

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

**The association between dementia parental family history and midlife modifiable risk factors for dementia: a cross-sectional study using propensity score matching within the Lifelines cohort**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-049918
Article Type:	Original research
Date Submitted by the Author:	06-Feb-2021
Complete List of Authors:	Vrijsen, Joyce; University of Groningen, Epidemiology Abu-Hanna, Ameen; University of Amsterdam, Amsterdam UMC, Medical Informatics de Rooij, Sophia; Medical Spectrum Twente, Medical School Twente Smidt, Nynke; University of Groningen, Epidemiology
Keywords:	Dementia < NEUROLOGY, PREVENTIVE MEDICINE, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1  
2  
3 1 **TITLE**  
4

5 2 The association between dementia parental family history and midlife modifiable risk factors for  
6  
7 3 dementia: a cross-sectional study using propensity score matching within the Lifelines cohort  
8

9 4  
10  
11 5 **AUTHORS**  
12

13 6 J. Vrijsen<sup>1\*</sup>, A. Abu-Hanna<sup>2</sup>, S.E. de Rooij<sup>3</sup>, N. Smidt<sup>1</sup>  
14

15 7 <sup>1</sup> University of Groningen, University Medical Centre Groningen, Department of Epidemiology,  
16  
17 Groningen, the Netherlands  
18

19 9 <sup>2</sup> University of Amsterdam, Amsterdam UMC, Department of Medical Informatics, Amsterdam Public  
20  
21 Health research institute, Amsterdam, the Netherlands  
22

23 10  
24 11 <sup>3</sup> Medical Spectrum Twente, Medical School Twente, Enschede, the Netherlands  
25

26 12  
27  
28 13 \*Corresponding author. University Medical Centre Groningen, Department of Epidemiology,  
29

30 14 Hanzeplein 1, PO Box 30 001, FA40, 9700 RB Groningen, the Netherlands. E-mail:  
31

32 15 j.vrijsen@umcg.nl; Tel: 06-25650782  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**17 ABSTRACT**

**18 OBJECTIVE:** Individuals with a parental family history (PFH) of dementia have an increased risk to  
**19** develop dementia, regardless of genetic risks. The aim of this study is to investigate the association  
**20** between a PFH of dementia and currently known modifiable risk factors for dementia among middle-  
**21** aged individuals, using propensity score matching (PSM).

**22 DESIGN:** A cross-sectional study

**23 SETTING AND PARTICIPANTS:** A subsample of Lifelines (35-65 years), a prospective  
**24** population-based cohort study in the Netherlands was used.

**25 OUTCOME MEASURES:** Fourteen modifiable risk factors for dementia and the overall Lifestyle  
**26** for Brain Health (LIBRA) score, indicating someone's potential for dementia risk reduction (DRR).

**27 RESULTS:** The study population included 89,869 participants of which 10,940 participants (12.2%)  
**28** with a PFH of dementia (mean(SD) age=52.95(7.2)) and 36,389 participants (40.5%) without a PFH of  
**29** dementia (mean(SD) age=43.19(5.5)). Of 42,540 participants (47.3%) PFH of dementia was imputed.  
**30** After PSM, potential confounding variables were balanced between individuals with and without PFH  
**31** of dementia. Individuals with a PFH of dementia had more often hypertension (OR; 95%-CI)=1.19;  
**32** 1.14-1.24), high cholesterol (OR=1.24; 1.18-1.30), diabetes (OR=1.26; 1.11-1.42), CVDs (OR=1.49;  
**33** 1.18-1.88)), depression (OR=1.23; 1.08-1.41), obesity (OR=1.14; 1.08-1.20), overweight (OR=1.10;  
**34** 1.05-1.17) and were more often current-smokers (OR=1.20; 1.14-1.27) and ex-smokers (OR=1.21;  
**35** 1.16-1.27). However, they were less often low/moderate alcohol consumers (OR=0.87; 0.83-0.91),  
**36** excessive alcohol consumers (OR=0.93; 0.89-0.98)), socially inactive (OR=0.84; 0.78-0.90) and  
**37** physically inactive (OR=0.93; 0.91-0.97). Having a PFH of dementia resulted in a higher LIBRA  
**38** score (RC=0.15; 0.11-0.19).

**39 CONCLUSION:** We found that having a PFH of dementia was associated with several modifiable  
**40** risk factors. This suggests that middle-aged individuals with a PFH of dementia are a group at risk and  
**41** could benefit from DRR. Further research should explore their knowledge, beliefs and attitudes  
**42** towards DRR, and whether they are willing to assess their risk and change their lifestyle to reduce  
**43** dementia risk.

1  
2  
3 45 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
4

- 5 46 • No other study investigating the association between a parental family history of dementia and  
6  
7 47 modifiable risk factors for dementia used a wide range of the currently known modifiable risk  
8  
9 48 factors for dementia.  
10  
11 49 • Our large study sample provided sufficient power to detect relevant associations independent  
12  
13 50 of confounding factors.  
14  
15 51 • We used sophisticated statistical techniques to prevent selection bias and calculated odds  
16  
17 52 ratios and regression coefficients with 95%-confidence intervals.  
18  
19 53 • Parental family history of dementia was based on self-reported questionnaires, which could  
20  
21 54 have led to misclassification.  
22  
23 55 • Results were based on cross-sectional data in which previous health behaviours were not taken  
24  
25 56 into account.  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

58 **KEY WORDS:**

- 59 • Dementia Risk Reduction
- 60 • Family History
- 61 • Modifiable Risk Factors
- 62 • Multiple Imputation
- 63 • Propensity Score Matching
- 64 • Middle Aged

For peer review only

## 66 INTRODUCTION

67 Since the world's population is ageing, the total number of people with dementia will increase (1). In  
68 2019, around 50 million people were living with dementia worldwide and the number of people with  
69 dementia is expected to increase to 152 million by 2050 (2). Dementia affects not only the individual  
70 living with dementia, but also their family, caregivers and society as a whole (2). Since treatment  
71 options for curing dementia are unavailable to date, prevention of dementia is the key in decreasing  
72 the burden of dementia. It is estimated that delaying dementia onset by one year would reduce the total  
73 worldwide number of people with dementia over 60 years old in 2050 by 11.8% (3).

