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Multiple risk factor control, mortality and cardiovascular events in type 2 diabetes and chronic kidney disease: a population-based cohort study

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6 **Multiple risk factor control, mortality and cardiovascular events in type 2 diabetes**
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9 **and chronic kidney disease: a population-based cohort study**
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Abstract

OBJECTIVES: This study aimed to evaluate the effectiveness of multiple risk factor control (MRFC) at reducing mortality and cardiovascular events in diabetes and chronic kidney disease (CKD) in clinical practice.

DESIGN: Population-based cohort study.

SETTING: Primary care database in the UK, linked with inpatient and mortality data.

PARTICIPANTS: Participants aged 40 to 79 years with type 2 diabetes and valid serum creatinine measurements, including 11,431 participants with CKD (eGFR 15–59 mL/min/1.73 m²) and 36,429 participants with non-CKD (eGFR ≥60 mL/min/1.73 m²).

EXPOSURES: MRFC consisted of four components: HbA1c <53 mmol/mol (<7.0%), blood pressure <140/90 mmHg, total cholesterol <5 mmol/L and no smoking. The main exposure variable was the number of risk factors controlled at the same time at baseline.

OUTCOME MEASURES: All-cause and cardiovascular mortality in the overall participants. Cardiovascular events, including coronary heart disease and stroke, in participants limited to those without a history of cardiovascular diseases at baseline (CKD N=7,216; non-CKD N=28,569).

RESULTS: In participants with CKD, 37% or 13% met three or four MRFC criteria, respectively. Increasing MRFC was associated with lower relative hazards for all

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6 outcomes studied compared with those meeting no or one criterion. For participants
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8 with CKD meeting four criteria, the adjusted hazard ratio (HR) for all-cause mortality
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10 was 0.59 (95% confidence interval (CI) 0.52 to 0.67) and the adjusted subdistribution
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12 HR for cardiovascular mortality was 0.58 (0.49 to 0.69), considering a competing risk
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14 of non-cardiovascular death. Participants meeting four criteria also had lower relative
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16 hazards for coronary heart disease (adjusted subdistribution HR 0.73, 95% CI 0.59 to
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18 0.91) and stroke (0.61, 0.43 to 0.86), considering death as a competing risk.
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25 **CONCLUSIONS:** MRFC may attenuate the increased risks for mortality and
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27 cardiovascular events in people with diabetes and CKD. The implementation of MRFC
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29 is suboptimal and should be ensured in this high-risk population.
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37 **Strengths and limitations of this study**

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39 • This study included >11,000 participants with type 2 diabetes and CKD sampled
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41 from a representative general population with about 6 years of follow-up, which
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43 enabled to determine the associations of cardiovascular risk factors with mortality
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45 and cardiovascular events.
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49 • Linked data for hospital care and death registration with a primary care database
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51 enhanced the validity of the study to evaluate mortality and cardiovascular events.
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6 • We could not determine the causal relationships between MRFC and mortality and
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8 cardiovascular events from this non-randomised study.
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11 • There is a possibility of confounding by indication; thus, healthier participants were
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13 managed more successfully and resulted in being categorised as those with greater
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15 number of risk factors controlled.
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Introduction

Diabetes and chronic kidney disease (CKD) are growing health problems worldwide, contributing to increased mortality [1]. Diabetes and CKD also impose a substantial economic burden on society, with particularly high costs relating to cardiovascular complications and renal replacement therapy [2,3]. The prevalence of CKD in patients with diabetes is between 4.2% and 17.9% (CKD stages 3 to 5) in European countries [4]. The leading cause of death in people with type 2 diabetes or CKD is cardiovascular disease rather than renal complications [5,6]. Prevention of cardiovascular events is a key focus in the management of patients with these conditions.

Recent epidemiological studies have demonstrated additional risks of CKD on mortality and cardiovascular diseases in people with diabetes [7], but treatment approaches in this population have not been well studied. Multifactorial interventions to reduce cardiovascular risks were shown to be effective at reducing mortality and cardiovascular events in patients with type 2 diabetes and persistent microalbuminuria in the Steno-2 randomised trial [8,9]. This study provided a high level of evidence, but included a relatively small number of participants with diabetes who were managed in specialist centres. Recently, the implementation and effectiveness of this approach have been

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6 evaluated in patients with diabetes in clinical practice settings [10-12]. However, no
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9 studies focused on multiple risk factor control (MRFC) in patients with both diabetes
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11 and CKD in a wide clinical practice setting. Generally, patients with kidney disease
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14 have been underrepresented in cardiovascular clinical trials [13]. This population may
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17 have an altered risk-benefit profile, and extrapolation of data based on patients with
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20 normal kidney function into patients with CKD may be unreliable [13]. We aimed to
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23 conduct a pragmatic evaluation of the effectiveness of MRFC on mortality and
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26 cardiovascular events in participants with type 2 diabetes and CKD in a
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29 population-based cohort study.
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34 **Methods**

35 *Data sources*

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37 This study employed a linked dataset derived from the UK Clinical Practice Research
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40 Datalink (CPRD), the UK National Health Service Hospital Episodes Statistics (HES)
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43 inpatient data, and the UK Office for National Statistics (ONS) mortality data. The
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46 CPRD contains anonymised electronic health records from general practices across the
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49 UK [14]. The CPRD collects data for diagnoses and clinical assessment, prescriptions
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52 and laboratory test results, such as HbA1c and serum creatinine. The HES inpatient data
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6 were comprised of inpatient records from all National Health Service hospitals in
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9 England. Information on the date of death and the causes of death were available in the
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11 ONS mortality data file. Diagnoses and clinical evaluation in the CPRD were coded
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14 with the Read codes, a hierarchical coding system used in primary care in the UK,
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17 whereas those in the HES and ONS were coded with the International Classification of
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20 Diseases, tenth revision (ICD-10). Linked data are available for general practices in
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23 England only and participants were limited to those with linked data for the HES and
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26 ONS available. The study was approved by the CPRD Independent Scientific Advisory
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29 Committee (ISAC Protocol 15_201R).

30 31 32 33 34 *Study population*

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37 The scheme of the study cohort selection is presented in figure S1. We initially sampled
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40 participants who were diagnosed with type 2 diabetes from the CPRD [15]. Using the
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43 CPRD records, the date of the first valid serum creatinine value between 2006 and 2010
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46 recorded more than one year after the first diagnosis of diabetes were defined as the
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49 index date. A similar approach was taken by Adamsson Eryd et al [16] to ensure that
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52 participants managed for diabetes had sufficient time available for recording of baseline
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55 values. To avoid misclassification of CKD status and stage, the index serum creatinine
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6 values were validated by confirmation of subsequent values within 30% of the index
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8 values. We restricted the sample to participants aged 40 to 79 years at the index date
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10 with at least one year of follow-up data available (ie, participants who died in the first
11
12 year of follow-up were excluded). Estimated glomerular filtration rate (eGFR) was
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14 calculated from a serum creatinine value, age, gender, and ethnicity, using the Chronic
15
16 Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [17]. Missing
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18 ethnicity was assumed as 'non-black' in the present study. Participants diagnosed with
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20 end-stage renal disease, those who had received renal replacement therapy, or those with
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22 index eGFR <15 mL/min/1.73 m² were excluded. We also excluded participants with
23
24 missing data for smoking status, body mass index (BMI), HbA1c, blood pressure, total
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26 cholesterol or with extreme BMI (<18.5 or ≥ 45 kg/m²) at baseline. Since it has been
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28 reported that low values of cardiovascular risk factors were not always associated with
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30 better outcomes in observational studies [15,18,19], possibly due to reverse causation
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32 [20,21], participants with low HbA1c (<42 mmol/mol or $<6.0\%$), blood pressure
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34 (systolic <120 or diastolic <60 mmHg) and total cholesterol (<3 mmol/L) were further
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36 excluded. Participants were categorised according to index eGFR into those with CKD
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38 (<60 mL/min/1.73 m²) and non-CKD (≥ 60 mL/min/1.73 m²).
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Multiple risk factor control

MRFC was defined in this study as consisting of four components: (1) HbA1c <53 mmol/mol (<7.0%), (2) blood pressure <140/90 mmHg (systolic <140 and diastolic <90 mmHg), (3) total cholesterol <5 mmol/L and (4) no smoking (non- or ex-smokers). The means of HbA1c, blood pressure, and total cholesterol records within one year before the index date were evaluated. The number of the risk factors controlled from four criteria was treated as the exposure and included as a categorical variable in the analyses, with those meeting no or one criterion as a reference category.

Outcomes

Main outcomes of interest in this study included all-cause and cardiovascular mortality, fatal and non-fatal coronary heart disease (CHD) and stroke. The date of death and causes of death were determined using the ONS mortality data. Patients who died from cardiovascular causes were identified if people had any of the ICD-10 codes I00 to I99 as a cause of death. All of the CPRD, HES and ONS were used to ascertain fatal and non-fatal CHD and stroke. Read codes for CHD and stroke reported previously [22,23] were updated for the present study. The ICD-10 codes for CHD and stroke were I20 to I25 and I60, I61, I63 and I64, respectively.

Analysis

Baseline characteristics of the study cohort were described according to CKD status.

Time-to-event analyses were conducted to evaluate the associations of MRFC with mortality and cardiovascular events. To address the issue of reverse causation and to avoid misclassification of the outcomes from those which had existed at baseline, person-years for participants who experienced outcomes of interest in the first year of follow-up were excluded from analyses. Cox proportional hazards models were used to evaluate the association of MRFC with all-cause mortality. Proportional hazards assumption was assessed by visual inspection of log-log plots, and no apparent violation was found. Competing risks regression with subdistribution hazard models were conducted for cardiovascular mortality and cardiovascular events, considering competing risks for non-cardiovascular and all-cause death, respectively [24].

Associations of MRFC with cardiovascular events were evaluated in participants without a known history of cardiovascular diseases at baseline. Participants were followed from the index date until the earliest of the events of interest, the last date of CPRD records, or 31 March 2015 for all-cause mortality evaluation. In the competing risks regression analyses for cardiovascular mortality and cardiovascular events,

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6 participants who experienced the corresponding competing events prior to the event of
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8 interest were also censored.
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14 Main analyses were conducted by CKD status, adjusting for a range of baseline
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16 covariates, including age (continuous), gender (male or female), CKD stage (3a, 3b and
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18 4; for CKD cohort), BMI (18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9 and 40.0–44.9
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20 kg/m²), deprivation level (quintile; 1, least deprived, to 5, most deprived), duration of
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22 diabetes (1.0–4.9 5.0–9.9 and 10+ years), a history of cardiovascular diseases, including
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24 CHD and stroke, and prescribing during six months prior to the index date of
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26 antidiabetic drugs (none, insulin with and without other antidiabetic drugs, and
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28 non-insulin drugs only), antihypertensive drugs (none, drugs acting on renin-angiotensin
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30 system with and without other antihypertensive drugs, and other classes of
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32 antihypertensive drugs only, including β -blockers, calcium channel blockers, and
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34 thiazide diuretics), statins and antiplatelet drugs, and index year (2006 to 2010). In
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36 addition, the association of CKD with the outcomes were evaluated according to the
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38 number of risk factors controlled, adjusting for the potential confounding factors
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40 described above.
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6 In this paper, the results for participants with CKD were focused on, with the results for
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8 those with non-CKD shown for comparative purposes. All analyses were performed
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10 using Stata version 14 (Stata Corp., College Station TX). The ‘forestplot’ package in R
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12 was used to present the results [25].
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20 **Results**

21 *Characteristics of the study population*

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23 Baseline characteristics of the study cohort are shown according to CKD status in table
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28 1. Mean index eGFR was 49 mL/min/1.73 m² for participants with CKD and 81
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30 mL/min/1.73 m² for those with non-CKD. Participants with CKD were older (71 vs 62
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32 years), included more women (52% vs 40%), had a longer duration of diabetes, and
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34 were more likely to have a history of cardiovascular diseases (37% vs 22%). HbA1c and
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36 total cholesterol were slightly lower in participants with CKD. Although diastolic blood
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38 pressure was lower in participants with CKD, systolic blood pressure was higher despite
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40 more people under antihypertensive medications. Participants with CKD were
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42 prescribed insulin, drugs on renin-angiotensin systems, statins, and antipatelet drugs
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44 more frequently.
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Implementation of MRFC

The number of risk factors controlled from four components of MRFC are shown in table 2. More detailed results of which of the components were controlled are available in table S1. Higher rates of control for HbA1c, total cholesterol and smoking status were observed in participants with CKD compared with those with non-CKD. However, blood pressure was less likely managed in participants with CKD (46% vs 51%). There were some differences in management status according to a history of cardiovascular diseases: in participants with CKD, higher rates of control of blood pressure (49% vs 44%) and total cholesterol (83% vs 76%) in participants with a history of cardiovascular diseases compared with those without. Participants meeting three or four criteria accounted for 37% or 13% in participants with CKD.

Effectiveness of MRFC

Absolute risks for mortality and cardiovascular diseases and adjusted relative hazards of the number of risk factors controlled for the outcomes are shown in figure 1. Increasing MRFC was associated with lower relative hazards for all outcomes studied relative to participants meeting no or one criterion. For participants with CKD meeting four MRFC criteria, the adjusted hazard ratio (HR) for all-cause mortality was 0.59 (95% CI 0.52 to

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6 0.67) and adjusted subdistribution HR for cardiovascular mortality was 0.58 (0.49 to
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8 0.69). Participants meeting four criteria also had lower relative risks for CHD (adjusted
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10 subdistribution HR 0.73, 95% CI 0.59 to 0.91) and stroke (0.61, 0.43 to 0.86) in
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12 participants with CKD. In participants with non-CKD, increasing MRFC was also
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14 associated with lower risks for all-cause and cardiovascular mortality, CHD and stroke.
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23 *Comparisons between CKD and non-CKD*

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25 Unadjusted absolute risks for mortality and cardiovascular diseases were higher in
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27 participants with CKD by 1.4- to 2.9-fold compared with those with non-CKD at the
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29 same MRFC category (figure 1). More participants with CKD died from cardiovascular
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31 causes compared with those without (63% vs 54%, $P<0.001$). Relative hazards of CKD
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33 for the outcomes are shown in figure 2. After adjustment with possible confounding
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35 factors, comorbid CKD remained to be associated with greater risks for all-cause
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37 mortality (adjusted HR, 1.18 to 1.32), cardiovascular mortality (adjusted subdistribution
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39 HR, 1.28 to 1.44) and CHD (1.08 to 1.25). However, the associations of comorbid CKD
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41 with stroke was observed in participants meeting four criteria only (1.64).
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54 **Discussion**

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6 In this population-based cohort study of 11,431 participants with type 2 diabetes and
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8 CKD stages 3 to 4, MRFC was associated with lower relative risks for mortality and
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10 cardiovascular diseases. We also confirmed that CKD was associated with increased
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12 risks for mortality and cardiovascular events. Higher absolute risks for mortality and
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14 cardiovascular events and great relative risk reduction associated with MRFC suggest
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16 that the MRFC strategy may be one of the main approaches to potentially reducing the
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18 burden of diabetes and CKD. Nevertheless, we found that the implementation of MRFC
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20 in patients with diabetes was suboptimal in the clinical practice setting, as reported in
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22 previous studies [10-12].
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34 This study evaluated the effectiveness of MRFC in patients with type 2 diabetes
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36 according to presence or absence of CKD in clinical practice. So far, the associations of
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38 MRFC with lower risks for mortality and cardiovascular events have been shown in
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40 people with diabetes, not focusing on CKD status. Participants with controlled three risk
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42 factors of HbA1c, blood pressure and LDL cholesterol had 62% and 60% risk reduction
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44 for cardiovascular events and CHD, respectively, in patients with diabetes without
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46 known cardiovascular diseases [11]. The associations of uncontrolled HbA1c, blood
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48 pressure, LDL cholesterol and smoking with mortality and cardiovascular events were
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6 individually evaluated in a large population-based study with >850,000 participants
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8 with diabetes [12]. The study cohort included 35.5% of CKD in those with
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10 cardiovascular diseases and 21.8% in those without, and CKD was included in the
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12 analyses for adjustment. This study suggested that uncontrolled risk factors attributed to
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14 about 1 in 3 major cardiovascular events and fewer 1 in 10 deaths.
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23 The strength of this study was the inclusion of a large size of >11,000 participants with
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25 diabetes and CKD with an observation of >62,000 person-years. In addition to the large
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27 sample size and long-term follow-up, representativeness from general population and
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29 data quality are also advantages of the CPRD [14], which should remain even if linked
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31 data for HES and ONS are only available for England practices. Instead, linked data for
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33 hospital care and death registration substantially enhanced the validity of the study to
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35 evaluate mortality and cardiovascular events.
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45 There are also some limitations in this study. First, despite our focus on the number of
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47 MRFC, the impact of each of the risks factor on mortality and cardiovascular events
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49 should be different. Second, we could not determine the causal relationships between
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51 MRFC and mortality and cardiovascular events from this non-randomised study. Third,
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6 there is a possibility of confounding by indication; thus, healthier participants were
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8 managed more successfully and resulted in being categorised as those with greater
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10 number of risk factors controlled. For example, stringent management of HbA1c might
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12 not be targeted for vulnerable participants due to concerns for greater risk of
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14 hypoglycaemia. Fourth, we cannot exclude the possibility of residual confounding
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16 despite adjustment with a range of covariates in the analyses, including physical activity
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18 and alcohol intake [26,27]. Albuminuria, not always available in our study, has been
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20 known as a risk factor for mortality and cardiovascular diseases [28,29]. A recent study
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22 suggested, however, that proteinuria status might not have substantial impact on
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24 cardiovascular outcomes in patients with diabetes and CKD [30]. Fifth, measurement
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26 and assay methods for HbA1c, blood pressure, cholesterol and serum creatinine might
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28 not have been standardised among general practices or laboratories. As well as missing
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30 data on ethnicity and fluctuations in serum creatinine values, these methodological
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32 limitations might influence the determination of CKD status or staging. Finally,
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34 although we used one of the largest primary care electronic health records database, it
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36 seemed to be insufficient to separately evaluate MRFC for participants with different
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38 stages of CKD. Further research is needed to focus on patients with more advanced
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40 CKD who may have altered risk-benefit profile compared with patients with less
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6 impaired renal function.
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11 In summary, based on the population-based cohort study of routine clinical practices,
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13 MRFC may attenuate the increased risks for mortality and cardiovascular events in
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15 people with diabetes and CKD. However, the implementation of MRFC is suboptimal,
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17 and further research is needed to clarify underlying reasons to ensure more improved
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19 achievement of MRFC in this population.
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34
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36
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38
39 license from the UK Medicines and Healthcare products Regulatory Agency. However,
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41 the interpretation and conclusions contained in this report are those of the authors alone
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43 and not necessarily those of the National Health Service, the NIHR or the Department
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6 **Contributors:** Both authors contributed to conception and study design of the study,
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8 data acquisition, statistical analysis, and interpretation. SH drafted the manuscript and
9
10
11 MCG revised it critically for important intellectual content.
12

