | |
| Cancer | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | -0.0001 | 0.0017 | | |

| | | | | | | | | | | | | |
|-----------|--------|--------|---------|---------|--------|--------|--------|--------|--------|--------|--------|--------|
| Intercept | 0.0000 | 0.0000 | -0.0001 | -0.0002 | 0.0002 | 0.0000 | 0.0002 | 0.0003 | 0.0000 | 0.0001 | 0.0022 | |
| Alpha | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0010 |

Whitehall II Statistical Model of Metabolic Trajectories

The metabolic trajectories used in the model are derived from statistical analysis of the longitudinal Whitehall II cohort (13). The parameters derived from this model are described in the following tables.

Table 43: Coefficient estimates for metabolic risk factor parallel growth models

| | Parameter Description | Estimated Mean | Standard error | p-value |
|-----------------------------|---|----------------|----------------|---------|
| BMI Intercept | | | | |
| α_{10} | Population mean BMI intercept | 2.2521 | 0.045 | <0.001 |
| γ_{10} | Age at baseline coefficient for BMI intercept | 0.0056 | 0.001 | <0.001 |
| | Sex coefficient for BMI intercept | -0.0311 | 0.012 | 0.009 |
| | Family history of CVD coefficient for BMI intercept | -0.0079 | 0.012 | 0.515 |
| ν_{10} | Random error term for BMI intercept | 0.1165 | 0.003 | <0.001 |
| BMI linear slope | | | | |
| α_{11} | Population mean BMI linear slope | 0.6409 | 0.042 | <0.001 |
| γ_{11} | Age at baseline coefficient for BMI linear slope | -0.0084 | 0.001 | <0.001 |
| | Sex coefficient for BMI linear slope | -0.0285 | 0.011 | 0.009 |
| | Family history of CVD coefficient for BMI linear slope | -0.0155 | 0.010 | 0.117 |
| ν_{11} | Random error term for BMI linear slope | 0.0222 | <0.001 | <0.001 |
| BMI quadratic slope | | | | |
| α_{12} | Population mean BMI quadratic slope | -0.2007 | 0.023 | <0.001 |
| γ_{12} | Age at baseline coefficient for quadratic slope | 0.0026 | <0.001 | <0.001 |
| | Sex coefficient for quadratic slope | 0.0089 | 0.006 | 0.147 |
| | Family history of CVD coefficient for quadratic slope | 0.0104 | 0.006 | 0.061 |
| ϵ_1 | Random error term for BMI | 0.0104 | <0.001 | <0.001 |
| Glyc Intercept | | | | |
| α_{20} | Population mean glyc intercept | 0 | NA | NA |
| γ_{20} | Smoker coefficient for glyc intercept | -0.1388 | 0.029 | <0.001 |
| τ_{20} | Association between BMI intercept and glyc intercept | 0.2620 | 0.024 | <0.001 |
| ν_{20} | Random error term for glyc intercept | 0.0851 | 0.008 | <0.001 |
| Glyc linear slope | | | | |
| α_{21} | Population mean glyc linear slope | -0.4255 | 0.071 | <0.001 |
| γ_{21} | Sex coefficient for glyc linear slope | 0.1486 | 0.045 | 0.001 |
| | Ethnicity coefficient for glyc linear slope | -0.0218 | 0.081 | 0.786 |
| | Family history of T2DM coefficient for glyc linear slope | -0.0512 | 0.054 | 0.345 |
| | Smoker coefficient for glyc linear slope | 0.1796 | 0.066 | 0.007 |
| τ_{21} | Association between BMI intercept and glyc linear slope | 0.0821 | 0.024 | 0.001 |
| τ_{22} | Association between BMI linear slope and glyc linear slope | 0.1984 | 0.073 | 0.007 |
| ν_{21} | Random error term for glyc linear slope | 0.0222 | 0.011 | 0.053 |
| Glyc quadratic slope | | | | |
| α_{22} | Population mean glyc quadratic slope | 0.1094 | 0.025 | <0.001 |
| γ_{22} | Sex coefficient for glyc quadratic slope | -0.0855 | 0.027 | 0.002 |
| | Ethnicity coefficient for glyc quadratic slope | 0.0899 | 0.049 | 0.067 |
| | Family history of T2DM coefficient for glyc quadratic slope | 0.0633 | 0.033 | 0.052 |
| | Smoker coefficient for glyc quadratic slope | -0.0390 | 0.040 | 0.330 |
| ν_{22} | Random error term for glyc quadratic slope | 0.0107 | 0.003 | 0.002 |
| ϵ_2 | Glyc measurement error | 0.0707 | 0.005 | <0.001 |
| SBP Intercept | | | | |
| α_{30} | Population mean SBP intercept | 0.6934 | 0.021 | <0.001 |
| γ_{30} | Age at baseline coefficient for SBP intercept | 0.0043 | <0.001 | <0.001 |