74  
75 Accumulating evidence shows that the development of dementia is a long-term pathological process  
76 that starts approximately ten to twenty years before dementia is clinically diagnosed (4–6). The  
77 evidence of modifiable risk factors influencing this process has been mounting (1,7,8). Livingston et  
78 al. (2020) found that 40% of the dementia cases is attributable to several lifestyle-related risk factors  
79 (i.e. less education, hypertension, hearing impairment, smoking, obesity, depression, physical  
80 inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury and air  
81 pollution) (9). Also support for several other factors was found, such as hyperlipidaemia, coronary  
82 heart disease, renal dysfunction, Mediterranean diet, cognitive activity and stress (8,10). The majority  
83 of these risk factors were combined in the Lifestyle for Brain Health (LIBRA) score, reflecting  
84 someone's potential for dementia risk reduction (DRR) (8,11,12). The predictive accuracy of the  
85 LIBRA score was examined and results showed that higher LIBRA scores (presence of more risk  
86 factors) were associated to dementia in middle-aged individuals (55–69 years) (HR=1.10, 1.02–  
87 1.18)(12), but not in very old individuals (84-102 years) (HR=0.93, 0.83-1.05) (13). Several multi-  
88 domain interventions to reduce dementia risk and prevent cognitive decline among older individuals  
89 were conducted, however only small or non-significant effects on cognition were found (14–16).

90  
91 These multi-domain interventions may be more effective among cognitively healthy middle-aged  
92 individuals with a higher risk for developing dementia, for instance individuals with a parental family  
93 history (PFH) of dementia. The average lifetime risk of developing dementia is 10-12% and increases



1  
2  
3 94 to 15-25% for individuals with a family history of dementia (17). This increased risk can be explained  
4  
5 95 by both genetic and lifestyle factors (18–21), which are passed on from parents to offspring (20,22).  
6  
7 96 The APOE  $\epsilon$ 4 allele is one of the genes to be consistently shown to increase the risk for dementia (23–  
8  
9 97 25). Individuals with a PFH of dementia are more often carrier of this allele compared to individuals  
10  
11 98 without a PFH of dementia (21,26–29). Nevertheless, several studies have shown that individuals with  
12  
13 99 a PFH of dementia have an increased risk, independent of their genetic risk (18,27,28).

14  
15  
16 100  
17  
18 101 Although the role of APOE genotype on dementia risk has been well studied, the risk factor of a PFH  
19  
20 102 remains rarely studied. Only a few studies investigated the association between family history of  
21  
22 103 dementia and modifiable risk factors for dementia (28,30,31). They found that family history of  
23  
24 104 dementia was associated with both higher diastolic (DBP) as systolic blood pressure (SBP) and  
25  
26 105 depression (28,31), while it was not associated with Body Mass Index (BMI), serum lipid profiles (e.g.  
27  
28 106 Total cholesterol, HDL, LDL), alcohol consumption and smoking behaviour (30). However, previous  
29  
30 107 studies did not take all currently known modifiable risk factors for dementia into account and included  
31  
32 108 a relatively small sample of participants. Moreover, these findings might be a result of confounding  
33  
34 109 bias. Propensity score matching (PSM) is a sophisticated analysis technique that can reduce this bias  
35  
36 110 by assembling a matched sample of people with and without a PFH of dementia, in which  
37  
38 111 confounding factors are balanced between groups (32). By matching, a greater proportion of the  
39  
40 112 systematic differences in characteristics of individuals with and without a PFH is eliminated compared  
41  
42 113 to the commonly used regression adjustment (32).

43  
44  
45 114  
46  
47 115 Finding differences in modifiable risk factors for dementia among middle-aged individuals with and  
48  
49 116 without a PFH of dementia, might help to identify individuals with an increased risk for dementia and  
50  
51 117 subsequently offer them tailor-made interventions for DRR. Therefore, the aim of this study was to  
52  
53 118 investigate the association between a PFH of dementia and modifiable risk factors for dementia among  
54  
55 119 middle-aged individuals from the general population.

56 120

## 57 121 **METHOD**

## 122 **Study population**

123 The Lifelines Cohort Study is a multi-disciplinary prospective population-based cohort study  
124 examining, in a unique three-generation design, the health and health-related behaviours of 167,729  
125 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in  
126 assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which  
127 contribute to the health and disease of the general population, with a special focus on multi-morbidity  
128 and complex genetics (33,34). The Lifelines Cohort study was conducted according to the guidelines  
129 in the Declaration of Helsinki, and approved by the Medical Ethics Committee of the University  
130 Medical Centre Groningen. All participants provided written informed consent. For the current study,  
131 we selected participants aged 35 to 65 years that participated in the baseline assessment and the first  
132 follow-up questionnaire.

## 134 **Measurement of independent and dependent variables**

### 135 **Independent variable**

136 Family history of dementia was assessed during the first follow-up questionnaire, on average 1.5 years  
137 after baseline measurement with the question 'Does your biological father and/or mother have or had  
138 one of the following diseases?'. Participants could indicate whether their father and/or mother had  
139 dementia. This variable was dichotomized into: (i) 'yes' (1 = having a parent with dementia) and (ii)  
140 'no' (0 = not having a parent with dementia). Furthermore, participants reported whether parents  
141 deceased and the year of birth and death of their father and/or mother if applicable. In case one of the  
142 parents deceased and no information was given about whether at least one parent had dementia, the  
143 PFH of dementia was recoded as missing. In these cases, dementia symptoms might not have been  
144 revealed yet. Therefore, it is unclear whether they would have developed dementia if they would still  
145 be alive. We attended to this by the use of multiple imputation (see Statistical analyses).