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17 **Competing interests:** None declared.
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20 **Provenance and peer review:** Not commissioned; externally peer reviewed.
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23 **Data sharing statement:** No additional data are available.
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Table 1. Baseline characteristics of the study cohort by CKD status

		CKD (N=11,431)	Non-CKD (N=36,429)	P value
Age (years)	Mean (SD)	71 (6)	62 (9)	<0.001
Gender	Male	5,481 (48)	22,006 (60)	<0.001
	Female	5,950 (52)	14,423 (40)	
eGFR (mL/min/1.73 m ²)	Mean (SD)	49 (9)	81 (13)	–
	15–29	558 (5)	–	
	30–44	2,655 (23)	–	
	45–59	8,218 (72)	–	
Smoking status	Non-smoker	5,426 (47)	16,511 (45)	<0.001
	Ex-smoker	4,327 (38)	12,217 (34)	
	Current smoker	1,678 (15)	7,701 (21)	
BMI (kg/m ²)	18.5–24.9	1,459 (13)	4,097 (11)	<0.001
	25.0–29.9	4,329 (38)	13,054 (36)	
	30.0–34.9	3,527 (31)	11,485 (32)	
	35.0–39.9	1,541 (13)	5,454 (15)	
	40.0–44.9	575 (5)	2,339 (6)	
Deprivation level (quintile)	1 (least deprived)	1,508 (13)	4,785 (13)	0.293
	2	2,331 (20)	7,300 (20)	
	3	2,374 (21)	7,640 (21)	
	4	2,637 (23)	8,172 (22)	
	5 (most deprived)	2,581 (23)	8,532 (23)	
Duration of diabetes (years)	1.0–4.9	5,208 (46)	22,527 (62)	<0.001
	5.0–9.9	2,954 (26)	8,356 (23)	
	≥10.0	3,269 (29)	5,546 (15)	
History of coronary heart disease and/or stroke		4,215 (37)	7,860 (22)	<0.001
HbA1c (mmol/mol/%)	42–47 (6.0–6.4)*	1,307 (11)	3,513 (10)	<0.001
	48–52 (6.5–6.9)	3,041 (27)	8,900 (24)	
	53–57 (7.0–7.4)	2,590 (23)	7,781 (21)	
	58–63 (7.5–7.9)	1,709 (15)	5,461 (15)	
	64–68 (8.0–8.4)	1,038 (9)	3,567 (10)	
	≥69 (≥8.5)	1,746 (15)	7,207 (20)	
Systolic blood pressure	120–129	1,777 (16)	7,203 (20)	<0.001

	(mmHg)				
		130–139	3,508 (31)	12,121 (33)	
		140–149	3,387 (30)	10,242 (28)	
		≥150	2,759 (24)	6,863 (19)	
	Diastolic blood pressure (mmHg)	60–79	7,238 (63)	16,803 (46)	<0.001
		80–89	3,599 (31)	15,816 (43)	
		≥90	594 (5)	3,810 (10)	
	Total cholesterol (mmol/L)	3.0–3.9	3,782 (33)	10,960 (30)	<0.001
		4.0–4.9	5,220 (46)	16,387 (45)	
		≥5.0	2,429 (21)	9,082 (25)	
	Medication	Antidiabetic drugs			<0.001
		Insulin (± non-insulin)	1,805 (16)	3,225 (9)	
		Non-insulin only	7,722 (68)	26,753 (73)	
		Antihypertensive drugs			<0.001
		Drugs on renin-angiotensin system (± others)	8,472 (74)	21,535 (59)	
		Other antihypertensive drugs only	1,610 (14)	4,751 (13)	
		Statins	9,004 (79)	27,011 (74)	<0.001
		Antiplatelet drugs	6,440 (56)	16,375 (45)	<0.001
	Index year	2006	9,091 (80)	24,192 (66)	<0.001
		2007	1,008 (9)	3,741 (10)	
		2008	545 (5)	2,880 (8)	
		2009	432 (4)	2,677 (7)	
		2010	355 (3)	2,939 (8)	

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

* Participants with HbA1c <48 mmol/mol (<6.5%) were only included if they were prescribed antidiabetic drugs.

Table 2. Risk factors controlled according to chronic kidney disease and a history of cardiovascular diseases

	CKD			Non-CKD		
	Total (N=11,431)	No CVD (N=7,216)	CVD (N=4,215)	Total (N=36,429)	No CVD (N=28,569)	CVD (N=7,860)
<i>Individual risk factor controlled</i>						
HbA1c <53 mmol/mol (<7.0%)	4,348 (38)	2,767 (38)	1,581 (38)	12,413 (34)	9,603 (34)	2,810 (36)
Blood pressure <140 & <90 mmHg	5,224 (46)	3,147 (44)	2,077 (49)	18,655 (51)	14,438 (51)	4,217 (54)
Total cholesterol <5 mmol/L	9,002 (79)	5,512 (76)	3,490 (83)	27,347 (75)	20,826 (73)	6,521 (83)
No smoking	9,753 (85)	6,193 (86)	3,560 (84)	28,728 (79)	22,565 (79)	6,163 (78)
<i>Number of risk factors controlled</i>						
0	138 (1)	87 (1)	51 (1)	806 (2)	678 (2)	128 (2)
1	1,427 (12)	971 (13)	456 (11)	5,372 (15)	4,421 (15)	951 (12)
2	4,162 (36)	2,693 (37)	1,469 (35)	13,288 (36)	10,602 (37)	2,686 (34)
3	4,240 (37)	2,598 (36)	1,642 (39)	12,657 (35)	9,665 (34)	2,992 (38)
4	1,464 (13)	867 (12)	597 (14)	4,306 (12)	3,203 (11)	1,103 (14)

CKD, chronic kidney disease; CVD, (a history of) cardiovascular diseases

Figure legends

Figure 1. Relative hazards of the number of risk factors controlled for mortality and cardiovascular events in (a) participants with chronic kidney disease (CKD) and (b) participants with non-CKD. Hazard ratios (HRs) for all-cause mortality and subdistribution hazard ratios (SHRs) for cardiovascular mortality, coronary heart disease and stroke were adjusted for age, gender, CKD stage (for CKD cohort) body mass index, deprivation level, duration of diabetes, a history of cardiovascular diseases (for mortality evaluation), prescribing of antidiabetic, antihypertensive, statins and antiplatelet drugs, and index year.

Figure 2. Relative hazards of presence of chronic kidney disease for mortality and cardiovascular events compared with non-CKD as reference. Hazard ratios (HRs) for all-cause mortality and subdistribution hazard ratios (SHRs) for cardiovascular mortality, coronary heart disease and stroke were adjusted for age, gender, body mass index, deprivation level, duration of diabetes, a history of cardiovascular diseases (for mortality evaluation), prescribing of antidiabetic, antihypertensive, statins and antiplatelet drugs, and index year.

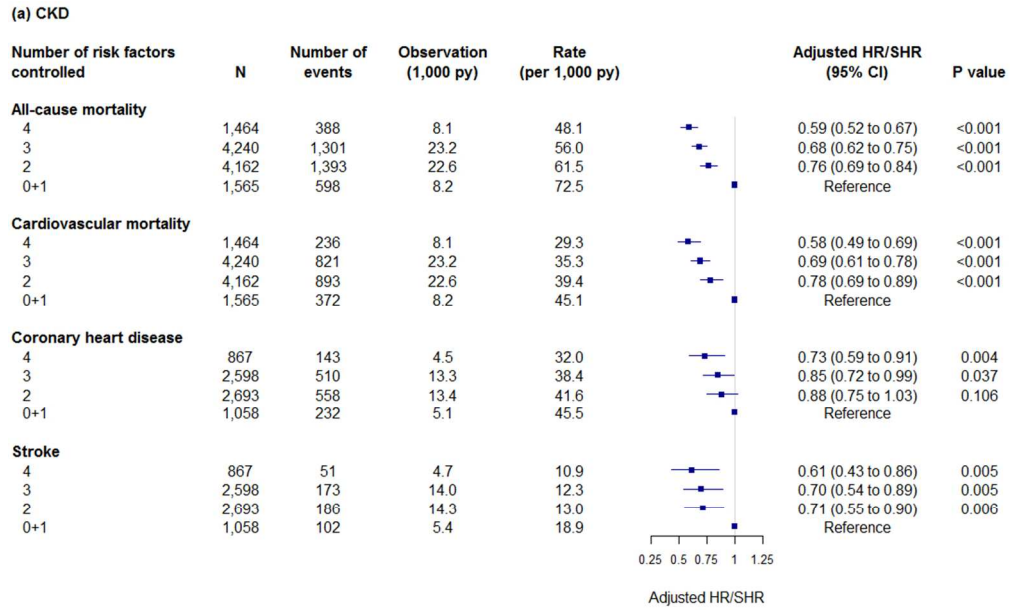


Figure 1a

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(b) Non-CKD

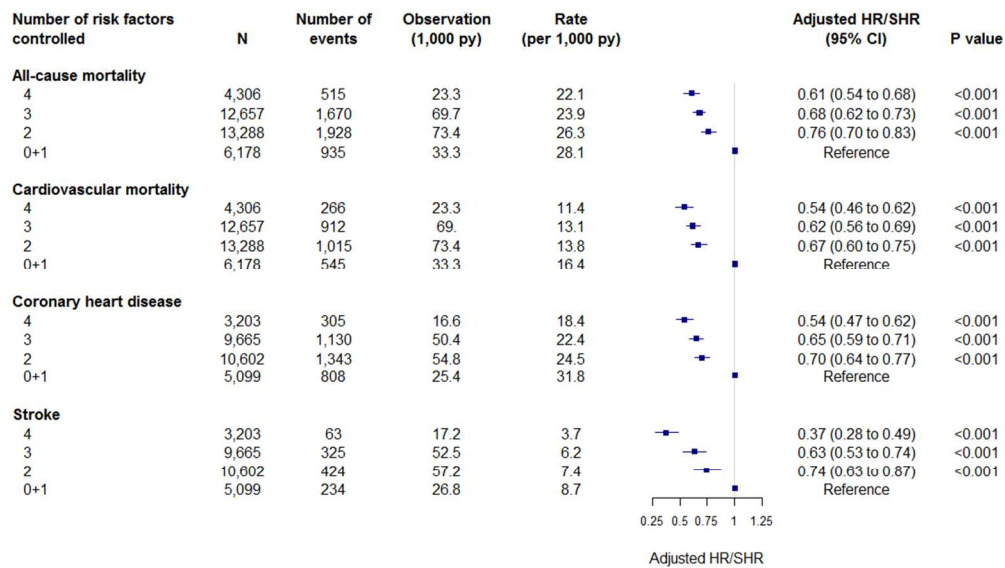


Figure 1b

287x172mm (96 x 96 DPI)

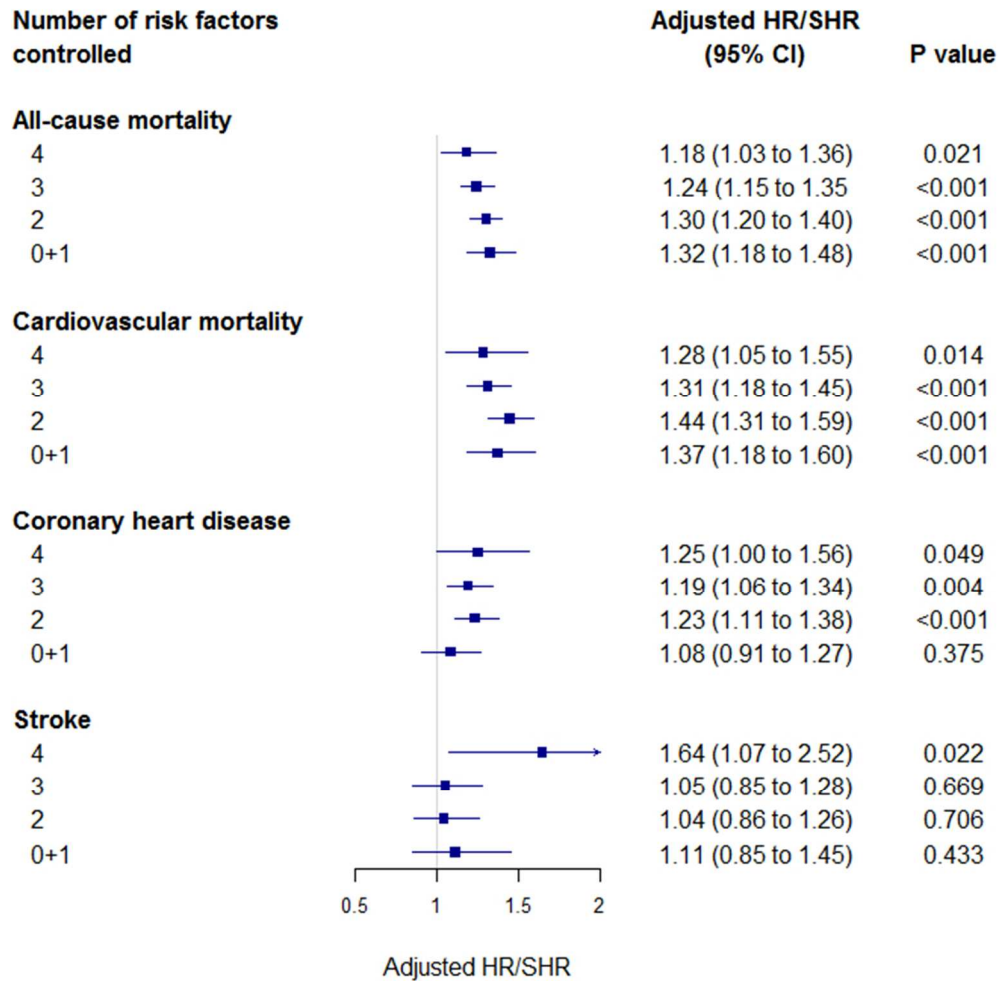
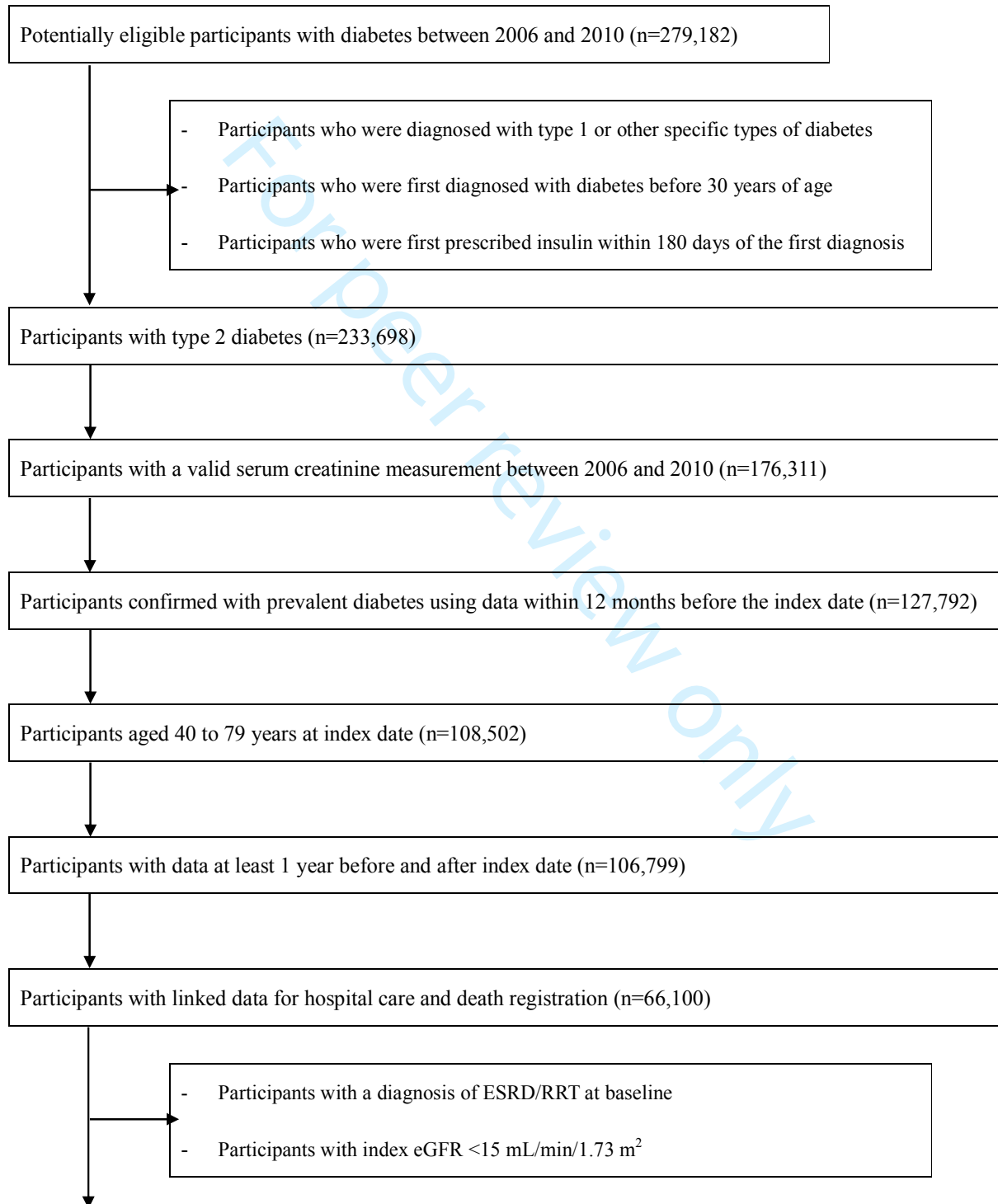
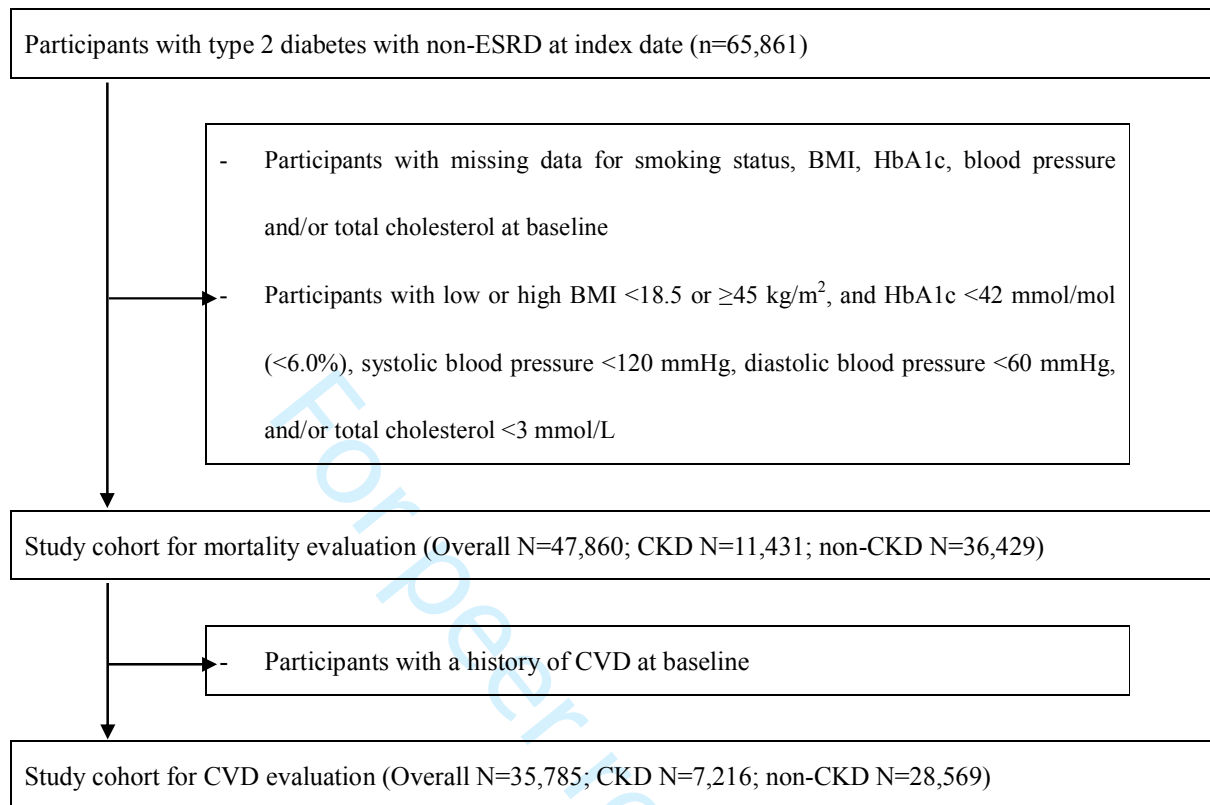