| | | | | |
|------------------|---|---------|--------|--------|
| | Sex coefficient for SBP intercept | 0.0380 | 0.004 | <0.001 |
| | Smoking coefficient for SBP intercept | -0.0243 | 0.006 | <0.001 |
| | Ethnicity coefficient for SBP intercept | 0.0078 | 0.007 | 0.300 |
| | Family history of CVD coefficient for SBP intercept | 0.0061 | 0.004 | 0.160 |
| τ_{31} | Association between BMI intercept and SBP intercept | 0.1080 | 0.006 | <0.001 |
| v_{30} | Random error term for SBP intercept | 0.0085 | 0.00 | <0.001 |
| SBP linear slope | | | | |
| α_{31} | Population mean SBP linear slope | -0.0227 | 0.021 | 0.278 |
| γ_{31} | Age at baseline coefficient for SBP linear slope | 0.0024 | <0.001 | <0.001 |
| | Sex coefficient for SBP linear slope | -0.0004 | 0.004 | 0.927 |
| | Smoking coefficient for SBP linear slope | 0.0205 | 0.005 | <0.001 |
| | Ethnicity coefficient for SBP linear slope | 0.0224 | 0.007 | 0.001 |
| | Family history of CVD coefficient for SBP linear slope | -0.0013 | 0.004 | 0.748 |
| τ_{31} | Association between BMI intercept and SBP linear slope | -0.0396 | 0.006 | <0.001 |
| | Association between BMI linear slope and SBP linear slope | 0.2325 | 0.019 | <0.001 |
| v_{31} | Random error term for SBP linear slope | 0.0024 | <0.001 | <0.001 |
| ϵ_3 | SBP measurement error variance | 0.0093 | <0.001 | <0.001 |
| TC Intercept | | | | |
| α_{40} | Population mean TC intercept | 2.9956 | 0.176 | <0.001 |
| γ_{40} | Age at baseline coefficient for TC intercept | 0.0456 | 0.003 | <0.001 |
| | Sex coefficient for TC intercept | 0.0660 | 0.036 | 0.070 |
| τ_{40} | Association between BMI intercept and TC intercept | 0.4459 | 0.049 | <0.001 |
| v_{40} | Random error term for TC intercept | 0.8960 | 0.025 | <0.001 |
| TC linear slope | | | | |
| α_{41} | Population mean TC linear slope | 2.1216 | 0.128 | <0.001 |
| γ_{41} | Age at baseline coefficient for TC linear slope | -0.0316 | 0.002 | <0.001 |
| | Sex coefficient for TC linear slope | -0.2677 | 0.026 | <0.001 |
| τ_{41} | Association between BMI intercept and TC linear slope | -0.4808 | 0.035 | <0.001 |
| τ_{42} | Association between BMI linear slope and TC linear slope | 0.9802 | 0.108 | <0.001 |
| v_{41} | Random error term for TC linear slope | 0.1583 | 0.011 | <0.001 |
| ϵ_4 | TC measurement error variance | 0.3426 | 0.006 | <0.001 |
| HDL Intercept | | | | |
| α_{50} | Population mean HDL intercept | 2.4124 | 0.054 | <0.001 |
| γ_{50} | Age at baseline coefficient for HDL intercept | 0.0032 | 0.011 | <0.001 |
| | Sex coefficient for HDL intercept | -0.3710 | 0.001 | <0.001 |
| τ_{51} | Association between BMI intercept and HDL intercept | -0.3514 | 0.015 | <0.001 |
| v_{50} | Random error term for HDL intercept | 0.0827 | -0.040 | <0.001 |
| HDL linear slope | | | | |
| α_{51} | Population mean HDL linear slope | 0.1241 | 0.034 | <0.001 |
| γ_{51} | Age at baseline coefficient for HDL linear slope | 0.0020 | 0.001 | <0.001 |
| | Sex coefficient for HDL linear slope | 0.0041 | 0.007 | 0.558 |
| τ_{51} | Association between BMI intercept and HDL linear slope | -0.0400 | 0.010 | <0.001 |
| v_{51} | Random error term for HDL linear slope | 0.0090 | 0.001 | <0.001 |
| ϵ_5 | HDL measurement error variance | 0.0333 | 0.001 | <0.001 |

Table 44: Coefficient estimates for latent glycaemic measurement model

| | Parameter Description | Estimated Mean | Standard error | p-value |
|---------------|-----------------------------------|----------------|----------------|---------|
| μ_0 | FPG intercept | 4.2903 | 0.089 | <0.001 |
| θ_{01} | Glycaemic factor to FPG | 1 | NA | NA |
| θ_{02} | Age to FPG | 0.0031 | 0.001 | 0.022 |
| θ_{03} | Sex to FPG | 0.2129 | 0.021 | <0.001 |
| θ_{04} | Ethnicity to FPG | 0.0100 | 0.037 | 0.786 |
| θ_{05} | Family history of diabetes to FPG | 0.1168 | 0.025 | <0.001 |
| ϵ_0 | FPG measurement error variance | 0.1649 | 0.007 | <0.001 |
| μ_1 | 2-hr Glucose intercept | 0.5707 | 0.223 | 0.011 |
| θ_{11} | Glycaemic factor to 2-hr glucose | 2.4384 | 0.078 | <0.001 |
| θ_{12} | Age to 2-hr glucose | 0.0716 | 0.003 | <0.001 |

| | | | | |
|-----------------|--|---------|-------|--------|
| θ_{13} | Sex to 2-hr glucose | -0.1411 | 0.058 | 0.014 |
| θ_{14} | Ethnicity to 2-hr glucose | 0.3047 | 0.100 | 0.002 |
| θ_{15} | Family history of diabetes to 2-hr glucose | 0.3496 | 0.068 | <0.001 |
| ε_1 | 2-hr measurement error variance | 2.3679 | 0.054 | <0.001 |
| μ_2 | HbA1c intercept | 4.4769 | 0.073 | <0.001 |
| θ_{21} | Glycaemic factor to HBA1c | 0.5074 | 0.016 | <0.001 |
| θ_{22} | Age to HBA1c | 0.0101 | 0.001 | <0.001 |
| θ_{23} | Sex to HBA1c | -0.0457 | 0.001 | <0.001 |
| θ_{24} | Ethnicity to HBA1c | 0.1854 | 0.030 | <0.001 |
| θ_{25} | Family history of diabetes to HBA1c | 0.0563 | 0.020 | 0.004 |
| ε_2 | HbA1c measurement error variance | 0.1166 | 0.003 | <0.001 |

Table 45: Covariance matrix Ω for individual random error

| | | | | | | | | | | | |
|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| | u_{10} | u_{11} | u_{20} | u_{21} | u_{22} | u_{30} | u_{31} | u_{40} | u_{41} | u_{50} | u_{51} |
| u_{10} | 0.1165 | | | | | | | | | | |
| u_{11} | 0.0095 | 0.0131 | | | | | | | | | |
| u_{20} | <0.0010 | <0.0010 | 0.0851 | | | | | | | | |
| u_{21} | <0.0010 | <0.0010 | 0.0222 | 0.0209 | | | | | | | |
| u_{22} | <0.0010 | <0.0010 | <0.0010 | <0.0010 | 0.0107 | | | | | | |
| u_{30} | <0.0010 | <0.0010 | 0.0080 | <0.0010 | <0.0010 | 0.0085 | | | | | |
| u_{31} | <0.0010 | <0.0010 | <0.0010 | 0.0018 | <0.0010 | <0.0017 | 0.0024 | | | | |
| u_{40} | <0.0010 | <0.0010 | 0.0324 | <0.0010 | <0.0010 | 0.0031 | <0.0010 | 0.8960 | | | |
| u_{41} | <0.0010 | <0.0010 | <0.0010 | <0.0012 | <0.0010 | <0.0010 | 0.0066 | -0.2229 | 0.1583 | | |
| u_{50} | <0.0010 | <0.0010 | -0.0118 | <0.0010 | <0.0010 | 0.0010 | <0.0010 | 0.0273 | <0.0010 | 0.0827 | |
| u_{51} | <0.0010 | <0.0010 | <0.0010 | -0.0059 | <0.0010 | <0.0010 | 0.0020 | <0.0010 | 0.0159 | 0.0061 | 0.0090 |

HbA1c trajectory in individuals diagnosed with type 2 diabetes

The input parameters for the initial reduction in HbA1c and long term trend in HbA1c following diagnosis, derived from analysis of the UKPDS outcomes model (15), are reported in Table 46 and Table 47 respectively.