### 147 **Dependent variables**

148 Dependent variables are risk and protective factors for dementia, and are based on data collection  
149 during physical examination (SBP, DBP, body weight and length), a fasting blood sample (glucose,

1  
2  
3 150 HbA1C, total cholesterol, HDL and serum creatinine) and questionnaires, including questions on  
4  
5 151 demographic characteristics, health behaviours, (parental) health and medication use. Participants  
6  
7 152 brought their medication to the research site, which was subsequently reported and categorized using  
8  
9 153 the Anatomical Therapeutic Chemical (ATC) codes (35).  
10

11 154

### 13 155 *Hypertension*

15 156 Hypertension was defined as: (i) SBP > 140 mmHg, or (ii) DBP > 90 mmHg, or (iii) using blood  
17 157 pressure lowering medication, which was based on the following ATC codes: C02 (antihypertensives),  
19 158 C03 (diuretics), C07 ( $\beta$ -blocking agents), C08 (calcium channel blockers) and C09 (agents acting on  
21 159 renin-angiotensin system) (35,36). In case the recorded SBP and DBP were missing and the participant  
23 160 did not use blood pressure lowering medication, the presence of hypertension was based on the answer  
25 161 of the self-reported questionnaire (Do you have hypertension?).  
27

28 162

### 30 163 *High cholesterol*

32 164 High cholesterol was defined as: (i) a ratio of total cholesterol (TC) and High Density Lipoprotein  
34 165 (HDL) higher than 5 mmol/l, or (iii) use of lipid lowering medication (ATC code C10 (lipid modifying  
36 166 agents)) (35,36). If TC and HDL levels were missing and the participant did not use any lipid lowering  
38 167 medication, high cholesterol was based on the answer of the self-reported questionnaire (Have you  
40 168 ever been diagnosed with high cholesterol?).  
42

43 169

### 45 170 *Renal dysfunction*

47 171 Renal dysfunction is categorized into low dysfunction (eGFR>90 ml/min/1.73 m<sup>2</sup>), moderate  
49 172 dysfunction (eGFR:60-89 ml/min/1.73 m<sup>2</sup>) and high dysfunction (eGFR<60 ml/min/1.73 m<sup>2</sup>) (37–39).  
51

52 173

### 53 174 *Obesity and overweight*

55 175 BMI was calculated using measured body weight (in kg) and length (in cm) (BMI = weight/length<sup>2</sup>).  
57 176 Subsequently, the presence or absence of overweight (BMI $\geq$  25.0) and obesity (BMI $\geq$  30.0) was  
59 177 determined (40,41).

1  
2  
3 1784  
5 179 ***Diabetes***

6  
7 180 Diabetes Mellitus was defined as: (i) glucose (fasting capillary blood) of 7.0 mmol/l or higher, or (ii)  
8  
9 181 HbA1C levels higher than 53 mmol/mol, or (iii) using blood glucose lowering medication (ATC code  
10  
11 182 A10 (drugs used in diabetes)) (35,42). In case glucose and HbA1c levels were missing and the  
12  
13 183 participant did not use any glucose lowering medication, the presence of diabetes mellitus was based  
14  
15 184 on the answer of the self-reported questionnaire (Do you have diabetes mellitus?).  
16  
17

18 185

19  
20 186 ***Cardiovascular diseases***

21  
22 187 Participants reported whether they have suffered or still suffer from one of the following  
23  
24 188 cardiovascular diseases (CVDs): myocardial infarction, stroke or peripheral arterial diseases. If at least  
25  
26 189 one of these CVDs was indicated with 'yes' in the self-reported questionnaire, participants were  
27  
28 190 known with CVDs.  
29

30 191

31  
32 192 ***Healthy diet***

33  
34 193 A quantitative Food Frequency Questionnaire (FFQ) was used to assess dietary intake over the  
35  
36 194 previous month (43,44). The Mediterranean diet was associated with slower cognitive decline (45–47),  
37  
38 195 however not all food groups of the Mediterranean diet were measured within the Lifelines population  
39  
40 196 on baseline. Therefore, the Lifelines diet score (LLDS) was used to determine adherence to a healthy  
41  
42 197 diet, which includes most food groups of the Mediterranean diet. The LLDS was based on the  
43  
44 198 consumption of nine positive food groups (vegetables, fruit, whole grain products, legumes and nuts,  
45  
46 199 fish, oils and soft margarines, unsweetened dairy, coffee and tea) and three negative food groups (red  
47  
48 200 and processed meat, butter and hard margarines and sugar-sweetened beverages). The consumption of  
49  
50 201 each food group was divided into quintiles to score an individual's consumption compared to the total  
51  
52 202 Lifelines population. For each food group, the quintiles ranged from 0 to 4 points, using 4 points for  
53  
54 203 the highest quintile of consumption for positive food groups and the lowest quintile for the negative  
55  
56 204 food groups. The total LLDS ranges from 0 to 48, with a higher score indicating a healthier diet (48).  
57  
58  
59

60 205

1  
2  
3 206 ***Alcohol consumption***  
4

5 207 Alcohol consumption is categorized into: (i) no alcohol consumption (0 alcohol units in the past  
6  
7 208 month), (ii) low/moderate alcohol consumption (average  $\leq 1$  alcohol unit per day and no binge  
8  
9 209 drinking) and (iii) excessive alcohol consumption (average  $> 1$  alcohol unit per day and/or binge  
10  
11 210 drinking, which is defined as more than three alcohol units per occasion for females and more than  
12  
13 211 four alcohol units per occasion for males).  
14