Figure 2

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SUPPLEMENTARY MATERIAL

Figure S1. Study cohort selection



BMI, body mass index; CKD, chronic kidney disease; CVD, Cardiovascular diseases; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RRT, renal replacement therapy

Table S1. Breakdown of risk factors controlled according to chronic kidney disease and a history of cardiovascular diseases

Number of risk factors controlled	HbA1c <53 mmol/mol (<7.0%)	Blood pressure <140/90 mmHg	Total cholesterol <5 mmol/L	No smoking	CKD			Non-CKD		
					Overall (N=11,431)	No CVD (N=7,216)	CVD (N=4,215)	Overall (N=36,429)	No CVD (N=28,569)	CVD (N=7,860)
0	–	–	–	–	138 (1)	87 (1)	51 (1)	806 (2)	678 (2)	128 (2)
1	Y	–	–	–	69 (0.6)	46 (0.6)	23 (0.6)	312 (1)	260 (0.9)	52 (0.7)
	–	Y	–	–	89 (0.8)	64 (0.9)	25 (0.6)	759 (2)	624 (2)	135 (2)
	–	–	Y	–	438 (4)	264 (4)	174 (4)	1,742 (5)	1,350 (5)	392 (5)
	–	–	–	Y	831 (7)	597 (8)	234 (6)	2,559 (7)	2,187 (8)	372 (5)
	Y	Y	–	–	62 (0.5)	43 (0.6)	19 (0.5)	304 (0.8)	268 (0.9)	36 (0.5)
2	Y	–	Y	–	245 (2)	152 (2)	93 (2)	794 (2)	590 (2)	204 (3)
	–	Y	–	Y	407 (4)	289 (4)	118 (3)	1,070 (3)	911 (3)	159 (2)
	–	–	Y	–	390 (3)	215 (3)	175 (4)	1,911 (5)	1,446 (5)	465 (6)
	–	Y	–	Y	531 (5)	379 (5)	152 (4)	2,205 (6)	1,910 (7)	295 (4)
	–	–	Y	Y	2,527 (22)	1,615 (22)	912 (22)	7,004 (19)	5,477 (19)	1,527 (19)
3	Y	Y	Y	–	247 (2)	152 (2)	95 (2)	1,073 (3)	788 (3)	285 (4)
	–	Y	–	Y	302 (3)	199 (3)	103 (2)	1,067 (3)	905 (3)	162 (2)
	–	–	Y	Y	1,552 (14)	1,019 (14)	533 (13)	3,487 (10)	2,678 (9)	809 (10)
	–	Y	Y	Y	2,139 (19)	1,228 (17)	911 (22)	7,030 (19)	5,294 (19)	1,736 (22)
4	Y	Y	Y	Y	1,464 (13)	867 (12)	597 (14)	4,306 (12)	3,203 (11)	1,103 (14)

Y, meeting the criterion; –, not meeting the criterion

CKD, chronic kidney disease; CVD, (a history of) cardiovascular diseases

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7,8,10
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-9
Bias	9	Describe any efforts to address potential sources of bias	10,11
Study size	10	Explain how the study size was arrived at	6-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11
		(b) Describe any methods used to examine subgroups and interactions	11
		(c) Explain how missing data were addressed	8
		(d) If applicable, explain how loss to follow-up was addressed	10
		(e) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12, Figure S1
		(b) Give reasons for non-participation at each stage	12, Figure S1
		(c) Consider use of a flow diagram	Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Figure S1
		(c) Summarise follow-up time (eg, average and total amount)	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Figure 1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(b) Report category boundaries when continuous variables were categorized	9
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16, 17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Multiple risk factor control, mortality and cardiovascular events in type 2 diabetes and chronic kidney disease: a population-based cohort study

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Secondary Subject Heading:	General practice / Family practice
Keywords:	cardiovascular diseases, chronic kidney disease, mortality, type 2 diabetes

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6 **Multiple risk factor control, mortality and cardiovascular events in type 2 diabetes**
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9 **and chronic kidney disease: a population-based cohort study**
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Abstract

OBJECTIVES: This study aimed to evaluate the effectiveness of multiple risk factor control (MRFC) at reducing mortality and cardiovascular events in diabetes and chronic kidney disease (CKD) in clinical practice.

DESIGN: Population-based cohort study.

SETTING: Primary care database in the UK, linked with inpatient and mortality data.

PARTICIPANTS: Participants aged 40 to 79 years with type 2 diabetes and valid serum creatinine measurements, including 11,431 participants with CKD (eGFR 15–59 mL/min/1.73 m²) and 36,429 participants with non-CKD (eGFR ≥60 mL/min/1.73 m²).

EXPOSURES: MRFC consisted of four components: HbA1c <53 mmol/mol (<7.0%), blood pressure <140/90 mmHg, total cholesterol <5 mmol/L, and no smoking. The main exposure variable was the number of risk factors controlled at baseline.

OUTCOME MEASURES: All-cause and cardiovascular mortality in the overall participants. Cardiovascular events, including coronary heart disease and stroke, in participants limited to those without a history of cardiovascular diseases at baseline.

RESULTS: In participants with CKD, 37% or 13% met three or four MRFC criteria, respectively. Increasing numbers of risk factors controlled were associated with lower relative hazards for all outcomes studied compared with those meeting no or one

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6 criterion. For participants with CKD meeting four criteria, the adjusted hazard ratio
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8 (HR) for all-cause mortality was 0.60 (95% confidence interval (CI) 0.53 to 0.69) and
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10 the adjusted subdistribution HR for cardiovascular mortality was 0.60 (0.50 to 0.70),
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12 considering a competing risk of non-cardiovascular death. Participants meeting four
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14 criteria also had lower relative hazards for coronary heart disease (adjusted
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16 subdistribution HR 0.73, 95% CI 0.59 to 0.91) and stroke (0.63, 0.45 to 0.89),
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18 considering death as a competing risk.
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25 **CONCLUSIONS:** MRFC may lower the increased risks for mortality and
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27 cardiovascular events in people with diabetes and CKD. Further research is needed to
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29 evaluate appropriateness of MRFC according to individual participants' health status for
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31 improved management of cardiovascular risks in this population.
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40 **Strengths and limitations of this study**

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42 • This study included a large number of participants with type 2 diabetes and CKD
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44 sampled from a representative general population with about 6 years of follow-up,
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46 which enabled to determine the associations of cardiovascular risk factors with
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48 mortality and cardiovascular events.
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52 • Linked data for hospital care and death registration with a primary care database
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6 enhanced the validity of the study to evaluate mortality and cardiovascular events.
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- 9 • We could not conclude that association represented causal relationships between
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11 MRFC and mortality and cardiovascular events in this non-randomised study.
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14 • There is a possibility of confounding if healthier participants were managed more
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16 successfully and this resulted in being categorised as those with greater number of
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18 risk factors controlled.
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Introduction

Diabetes and chronic kidney disease (CKD) are growing health problems worldwide, contributing to increased mortality [1]. Diabetes and CKD also impose a substantial economic burden on society, with particularly high costs relating to cardiovascular complications and renal replacement therapy [2,3]. The prevalence of CKD in patients with diabetes is between 4.2% and 17.9% (CKD stages 3 to 5) in European countries [4]. The leading cause of death in people with type 2 diabetes or CKD is cardiovascular disease rather than renal complications [5,6]. Prevention of cardiovascular events is a key focus in the management of patients with these conditions.

Multifactorial interventions to reduce cardiovascular risks were shown to be effective at reducing mortality and cardiovascular events in patients with type 2 diabetes and persistent microalbuminuria in the Steno-2 randomised trial [7,8]. This study provided a high level of evidence, but included a relatively small number of participants with diabetes who were managed in specialist centres. Recently, the implementation and effectiveness of this approach have been evaluated in patients with diabetes in clinical practice settings [9-11]. Epidemiological studies have demonstrated additional risks of CKD on mortality and cardiovascular diseases in people with diabetes [12], but

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6 treatment approaches in this population have not been well studied. No studies focused
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9 on multiple risk factor control (MRFC) in patients with both diabetes and CKD in a
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11 wide clinical practice setting. Generally, patients with kidney disease have been
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13 underrepresented in cardiovascular clinical trials [13]. This population may have an
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15 altered risk-benefit profile, and extrapolation of data based on patients with normal
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17 kidney function into patients with CKD may be unreliable [13]. We aimed to conduct a
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19 pragmatic evaluation of the effectiveness of MRFC on mortality and cardiovascular
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21 events in participants with type 2 diabetes and CKD in a population-based cohort study.
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31 **Methods**

32 *Data sources*

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34 This study employed a linked dataset derived from the UK Clinical Practice Research
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36 Datalink (CPRD), the UK National Health Service Hospital Episodes Statistics (HES)
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38 inpatient data, and the UK Office for National Statistics (ONS) mortality data. The
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40 CPRD contains anonymised electronic health records from general practices across the
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42 UK [14]. The CPRD collects data for diagnoses and clinical assessment, prescriptions
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44 and laboratory test results, such as HbA1c and serum creatinine. The HES inpatient data
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46 were comprised of inpatient records from all National Health Service hospitals in
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6 England. Information on the date of death and the causes of death were available in the
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8 ONS mortality data file. Multiple causes of death can be recorded in the mortality data.
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11 Diagnoses and clinical evaluation in the CPRD were coded with the Read codes, a
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13 hierarchical coding system used in primary care in the UK, whereas those in the HES
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15 and ONS were coded with the International Classification of Diseases, tenth revision
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17 (ICD-10). Linked data are available for general practices in England only and
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20 participants were limited to those with linked data for the HES and ONS available. The
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23 study was approved by the CPRD Independent Scientific Advisory Committee (ISAC
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26 Protocol 15_201R).
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34 *Study population*

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37 The scheme of the study cohort selection is presented in figure S1. We initially sampled
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39 participants who were diagnosed with type 2 diabetes from the CPRD [15]. Using the
40
41 CPRD records, the date of the first valid serum creatinine value between 2006 and 2010
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43 recorded more than one year after the first diagnosis of diabetes were defined as the
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45 index date. A similar approach was taken by Adamsson Eryd et al [16] to ensure that
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48 participants managed for diabetes had sufficient time available for recording of baseline
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51 values. To avoid misclassification of CKD status and stage, the index serum creatinine
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6 values were validated by confirmation of subsequent values within 30% of the index
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8 values. We restricted the sample to participants aged 40 to 79 years at the index date
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10 with at least one year of follow-up data available (ie, participants who died in the first
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12 year of follow-up were excluded). Estimated glomerular filtration rate (eGFR) was
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14 calculated from a serum creatinine value, age, gender, and ethnicity, using the Chronic
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16 Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [17]. Missing
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18 ethnicity was assumed as 'non-black' in the present study. Participants diagnosed with
19
20 end-stage renal disease, those who had received renal replacement therapy, or those with
21
22 index eGFR <15 mL/min/1.73 m² were excluded. We also excluded participants with
23
24 missing data for smoking status, body mass index (BMI), HbA1c, blood pressure, or
25
26 total cholesterol, or those with extreme BMI (<18.5 or ≥ 45 kg/m²) at baseline. Since it
27
28 has been reported that low values of cardiovascular risk factors were not always
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30 associated with better outcomes in observational studies [15,18,19], possibly due to
31
32 reverse causation [20,21], participants with low HbA1c (<42 mmol/mol or $<6.0\%$),
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34 blood pressure (systolic <120 or diastolic <60 mmHg), and total cholesterol (<3
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36 mmol/L) were further excluded. Participants were categorised according to index eGFR
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38 into participants with CKD (<60 mL/min/1.73 m²) and those with non-CKD (≥ 60
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40 mL/min/1.73 m²).
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Multiple risk factor control

MRFC was defined in this study as consisting of four components: (1) HbA1c <53 mmol/mol (<7.0%), (2) blood pressure <140/90 mmHg (systolic <140 and diastolic <90 mmHg), (3) total cholesterol <5 mmol/L, and (4) no smoking (non- or ex-smokers). The means of HbA1c, blood pressure, and total cholesterol records within one year before the index date were evaluated. The number of the risk factors controlled from four criteria was treated as the exposure and included as a categorical variable in the analyses, with those meeting no or one criterion as a reference category.

Outcomes

Main outcomes of interest in this study included all-cause and cardiovascular mortality, fatal and non-fatal coronary heart disease (CHD) and stroke. The date of death and causes of death were determined using the ONS mortality data. Participants who died from cardiovascular causes were identified if people had any of the ICD-10 codes I00 to I99 as a cause of death. Similarly, participants who died from renal causes were identified by the ICD-10 codes N17 to N19. All of the CPRD, HES and ONS were used to ascertain fatal and non-fatal CHD and stroke. Read codes for CHD and stroke

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6 reported previously [22,23] were updated for the present study. The ICD-10 codes for
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8 CHD and stroke were I20 to I25 and I60, I61, I63 and I64, respectively.
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10 11 12 13 14 *Analysis*

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17 Baseline characteristics of the study cohort were described according to CKD status.

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20 Time-to-event analyses were conducted to evaluate the associations of MRFC with
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22 mortality and cardiovascular events. To address the issue of reverse causation and to
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24 avoid misclassification of the outcomes from those which had existed at baseline,
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26 person-years for participants who experienced outcomes of interest in the first year of
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28 follow-up were excluded from analyses (figure S1). Cox proportional hazards models
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30
31 were used to evaluate the association of MRFC with all-cause mortality. Proportional
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33 hazards assumption was assessed by visual inspection of log-log plots, and no apparent
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35 violation was found. Competing risks regression with subdistribution hazard models
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37 were conducted for cardiovascular mortality and cardiovascular events, considering
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39 competing risks for non-cardiovascular and all-cause death, respectively [24].
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48 Associations of MRFC with cardiovascular events were evaluated in participants
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50 without a known history of cardiovascular diseases at baseline (figure S1). Participants
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52 were followed from the index date until the earliest of the events of interest, the last date
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6 of CPRD records, or 31 March 2015 for all-cause mortality evaluation. In the competing
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8 risks regression analyses for cardiovascular mortality and cardiovascular events,
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10 participants who experienced the corresponding competing events prior to the event of
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12 interest were also censored.
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19 Main analyses were conducted by CKD status, adjusting for a range of baseline
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21 covariates, including age (continuous), gender (male or female), CKD stage (3a, 3b, and
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23 4; for CKD cohort), BMI (18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, and 40.0–44.9
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25 kg/m²), deprivation level (quintile; 1, least deprived, to 5, most deprived), duration of
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27 diabetes (1.0–4.9, 5.0–9.9, and 10+ years), proteinuria status, including
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29 microalbuminuria (yes, no, and a missing category), a history of cardiovascular diseases,
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31 including CHD and stroke (for mortality evaluation), and prescribing during six months
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33 prior to the index date of antidiabetic drugs (none, insulin with and without other
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35 antidiabetic drugs, and non-insulin drugs only), antihypertensive drugs (none, drugs
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37 acting on renin-angiotensin system with and without other antihypertensive drugs, and
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39 other classes of antihypertensive drugs only, including β -blockers, calcium channel
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41 blockers, and thiazide diuretics), statins and antiplatelet drugs, and index year (2006 to
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43 2010). In addition, the associations of CKD with the outcomes were evaluated
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6 according to the number of risk factors controlled, adjusting for the potential
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8 confounding factors described above.
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14 In this paper, the results for participants with CKD were focused on, with the results for
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16 those with non-CKD shown for comparative purposes. The associations of each
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18 component of MRFC with the outcomes were also evaluated to aid interpretation of the
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20 study results. All analyses were performed using Stata version 14 (Stata Corp., College
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22 Station TX). The ‘forestplot’ package in R was used to present the results [25].
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31 **Results**

32 *Characteristics of the study population*

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35 Baseline characteristics of the study cohort are shown according to CKD status in table
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39 1. Mean index eGFR was 49 mL/min/1.73 m² for participants with CKD and 81
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41 mL/min/1.73 m² for those with non-CKD. Participants with CKD were older (71 vs 62
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43 years), included more women (52% vs 40%), had a longer duration of diabetes, and
44
45 were more likely to have a history of cardiovascular diseases (37% vs 22%). A higher
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47 frequency of proteinuria was recorded in participants with CKD (18% vs 12% among
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49 participants with records of proteinuria status). HbA1c and total cholesterol were
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6 slightly lower in participants with CKD. Although diastolic blood pressure was lower in
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8 participants with CKD, systolic blood pressure was higher despite more people under
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10 antihypertensive medications. Participants with CKD were prescribed insulin, drugs on
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12 renin-angiotensin systems, statins, and antiplatelet drugs more frequently.
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20 *Implementation of MRFC*