Table 46: Estimated change in HbA1c in first year following diabetes diagnosis

| | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|---------------------------|--------------|-------------|-------------|------------------|
| Change in HbA1c Intercept | NORMAL | -2.9465 | 0.0444513 | -2.9465 |
| HbA1c at baseline | NORMAL | 0.5184 | 0.4521958 | 0.5184 |

Table 47: Estimated change in HbA1c following diabetes diagnosis over long term

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|---|--------------|-------------|-------------|------------------|
| Longitudinal HbA1c for diabetes intercept | NORMAL | -0.024 | 0.017 | -0.024 |
| Longitudinal HbA1c for diabetes log(time since diagnosis) | NORMAL | 0.144 | 0.009 | 0.144 |
| Longitudinal HbA1c for diabetes Second year | NORMAL | -0.333 | 0.05 | -0.333 |
| Longitudinal HbA1c for diabetes lag HbA1c | NORMAL | 0.759 | 0.004 | 0.759 |
| Longitudinal HbA1c for diabetes HbA1c at diagnosis | NORMAL | 0.085 | 0.004 | 0.0896 |

Systolic blood pressure and cholesterol trajectory following treatment

The changes in systolic blood pressure and total cholesterol following treatment with anti-hypertensives or statins, and statin uptake are reported in Table 48.

Table 48: Treatment effects following treatment

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|------------------------------------|--------------|-------------|-------------|------------------|--------|
| Simvastatin treatment effects | NORMAL | -1.45 | 0.11 | -1.45 | (20) |
| Anti-hypertensive treatment effect | NORMAL | -8.4 | 0.638 | -8.4 | (22) |
| Statin Uptake | UNIFORM | 0.65 | (0.4-0.9) | 0.65 | (21) |

Metabolic Risk Factor screening

The distribution for the HbA1c threshold at which opportunistic screening for type 2 Diabetes is initiated even if the individual does not have a history of cardiovascular disease, microvascular disease or identified impaired glucose regulation is reported in Table 49.

Table 49: Threshold for HbA1c opportunistic diagnosis

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|-----------------------|--------------|-------------|-------------|------------------|--------|
| HbA1c at diagnosis | NORMAL | 8.1 | 0.073 | 8.1 | (16) |

COMORBID OUTCOMES AND MORTALITY

Cardiovascular Disease

Cardiovascular risk is estimated using the QRISK2 model (25). Parameter distributions for men and women are reported in Table 50.

Table 50: Input parameters of the QRISK2 risk model

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|--------------------------|--------------|-------------|-------------|------------------|
| QRISK female ethnicity 2 | NORMAL | 0.2163 | 0.0537 | 0.2163 |
| QRISK female ethnicity 3 | NORMAL | 0.6905 | 0.069 | 0.6905 |
| QRISK female ethnicity 4 | NORMAL | 0.3423 | 0.1073 | 0.3423 |
| QRISK female ethnicity 5 | NORMAL | 0.0731 | 0.1071 | 0.0731 |
| QRISK female ethnicity 6 | NORMAL | -0.0989 | 0.0619 | -0.0989 |
| QRISK female ethnicity 7 | NORMAL | -0.2352 | 0.1275 | -0.2352 |
| QRISK female ethnicity 8 | NORMAL | -0.2956 | 0.1721 | -0.2956 |
| QRISK female ethnicity 9 | NORMAL | -0.1010 | 0.0793 | -0.1010 |
| QRISK female smoke 2 | NORMAL | 0.2033 | 0.0152 | 0.2033 |
| QRISK female smoke 3 | NORMAL | 0.48200 | 0.0220 | 0.4820 |
| QRISK female smoke 4 | NORMAL | 0.6126 | 0.0178 | 0.6126 |
| QRISK female smoke 5 | NORMAL | 0.7481 | 0.0194 | 0.7481 |
| QRISK female age 1 | NORMAL | 5.0373 | 1.0065 | 5.0327 |
| QRISK female age 2 | NORMAL | -0.0108 | 0.0022 | -0.0108 |
| QRISK female bmi | NORMAL | 0.4724 | 0.0423 | 0.4724 |
| QRISK female cholesterol | NORMAL | 0.6375 | 0.0143 | 0.6375 |