15  
16 212

17  
18 213 ***Physical inactivity***  
19

20 214 Physical inactivity was measured with the Short Questionnaire to Assess Health enhancing physical  
21  
22 215 activity (SQUASH) (49). The results are converted to minutes per week spent in physical activity of  
23  
24 216 light intensity and physical activity of moderate to vigorous intensity (MVPA), based on Metabolic  
25  
26 217 Equivalent Tasks (METs) derived from the Ainsworth's compendium of physical activity (50).  
27  
28 218 Physical inactivity is defined as less than 150 minutes per week MVPA (51).  
29

30 219

31  
32  
33 220 ***Smoking***  
34

35 221 Smoking behaviour was assessed with the self-reported questionnaire, including the following two  
36  
37 222 questions: (i) 'Do you smoke now, or have you smoked in the past month?' and (ii) 'Have you ever  
38  
39 223 smoked for a full year?'. Subsequently, smoking behaviour was categorized into: (i) non-smoker, (ii)  
40  
41 224 ex-smoker and (iii) current smoker. Current smokers are defined as people who reported smoking in  
42  
43 225 the past month. Ex-smokers reported smoking for at least one year, but did not smoke in the past  
44  
45 226 month.  
46

47 227

48  
49 228 ***Social activity***  
50

51 229 Social activity was measured with the following question 'On average how many people did you have  
52  
53 230 contact with in the past two weeks?'. Subsequently, social activity is categorized into low  
54  
55 231 (contacts $<4$ ), moderate (contacts: 4-7) and high (contacts $\geq 8$ ) (52).  
56  
57

58 232

59  
60 233 ***Depression***

1  
2  
3 234 The presence of a major depression was measured with the Mini International Neuropsychiatric  
4  
5 235 Interview (MINI) (53). Major depression was defined as having at least one key symptom of  
6  
7 236 depression (e.g. depressed mood or loss of interest) and four additional symptoms in the past month,  
8  
9 237 according the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) (54).

11  
12 238

13  
14 239 ***Stress***

15  
16 240 Chronic stress was measured by the Long-term Difficulties Inventory (LDI) (55,56), which consists of  
17  
18 241 twelve items that refer to twelve stressful life events, with regard to housing, work, social  
19  
20 242 relationships, free time, finances, health, school/study and religion. Participants indicated how much  
21  
22 243 stress they experienced over the past twelve months with regard to each aspect on a three-point scale  
23  
24 244 (0=not stressful; 1=slightly stressful; 2=very stressful). Total scores range from 0 (no stress) to 24  
25  
26 245 (very stressful).

28  
29 246

30  
31 247 ***LIBRA score***

32  
33 248 The LIBRA score reflects an individual's potential to reduce their risk on developing dementia and is  
34  
35 249 based on a total of twelve protective (i.e. Mediterranean diet, low/moderate alcohol consumption, high  
36  
37 250 cognitive activity) and risk factors (i.e. physical inactivity, smoking, CVDs, hypertension, high  
38  
39 251 cholesterol, diabetes mellitus, obesity, renal dysfunction, depression) for dementia (8,11–13). Using  
40  
41 252 the relative risks derived from the systematic review of Deckers et al. (2015), the LIBRA score was  
42  
43 253 calculated (8). Since cognitive activities were not measured in Lifelines, LIBRA scores could range  
44  
45 254 from -2.7 (low risk for dementia) to 12.7 (high risk for dementia). In **Table 1** the definitions and  
46  
47 255 corresponding scores for each protective and risk factor for dementia are presented.

49  
50 256

51  
52 257 **INSERT TABLE 1 ABOUT HERE**

53  
54 258

55  
56 259 ***Covariates***

57  
58 260 The demographic factors such as age, sex and education were measured at baseline. Age (in years) is  
59  
60 261 included as a continuous variable. Sex is included as a dichotomous variable (male/female). Education

1  
2  
3 262 was based on the question ‘What is your highest completed level of education?’. Highest level of  
4  
5 263 education was categorized into: (i) elementary (no education or primary education), (ii) lower  
6  
7 264 secondary (lower or preparatory vocational education or lower general secondary education), (iii)  
8  
9 265 upper secondary (intermediate vocational education) and (iv) tertiary (higher general secondary  
10  
11 266 education or pre-university secondary education, higher vocational education and university) (57).

12 267

## 13 268 **Statistical methods**

14  
15  
16  
17 269 The baseline characteristics of the total study population were described and differences between  
18  
19 270 participants with and without a PFH of dementia were calculated using Standardized Mean  
20  
21 271 Differences (SMD). Five imputed datasets were generated to replace missing values, using Multiple  
22  
23 272 Imputation using Chained Equations (MICE). In each imputed dataset, we assessed the association  
24  
25 273 between PFH of dementia and each modifiable risk factor in two steps. First, to eliminate selection  
26  
27 274 bias, PSM was used to match each individual with a PFH of dementia to an individual without a PFH  
28  
29 275 of dementia (ratio 1:1) (caliper=0.2), based on the standard potential confounders age, sex and  
30  
31 276 educational level (model 1) and other potential confounders (model 2) (see **Supplementary file 1**)  
32  
33 277 (32). After PSM, we checked if the balance in the covariates was achieved (SMD < 0.2). Second,  
34  
35 278 logistic (dichotomous outcomes), linear (continuous outcomes) and multinomial (categorical  
36  
37 279 outcomes) regression analyses were used to examine the association between a PFH of dementia and  
38  
39 280 each modifiable risk factor. These analyses were conducted for each imputed matched dataset to  
40  
41 281 obtain the estimates, which were pooled using Rubin’s rules (58). Since the LIBRA score is a  
42  
43 282 composite score and includes all individual modifiable risk factors for dementia, this analysis is based  
44  
45 283 on model 1 (only matched on sex, age and educational level). Results are presented as odds ratios  
46  
47 284 (OR) or regression coefficients (RC) with 95% confidence intervals (95%-CI). Sensitivity analyses  
48  
49 285 were conducted in which covariate adjustment is used instead of PSM. R statistical software  
50  
51 286 environment version 1.3.383 was used (59). In particular, we used the ‘MatchThem’, ‘tableone’ and  
52  
53 287 ‘cobalt’ package in R.  
54  
55  
56  
57  
58  
59

## 60 289 **Patient and Public Involvement**

290 Participants of the Lifelines Cohort study were not involved in the design, conduct reporting or  
291 dissemination plans of our research.