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22 The number of risk factors controlled from four components of MRFC are shown in
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24 table 2. More detailed results of which of the components were controlled are available
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26 in table S1. Higher rates of control for HbA1c, total cholesterol, and smoking status
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28 were observed in participants with CKD compared with those with non-CKD. However,
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30 blood pressure was less likely managed in participants with CKD (46% vs 51%). There
31
32 were some differences in management status according to a history of cardiovascular
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34 diseases: in participants with CKD, higher rates of control of blood pressure (49% vs
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36 44%) and total cholesterol (83% vs 76%) in participants with a history of cardiovascular
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38 diseases compared with those without. Participants meeting three or four criteria
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40 accounted for 37% or 13% in participants with CKD.
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53 *Effectiveness of MRFC*

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6 Absolute risks for mortality and cardiovascular diseases and adjusted relative hazards of
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8 the number of risk factors controlled for the outcomes are shown in figure 1. Increasing
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10 numbers of risk factors controlled were associated with lower relative hazards for all
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12 outcomes studied relative to participants meeting no or one criterion. For participants
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14 with CKD meeting four MRFC criteria, the adjusted hazard ratio (HR) for all-cause
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16 mortality was 0.60 (95% CI 0.53 to 0.69), and adjusted subdistribution HR for
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18 cardiovascular mortality was 0.60 (0.50 to 0.70). Participants meeting four criteria also
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20 had lower relative risks for CHD (adjusted subdistribution HR 0.73, 95% CI 0.59 to
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22 0.91) and stroke (0.63, 0.45 to 0.89) in participants with CKD. In participants with
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24 non-CKD, increasing numbers of risk factors controlled were also associated with lower
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26 risks for all-cause and cardiovascular mortality, CHD, and stroke. As shown in figure S2,
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28 the strengths of associations of each component of MRFC with mortality and
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30 cardiovascular diseases were different; for example, the greatest associations of no
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32 smoking with all-cause and cardiovascular mortality were observed in participants with
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34 and without CKD.
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51 *Comparisons between CKD and non-CKD*

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53 Unadjusted absolute risks for mortality and cardiovascular diseases were higher in
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6 participants with CKD by 1.4- to 2.9-fold compared with those with non-CKD at the
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8 same MRFC category (figure 1). More participants with CKD died from cardiovascular
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10 causes compared with those without (63% vs 54%, $P<0.001$). More participants with
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12 CKD died from renal causes ($n=631$ or 5% vs $n=326$ or 0.9%, $P<0.001$), but the
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14 proportions were much smaller than cardiovascular causes of death. Relative hazards of
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16 CKD for the outcomes are shown in figure 2. After adjustment with possible
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18 confounding factors, comorbid CKD remained to be associated with greater risks for
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20 all-cause mortality (adjusted HR, 1.16 to 1.30) and cardiovascular mortality (adjusted
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22 subdistribution HR, 1.25 to 1.41). In participants meeting two or more criteria,
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24 comorbid CKD was associated with a higher risk for CHD (1.18 to 1.25). The
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26 associations of comorbid CKD with stroke was observed in participants meeting four
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28 criteria only (1.64).
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43 Discussion

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45 In this population-based cohort study of participants with type 2 diabetes and CKD
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47 stages 3 to 4, MRFC was associated with lower relative risks for mortality ($N>11,000$)
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49 and cardiovascular diseases ($N>7,000$). We also confirmed that CKD was associated
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51 with increased risks for mortality and cardiovascular events. Higher absolute risks for
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6 mortality and cardiovascular events and great relative risk reduction associated with
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8 MRFC suggest that the MRFC strategy may be one of the main approaches to
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11 potentially reducing the burden of diabetes and CKD.
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17 This study evaluated the effectiveness of MRFC in patients with type 2 diabetes
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19 according to presence or absence of CKD in clinical practice. So far, the associations of
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21 MRFC with lower risks for mortality and cardiovascular events have been shown in
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23 people with diabetes, not focusing on CKD status. Participants with controlled three risk
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25 factors of HbA1c, blood pressure, and LDL cholesterol had 62% and 60% risk reduction
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27 for cardiovascular events and CHD, respectively, in patients with diabetes without
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29 known cardiovascular diseases [10]. The associations of uncontrolled HbA1c, blood
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31 pressure, LDL cholesterol, and smoking with mortality and cardiovascular events were
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33 individually evaluated in a large population-based study with >850,000 participants
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35 with diabetes [11]. The study cohort included 35.5% of participants with CKD in those
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37 with cardiovascular diseases and 21.8% in those without, and CKD was included in the
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39 analyses for adjustment. This study suggested that uncontrolled risk factors attributed to
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41 about 1 in 3 major cardiovascular events and fewer 1 in 10 deaths.
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6 The strength of this study was the inclusion of a large size of >11,000 participants with
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8 diabetes and CKD with an observation of >62,000 person-years. In addition to the large
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10 sample size and long-term follow-up, representativeness from general population and
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12 data quality are also advantages of the CPRD [14], which should remain even if linked
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14 data for HES and ONS are only available for England practices. Instead, linked data for
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16 hospital care and death registration substantially enhanced the validity of the study to
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18 evaluate mortality and cardiovascular events.
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28 There are also some limitations in this study. First, despite our focus on the number of
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30 MRFC, the impacts of each component of MRFC on mortality and cardiovascular
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32 events were different. Different cut-off points for HbA1c, blood pressure, and total
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34 cholesterol may bring different results. Next, we could not conclude that associations
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36 represented causal relationships between MRFC and mortality and cardiovascular
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38 events in this non-randomised study. There is a possibility of confounding if healthier
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40 participants were managed more successfully and this resulted in being categorised as
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42 those with greater number of risk factors controlled. For example, stringent
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44 management of HbA1c might not be targeted for vulnerable participants due to concerns
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46 for greater risk of hypoglycaemia, a form of confounding by contra-indication. We
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6 cannot exclude the possibility of residual confounding despite adjustment with a range
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9 of covariates in the analyses, including physical activity and alcohol intake [26,27].
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11 Then, measurement and assay methods for HbA1c, blood pressure, cholesterol and
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13 serum creatinine might not have been standardised among general practices or
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15 laboratories. As well as missing data on ethnicity and fluctuations in serum creatinine
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17 values, these methodological limitations might influence the determination of CKD
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19 status or staging. Finally, although we used one of the largest primary care electronic
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21 health records database, it seemed to be insufficient to separately evaluate MRFC for
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23 participants with different stages of CKD. Further research is needed to focus on
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25 patients with more advanced CKD who may have altered risk-benefit profile compared
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27 with patients with less impaired renal function.
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40 In summary, based on the population-based cohort study of routine clinical practices,
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42 MRFC may lower the increased risks for mortality and cardiovascular events in people
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44 with diabetes and CKD. Further research is needed to evaluate appropriateness of
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46 MRFC according to individual participants' health status for improved management of
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48 cardiovascular risks in this population.
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Table 1. Baseline characteristics of the study cohort by CKD status

		CKD (N=11,431)	Non-CKD (N=36,429)	P value
Age (years)	Mean (SD)	71 (6)	62 (9)	<0.001
Gender	Male	5,481 (48)	22,006 (60)	<0.001
	Female	5,950 (52)	14,423 (40)	
eGFR (mL/min/1.73 m ²)	Mean (SD)	49 (9)	81 (13)	–
	15–29	558 (5)	–	
	30–44	2,655 (23)	–	
	45–59	8,218 (72)	–	
Smoking status	Non-smoker	5,426 (47)	16,511 (45)	<0.001
	Ex-smoker	4,327 (38)	12,217 (34)	
	Current smoker	1,678 (15)	7,701 (21)	
BMI (kg/m ²)	18.5–24.9	1,459 (13)	4,097 (11)	<0.001
	25.0–29.9	4,329 (38)	13,054 (36)	
	30.0–34.9	3,527 (31)	11,485 (32)	
	35.0–39.9	1,541 (13)	5,454 (15)	
	40.0–44.9	575 (5)	2,339 (6)	
Deprivation level (quintile)	1 (least deprived)	1,508 (13)	4,785 (13)	0.293
	2	2,331 (20)	7,300 (20)	
	3	2,374 (21)	7,640 (21)	
	4	2,637 (23)	8,172 (22)	
	5 (most deprived)	2,581 (23)	8,532 (23)	
Duration of diabetes (years)	1.0–4.9	5,208 (46)	22,527 (62)	<0.001
	5.0–9.9	2,954 (26)	8,356 (23)	
	≥10.0	3,269 (29)	5,546 (15)	
Proteinuria	Yes	1,714 (15)	3,279 (9)	<0.001
	No	7,666 (67)	24,110 (66)	
	Missing	2,051 (18)	9,040 (25)	
History of coronary heart disease and/or stroke		4,215 (37)	7,860 (22)	<0.001
HbA _{1c} (mmol/mol/%)	42–47 (6.0–6.4)*	1,307 (11)	3,513 (10)	<0.001
	48–52 (6.5–6.9)	3,041 (27)	8,900 (24)	
	53–57 (7.0–7.4)	2,590 (23)	7,781 (21)	
	58–63 (7.5–7.9)	1,709 (15)	5,461 (15)	

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		64–68 (8.0–8.4)	1,038 (9)	3,567 (10)	
		≥69 (≥8.5)	1,746 (15)	7,207 (20)	
Systolic blood pressure (mmHg)		120–129	1,777 (16)	7,203 (20)	<0.001
		130–139	3,508 (31)	12,121 (33)	
		140–149	3,387 (30)	10,242 (28)	
		≥150	2,759 (24)	6,863 (19)	
Diastolic blood pressure (mmHg)		60–79	7,238 (63)	16,803 (46)	<0.001
		80–89	3,599 (31)	15,816 (43)	
		≥90	594 (5)	3,810 (10)	
Total cholesterol (mmol/L)		3.0–3.9	3,782 (33)	10,960 (30)	<0.001
		4.0–4.9	5,220 (46)	16,387 (45)	
		≥5.0	2,429 (21)	9,082 (25)	
Medication		Antidiabetic drugs			<0.001
		Insulin (± non-insulin)	1,805 (16)	3,225 (9)	
		Non-insulin only	7,722 (68)	26,753 (73)	
		Antihypertensive drugs			<0.001
		Drugs on renin-angiotensin system (± others)	8,472 (74)	21,535 (59)	
		Other antihypertensive drugs only	1,610 (14)	4,751 (13)	
		Statins	9,004 (79)	27,011 (74)	<0.001
		Antiplatelet drugs	6,440 (56)	16,375 (45)	<0.001
Index year		2006	9,091 (80)	24,192 (66)	<0.001
		2007	1,008 (9)	3,741 (10)	
		2008	545 (5)	2,880 (8)	
		2009	432 (4)	2,677 (7)	
		2010	355 (3)	2,939 (8)	

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Frequencies (percentages) are shown otherwise specified.

* Participants with HbA1c <48 mmol/mol (<6.5%) were only included if they were prescribed antidiabetic drugs.

Table 2. Risk factors controlled according to chronic kidney disease and a history of cardiovascular diseases

	CKD			Non-CKD		
	Total (N=11,431)	No CVD (N=7,216)	CVD (N=4,215)	Total (N=36,429)	No CVD (N=28,569)	CVD (N=7,860)
<i>Individual risk factor controlled</i>						
HbA1c <53 mmol/mol (<7.0%)	4,348 (38)	2,767 (38)	1,581 (38)	12,413 (34)	9,603 (34)	2,810 (36)
Blood pressure <140 & <90 mmHg	5,224 (46)	3,147 (44)	2,077 (49)	18,655 (51)	14,438 (51)	4,217 (54)
Total cholesterol <5 mmol/L	9,002 (79)	5,512 (76)	3,490 (83)	27,347 (75)	20,826 (73)	6,521 (83)
No smoking	9,753 (85)	6,193 (86)	3,560 (84)	28,728 (79)	22,565 (79)	6,163 (78)
<i>Number of risk factors controlled</i>						
0	138 (1)	87 (1)	51 (1)	806 (2)	678 (2)	128 (2)
1	1,427 (12)	971 (13)	456 (11)	5,372 (15)	4,421 (15)	951 (12)
2	4,162 (36)	2,693 (37)	1,469 (35)	13,288 (36)	10,602 (37)	2,686 (34)
3	4,240 (37)	2,598 (36)	1,642 (39)	12,657 (35)	9,665 (34)	2,992 (38)
4	1,464 (13)	867 (12)	597 (14)	4,306 (12)	3,203 (11)	1,103 (14)

CKD, chronic kidney disease; CVD, (a history of) cardiovascular diseases

Frequencies (percentages) are shown.

Figure legends

Figure 1. Relative hazards of the number of risk factors controlled for mortality and cardiovascular events in (a) participants with chronic kidney disease (CKD) and (b) participants with non-CKD. Hazard ratios (HRs) for all-cause mortality and subdistribution hazard ratios (SHRs) for cardiovascular mortality, coronary heart disease, and stroke were adjusted for age, gender, CKD stage (for CKD cohort), body mass index, deprivation level, duration of diabetes, proteinuria status, a history of cardiovascular diseases (for mortality evaluation), prescribing of antidiabetic, antihypertensive, statins and antiplatelet drugs, and index year.

Figure 2. Relative hazards of presence of chronic kidney disease for mortality and cardiovascular events compared with non-CKD as reference. Hazard ratios (HRs) for all-cause mortality and subdistribution hazard ratios (SHRs) for cardiovascular mortality, coronary heart disease, and stroke were adjusted for age, gender, body mass index, deprivation level, duration of diabetes, proteinuria status, a history of cardiovascular diseases (for mortality evaluation), prescribing of antidiabetic, antihypertensive, statins and antiplatelet drugs, and index year.