| | | | | | |
|----|--|----------|-----------|----------|-----------|
| 1 | QRISK female sbp | NORMAL | 0.0106 | 0.0045 | 0.0106 |
| 2 | QRISK female townsend | NORMAL | 0.060 | 0.0068 | 0.060 |
| 3 | QRISK female fibrillation | NORMAL | 1.3261 | 0.0310 | 1.3261 |
| 4 | QRISK female RA | NORMAL | 0.3626 | 0.0319 | 0.3626 |
| 5 | QRISK female Renal | NORMAL | 0.7636 | 0.0639 | 0.7636 |
| 6 | QRISK female Hypertension | NORMAL | 0.5421 | 0.0115 | 0.5421 |
| 7 | QRISK female diabetes | NORMAL | 0.8940 | 0.0199 | 0.8940 |
| 8 | QRISK female family history cvd | NORMAL | 0.5997 | 0.0122 | 0.5997 |
| 9 | QRISK female age 1 * smoke 1 | NORMAL | 0.1774 | 0.0355 | 0.1774 |
| 10 | QRISK female age 1 * smoke 2 | NORMAL | -0.3277 | 0.0655 | -0.3277 |
| 11 | QRISK age1 * smoke 3 | NORMAL | -1.1533 | 0.2307 | -1.1533 |
| 12 | QRISK female age 1 * smoke 4 | NORMAL | -1.5397 | 0.3079 | -1.5397 |
| 13 | QRISK female age 1 * atrial fibrillation | NORMAL | -4.6084 | 0.922 | -4.6084 |
| 14 | QRISK female age 1 * renal | NORMAL | -2.6401 | 0.5280 | -2.6401 |
| 15 | QRISK female age 1 * hypertension | NORMAL | -2.2480 | 0.4496 | -2.2480 |
| 16 | QRISK female age 1 * diabetes | NORMAL | -1.8452 | 0.3690 | -1.8452 |
| 17 | QRISK female age 1 * bmi | NORMAL | -3.0851 | 0.6170 | -3.0851 |
| 18 | QRISK female age 1 * family history cvd | NORMAL | -0.2481 | 0.0496 | -0.2481 |
| 19 | QRISK female age 1 * sbp | NORMAL | -0.0132 | 0.0026 | -0.0132 |
| 20 | QRISK female age 1 * town | NORMAL | -0.0369 | 0.0074 | -0.0369 |
| 21 | QRISK female age 2 * smoke 1 | NORMAL | -0.0053 | 0.0001 | -0.0053 |
| 22 | QRISK female age 2 * smoke 2 | NORMAL | -0.0005 | 0.0001 | -0.0005 |
| 23 | QRISK female age 2 * smoke 3 | NORMAL | -0.0105 | 0.0021 | -0.0105 |
| 24 | QRISK female age 2 * smoke 4 | NORMAL | -0.0155 | 0.0031 | -0.0155 |
| 25 | QRISK female age 2 * fibrillation | NORMAL | -0.0507 | 0.0101 | -0.0507 |
| 26 | QRISK female age 2 * renal | NORMAL | 0.0343 | 0.0069 | 0.0343 |
| 27 | QRISK female age 2 * hypertension | NORMAL | 0.0258 | 0.0051 | 0.0258 |
| 28 | QRISK female age 2 * diabetes | NORMAL | 0.0180 | 0.0036 | 0.0180 |
| 29 | QRISK female age 2 * bmi | NORMAL | 0.0345 | 0.0069 | 0.0345 |
| 30 | QRISK female age 2 * family history cardiovascular | NORMAL | -0.0062 | 0.0012 | -0.0062 |
| 31 | QRISK female age 2 * sbp | NORMAL | -0.000029 | 0.000006 | -0.000029 |
| 32 | QRISK female age 2 * townsend | NORMAL | -0.0011 | 0.0002 | -0.0011 |
| 33 | QRISK female 1 year survival | CONSTANT | 0.9983 | NA | NA |
| 34 | QRISK male ethnicity 2 | NORMAL | 0.3163 | 0.0425 | 0.3163 |
| 35 | QRISK male ethnicity 3 | NORMAL | 0.6092 | 0.0547 | 0.6092 |
| 36 | QRISK male ethnicity 4 | NORMAL | 0.5958 | 0.0727 | 0.5958 |
| 37 | QRISK male ethnicity 5 | NORMAL | 0.1142 | 0.0845 | 0.1142 |
| 38 | QRISK male ethnicity 6 | NORMAL | -0.3489 | 0.0641 | -0.3489 |
| 39 | QRISK male ethnicity 7 | NORMAL | -0.3604 | 0.1094 | -0.3604 |
| 40 | QRISK male ethnicity 8 | NORMAL | -0.2666 | 0.1538 | -0.2666 |
| 41 | QRISK male ethnicity 9 | NORMAL | -0.1208 | 0.0734 | -0.1208 |
| 42 | QRISK male SMOKE 2 | NORMAL | 0.2033 | 0.0152 | 0.2033 |
| 43 | QRISK male SMOKE 3 | NORMAL | 0.4820 | 0.0220 | 0.4820 |
| 44 | QRISK male SMOKE 4 | NORMAL | 0.6126 | 0.0178 | 0.6126 |
| 45 | QRISK male SMOKE 5 | NORMAL | 0.7481 | 0.0194 | 0.7481 |
| 46 | QRISK male age 1 | NORMAL | 47.316 | 9.4630 | 47.316 |
| 47 | QRISK male age 2 | NORMAL | -101.236 | 20.247 | -101.236 |
| 48 | QRISK male bmi | NORMAL | 0.5425 | 0.0299 | 0.5425 |
| 49 | QRISK male cholesterol | NORMAL | 0.14425 | 0.0022 | 0.14425 |
| 50 | QRISK male sbp | NORMAL | 0.0081 | 0.0046 | 0.0081 |
| 51 | QRISK male townsend | NORMAL | 0.0365 | 0.0048 | 0.0365 |
| 52 | QRISK male fibrillation | NORMAL | 0.7547 | 0.1018 | 0.7547 |
| 53 | QRISK male RA | NORMAL | 0.3089 | 0.0445 | 0.3089 |
| 54 | QRISK male renal | NORMAL | 0.7441 | 0.0702 | 0.7441 |
| 55 | QRISK male hypertension | NORMAL | 0.6965 | 0.011 | 0.6965 |
| 56 | QRISK male age 1 smoke 1 | NORMAL | -3.8805 | 0.7761 | -3.8805 |
| 57 | QRISK male age 1 smoke 2 | NORMAL | -16.703 | 3.3406 | -16.703 |
| 58 | QRISK male age 1 smoke 3 | NORMAL | -15.3738 | 3.5291 | -15.3738 |
| 59 | QRISK male age 1 smoke 4 | NORMAL | -17.6453 | 3.5291 | -17.6453 |

| | | | | |
|-------------------------------|----------|----------|--------|----------|
| QRISK male age 1 fibrillation | NORMAL | -7.0146 | 1.4056 | -7.0282 |
| QRISK male age 1 renal | NORMAL | -17.015 | 3.4029 | -17.015 |
| QRISK male age 1 hypertension | NORMAL | 33.9625 | 6.7925 | 33.9625 |
| QRISK male age 1 diabetes | NORMAL | 12.7886 | 2.5577 | 12.7886 |
| QRISK male age 1 bmi | NORMAL | 3.2680 | 0.6536 | 3.2680 |
| QRISK male age 1 fxcd | NORMAL | -17.9219 | 3.5844 | -17.9219 |
| QRISK male age 1 sbp | NORMAL | -0.1511 | 0.030 | -0.1511 |
| QRISK male age 1 town | NORMAL | -2.5502 | 0.5100 | -2.5502 |
| QRISK male age 2 SMOKE 1 | NORMAL | 7.9709 | 1.5942 | 7.9709 |
| QRISK male age 2 SMOKE 2 | NORMAL | 23.6859 | 4.7372 | 23.6859 |
| QRISK male age 2 SMOKE 3 | NORMAL | 23.1371 | 4.6274 | 23.1371 |
| QRISK male age 2 SMOKE 4 | NORMAL | 26.8674 | 5.3735 | 26.8674 |
| QRISK male age 2 Fibrillation | NORMAL | 14.4518 | 2.8904 | 14.4518 |
| QRISK male age 2 renal | NORMAL | 28.2702 | 5.654 | 28.2702 |
| QRISK male age 2 hypertension | NORMAL | -18.8167 | 3.7633 | -18.8167 |
| QRISK male age 2 diabetes | NORMAL | 0.9630 | 0.1926 | 0.963 |
| QRISK male age 2 bmi | NORMAL | 10.5517 | 2.1103 | 10.5517 |
| QRISK male age 2 FXCD | NORMAL | 26.6047 | 5.3209 | 26.6047 |
| QRISK male age 2 sbp | NORMAL | 0.2911 | 0.0582 | 0.2911 |
| QRISK male age 2 town | NORMAL | 3.007 | 0.6014 | 3.007 |
| QRISK2 male 1 year survival | CONSTANT | 0.997 | NA | NA |

The QRISK2 model was modified to allow a linear relationship between HbA1c and the risk of cardiovascular disease for individuals with IGR and type 2 Diabetes (HbA1c>42 mmol/mol). The parameter distributions for these additional inputs are reported in Table 51.