292

## 293 RESULTS

### 294 Baseline characteristics

295 A total of 106,884 Lifelines participants aged 35-65 years at baseline completed the baseline  
296 assessment. For 17,015 participants no data was available on PFH of dementia, since they did not  
297 participate in the first follow-up questionnaire and were therefore excluded from the analyses. This  
298 resulted in 89,869 participants of which 10,940 participants (12.2%) with a PFH of dementia and  
299 36,389 participants (40.5%) without a PFH of dementia. Of 42,540 participants (47.3%) PFH of  
300 dementia was recoded as missing, since at least one parent was deceased (see flowchart in  
301 **Supplementary file 2**). **Table 2** presents the characteristics of participants with and without a PFH of  
302 dementia. In the observed data, we found an imbalance in age (SMD=1.534), education (SMD=0.271),  
303 hypertension (SMD=0.304), high cholesterol (SMD=0.265), renal dysfunction (SMD=0.334), physical  
304 inactivity (SMD=0.375), diet (SMD=0.278) and smoking (SMD=0.333). After PSM on potential  
305 confounders, the balance in confounding variables was improved (see **Supplementary file 3**). We  
306 focused further on the results of the final model (model 2).

307

308 **INSERT TABLE 2 ABOUT HERE**

309

### 310 The association between a PFH of dementia and modifiable risk factors for dementia

311 The results of the logistic, linear and multinomial regression analyses on the association between a  
312 PFH of dementia and modifiable risk factors for dementia are presented in **Table 3**. Individuals with a  
313 PFH of dementia had more often hypertension (OR=1.19, 95%-CI: 1.14,1.24), high cholesterol  
314 (OR=1.24, 95%-CI: 1.18,1.30), diabetes (OR=1.26, 95%-CI: 1.11,1.42), CVDs (OR=1.49, 95%-CI:  
315 1.18,1.88), obesity (OR=1.14, 95%-CI: 1.08,1.20), overweight (OR=1.10, 95%-CI: 1.05,1.17), and  
316 depressive symptoms (OR=1.23, 95%-CI: 1.08,1.41) compared to their peers without a PFH of  
317 dementia. Further, individuals with a PFH of dementia were more often current-smokers (OR=1.20,



1  
2  
3 318 95%-CI: 1.14,1.27) and ex-smokers (OR=1.21, 95%-CI:1.16,1.27), but were less often low/moderate  
4  
5 319 alcohol consumers (OR=0.87, 95%-CI: 0.83,0.91), excessive alcohol consumers (OR=0.93, 95%-  
6  
7 320 CI:0.89,0.98), physically inactive (OR=0.93, 95%-CI: 0.91,0.97) and had less often a low social  
8  
9 321 activity (OR=0.84, 95%-CI:0.78,0.90). Finally, individuals with a PFH of dementia also had an overall  
10  
11 322 higher risk to develop dementia (LIBRA score RC=0.15, 95%-CI: 0.11,0.19) compared to their peers  
12  
13 323 without a PFH of dementia.  
14  
15  
16 324

17  
18 325 **INSERT TABLE 3 ABOUT HERE**  
19

20 326

## 21 327 **DISCUSSION**

22  
23  
24 328 In this study, we investigated the association between having a PFH of dementia and fourteen  
25  
26 329 modifiable risk factors for dementia among middle-aged individuals from the general population. We  
27  
28 330 found that several modifiable risk factors for dementia were more common in individuals with a PFH  
29  
30 331 of dementia independent of their age, sex and educational level. They had more often hypertension,  
31  
32 332 high cholesterol, diabetes, CVDs, obesity, overweight, depression and were also more often ex-smoker  
33  
34 333 and current smoker than never smoker. However, they were more often non-alcohol consumers,  
35  
36 334 physically active and socially active compared to their peers without a PFH of dementia. Overall,  
37  
38 335 individuals with a PFH of dementia had a higher risk of developing dementia, based on the LIBRA  
39  
40 336 score, which suggests that they are a group at risk for dementia.  
41  
42

43 337

44  
45 338 In general, most findings are in line with our expectations, except that individuals with a PFH of  
46  
47 339 dementia were less often physically and socially inactive, and less often low/moderate alcohol  
48  
49 340 consumer and excessive alcohol consumer than no alcohol consumer. Since individuals with a PFH of  
50  
51 341 dementia had more often cardiovascular risk factors, it might be that they did not consume alcohol due  
52  
53 342 to health concerns or use of medication (60). Furthermore, in our study, PFH of dementia was  
54  
55 343 determined by the first follow-up questionnaire. In case dementia was diagnosed before baseline  
56  
57 344 assessment, individuals with a PFH of dementia could already have adjusted their lifestyle. Therefore,  
58  
59  
60

1  
2  
3 345 these findings may reflect a reverse causality from having a parent with dementia to more physical and  
4  
5 346 social activity. No data was available on the date of onset of dementia.  
6