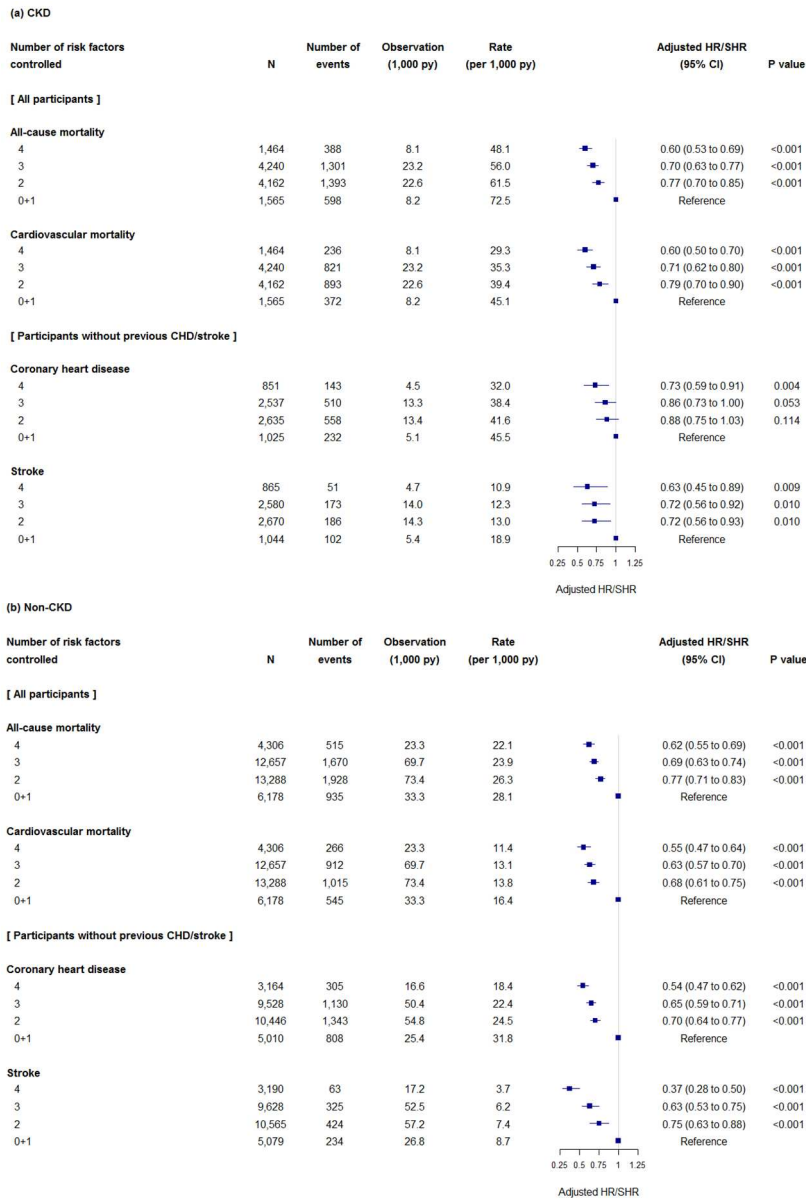


figure1

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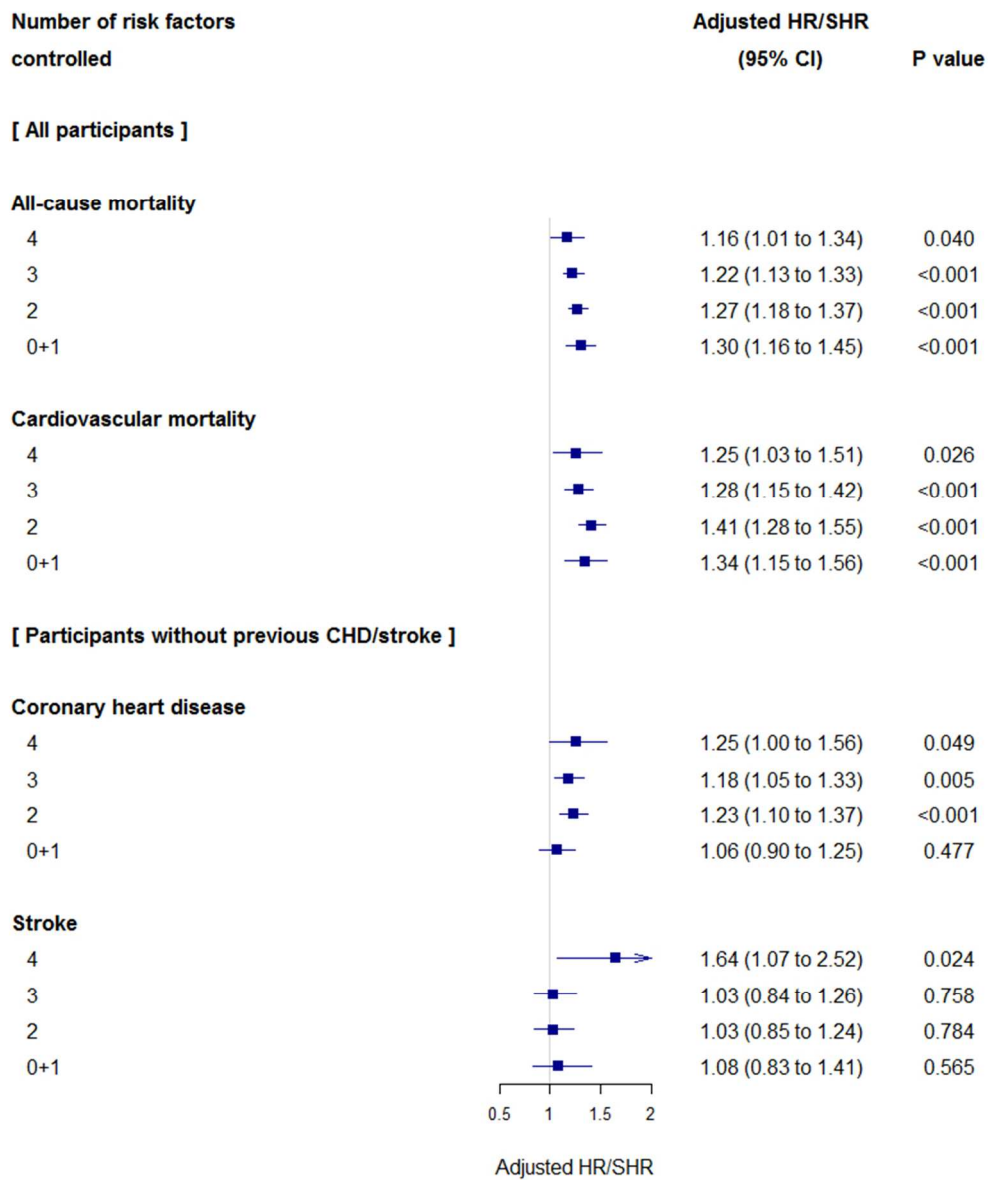
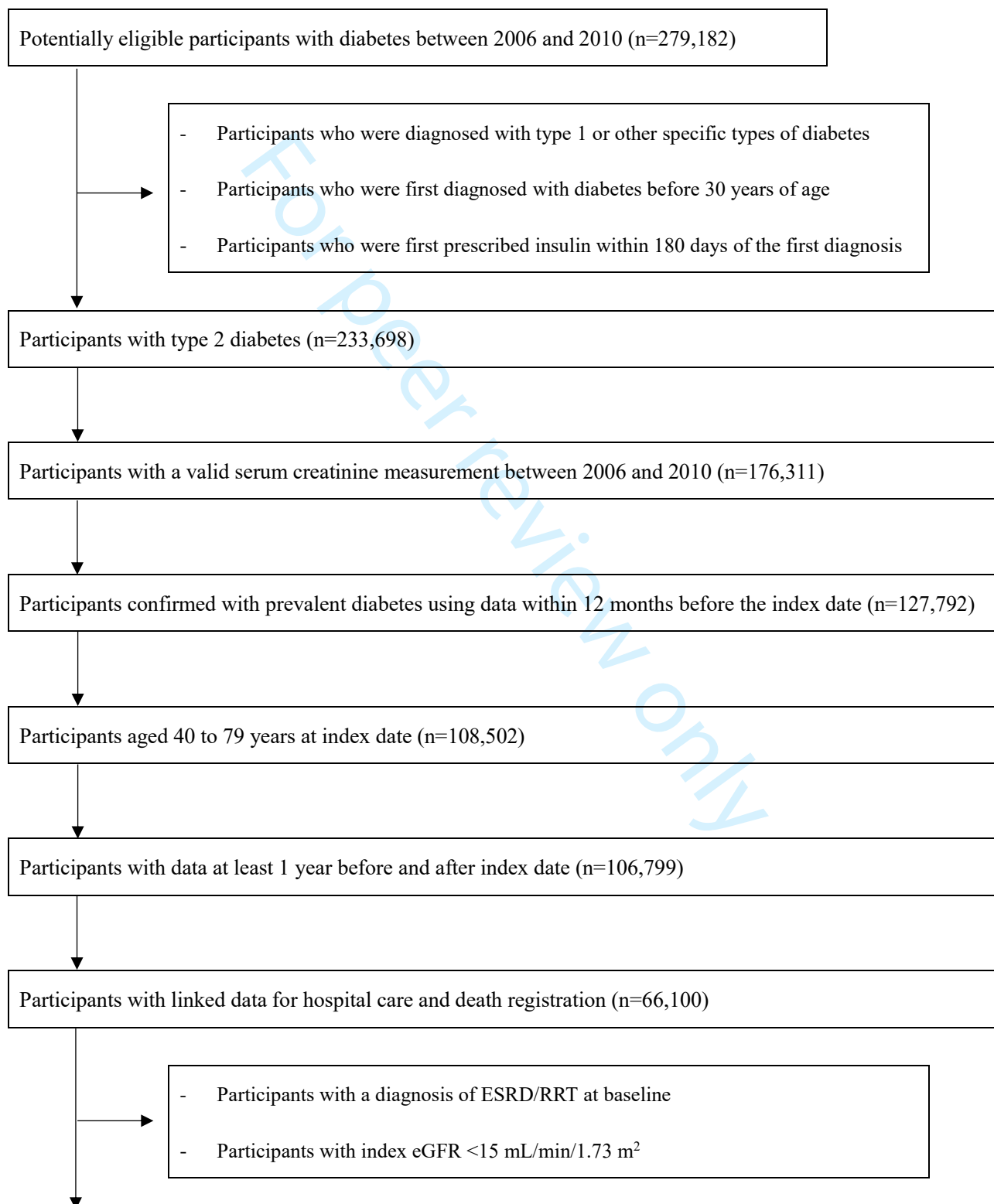


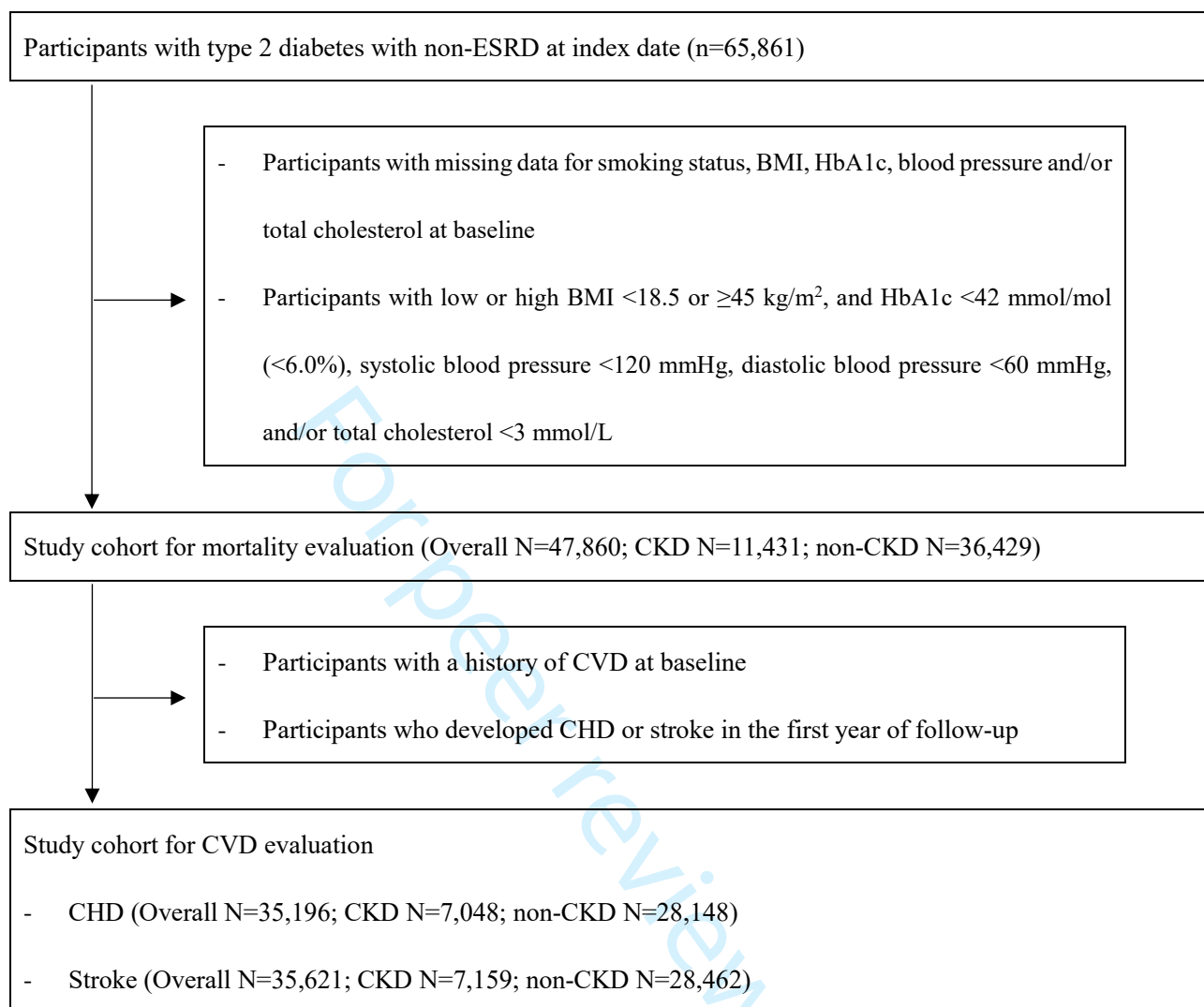
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SUPPLEMENTARY MATERIAL

Figure S1. Study cohort selection





BMI, body mass index; CKD, chronic kidney disease; CHD, coronary heart disease; CVD, Cardiovascular diseases; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RRT, renal replacement therapy

Table S1. Breakdown of risk factors controlled according to chronic kidney disease and a history of cardiovascular diseases

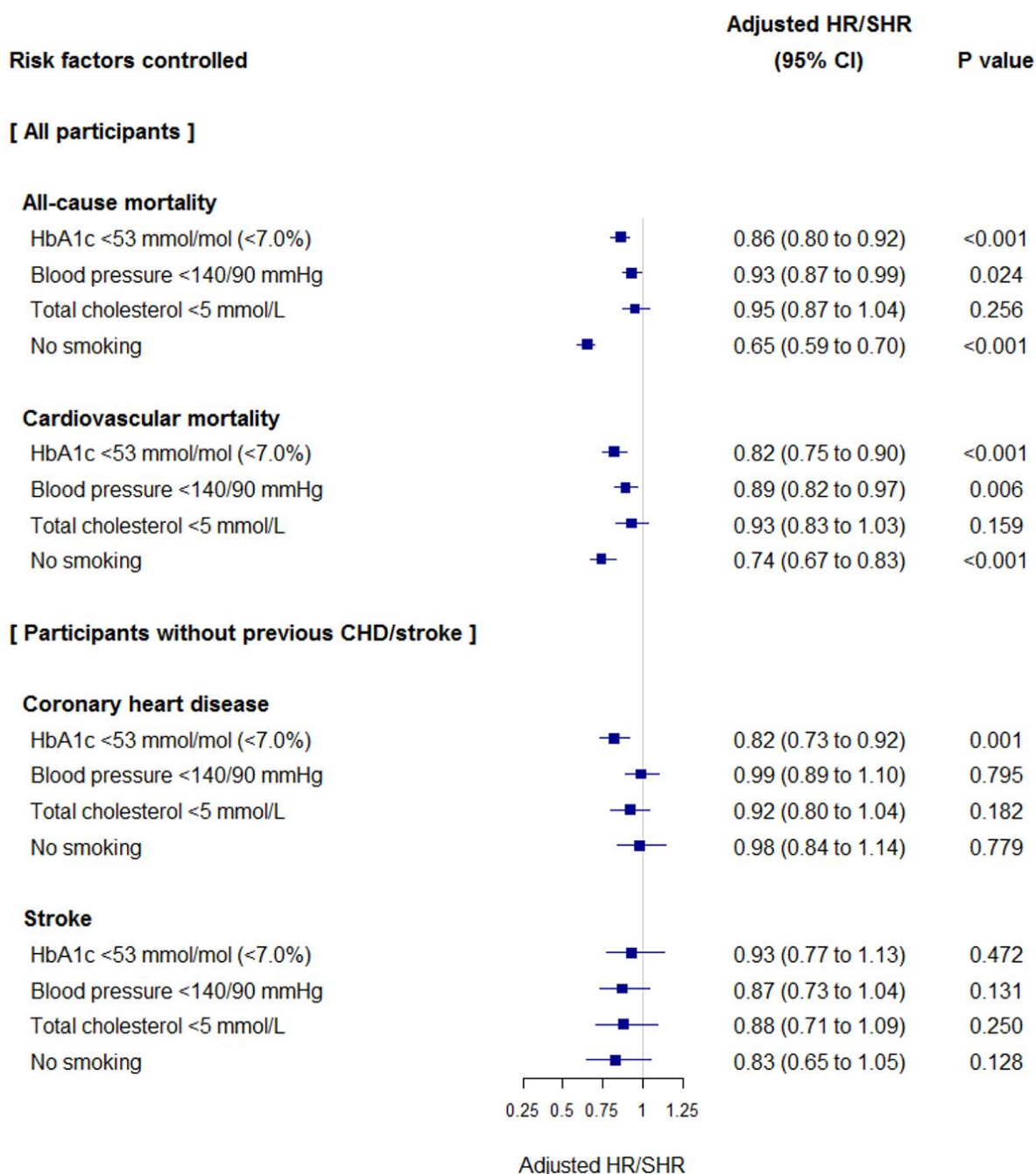
Number of risk factors controlled	HbA1c <53 mmol/mol (<7.0%)	Blood pressure <140/90 mmHg	Total cholesterol <5 mmol/L	No smoking	CKD (N=11,431)			Non-CKD (N=36,429)		
					Overall (N=11,431)	No CVD (N=7,216)	CVD (N=4,215)	Overall (N=36,429)	No CVD (N=28,569)	CVD (N=7,860)
0	–	–	–	–	138 (1)	87 (1)	51 (1)	806 (2)	678 (2)	128 (2)
1	Y	–	–	–	69 (0.6)	46 (0.6)	23 (0.6)	312 (1)	260 (0.9)	52 (0.7)
	–	Y	–	–	89 (0.8)	64 (0.9)	25 (0.6)	759 (2)	624 (2)	135 (2)
2	–	–	Y	–	438 (4)	264 (4)	174 (4)	1,742 (5)	1,350 (5)	392 (5)
	–	–	–	Y	831 (7)	597 (8)	234 (6)	2,559 (7)	2,187 (8)	372 (5)
	Y	Y	–	–	62 (0.5)	43 (0.6)	19 (0.5)	304 (0.8)	268 (0.9)	36 (0.5)
	Y	–	Y	–	245 (2)	152 (2)	93 (2)	794 (2)	590 (2)	204 (3)
	Y	–	–	Y	407 (4)	289 (4)	118 (3)	1,070 (3)	911 (3)	159 (2)
3	–	Y	Y	–	390 (3)	215 (3)	175 (4)	1,911 (5)	1,446 (5)	465 (6)
	–	Y	–	Y	531 (5)	379 (5)	152 (4)	2,205 (6)	1,910 (7)	295 (4)
	–	–	Y	Y	2,527 (22)	1,615 (22)	912 (22)	7,004 (19)	5,477 (19)	1,527 (19)
	Y	Y	Y	–	247 (2)	152 (2)	95 (2)	1,073 (3)	788 (3)	285 (4)
	Y	Y	–	Y	302 (3)	199 (3)	103 (2)	1,067 (3)	905 (3)	162 (2)
4	Y	–	Y	Y	1,552 (14)	1,019 (14)	533 (13)	3,487 (10)	2,678 (9)	809 (10)
	–	Y	Y	Y	2,139 (19)	1,228 (17)	911 (22)	7,030 (19)	5,294 (19)	1,736 (22)
	Y	Y	Y	Y	1,464 (13)	867 (12)	597 (14)	4,306 (12)	3,203 (11)	1,103 (14)

Y, meeting the criterion; –, not meeting the criterion

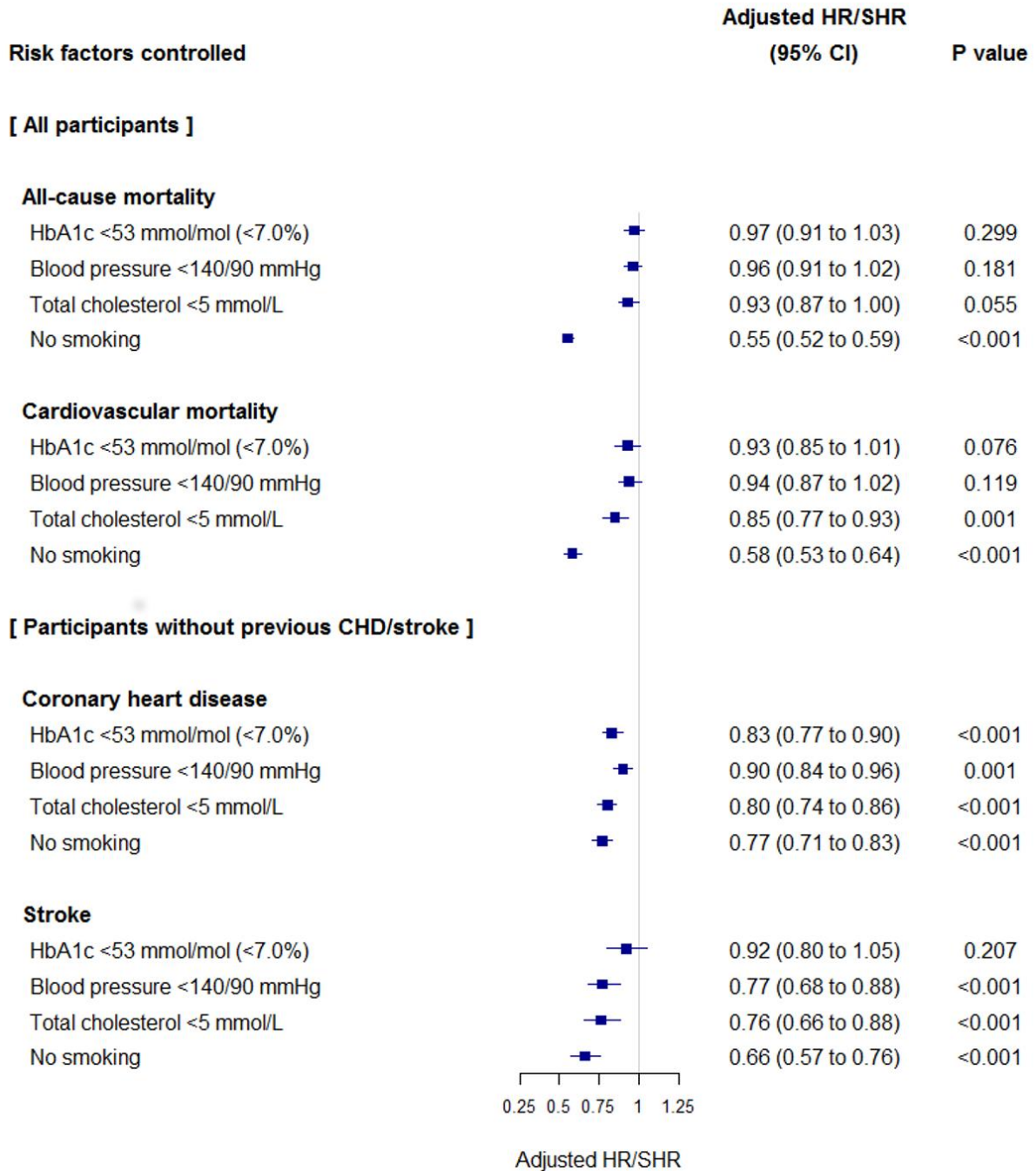
CKD, chronic kidney disease; CVD, (a history of) cardiovascular diseases

Figure S2. Relative hazards of individual risk factors controlled for mortality and cardiovascular events in (a) participants with chronic kidney disease (CKD) and (b) participants with non-CKD. Hazard ratios (HRs) for all-cause mortality and subdistribution hazard ratios (SHRs) for cardiovascular mortality, coronary heart disease, and stroke were adjusted for age, gender, CKD stage (for CKD cohort), body mass index, deprivation level, duration of diabetes, proteinuria status, a history of cardiovascular diseases (for mortality evaluation), prescribing of antidiabetic, antihypertensive, statins and antiplatelet drugs, and index year.