Table 51: Additional parameters for linear relationship between HbA1c and cardiovascular disease

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|---|--------------|-------------|-------------|------------------|--------|
| Female RR of MI due to HbA1c in diabetics | LOGNORMAL | 0.078 | 0.030 | 1.08 | (25) |
| Male RR of MI due to HbA1c in diabetics | LOGNORMAL | 0.108 | 0.023 | 1.11 | (25) |
| RR of stroke due to HbA1c in diabetics | LOGNORMAL | 0.092 | 0.026 | 1.096 | (25) |
| Log(RR) of cvd due to IGR | NORMAL | 0.223 | 0.043 | 1.25 | (28) |

Congestive Heart Failure

The parameter distributions for congestive heart failure based on the Framingham Heart Study (29) are reported in Table 52.

Table 52: Input parameters for Congestive Heart Failure Risk model for men and women

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|--|--------------|-------------|-------------|------------------|
| Male Heart failure baseline hazard | NORMAL | -9.2087 | 0.9209 | -9.2087 |
| Male Heart failure Age | NORMAL | 0.0412 | 0.0278 | 0.0412 |
| Male Heart failure LVH | NORMAL | 0.9026 | 1.0359 | 0.9026 |
| Male Heart failure Heart rate | NORMAL | 0.0166 | 0.0174 | 0.0166 |
| Male Heart failure Systolic blood pressure | NORMAL | 0.00804 | 0.0117 | 0.00804 |
| Male Heart failure CHD | NORMAL | 1.6079 | 0.5336 | 1.6079 |
| Male Heart failure Valve disease | NORMAL | 0.9714 | 0.6557 | 0.9714 |
| Male Heart failure Diabetes | NORMAL | 0.2244 | 0.6682 | 0.2244 |
| Female Heart failure baseline hazard | NORMAL | -10.7988 | 1.0799 | -10.7988 |

| | | | | |
|---|--------|---------|--------|---------|
| Female Heart failure Age | NORMAL | 0.0503 | 0.0301 | 0.0503 |
| Female Heart failure LVH | NORMAL | 1.3402 | 0.8298 | 1.3402 |
| Female Heart failure Heart rate | NORMAL | 0.0105 | 0.0193 | 0.0105 |
| Female Heart failure Systolic blood pressure | NORMAL | 0.00337 | 0.0109 | 0.00337 |
| Female Heart failure CHD | NORMAL | 1.5549 | 0.5973 | 1.5549 |
| Female Heart failure Valve disease | NORMAL | 1.3929 | 0.6707 | 1.3929 |
| Female Heart failure Diabetes | NORMAL | 1.3857 | 0.7105 | 1.3857 |
| Female Heart failure BMI | NORMAL | 0.0578 | 0.0555 | 0.0578 |
| Female Heart failure Valve disease & Diabetes | NORMAL | -0.986 | 1.4370 | -0.986 |

Microvascular Complications

The parameter distributions for the risk models for foot ulcer, blindness, renal failure, first amputation and second amputation are reported in Table 53. Parameters for renal failure were based on the UKPDS Outcomes Model 1 (15), whereas parameters for other microvascular complications were based on the UKPDS Outcomes Model 2 (23).

Table 53: Input parameters for microvascular complications

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|--|--------------|-------------|-------------|------------------|
| Renal failure baseline hazard | NORMAL | -10.016 | 0.939 | -10.016 |
| Renal failure Weibull shape | NORMAL | 1.865 | 1.4352 | 1.865 |
| Renal failure systolic blood pressure | NORMAL | 0.404 | 0.106 | 0.404 |
| Renal failure blindness | NORMAL | 2.082 | 0.551 | 2.082 |
| Foot ulcer baseline hazard | NORMAL | -11.295 | 1.13 | -11.295 |
| Foot ulcer age at diagnosis | NORMAL | 0.043 | 0.014 | 0.043 |
| Foot ulcer female | NORMAL | -0.962 | 0.255 | -0.962 |
| Foot ulcer BMI | NORMAL | 0.053 | 0.019 | 0.053 |
| Foot ulcer HbA1c | NORMAL | 0.16 | 0.056 | 0.16 |
| Foot ulcer PVD | NORMAL | 0.968 | 0.258 | 0.968 |
| Amputation baseline hazard | NORMAL | -14.844 | 1.205 | -14.844 |
| Amputation age at diagnosis | NORMAL | 0.023 | 0.011 | 0.023 |
| Amputation female | NORMAL | -0.445 | 0.189 | -0.445 |
| Amputation atrial fibrillation | NORMAL | 1.088 | 0.398 | 1.088 |
| Amputation HbA1c | NORMAL | 0.248 | 0.042 | 0.248 |
| Amputation HDL | NORMAL | -0.059 | 0.032 | -0.059 |
| Amputation heart rate | NORMAL | 0.098 | 0.05 | 0.098 |
| Amputation MMALB | NORMAL | 0.602 | 0.18 | 0.602 |
| Amputation peripheral vascular disease | NORMAL | 1.01 | 0.189 | 1.01 |
| Amputation white blood count | NORMAL | 0.04 | 0.017 | 0.04 |
| Amputation Stroke | NORMAL | 1.299 | 0.245 | 1.299 |
| Amputation shape | NORMAL | 2.067 | 0.193 | 2.067 |
| Amputation with Ulcer lambda | NORMAL | -0.881 | 0.139 | -0.881 |
| Amputation with Ulcer age at diagnosis | NORMAL | -0.065 | 0.027 | -0.065 |
| Amputation with Ulcer PVD | NORMAL | 1.769 | 0.449 | 1.769 |
| Second Amputation baseline hazard | NORMAL | -3.455 | 0.565 | -3.455 |
| Second Amputation HbA1c | NORMAL | 0.127 | 0.06 | 0.127 |
| Blindness baseline hazard | NORMAL | -10.6774 | 0.759 | -10.6774 |
| Blindness age at diagnosis | NORMAL | 0.047 | 0.009 | 0.047 |
| Blindness HbA1c | NORMAL | 0.171 | 0.032 | 0.171 |
| Blindness heart rate | NORMAL | 0.08 | 0.039 | 0.08 |
| Blindness systolic blood pressure | NORMAL | 0.068 | 0.032 | 0.068 |
| Blindness white blood cells | NORMAL | 0.052 | 0.019 | 0.052 |

| | | | | |
|---------------|--------|-------|-------|-------|
| Blindness CHF | NORMAL | 0.841 | 0.287 | 0.841 |
| Blindness IHD | NORMAL | 0.61 | 0.208 | 0.61 |

Cancer

The parameter distributions for the incidence and hazard ratios for breast cancer and colorectal cancer are reported in Table 54.