7 347

8  
9 348 To our knowledge, this is the first study that investigated the association between having a PFH of  
10  
11 349 dementia and currently known modifiable risk factors for dementia among middle-aged individuals  
12  
13 350 using a large sample size and PSM. Only few studies have been conducted to test the differences in  
14  
15 351 several modifiable risk factors of dementia between individuals with and without a family history of  
16  
17 352 dementia (28,30,31). However, it is likely that these studies were hampered by small sample sizes of  
18  
19 353 the study population. For instance, Luckhoff et al. (2016) did not find differences in BMI (objectively  
20  
21 354 measured), total cholesterol, HDL, LDL, alcohol intake and smoking behaviour between middle-aged  
22  
23 355 individuals with (n=75) and without (n=505) a self-reported family history of dementia ( $p>0.05$ )(30).  
24  
25 356 Exel et al. (2009) found that middle-aged individuals with an objectively measured PFH of dementia  
26  
27 357 (n=206) had more often hypertension and caregiver burden stress compared to their peers (n=200)  
28  
29 358 ( $p<0.05$ )(28). However, no differences were found in high cholesterol, glucose levels and lifestyle-  
30  
31 359 related risk factors such as smoking and physical activity ( $p>0.05$ ) (61). La Rue et al. (2008) also  
32  
33 360 showed that individuals with a PFH of dementia (n=623) had higher cholesterol levels, higher DBP  
34  
35 361 and SBP and higher depression rates compared to individuals without a PFH of dementia (n=157)  
36  
37 362 ( $p<0.01$ )(31). Although differences with the current study could be explained by the use of different  
38  
39 363 statistical methods, sensitivity analyses in which covariate adjustment is used showed similar results  
40  
41 364 when using PSM (see **Supplementary file 4**). A major advantage of PSM is that the balance in  
42  
43 365 potential confounders can be inspected between individuals with and without a PFH of dementia  
44  
45 366 before conducting the analyses. After PSM most potential confounders were balanced between  
46  
47 367 participants with and without a PFH of dementia (SMD<0.2), except for the variable renal dysfunction  
48  
49 368 (SMD=-0.207). Therefore, it is possible that the associations between having a PFH of dementia and  
50  
51 369 lifestyle-related risk factors for dementia are slightly biased.  
52  
53  
54  
55

56 370

57  
58 371 **Strengths and limitations**  
59  
60

1  
2  
3 372 Our large study sample provided sufficient power to detect relevant associations independent of  
4  
5 373 confounding factors. In addition, no other study investigating the association between a PFH of  
6  
7 374 dementia and modifiable risk factors for dementia used a wide range of the currently known  
8  
9 375 modifiable risk factors for dementia. A large part of these modifiable risk factors (e.g., hypertension,  
10  
11 376 high cholesterol, diabetes mellitus, obesity, overweight, renal dysfunction) were objectively measured  
12  
13 377 through physical examination and fasting blood samples. Further, we used sophisticated statistical  
14  
15 378 techniques to prevent selection bias. The potential confounders used in PSM were carefully chosen per  
16  
17 379 outcome measure. Finally, in contrast to previous studies, we reported adjusted ORs and RCs with  
18  
19 380 95%-confidence intervals instead of p-values, which gives more information on the magnitude and  
20  
21 381 direction of the association studied.  
22

23  
24 382  
25  
26 383 This study also had certain limitations. One drawback is that PFH of dementia was based on self-  
27  
28 384 reported questionnaires and could have led to misclassification. Nonetheless, it is likely that the  
29  
30 385 misclassification was non-differential and would have led to an underestimation of our results.  
31  
32 386 Second, no data was available on the APOE genotype, which may be an important effect modifier  
33  
34 387 (19). Previous literature showed that a healthy lifestyle might especially be beneficial for the cognition  
35  
36 388 of APOE e4 carriers (19,62). Since individuals with a PFH of dementia are more often carrier of the  
37  
38 389 APOE e4 allele, a healthy lifestyle might also be especially beneficial for individuals with a PFH of  
39  
40 390 dementia. Therefore, absence of APOE genotype data could have led to an underestimation of the  
41  
42 391 results for APOE e4 carriers with a PFH of dementia. Third, the results were based on cross-sectional  
43  
44 392 data in which previous health behaviours were not taken into account. It might be possible that  
45  
46 393 individuals with a PFH of dementia adopted a healthier lifestyle after their parent got diagnosed with  
47  
48 394 dementia. In other words, our findings may reflect a reverse causality from PFH of dementia to health  
49  
50 395 behaviour, indicating that our estimates may be underestimated. Finally, we imputed PFH of dementia  
51  
52 396 of all participants without a PFH of dementia with at least one deceased parent. We did not distinguish  
53  
54 397 in the age of death of deceased parents, since the incidence of dementia increases with age and the  
55  
56 398 average age of onset of dementia differs between types of dementia (63). However, relatively young  
57  
58 399 parents are less likely to develop dementia compared to older parents. Nevertheless, sensitivity  
59  
60

1  
2  
3 400 analyses in which individuals with deceased fathers who survived to at least the age of 70 or mothers  
4  
5 401 who survived to at least the age of 75 were assigned to the group without having a PFH of dementia  
6  
7 402 instead of PFH being imputed, showed similar results (31).  
8

9 403

11 404 These findings support a high-risk prevention strategy for dementia by identifying the individuals with  
12  
13 405 a PFH of dementia, screening them for modifiable risk factors for dementia, and implementing multi-  
14  
15 406 domain interventions targeting these modifiable risk factors. Future studies should first explore the  
16  
17 407 knowledge, beliefs and attitudes towards dementia (risk reduction) among middle-aged individuals  
18  
19 408 with a PFH of dementia, and whether they are willing to assess their protective and risk factors for  
20  
21 409 dementia and adopt a healthier lifestyle. Next, the effectiveness of these multi-domain interventions in  
22  
23 410 changing health behaviour for DRR among middle-aged individuals with a PFH of dementia should be  
24  
25 411 investigated.  
26  
27

28 412

## 30 413 CONCLUSION

32 414 We found that a PFH of dementia was associated with several modifiable risk factors for dementia  
33  
34 415 independent of age, sex and educational level, including hypertension, high cholesterol, diabetes  
35  
36 416 mellitus, CVDs, obesity, overweight and depression. This suggests that middle-aged individuals with a  
37  
38 417 PFH of dementia are a group at risk for dementia and might benefit from DRR. Further research  
39  
40 418 should examine knowledge, beliefs and attitudes towards DRR among middle-aged individuals with a  
41  
42 419 PFH of dementia, and their willingness to address and tackle their personal risk factors for dementia in  
43  
44 420 order to prevent or postpone dementia.  
45  
46

47 421

49 422 **Acknowledgements:** The Lifelines Biobank initiative has been made possible by subsidy from the  
50  
51 423 Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University  
52  
53 424 Medical Centre Groningen (UMCG the Netherlands), University Groningen and the Northern  
54  
55 425 Provinces of the Netherlands.  
56  
57  
58  
59  
60

1  
2  
3 426 **Author contributions:** JV, AAH, SR and NS were involved in the design of the study. JV conducted  
4  
5 427 the analysis with support of AAH. JV wrote the manuscript and AAH, SR and NS revised the  
6  
7 428 manuscript. All authors read and approved the final manuscript.