(a) CKD



(b) Non-CKD



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7,8,10
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-9
Bias	9	Describe any efforts to address potential sources of bias	10,11
Study size	10	Explain how the study size was arrived at	6-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11
		(b) Describe any methods used to examine subgroups and interactions	11
		(c) Explain how missing data were addressed	8,11
		(d) If applicable, explain how loss to follow-up was addressed	10
		(e) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12, Figure S1
		(b) Give reasons for non-participation at each stage	12, Figure S1
		(c) Consider use of a flow diagram	Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1, Figure S1
		(c) Summarise follow-up time (eg, average and total amount)	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Figure 1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-15
		(b) Report category boundaries when continuous variables were categorized	9, 11
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Multiple risk factor control, mortality and cardiovascular events in type 2 diabetes and chronic kidney disease: a population-based cohort study

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Keywords:	cardiovascular diseases, chronic kidney disease, mortality, type 2 diabetes

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6 **Multiple risk factor control, mortality and cardiovascular events in type 2 diabetes**
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9 **and chronic kidney disease: a population-based cohort study**
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14 Shota Hamada^{1,2}, Martin C Gulliford^{1,3}
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Abstract

OBJECTIVES: This study aimed to evaluate the effectiveness of multiple risk factor control (MRFC) at reducing mortality and cardiovascular events in diabetes and chronic kidney disease (CKD) in clinical practice.

DESIGN: Population-based cohort study.

SETTING: Primary care database in the UK, linked with inpatient and mortality data.

PARTICIPANTS: Participants aged 40 to 79 years with type 2 diabetes and valid serum creatinine measurements, including 11,431 participants with CKD (eGFR 15–59 mL/min/1.73 m²) and 36,429 participants with non-CKD (eGFR ≥60 mL/min/1.73 m²).

EXPOSURES: MRFC consisted of four components: HbA1c <53 mmol/mol (<7.0%), blood pressure <140/90 mmHg, total cholesterol <5 mmol/L, and no smoking. The main exposure variable was the number of risk factors controlled at baseline.

OUTCOME MEASURES: All-cause and cardiovascular mortality in the overall participants. Cardiovascular events, including coronary heart disease and stroke, in participants limited to those without a history of cardiovascular diseases at baseline.

RESULTS: In participants with CKD, 37% or 13% met three or four MRFC criteria, respectively. Increasing numbers of risk factors controlled were associated with lower relative hazards for all outcomes studied compared with those meeting no or one

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6 criterion. For participants with CKD meeting four criteria, the adjusted hazard ratio
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8 (HR) for all-cause mortality was 0.60 (95% confidence interval (CI) 0.53 to 0.69) and
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10 the adjusted subdistribution HR for cardiovascular mortality was 0.60 (0.50 to 0.70),
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12 considering a competing risk of non-cardiovascular death. Participants meeting four
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14 criteria also had lower relative hazards for coronary heart disease (adjusted
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16 subdistribution HR 0.73, 95% CI 0.59 to 0.91) and stroke (0.63, 0.45 to 0.89),
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18 considering death as a competing risk.
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25 **CONCLUSIONS:** MRFC may lower the increased risks for mortality and
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27 cardiovascular events in people with diabetes and CKD. Further research is needed to
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29 evaluate appropriateness of MRFC according to individual participants' health status for
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31 improved management of cardiovascular risks in this population.
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40 **Strengths and limitations of this study**

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42 • This study included a large number of participants with type 2 diabetes and CKD
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44 sampled from a representative general population with about 6 years of follow-up,
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46 which enabled to determine the associations of cardiovascular risk factors with
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48 mortality and cardiovascular events.
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52 • Linked data for diagnostic data in hospitals and death registration with a primary
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6 care database enhanced the validity of the study to evaluate mortality and
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8 cardiovascular events.
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11 • We could not conclude that associations represented causal relationships between
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13 MRFC and mortality and cardiovascular events in this non-randomised study.
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17 • There is a possibility of confounding if healthier participants were managed more
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19 successfully and this resulted in being categorised as those with greater number of
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21 risk factors controlled.
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Introduction

Diabetes and chronic kidney disease (CKD) are growing health problems worldwide, contributing to increased mortality [1]. Diabetes and CKD also impose a substantial economic burden on society, with particularly high costs relating to cardiovascular complications and renal replacement therapy [2,3]. The prevalence of CKD in patients with diabetes is between 4.2% and 17.9% (CKD stages 3 to 5) in European countries [4]. The leading cause of death in people with type 2 diabetes or CKD is cardiovascular disease rather than renal complications [5,6]. Prevention of cardiovascular events is a key focus in the management of patients with these conditions.

Multifactorial interventions to reduce cardiovascular risks were shown to be effective at reducing mortality and cardiovascular events in patients with type 2 diabetes and persistent microalbuminuria in the Steno-2 randomised trial [7,8]. This study provided a high level of evidence, but included a relatively small number of participants with diabetes who were managed in specialist centres. Recently, the implementation and effectiveness of this approach have been evaluated in patients with diabetes in clinical practice settings [9-11]. Epidemiological studies have demonstrated additional risks of CKD on mortality and cardiovascular diseases in people with diabetes [12], but

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6 treatment approaches in this population have not been well studied. No studies focused
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9 on multiple risk factor control (MRFC) in patients with both diabetes and CKD in a
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11 wide clinical practice setting. Generally, patients with kidney disease have been
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13 underrepresented in cardiovascular clinical trials [13]. This population may have an
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15 altered risk-benefit profile, and extrapolation of data based on patients with normal
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17 kidney function into patients with CKD may be unreliable [13]. We aimed to conduct a
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19 pragmatic evaluation of the effectiveness of MRFC on mortality and cardiovascular
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21 events in participants with type 2 diabetes and CKD in a population-based cohort study.
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31 **Methods**

32 *Data sources*

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34 This study employed a linked dataset derived from the UK Clinical Practice Research
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36 Datalink (CPRD), the UK National Health Service Hospital Episodes Statistics (HES)
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38 inpatient data, and the UK Office for National Statistics (ONS) mortality data. The
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40 CPRD contains anonymised electronic health records from general practices across the
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42 UK [14]. The CPRD collects data for diagnoses and clinical assessment, prescriptions
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44 and laboratory test results, such as HbA1c and serum creatinine. The HES inpatient data
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46 were comprised of inpatient records from all National Health Service hospitals in
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6 England. Information on the date of death and the causes of death were available in the
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8 ONS mortality data file. Multiple causes of death can be recorded in the mortality data.
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11 Diagnoses and clinical evaluation in the CPRD were coded with the Read codes, a
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14 hierarchical coding system used in primary care in the UK, whereas those in the HES
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17 and ONS were coded with the International Classification of Diseases, tenth revision
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19
20 (ICD-10). Linked data are available for general practices in England only and
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23 participants were limited to those with linked data for the HES and ONS available. The
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26 study was approved by the CPRD Independent Scientific Advisory Committee (ISAC
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28 Protocol 15_201R).

31 32 33 34 *Study population*

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37 The scheme of the study cohort selection is presented in figure S1. We initially sampled
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40 participants who were diagnosed with type 2 diabetes from the CPRD [15]. Using the
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43 CPRD records, the date of the first valid serum creatinine value between 2006 and 2010
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46 recorded more than one year after the first diagnosis of diabetes were defined as the
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49 index date. A similar approach was taken by Adamsson Eryd et al [16] to ensure that
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52 participants managed for diabetes had sufficient time available for recording of baseline
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55 values. To avoid misclassification of CKD status and stage, the index serum creatinine
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6 values were validated by confirmation of subsequent values within 30% of the index
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8 values. We restricted the sample to participants aged 40 to 79 years at the index date
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10 with at least one year of follow-up data available (ie, participants who died in the first
11
12 year of follow-up were excluded). Estimated glomerular filtration rate (eGFR) was
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14 calculated from a serum creatinine value, age, gender, and ethnicity, using the Chronic
15
16 Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [17]. Missing
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18 ethnicity was assumed as 'non-black' in the present study. Participants diagnosed with
19
20 end-stage renal disease, those who had received renal replacement therapy, or those with
21
22 index eGFR <15 mL/min/1.73 m² were excluded. We also excluded participants with
23
24 missing data for smoking status, body mass index (BMI), HbA1c, blood pressure, or
25
26 total cholesterol, or those with extreme BMI (<18.5 or ≥ 45 kg/m²) at baseline. Since it
27
28 has been reported that low values of cardiovascular risk factors were not always
29
30 associated with better outcomes in observational studies [15,18,19], possibly due to
31
32 reverse causation [20,21], participants with low HbA1c (<42 mmol/mol or $<6.0\%$),
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34 blood pressure (systolic <120 or diastolic <60 mmHg), and total cholesterol (<3
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36 mmol/L) were further excluded. Participants were categorised according to index eGFR
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38 into participants with CKD (<60 mL/min/1.73 m²) and those with non-CKD (≥ 60
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40 mL/min/1.73 m²).
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Multiple risk factor control

MRFC was defined in this study as consisting of four components: (1) HbA1c <53 mmol/mol (<7.0%), (2) blood pressure <140/90 mmHg (systolic <140 and diastolic <90 mmHg), (3) total cholesterol <5 mmol/L, and (4) no smoking (non- or ex-smokers). The means of HbA1c, blood pressure, and total cholesterol records within one year before the index date were evaluated. The number of the risk factors controlled from four criteria was treated as the exposure and included as a categorical variable in the analyses, with those meeting no or one criterion as a reference category.

Outcomes

Main outcomes of interest in this study included all-cause and cardiovascular mortality, fatal and non-fatal coronary heart disease (CHD) and stroke. The date of death and causes of death were determined using the ONS mortality data. Participants who died from cardiovascular causes were identified if people had any of the ICD-10 codes I00 to I99 as a cause of death. Similarly, participants who died from renal causes were identified by the ICD-10 codes N17 to N19. All of the CPRD, HES and ONS were used to ascertain fatal and non-fatal CHD and stroke. Read codes for CHD and stroke

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6 reported previously [22,23] were updated for the present study. The ICD-10 codes for
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8 CHD and stroke were I20 to I25 and I60, I61, I63 and I64, respectively.
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10 11 12 13 14 *Analysis*

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17 Baseline characteristics of the study cohort were described according to CKD status.

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20 Time-to-event analyses were conducted to evaluate the associations of MRFC with
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22 mortality and cardiovascular events. To address the issue of reverse causation and to
23
24 avoid misclassification of the outcomes from those which had existed at baseline,
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26 person-years for participants who experienced outcomes of interest in the first year of
27
28 follow-up were excluded from analyses (figure S1). Cox proportional hazards models
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30
31 were used to evaluate the association of MRFC with all-cause mortality. Proportional
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33 hazards assumption was assessed by visual inspection of log-log plots, and no apparent
34
35 violation was found. Competing risks regression with subdistribution hazard models
36
37 were conducted for cardiovascular mortality and cardiovascular events, considering
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39 competing risks for non-cardiovascular and all-cause death, respectively [24].
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45 Associations of MRFC with cardiovascular events were evaluated in participants
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48 without a known history of cardiovascular diseases at baseline (figure S1). Participants
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51 were followed from the index date until the earliest of the events of interest, the last date
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6 of CPRD records, or 31 March 2015 for all-cause mortality evaluation. In the competing
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8 risks regression analyses for cardiovascular mortality and cardiovascular events,
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10 participants who experienced the corresponding competing events prior to the event of
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12 interest were also censored.
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19 Main analyses were conducted by CKD status, adjusting for a range of baseline
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21 covariates, including age (continuous), gender (male or female), CKD stage (3a, 3b, and
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23 4; for CKD cohort), BMI (18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, and 40.0–44.9
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25 kg/m²), deprivation level (quintile; 1, least deprived, to 5, most deprived), duration of
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27 diabetes (1.0–4.9, 5.0–9.9, and 10+ years), proteinuria status, including
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29 microalbuminuria (yes, no, and a missing category), a history of cardiovascular diseases,
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31 including CHD and stroke (for mortality evaluation), and prescribing during six months
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33 prior to the index date of antidiabetic drugs (none, insulin with and without other
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35 antidiabetic drugs, and non-insulin drugs only), antihypertensive drugs (none, drugs
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37 acting on renin-angiotensin system with and without other antihypertensive drugs, and
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39 other classes of antihypertensive drugs only, including β -blockers, calcium channel
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41 blockers, and thiazide diuretics), statins and antiplatelet drugs, and index year (2006 to
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43 2010). In addition, the associations of CKD with the outcomes were evaluated
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6 according to the number of risk factors controlled, adjusting for the potential
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8 confounding factors described above.
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14 In this paper, the results for participants with CKD were focused on, with the results for
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16 those with non-CKD shown for comparative purposes. The associations of each
17
18 component of MRFC with the outcomes were also evaluated to aid interpretation of the
19
20 study results. All analyses were performed using Stata version 14 (Stata Corp., College
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22 Station TX). The ‘forestplot’ package in R was used to present the results [25].
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31 *Patient and Public Involvement*

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34 No patients were involved in setting the research question or the outcome measures, nor
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36 were they involved in developing plans for design or implementation of the study. No
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38 patients were asked to advise on interpretation or writing up of results. Results will be
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40 disseminated to relevant patient communities through news media.
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48 **Results**

49 *Characteristics of the study population*

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54 Baseline characteristics of the study cohort are shown according to CKD status in table
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6 1. Mean index eGFR was 49 mL/min/1.73 m² for participants with CKD and 81
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8 mL/min/1.73 m² for those with non-CKD. Participants with CKD were older (71 vs 62
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10 years), included more women (52% vs 40%), had a longer duration of diabetes, and
11
12 were more likely to have a history of cardiovascular diseases (37% vs 22%). A higher
13
14 frequency of proteinuria was recorded in participants with CKD (18% vs 12% among
15
16 participants with records of proteinuria status). HbA1c and total cholesterol were
17
18 slightly lower in participants with CKD. Although diastolic blood pressure was lower in
19
20 participants with CKD, systolic blood pressure was higher despite more people under
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22 antihypertensive medications. Participants with CKD were prescribed insulin, drugs on
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24 renin-angiotensin system, statins, and antiplatelet drugs more frequently.
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37 *Implementation of MRFC*

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39 The number of risk factors controlled from four components of MRFC are shown in
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41 table 2. More detailed results of which of the components were controlled are available
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43 in table S1. Higher rates of control for HbA1c, total cholesterol, and smoking status
44
45 were observed in participants with CKD compared with those with non-CKD. However,
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47 blood pressure was less likely managed in participants with CKD (46% vs 51%). There
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49 were some differences in management status according to a history of cardiovascular
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6 diseases; in participants with CKD, higher rates of control of blood pressure (49% vs
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8 44%) and total cholesterol (83% vs 76%) in participants with a history of cardiovascular
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10 diseases compared with those without. Participants meeting three or four criteria
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12 accounted for 37% or 13% in participants with CKD.
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16 17 18 19 20 *Effectiveness of MRFC*

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22 Absolute risks for mortality and cardiovascular diseases and adjusted relative hazards of
23
24 the number of risk factors controlled for the outcomes are shown in figure 1. Increasing
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26 numbers of risk factors controlled were associated with lower relative hazards for all
27
28 outcomes studied relative to participants meeting no or one criterion. For participants
29
30 with CKD meeting four MRFC criteria, the adjusted hazard ratio (HR) for all-cause
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32 mortality was 0.60 (95% CI 0.53 to 0.69), and adjusted subdistribution HR for
33
34 cardiovascular mortality was 0.60 (0.50 to 0.70). Participants meeting four criteria also
35
36 had lower relative risks for CHD (adjusted subdistribution HR 0.73, 95% CI 0.59 to
37
38 0.91) and stroke (0.63, 0.45 to 0.89) in participants with CKD. In participants with
39
40 non-CKD, increasing numbers of risk factors controlled were also associated with lower
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42 risks for all-cause and cardiovascular mortality, CHD, and stroke. As shown in figure S2,
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44 the strengths of associations of each component of MRFC with mortality and
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6 cardiovascular diseases were different; for example, the greatest associations of no
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8 smoking with all-cause and cardiovascular mortality were observed in participants with
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11 and without CKD.
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13 14 15 16 17 *Comparisons between CKD and non-CKD* 18

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20 Unadjusted absolute risks for mortality and cardiovascular diseases were higher in
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22 participants with CKD by 1.4- to 2.9-fold compared with those with non-CKD at the
23
24 same MRFC category (figure 1). More participants with CKD died from cardiovascular
25
26 causes compared with those without (63% vs 54%, $P<0.001$). More participants with
27
28 CKD died from renal causes ($n=631$ or 5% vs $n=326$ or 0.9%, $P<0.001$), but the
29
30 proportions were much smaller than cardiovascular causes of death. Relative hazards of
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32 CKD for the outcomes are shown in figure 2. After adjustment with possible
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34 confounding factors, comorbid CKD remained to be associated with greater risks for
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36 all-cause mortality (adjusted HR, 1.16 to 1.30) and cardiovascular mortality (adjusted
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38 subdistribution HR, 1.25 to 1.41). In participants meeting two or more criteria,
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40 comorbid CKD was associated with a higher risk for CHD (1.18 to 1.25). The
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42 associations of comorbid CKD with stroke was observed in participants meeting four
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44 criteria only (1.64).
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Discussion

In this population-based cohort study of participants with type 2 diabetes and CKD stages 3 or 4, MRFC was associated with lower relative risks for mortality (N>11,000) and cardiovascular diseases (N>7,000). We also confirmed that CKD was associated with increased risks for mortality and cardiovascular events. Higher absolute risks for mortality and cardiovascular events and great relative risk reduction associated with MRFC suggest that the MRFC strategy may be one of the main approaches to potentially reducing the burden of diabetes and CKD.