Table 54: Input parameters for breast cancer and colorectal cancer risk models

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|--|--------------|-------------|-------------|------------------|-----------------|
| Colorectal cancer men | NORMAL | 0.0011 | 0.0001 | 0.0011 | ⁽³⁶⁾ |
| Colorectal cancer women | NORMAL | 0.0005 | 0.0000 | 0.0005 | ⁽³⁶⁾ |
| Breast cancer pre-menopause | NORMAL | 0.0010 | 0.0001 | 0.0010 | ⁽³⁴⁾ |
| Breast cancer post-menopause | NORMAL | 0.0028 | 0.0002 | 0.0028 | ⁽³⁴⁾ |
| Colorectal cancer BMI relative risk for men | LOGNORMAL | 0.1906 | 0.0111 | 1.21 | ⁽³⁵⁾ |
| Colorectal cancer BMI relative risk for women | LOGNORMAL | 0.0392 | 0.0151 | 1.04 | ⁽³⁵⁾ |
| Breast cancer BMI relative risk for pre-menopause | LOGNORMAL | -0.1165 | 0.0251 | 0.89 | ⁽³⁵⁾ |
| Breast cancer BMI relative risk for post-menopause | LOGNORMAL | 0.0862 | 0.0205 | 1.09 | ⁽³⁵⁾ |

The parameter distributions for breast and colorectal cancer mortality are reported in Table 55.

Table 55: Input parameters for breast cancer and colorectal cancer mortality (41)

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|-----------------------------------|--------------|-------------|-------------|------------------|
| Breast cancer 5 year survival | BETA | 439.69 | 2354.44 | 0.157 |
| Colorectal cancer 5 year survival | BETA | 1457.56 | 1806.35 | 0.447 |

Osteoarthritis

The parameter distributions for the incidence and hazard ratios for osteoarthritis are reported below.

Table 56: Input parameters for the osteoarthritis risk model (37)

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate |
|-------------------------------|--------------|-------------|-------------|------------------|
| Osteoarthritis incidence | NORMAL | 0.0053 | 0.0000004 | 0.0053 |
| Osteoarthritis RR of diabetes | LOGNORMAL | 0.723 | 0.317 | 2.06 |
| Osteoarthritis RR of BMI | LOGNORMAL | 0.073 | 0.026 | 1.076 |

Depression

The parameter distributions for the incidence and hazard ratios for depression are reported below.

Table 57: Input parameters for the depression risk model

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|-------------------------|--------------|-------------|-------------|------------------|--------|
| Odds of depression | BETA | 336 | 8803 | 0.0397 | (39) |
| Odds ratio for diabetes | LOGNORMAL | 0.4187 | 0.1483 | 1.52 | (39) |
| Odds ratio for stroke | LOGNORMAL | 1.8406 | 0.5826 | 6.3 | (40) |

UTILITIES

The parameter distributions used to estimate health state utilities in the model are reported below.

Table 58: Utility input parameters

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|---|--------------|-------------|-------------|------------------|--------|
| Renal/ulcer baseline utility | NORMAL | 0.689 | 0.014 | 0.689 | (47) |
| Renal dialysis | NORMAL | -0.078 | 0.026 | -0.078 | (47) |
| Foot ulcer | NORMAL | -0.099 | 0.013 | -0.099 | (47) |
| Amputation/heart failure baseline utility | NORMAL | 0.807 | 0.005 | 0.807 | (23) |
| Heart failure | NORMAL | -0.101 | 0.032 | -0.101 | (23) |
| Amputation | NORMAL | -0.172 | 0.045 | -0.172 | (23) |
| Stable angina multiplicative factor decrement | NORMAL | 0.801 | 0.038 | 0.801 | (21) |
| Unstable angina multiplicative factor decrement | NORMAL | 0.77 | 0.038 | 0.77 | (21) |
| MI multiplicative factor decrement | NORMAL | 0.76 | 0.018 | 0.76 | (21) |
| Stroke multiplicative factor decrement | NORMAL | 0.629 | 0.04 | 0.629 | (21) |
| Cancer baseline utility | NORMAL | 0.8 | 0.0026 | 0.8 | (48) |
| Cancer decrement | NORMAL | -0.06 | 0.008 | -0.06 | (48) |
| Osteoarthritis utility | NORMAL | 0.69 | 0.069 | 0.69 | (49) |
| Depression baseline utility | NORMAL | 0.48 | 0.048 | 0.48 | (51) |
| Depression remitters | NORMAL | 0.31 | 0.031 | 0.31 | (51) |
| Depression responders | NORMAL | 0.20 | 0.020 | 0.20 | (51) |
| Depression non-responders | NORMAL | 0.070 | 0.007 | 0.070 | (51) |
| Depression drop-outs | NORMAL | 0.050 | 0.005 | 0.050 | (51) |
| Age utility decrement | NORMAL | -0.004 | 0.0001 | -0.004 | (21) |

UNIT HEALTH CARE COSTS

The parameter distributions used to estimate health state utilities in the model are reported below.

Table 59: Cost input parameters

| Parameter Description | Distribution | Parameter 1 | Parameter 2 | Central estimate | Source |
|---------------------------|--------------|-------------|-------------|------------------|--------|
| DPP Intervention | GAMMA | | | £270 | PHE |
| DIABETES COSTS | | | | | |
| Insulin (annual cost) | GAMMA | 3.367 | 408.6 | £1375.72 | (58) |
| Metformin (annual cost) | CONSTANT | NA | NA | £18.83 | (54) |
| Sitagliptin (annual cost) | CONSTANT | NA | NA | £433.77 | (54) |