8  
9 429 **Funding:** None declared.

10  
11 430 **Competing Interests:** The authors declare that no conflict of interest exists.

12  
13 431 **Patient consent:** Not applicable.

14  
15 432 **Data sharing statement:** Lifelines is a facility that is open for all researchers ([www.lifelines.net](http://www.lifelines.net)).

16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

434 **REFERENCES**

- 435 1. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. The Lancet  
436 Commissions Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673–  
437 734.
- 438 2. World Health Organization. Dementia [Internet]. 2019. Available from:  
439 <https://www.who.int/news-room/fact-sheets/detail/dementia>
- 440 3. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of  
441 Alzheimer's disease. *Alzheimer's Dement*. 2007 Jul;3(3):186–91.
- 442 4. Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, et al. Timing of  
443 onset of cognitive decline: results from Whitehall II prospective cohort study. *BMJ*. 2012 Jan  
444 5;344:d7622.
- 445 5. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining  
446 the preclinical stages of Alzheimer's disease: recommendations from the National Institute on  
447 Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.  
448 *Alzheimers Dement*. 2011 May;7(3):280–92.
- 449 6. Rajan KB, Wilson RS, Weuve J, Barnes LL, Evans DA. Cognitive impairment 18 years before  
450 clinical diagnosis of Alzheimer disease dementia. *Neurology*. 2015 Sep 8;85(10):898–904.
- 451 7. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C, Ministers GH and S, et al. Potential  
452 for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet*  
453 *Neurol*. 2014 Aug;13(8):788–94.
- 454 8. Deckers K, van Boxtel MPJ, Schiepers OJG, de Vugt M, Muñoz Sánchez JL, Anstey KJ, et al.  
455 Target risk factors for dementia prevention: a systematic review and Delphi consensus study on  
456 the evidence from observational studies. *Int J Geriatr Psychiatry*. 2015 Mar;30(3):234–46.
- 457 9. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia  
458 prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*.  
459 2020;396(10248):413–46.
- 460 10. Li X-Y, Zhang M, Xu W, Li J-Q, Cao X-P, Yu J-T, et al. Midlife Modifiable Risk Factors for  
461 Dementia: A Systematic Review and Meta-analysis of 34 Prospective Cohort Studies. *Curr*

- 1  
2  
3 462 Alzheimer Res. 2019;16(14):1254–68.  
4  
5 463 11. Schiepers OJG, Köhler S, Deckers K, Irving K, O'Donnell CA, van den Akker M, et al.  
6  
7 464 Lifestyle for Brain Health (LIBRA): a new model for dementia prevention. *Int J Geriatr*  
8  
9 465 *Psychiatry*. 2018 Feb 28;33:167–75.  
10  
11 466 12. Vos SJB, van Boxtel MPJ, Schiepers OJG, Deckers K, de Vugt M, Carrière I, et al. Modifiable  
12  
13 467 Risk Factors for Prevention of Dementia in Midlife, Late Life and the Oldest-Old: Validation  
14  
15 468 of the LIBRA Index. *J Alzheimer's Dis*. 2017 May 11;58(2):537–47.  
16  
17 469 13. Deckers K, Köhler S, van Boxtel M, Verhey F, Brayne C, Fleming J, et al. Lack of associations  
18  
19 470 between modifiable risk factors and dementia in the very old: findings from the Cambridge  
20  
21 471 City over-75s cohort study. *Aging Ment Health*. 2017 Feb;1–7.  
22  
23 472 14. Ngandu T, Lehtisalo J, Solomon A, Levälähti E, Ahtiluoto S, Antikainen R, et al. A 2 year  
24  
25 473 multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring  
26  
27 474 versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised  
28  
29 475 controlled trial. *Lancet*. 2015 Jun;385(9984):2255–63.  
30  
31 476 15. van Charante EPM, Richard E, Eurelings LS, van Dalen J-W, Ligthart SA, van Bussel EF, et  
32  
33 477 al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia  
34  
35 478 (preDIVA): a cluster-randomised controlled trial. *Lancet*. 2016;388(10046):797–805.  
36  
37 479 16. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term  
38  
39 480 omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention  
40  
41 481 on cognitive function in elderly adults with memory complaints (MAPT): a randomised,  
42  
43 482 placebo-controlled trial. *Lancet Neurol*. 2017 May 1;16(5):377–89.  
44  
45 483 17. Goldman JS, Hahn SE, Catania JW, LaRusse-Eckert S, Butson MB, Rumbaugh M, et al.  
46  
47 484 Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American  
48  
49 485 College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med*. 2011  
50  
51 486 Jun;13(6):597–605.  
52  
53 487 18. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hyppönen E, Kuzma E, et al. Association of  
54  
55 488 lifestyle and genetic risk with incidence of dementia. *JAMA*. 2019 Aug 6;322(5):430.  
56  
57 489 19. Kivipelto M, Rovio S, Ngandu T, Kåreholt I, Eskelinen M, Winblad B, et al. Apolipoprotein E  
58  
59  
60