This study evaluated the effectiveness of MRFC in patients with type 2 diabetes according to presence or absence of CKD in clinical practice. So far, the associations of MRFC with lower risks for mortality and cardiovascular events have been shown in people with diabetes, not focusing on CKD status. Participants with controlled three risk factors of HbA1c, blood pressure, and LDL cholesterol had 62% and 60% risk reduction for cardiovascular events and CHD, respectively, in patients with diabetes without known cardiovascular diseases [10]. The associations of uncontrolled HbA1c, blood pressure, LDL cholesterol, and smoking with mortality and cardiovascular events were

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6 individually evaluated in a large population-based study with >850,000 participants
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8 with diabetes [11]. The study cohort included 35.5% of participants with CKD in those
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10 with cardiovascular diseases and 21.8% in those without, and CKD was included in the
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12 analyses for adjustment. This study suggested that uncontrolled risk factors attributed to
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14 about 1 in 3 major cardiovascular events and fewer 1 in 10 deaths.
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23 The strength of this study was the inclusion of a large size of >11,000 participants with
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25 diabetes and CKD with an observation of >62,000 person-years. In addition to the large
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27 sample size and long-term follow-up, representativeness from general population and
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29 data quality are also advantages of the CPRD [14], which should remain even if linked
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31 data for HES and ONS are only available for England practices. Instead, linked data for
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33 diagnoses in hospitals and death registration substantially enhanced the validity of the
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35 study to evaluate mortality and cardiovascular events.
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45 There are also some limitations in this study. First, despite our focus on the number of
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47 MRFC, the impacts of each component of MRFC on mortality and cardiovascular
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49 events were different. Different cut-off points for HbA1c, blood pressure, and total
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51 cholesterol may bring different results. Next, we could not conclude that associations
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6 represented causal relationships between MRFC and mortality and cardiovascular
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8 events in this non-randomised study. There is a possibility of confounding if healthier
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10 participants were managed more successfully and this resulted in being categorised as
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12 those with greater number of risk factors controlled. For example, stringent
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14 management of HbA1c might not be targeted for vulnerable participants due to concerns
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16 for greater risk of hypoglycaemia, a form of confounding by contra-indication. We
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18 cannot exclude the possibility of residual confounding, despite adjustment with a range
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20 of covariates in the analyses, including physical activity and alcohol intake [26,27].
21
22 Then, measurement and assay methods for HbA1c, blood pressure, cholesterol and
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24 serum creatinine might not have been standardised among general practices or
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26 laboratories. As well as missing data on ethnicity and fluctuations in serum creatinine
27
28 values, these methodological limitations might influence the determination of CKD
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30 status or staging. Although proteinuria has been known as a risk factor for mortality and
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32 cardiovascular diseases [28,29], we could not determine proteinuria status completely as
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34 reported previously [30,31]. Incomplete records on proteinuria may introduce a bias for
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36 proteinuria status and possibly influence the study results. Finally, although we used one
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38 of the largest primary care electronic health records database, it seemed to be
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40 insufficient to separately evaluate MRFC for participants with different stages of CKD.
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6 Further research is needed to focus on patients with more advanced CKD who may have
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8 altered risk-benefit profile compared with patients with less impaired renal function.
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14 In summary, based on the population-based cohort study of routine clinical practices,
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16 MRFC may lower the increased risks for mortality and cardiovascular events in people
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18 with diabetes and CKD. Further research is needed to evaluate appropriateness of
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20 MRFC according to individual participants' health status for improved management of
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22 cardiovascular risks in this population.
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33
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35
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37
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39
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41
42 license from the UK Medicines and Healthcare products Regulatory Agency. However,
43
44 the interpretation and conclusions contained in this report are those of the authors alone
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46 and not necessarily those of the National Health Service, the NIHR or the Department
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9 **Contributors:** Both authors contributed to conception and study design of the study,
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11 data acquisition, statistical analysis, and interpretation. SH drafted the manuscript and
12
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14 MCG revised it critically for important intellectual content.
15

16
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20 **Competing interests:** None declared.
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23 **Provenance and peer review:** Not commissioned; externally peer reviewed.
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26 **Data sharing statement:** No additional data are available.
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Table 1. Baseline characteristics of the study cohort by CKD status

		CKD (N=11,431)	Non-CKD (N=36,429)	P value
Age (years)	Mean (SD)	71 (6)	62 (9)	<0.001
Gender	Male	5,481 (48)	22,006 (60)	<0.001
	Female	5,950 (52)	14,423 (40)	
eGFR (mL/min/1.73 m ²)	Mean (SD)	49 (9)	81 (13)	–
	15–29	558 (5)	–	
	30–44	2,655 (23)	–	
	45–59	8,218 (72)	–	
Smoking status	Non-smoker	5,426 (47)	16,511 (45)	<0.001
	Ex-smoker	4,327 (38)	12,217 (34)	
	Current smoker	1,678 (15)	7,701 (21)	
BMI (kg/m ²)	18.5–24.9	1,459 (13)	4,097 (11)	<0.001
	25.0–29.9	4,329 (38)	13,054 (36)	
	30.0–34.9	3,527 (31)	11,485 (32)	
	35.0–39.9	1,541 (13)	5,454 (15)	
	40.0–44.9	575 (5)	2,339 (6)	
Deprivation level (quintile)	1 (least deprived)	1,508 (13)	4,785 (13)	0.293
	2	2,331 (20)	7,300 (20)	
	3	2,374 (21)	7,640 (21)	
	4	2,637 (23)	8,172 (22)	
	5 (most deprived)	2,581 (23)	8,532 (23)	
Duration of diabetes (years)	1.0–4.9	5,208 (46)	22,527 (62)	<0.001
	5.0–9.9	2,954 (26)	8,356 (23)	
	≥10.0	3,269 (29)	5,546 (15)	
Proteinuria	Yes	1,714 (15)	3,279 (9)	<0.001
	No	7,666 (67)	24,110 (66)	
	Missing	2,051 (18)	9,040 (25)	
History of coronary heart disease and/or stroke		4,215 (37)	7,860 (22)	<0.001
HbA _{1c} (mmol/mol or %)	42–47 (6.0–6.4)*	1,307 (11)	3,513 (10)	<0.001
	48–52 (6.5–6.9)	3,041 (27)	8,900 (24)	
	53–57 (7.0–7.4)	2,590 (23)	7,781 (21)	
	58–63 (7.5–7.9)	1,709 (15)	5,461 (15)	

	64–68 (8.0–8.4)	1,038 (9)	3,567 (10)	
	≥69 (≥8.5)	1,746 (15)	7,207 (20)	
Systolic blood pressure (mmHg)	120–129	1,777 (16)	7,203 (20)	<0.001
	130–139	3,508 (31)	12,121 (33)	
	140–149	3,387 (30)	10,242 (28)	
	≥150	2,759 (24)	6,863 (19)	
Diastolic blood pressure (mmHg)	60–79	7,238 (63)	16,803 (46)	<0.001
	80–89	3,599 (31)	15,816 (43)	
	≥90	594 (5)	3,810 (10)	
Total cholesterol (mmol/L)	3.0–3.9	3,782 (33)	10,960 (30)	<0.001
	4.0–4.9	5,220 (46)	16,387 (45)	
	≥5.0	2,429 (21)	9,082 (25)	
Medication	Antidiabetic drugs			<0.001
	Insulin (± non-insulin)	1,805 (16)	3,225 (9)	
	Non-insulin only	7,722 (68)	26,753 (73)	
	Antihypertensive drugs			<0.001
	Drugs on renin-angiotensin system (± others)	8,472 (74)	21,535 (59)	
	Other antihypertensive drugs only	1,610 (14)	4,751 (13)	
	Statins	9,004 (79)	27,011 (74)	<0.001
	Antiplatelet drugs	6,440 (56)	16,375 (45)	<0.001
Index year	2006	9,091 (80)	24,192 (66)	<0.001
	2007	1,008 (9)	3,741 (10)	
	2008	545 (5)	2,880 (8)	
	2009	432 (4)	2,677 (7)	
	2010	355 (3)	2,939 (8)	

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Frequencies (percentages) are shown otherwise specified.

* Participants with HbA1c <48 mmol/mol (<6.5%) were only included if they were prescribed antidiabetic drugs.

Table 2. Risk factors controlled according to chronic kidney disease and a history of cardiovascular diseases

	CKD			Non-CKD		
	Total (N=11,431)	No CVD (N=7,216)	CVD (N=4,215)	Total (N=36,429)	No CVD (N=28,569)	CVD (N=7,860)
<i>Individual risk factor controlled</i>						
HbA1c <53 mmol/mol (<7.0%)	4,348 (38)	2,767 (38)	1,581 (38)	12,413 (34)	9,603 (34)	2,810 (36)
Blood pressure <140 & <90 mmHg	5,224 (46)	3,147 (44)	2,077 (49)	18,655 (51)	14,438 (51)	4,217 (54)
Total cholesterol <5 mmol/L	9,002 (79)	5,512 (76)	3,490 (83)	27,347 (75)	20,826 (73)	6,521 (83)
No smoking	9,753 (85)	6,193 (86)	3,560 (84)	28,728 (79)	22,565 (79)	6,163 (78)
<i>Number of risk factors controlled</i>						
0	138 (1)	87 (1)	51 (1)	806 (2)	678 (2)	128 (2)
1	1,427 (12)	971 (13)	456 (11)	5,372 (15)	4,421 (15)	951 (12)
2	4,162 (36)	2,693 (37)	1,469 (35)	13,288 (36)	10,602 (37)	2,686 (34)
3	4,240 (37)	2,598 (36)	1,642 (39)	12,657 (35)	9,665 (34)	2,992 (38)
4	1,464 (13)	867 (12)	597 (14)	4,306 (12)	3,203 (11)	1,103 (14)

CKD, chronic kidney disease; CVD, (a history of) cardiovascular diseases

Frequencies (percentages) are shown.

Figure legends

Figure 1. Relative hazards of the number of risk factors controlled for mortality and cardiovascular events in (a) participants with chronic kidney disease (CKD) and (b) participants with non-CKD. Hazard ratios (HRs) for all-cause mortality and subdistribution hazard ratios (SHRs) for cardiovascular mortality, coronary heart disease, and stroke were adjusted for age, gender, CKD stage (for CKD cohort), body mass index, deprivation level, duration of diabetes, proteinuria status, a history of cardiovascular diseases (for mortality evaluation), prescribing of antidiabetic, antihypertensive, statins and antiplatelet drugs, and index year.

Figure 2. Relative hazards of presence of chronic kidney disease (CKD) for mortality and cardiovascular events compared with non-CKD as reference. Hazard ratios (HRs) for all-cause mortality and subdistribution hazard ratios (SHRs) for cardiovascular mortality, coronary heart disease, and stroke were adjusted for age, gender, body mass index, deprivation level, duration of diabetes, proteinuria status, a history of cardiovascular diseases (for mortality evaluation), prescribing of antidiabetic, antihypertensive, statins and antiplatelet drugs, and index year.

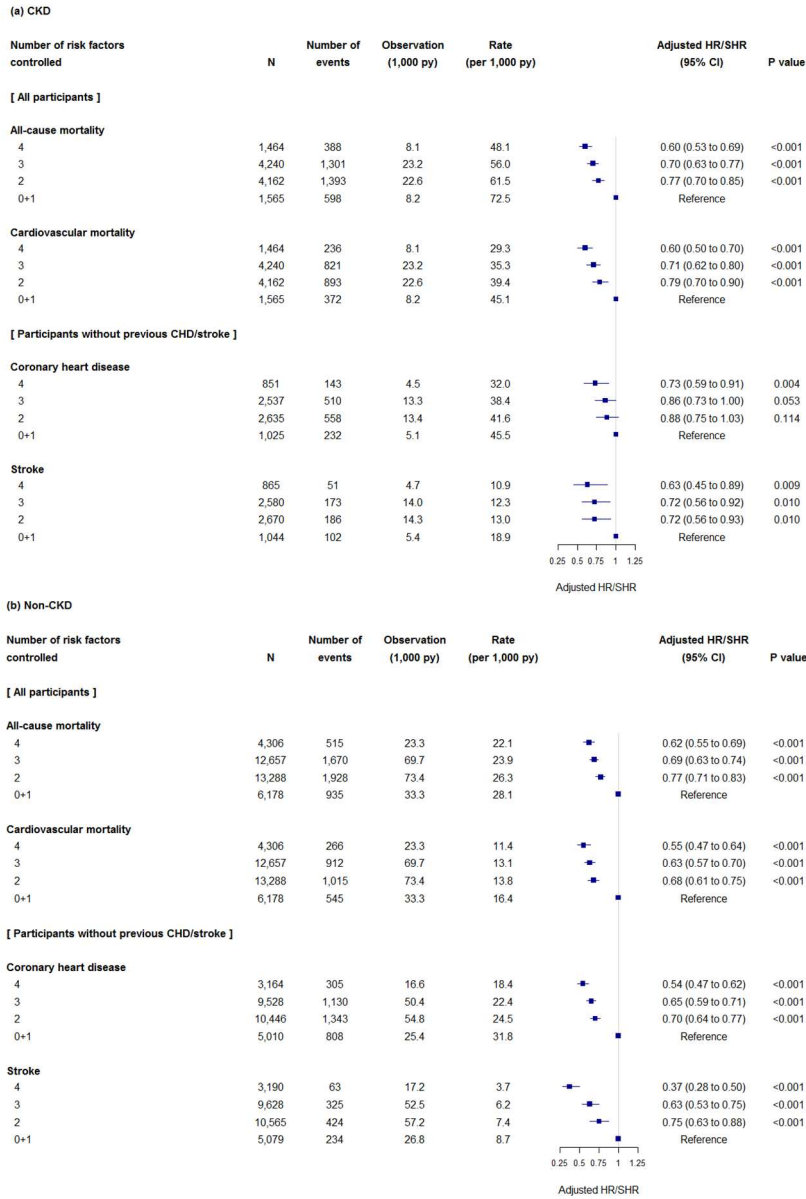


figure1

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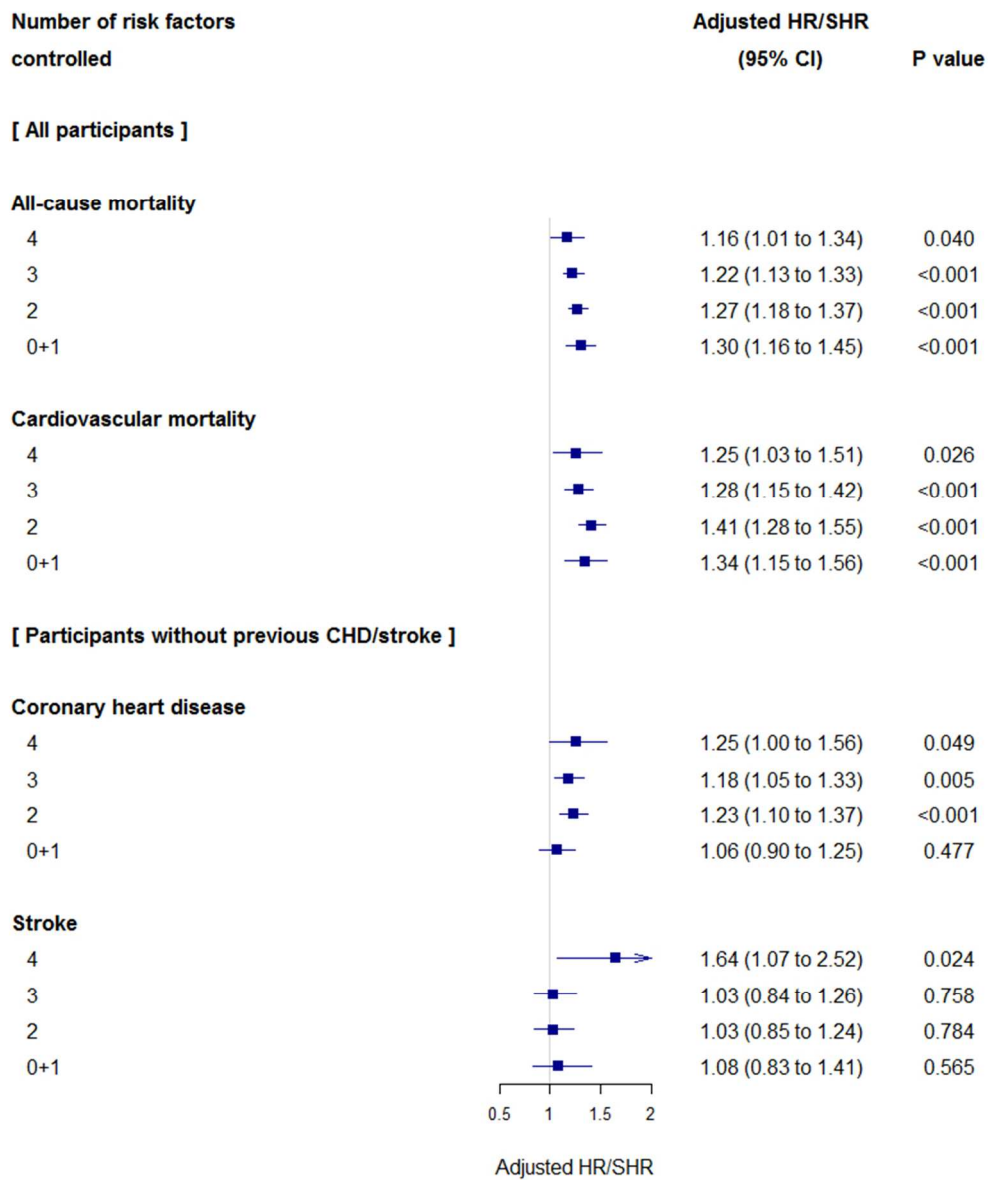
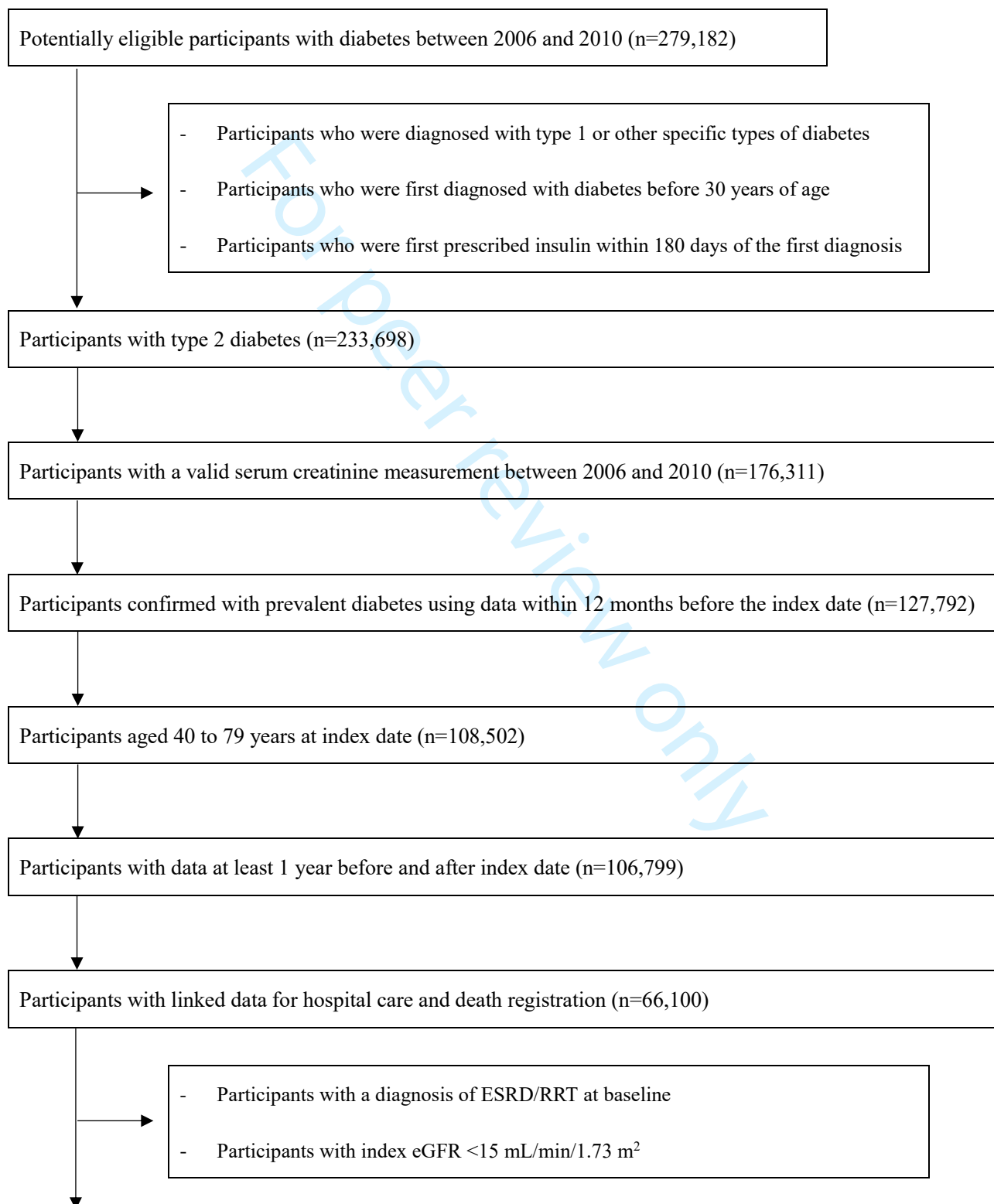