| | | | | | |
|---------------------------------------|----------|----------|----------|-----------|------|
| Nurse appointment (Advanced) | GAMMA | 100 | 0.26 | £25.52 | (53) |
| Health care assistant appointment | GAMMA | 100 | 0.03 | £3.40 | (53) |
| Eye screening | GAMMA | 15.3664 | 1.58219 | £24.31 | (56) |
| HbA1c test | GAMMA | 100 | 0.03 | £3.00 | (55) |
| Lipids test | GAMMA | 100 | 0.01 | £1.00 | (55) |
| LfT test | GAMMA | 100 | 0.01 | £1.00 | (55) |
| B12 test | GAMMA | 100 | 0.01 | £1.00 | (55) |
| Urine test | GAMMA | 100 | 0.01 | £1.00 | (55) |
| Nicotine replacement therapy | GAMMA | 100 | 1.03 | £103.00 | (53) |
| CVD COSTS | | | | | |
| Unstable Angina hospital admission | GAMMA | 100 | 12.75591 | £1275.59 | (20) |
| Revascularisation in hospital | GAMMA | 100 | 60.36846 | £6036.85 | (20) |
| MI Hospital admission | GAMMA | 100 | 15.54896 | £1554.90 | (20) |
| First Outpatient appointment | GAMMA | 100 | 1.653571 | £165.36 | (20) |
| Subsequent outpatient appointments | GAMMA | 100 | 1.100574 | £110.06 | (20) |
| Fatal CHD | GAMMA | 100 | 7.125001 | £712.50 | (38) |
| Fatal Stroke | GAMMA | 100 | 44.42562 | £4442.56 | (60) |
| First year stroke | GAMMA | 100 | 97.15908 | £9715.91 | (60) |
| Subsequent year stroke | GAMMA | 100 | 27.29644 | £2729.64 | (20) |
| Glytrin Spray | CONSTANT | NA | NA | £12.61 | (20) |
| Isosorbide mononitrate | CONSTANT | NA | NA | £13.54 | (20) |
| Verapamil | CONSTANT | NA | NA | £50.57 | (20) |
| Atenolol | CONSTANT | NA | NA | £36.42 | (20) |
| Aspirin | CONSTANT | NA | NA | £8.01 | (20) |
| Ramipril | CONSTANT | NA | NA | £90.45 | (20) |
| ARB | CONSTANT | NA | NA | £253.28 | (20) |
| Clopidogrel | CONSTANT | NA | NA | £554.41 | (20) |
| Congestive Heart Failure | GAMMA | 67.20788 | 45.99274 | £3091.07 | (62) |
| MICROVASCULAR COSTS | | | | | |
| Blindness year 1 | GAMMA | 10.26317 | 139.7079 | £1433.85 | (66) |
| Blindness subsequent years | GAMMA | 11.31099 | 42.37999 | £479.36 | (66) |
| Amputation year 1 | GAMMA | 19.37193 | 521.4492 | £10101.48 | (66) |
| Amputation subsequent years | GAMMA | 4.597909 | 412.4212 | £1896.28 | (66) |
| Renal Haemodialysis | GAMMA | 100 | 420.49 | £42049.00 | (63) |
| Renal Automated Peritoneal dialysis | GAMMA | 100 | 272.1714 | £27217.14 | (63) |
| Renal Ambulatory peritoneal dialysis | GAMMA | 100 | 197.4225 | £19742.25 | (63) |
| Renal transplant | GAMMA | 100 | 236.5973 | £23659.73 | (64) |
| Immunosuppressants | GAMMA | 100 | 69.58745 | £6958.75 | (64) |
| Foot ulcer not infected | GAMMA | 100 | 1.677526 | £167.75 | (65) |
| Foot ulcer with cellulitis | GAMMA | 100 | 4.431003 | £443.10 | (65) |
| Foot ulcer with osteomyelitis | GAMMA | 100 | 8.215817 | £821.58 | (65) |
| OTHER DISEASE COSTS | | | | | |
| Breast Cancer | GAMMA | 100 | 138.1811 | £13818.11 | (67) |
| Colorectal cancer Dukes A | GAMMA | 100 | 100.9135 | £10091.35 | (68) |
| Colorectal cancer Dukes B | GAMMA | 100 | 173.1532 | £17315.32 | (68) |
| Colorectal cancer Dukes C | GAMMA | 100 | 265.5026 | £26550.26 | (68) |
| Colorectal cancer Dukes D | GAMMA | 100 | 166.2553 | £16625.53 | (68) |
| Osteoarthritis | GAMMA | 100 | 9.616886 | £961.69 | (69) |
| Depression – Practice nurse surgery | GAMMA | 100 | 0.090154 | £9.02 | (70) |
| Depression – Practice nurse home | GAMMA | 100 | 0.270463 | 27.05 | (70) |
| Depression – Practice nurse telephone | GAMMA | 100 | 0.090154 | 9.02 | (70) |
| Depression – Health visitor | GAMMA | 100 | 0.387834 | 38.78 | (70) |
| Depression – District nurse | GAMMA | 100 | 0.377628 | 37.76 | (70) |
| Depression – Other nurse | GAMMA | 100 | 0.090154 | 9.02 | (70) |
| Depression – HCA phlebotomist | GAMMA | 100 | 0.034021 | 3.40 | (70) |
| Depression – Other primary care | GAMMA | 100 | 0.255154 | 25.52 | (70) |
| Depression – Out of Hours | GAMMA | 100 | 0.268661 | 26.87 | (70) |
| Depression – NHS Direct | GAMMA | 100 | 0.25295 | 25.30 | (70) |
| Depression – Walk-in Centre | GAMMA | 100 | 0.388316 | 38.83 | (70) |
| Depression – Prescribed medicines | GAMMA | 100 | 0.096144 | 9.61 | (70) |

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|-----------------------------|----------|-----|------|---------|------|
| Depression – Secondary Care | GAMMA | 100 | 0.81 | 81.00 | (70) |
| DIAGNOSIS AND OTHER COSTS | | | | | |
| GP appointment | GAMMA | 100 | 0.47 | £46.95 | (53) |
| Diabetes diagnosis | GAMMA | 100 | 0.12 | £14.81 | (55) |
| Hypertension diagnosis | GAMMA | 100 | 0.57 | £56.51 | (19) |
| Anti-hypertensives | GAMMA | 100 | 1.96 | £195.94 | (59) |
| Simvastatin | CONSTANT | NA | NA | £26.59 | (54) |

QUALITY ASSURANCE

Within ScHARR, research is conducted within a framework of standards and systems that ensure high quality science and governance. This includes ensuring staff receive appropriate training and operate within a culture of high quality research, building sufficient time into each project for quality assurance (including error checking and validation), internal and external review of models and ideally external peer review through publication in academic journals.

The SPHR Diabetes Prevention Model has undergone an extensive process of quality assurance and error checking, both during its development and during the adaptations required for this analysis. Face validity around the model structure and assumptions was provided during model development by means of regular input from a group of stakeholders, including clinicians, diabetes researchers, patients and public health commissioners, and during model adaptation by a group of stakeholders representing the seven DPP demonstrator sites.

A guide to checking, avoiding and identifying errors in health economic models has recently been developed within ScHARR (81). Where possible, the suggested black box verification tests were carried out as part of model development. A more complex set of internal validations were also carried out to ensure that the model was behaving as planned (e.g. that metabolic trajectories and risk equations work in the intended way). The model has also undergone a series of validations against external data (82), and the structure and model assumptions have undergone formal peer review for a publications associated with the model (12). Finally, in addition to ScHARR's own process of model quality assurance and error checking, the model code was externally reviewed and refactored as part of the PHE project adaptation by Dr Mat Hall, a software engineer from the Department of Computer Science at the University of Sheffield.

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The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been endorsed and co-published by the following journals:

- BJOG: An International Journal of Obstetrics and Gynaecology
- [BMC Medicine 2013; 11:80](#)
- [BMJ 2013;346:f1049](#)
- [Clinical Therapeutics 27 March 2013 \(Article in Press DOI: 10.1016/j.clinthera.2013.03.003\)](#)
- [Cost Effectiveness and Resource Allocation 2013 11:6.](#)
- [The European Journal of Health Economics 2013 Mar 26. \[Epub ahead of print\]](#)
- International Journal of Technology Assessment in Health Care
- [Journal of Medical Economics 2013 Mar 25. \[Epub ahead of print\]](#)
- [Pharmacoeconomics 2013 Mar 26. \[Epub ahead of print\]](#)
- [Value in Health 2013 March - April;16\(2\):e1-e5](#)

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

| Section/item | Item No | Recommendation | Reported on page No/line No |
|---------------------------------|---------|---|--|
| Title and abstract | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared. | <u>Page 1 Line 1</u> |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | <u>Pages 5 & 6</u> |
| Introduction | | | |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions. | <u>Page 8 paragraph 1</u> <u>Page 8 Lines 22-26</u> |
| Methods | | | |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | <u>Page 9 Lines 10-14 & Page 11 Lines 18-26</u> |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | <u>Page 8 Lines 22-23</u> |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | <u>Page 9 Lines 23-24</u> |
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | <u>Pages 10-11</u> |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | <u>Page 12 Lines 2-4</u> |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and | <u>Page 12 Lines 6-7</u> |



| | | | | |
|----|-------------------------|-----|---|--------------------|
| 1 | | | outcomes and say why appropriate. | Page 12 Lines 6-7 |
| 2 | | | | |
| 3 | Choice of health | 10 | Describe what outcomes were used as the measure(s) of | |
| 4 | outcomes | | benefit in the evaluation and their relevance for the type of | |
| 5 | | | analysis performed. | Page 12 Lines 2-3 |
| 6 | | | | |
| 7 | Measurement of | 11a | <i>Single study-based estimates:</i> Describe fully the design | |
| 8 | effectiveness | | features of the single effectiveness study and why the single | |
| 9 | | | study was a sufficient source of clinical effectiveness data. | Page 10 Lines 9-13 |
| 10 | | | | |
| 11 | | 11b | <i>Synthesis-based estimates:</i> Describe fully the methods used for | |
| 12 | | | identification of included studies and synthesis of clinical | |
| 13 | | | effectiveness data. | N/A |
| 14 | Measurement and | 12 | If applicable, describe the population and methods used to | |
| 15 | valuation of preference | | elicit preferences for outcomes. | |
| 16 | based outcomes | | | N/A |
| 17 | | | | |
| 18 | Estimating resources | 13a | <i>Single study-based economic evaluation:</i> Describe approaches | |
| 19 | and costs | | used to estimate resource use associated with the alternative | |
| 20 | | | interventions. Describe primary or secondary research methods | |
| 21 | | | for valuing each resource item in terms of its unit cost. | |
| 22 | | | Describe any adjustments made to approximate to opportunity | |
| 23 | | | costs. | N/A |
| 24 | | | | |
| 25 | | | | |
| 26 | | 13b | <i>Model-based economic evaluation:</i> Describe approaches and | |
| 27 | | | data sources used to estimate resource use associated with | |
| 28 | | | model health states. Describe primary or secondary research | |
| 29 | | | methods for valuing each resource item in terms of its unit | Page 11 Lines 4-10 |
| 30 | | | cost. Describe any adjustments made to approximate to | & Supplementary |
| 31 | | | opportunity costs. | Appendix |
| 32 | | | | Pages 44-49 |
| 33 | | | | |
| 34 | Currency, price date, | 14 | Report the dates of the estimated resource quantities and unit | |
| 35 | and conversion | | costs. Describe methods for adjusting estimated unit costs to | |
| 36 | | | the year of reported costs if necessary. Describe methods for | Page 9 Line 23 |
| 37 | | | converting costs into a common currency base and the | & Supplementary |
| 38 | | | exchange rate. | Appendix |
| 39 | | | | Pages 44-49 |
| 40 | Choice of model | 15 | Describe and give reasons for the specific type of decision- | Page 9 Line 8 & |
| 41 | | | analytical model used. Providing a figure to show model | Figure S1 in |
| 42 | | | structure is strongly recommended. | Supplementary |
| 43 | | | | Appendix |
| 44 | Assumptions | 16 | Describe all structural or other assumptions underpinning the | Supplementary |
| 45 | | | decision-analytical model. | Appendix |
| 46 | | | | Pages 10-70 |
| 47 | Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This | |
| 48 | | | could include methods for dealing with skewed, missing, or | |
| 49 | | | censored data; extrapolation methods; methods for pooling | |
| 50 | | | data; approaches to validate or make adjustments (such as half | |
| 51 | | | cycle corrections) to a model; and methods for handling | Supplementary |
| 52 | | | population heterogeneity and uncertainty. | Appendix |
| 53 | | | | Pages 10-70 |
| 54 | | | | |
| 55 | Results | | | |
| 56 | Study parameters | 18 | Report the values, ranges, references, and, if used, probability | |
| 57 | | | distributions for all parameters. Report reasons or sources for | |
| 58 | | | distributions used to represent uncertainty where appropriate. | |
| 59 | | | Providing a table to show the input values is strongly | Supplementary |
| 60 | | | recommended. | Appendix |
| | | | | Pages 53-70 |

| | | | | |
|---|---|-----|---|--|
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 | Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | Page 13 Table 1 |
| 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 | Characterising uncertainty | 20a | <i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). | N/A |
| | | 20b | <i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | Pages 15-16 Figure 3 Tables S3 & S4 |
| 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 | Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | Pages 14-15 Figures 1,2,4,S3 & S4 Table S4 |
| 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 | Discussion Study findings, limitations, generalisability, and current knowledge | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | Pages 17-19 |
| 31 32 33 34 35 36 37 38 39 40 41 | Other Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | Page 3 Lines 5-9 |
| 36 37 38 39 40 41 | Conflicts of interest | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | Page 2 Lines 19-23 |

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The CHEERS Statement may be accessed by the publication links above.

The ISPOR CHEERS Task Force Report provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

The citation for the CHEERS Task Force Report is:

Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. *Value Health* 2013;16:231-50.