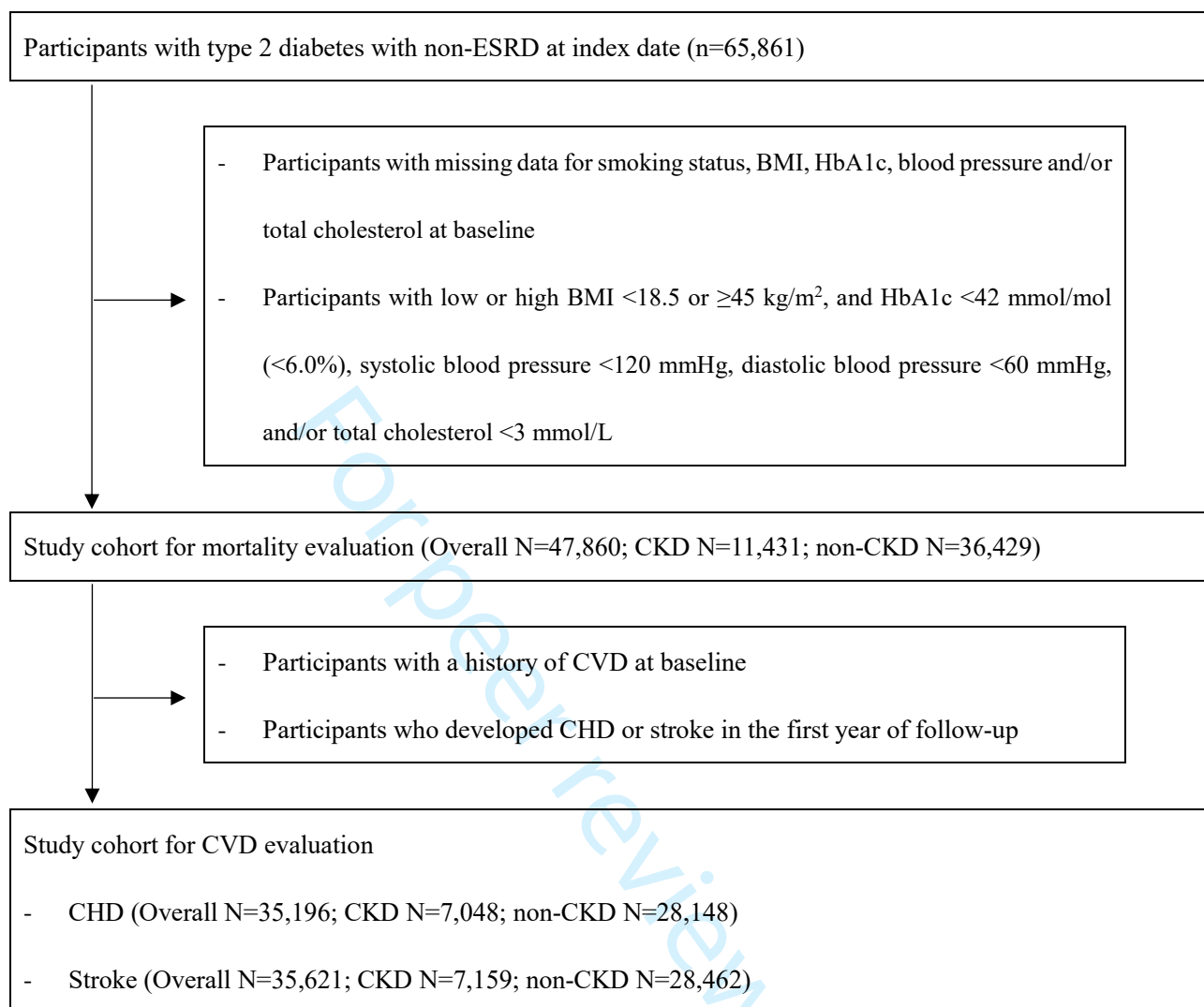
figure2

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SUPPLEMENTARY MATERIAL

Figure S1. Study cohort selection





BMI, body mass index; CKD, chronic kidney disease; CHD, coronary heart disease; CVD, Cardiovascular diseases; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RRT, renal replacement therapy

Table S1. Breakdown of risk factors controlled according to chronic kidney disease and a history of cardiovascular diseases

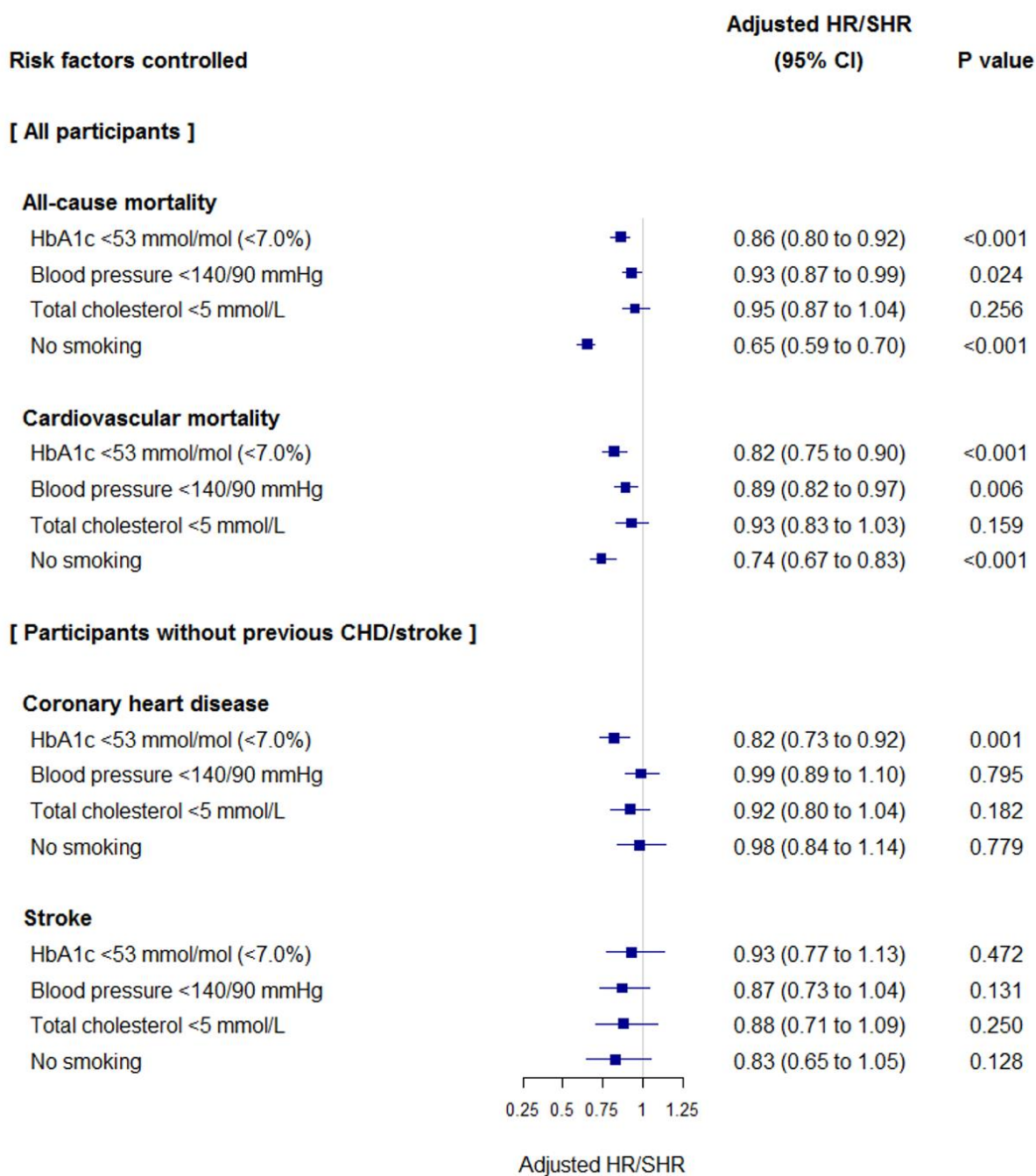
Number of risk factors controlled	HbA1c <53 mmol/mol (<7.0%)	Blood pressure <140/90 mmHg	Total cholesterol <5 mmol/L	No smoking	CKD (N=11,431)			Non-CKD (N=36,429)		
					Overall	No CVD	CVD	Overall	No CVD	CVD
0	-	-	-	-	138 (1)	87 (1)	51 (1)	806 (2)	678 (2)	128 (2)
1	Y	-	-	-	69 (0.6)	46 (0.6)	23 (0.6)	312 (1)	260 (0.9)	52 (0.7)
	-	Y	-	-	89 (0.8)	64 (0.9)	25 (0.6)	759 (2)	624 (2)	135 (2)
2	-	-	Y	-	438 (4)	264 (4)	174 (4)	1,742 (5)	1,350 (5)	392 (5)
	-	-	-	Y	831 (7)	597 (8)	234 (6)	2,559 (7)	2,187 (8)	372 (5)
	Y	Y	-	-	62 (0.5)	43 (0.6)	19 (0.5)	304 (0.8)	268 (0.9)	36 (0.5)
	Y	-	Y	-	245 (2)	152 (2)	93 (2)	794 (2)	590 (2)	204 (3)
	Y	-	-	Y	407 (4)	289 (4)	118 (3)	1,070 (3)	911 (3)	159 (2)
	-	Y	Y	-	390 (3)	215 (3)	175 (4)	1,911 (5)	1,446 (5)	465 (6)
3	-	Y	-	Y	531 (5)	379 (5)	152 (4)	2,205 (6)	1,910 (7)	295 (4)
	-	-	Y	Y	2,527 (22)	1,615 (22)	912 (22)	7,004 (19)	5,477 (19)	1,527 (19)
	Y	Y	Y	-	247 (2)	152 (2)	95 (2)	1,073 (3)	788 (3)	285 (4)
	Y	Y	-	Y	302 (3)	199 (3)	103 (2)	1,067 (3)	905 (3)	162 (2)
	Y	-	Y	Y	1,552 (14)	1,019 (14)	533 (13)	3,487 (10)	2,678 (9)	809 (10)
4	-	Y	Y	Y	2,139 (19)	1,228 (17)	911 (22)	7,030 (19)	5,294 (19)	1,736 (22)
	Y	Y	Y	Y	1,464 (13)	867 (12)	597 (14)	4,306 (12)	3,203 (11)	1,103 (14)

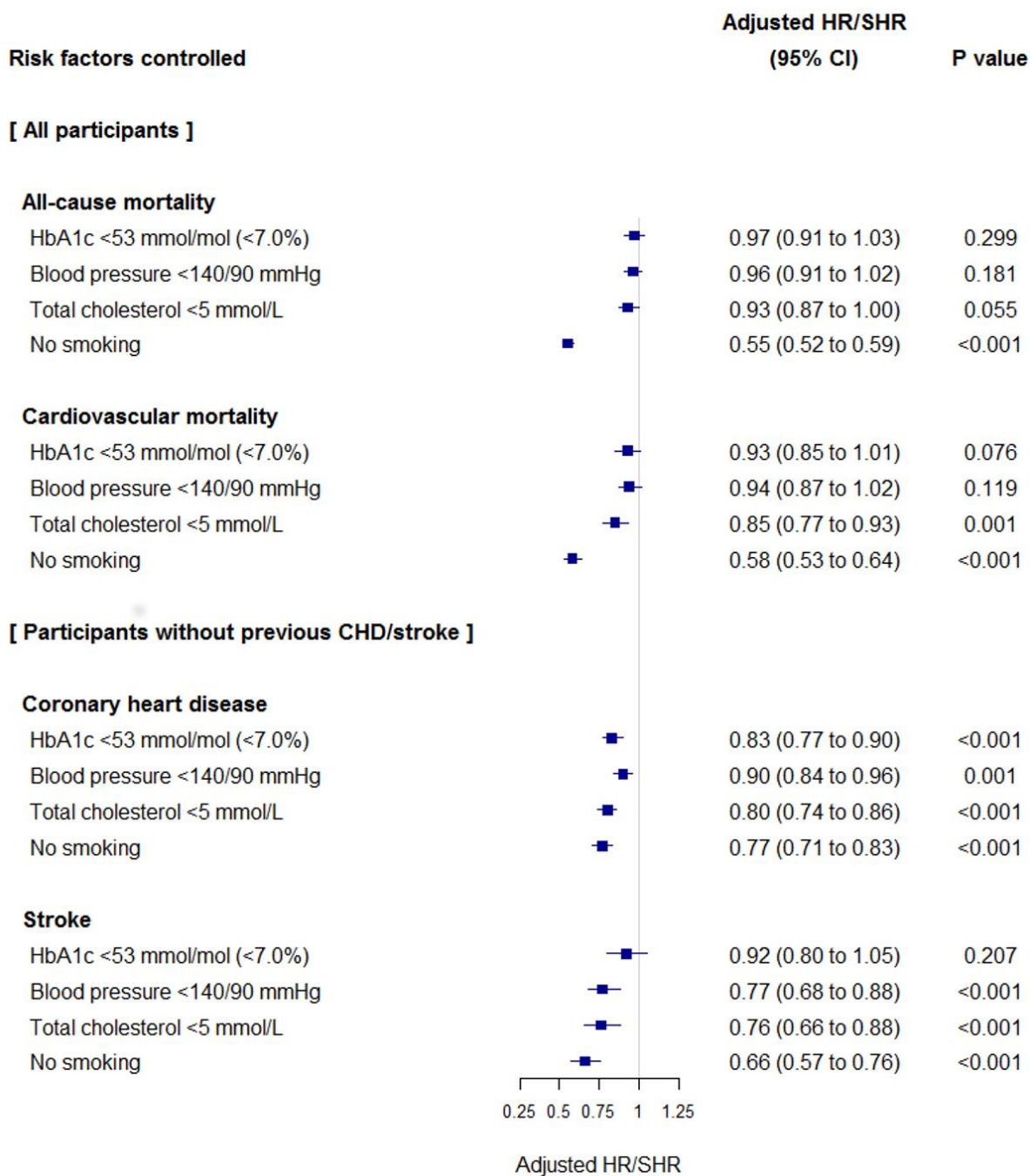
Y, meeting the criterion; -, not meeting the criterion

CKD, chronic kidney disease; CVD, (a history of) cardiovascular diseases

Figure S2. Relative hazards of individual risk factors controlled for mortality and cardiovascular events in (a) participants with chronic kidney disease (CKD) and (b) participants with non-CKD. Hazard ratios (HRs) for all-cause mortality and subdistribution hazard ratios (SHRs) for cardiovascular mortality, coronary heart disease, and stroke were adjusted for age, gender, CKD stage (for CKD cohort), body mass index, deprivation level, duration of diabetes, proteinuria status, a history of cardiovascular diseases (for mortality evaluation), prescribing of antidiabetic, antihypertensive, statins and antiplatelet drugs, and index year.

(a) CKD



(b) Non-CKD

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7,8,10
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-9
Bias	9	Describe any efforts to address potential sources of bias	10,11
Study size	10	Explain how the study size was arrived at	6-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11
		(b) Describe any methods used to examine subgroups and interactions	11
		(c) Explain how missing data were addressed	8,11
		(d) If applicable, explain how loss to follow-up was addressed	10
		(e) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12,Figure S1
		(b) Give reasons for non-participation at each stage	12,Figure S1
		(c) Consider use of a flow diagram	Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12,13,Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1,Figure S1
		(c) Summarise follow-up time (eg, average and total amount)	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Figure 1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-15
		(b) Report category boundaries when continuous variables were categorized	9,11
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17,18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.