- 1  
2  
3 490 epsilon4 magnifies lifestyle risks for dementia: a population-based study. *J Cell Mol Med.*  
4  
5 491 2008 Dec;12(6B):2762–71.  
6  
7 492 20. Borenstein AR, Copenhaver CI, Mortimer JA. Early-Life Risk Factors for Alzheimer Disease.  
8  
9 493 *Alzheimer Dis Assoc Disord.* 2006 Jan;20(1):63–72.  
10  
11 494 21. Donix M, Small GW, Bookheimer SY. Family History and APOE-4 Genetic Risk in  
12  
13 495 Alzheimer’s Disease. *Neuropsychol Rev.* 2012 Sep 23;22(3):298–309.  
14  
15 496 22. Muñoz M, Pong-Wong R, Canela-Xandri O, Rawlik K, Haley CS, Tenesa A. Evaluating the  
16  
17 497 contribution of genetics and familial shared environment to common disease using the UK  
18  
19 498 Biobank. *Nat Genet.* 2016 Jul 18;48(9):980–3.  
20  
21 499 23. Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC, et al.  
22  
23 500 Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat Genet.*  
24  
25 501 1994 Jun;7(2):180–4.  
26  
27 502 24. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of Age,  
28  
29 503 Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer  
30  
31 504 Disease. *JAMA.* 1997 Oct 22;278(16):1349.  
32  
33 505 25. Choudhury P, Ramanan VK, Boeve BF. APOE ε 4 Allele Testing and Risk of Alzheimer  
34  
35 506 Disease. *JAMA.* 2021 Jan 14;  
36  
37 507 26. Sager MA, Hermann B, La Rue A. Middle-aged children of persons with Alzheimer’s disease:  
38  
39 508 APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer’s Prevention.  
40  
41 509 *J Geriatr Psychiatry Neurol.* 2005 Dec 29;18(4):245–9.  
42  
43 510 27. Scarabino D, Gambina G, Broggio E, Pelliccia F, Corbo RM. Influence of family history of  
44  
45 511 dementia in the development and progression of late-onset Alzheimer’s disease. *Am J Med*  
46  
47 512 *Genet Part B Neuropsychiatr Genet.* 2016 Mar;171(2):250–6.  
48  
49 513 28. van Exel E, Eikelenboom P, Comijs H, Frölich M, Smit JH, Stek ML, et al. Vascular factors  
50  
51 514 and markers of inflammation in offspring with a parental history of late-onset Alzheimer  
52  
53 515 disease. *Arch Gen Psychiatry.* 2009 Nov 1;66(11):1263–70.  
54  
55 516 29. Johnson SC, Kosciak RL, Jonaitis EM, Clark LR, Mueller KD, Berman SE, et al. The  
56  
57 517 Wisconsin Registry for Alzheimer’s Prevention: A review of findings and current directions.



- 1  
2  
3 518 Alzheimer's Dement (Amsterdam, Netherlands). 2018;10:130–42.  
4  
5 519 30. Lückhoff HK, Kidd M, van Rensburg SJ, van Velden DP, Kotze MJ. Apolipoprotein E  
6  
7 520 genotyping and questionnaire-based assessment of lifestyle risk factors in dyslipidemic patients  
8  
9 521 with a family history of Alzheimer's disease: test development for clinical application. *Metab*  
10  
11 522 *Brain Dis.* 2016 Feb 20;31(1):213–24.  
12  
13 523 31. Rue A La, Hermann B, Jones JE, Johnson S, Asthana S, Sager MA. Effect of parental family  
14  
15 524 history of Alzheimer's disease on serial position profiles. *Alzheimer's Dement.* 2008 Jul  
16  
17 525 1;4(4):285–90.  
18  
19 526 32. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of  
20  
21 527 Confounding in Observational Studies. *Multivariate Behav Res.* 2011 May;46(3):399–424.  
22  
23 528 33. Scholtens S, Smidt N, Swertz MA, Bakker SJL, Dotinga A, Vonk JM, et al. Cohort Profile:  
24  
25 529 LifeLines, a three-generation cohort study and biobank. *Int J Epidemiol.* 2015  
26  
27 530 Aug;44(4):1172–80.  
28  
29 531 34. Stolk RP, Rosmalen JGM, Postma DS, de Boer RA, Navis G, Slaets JPJ, et al. Universal risk  
30  
31 532 factors for multifactorial diseases. *Eur J Epidemiol.* 2008 Jan 13;23(1):67–74.  
32  
33 533 35. World Health Organization. ATC/DDD Index 2020. Oslo, Norway; 2020.  
34  
35 534 36. van Dis SJ, Kromhout D, Geleijnse JM, Boer JMA, Verschuren WMM. Evaluation of  
36  
37 535 cardiovascular risk predicted by different score equations: the Netherlands as an example. *Eur J*  
38  
39 536 *Cardiovasc Prev Rehabil.* 2010;17:244–9.  
40  
41 537 37. De Grauw W, De Leest K, Schenk P, Scherpbier-De Haan N, Tjin-A-Ton J, Tuut M, et al.  
42  
43 538 NHG-Standaard Chronische Nierschade. *TPO - Prakt.* 2018;13(5):26–9.  
44  
45 539 38. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation  
46  
47 540 to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604–12.  
48  
49 541 39. Levey AS, Inker LA, Coresh J. GFR estimation: From physiology to public health. *Am J*  
50  
51 542 *Kidney Dis.* 2014;63(5):820–34.  
52  
53 543 40. Centers for Disease Control and Prevention (CDC). Body Mass Index (BMI) [Internet]. [cited  
54  
55 544 2020 Sep 9]. Available from:  
56  
57 545 [https://www.cdc.gov/healthyweight/assessing/bmi/adult\\_bmi/index.html](https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html)

- 1  
2  
3 546 41. World Health Organization (WHO). Body mass index (BMI) [Internet]. World Health  
4  
5 547 Organization; [cited 2019 May 6]. Available from: [http://www.euro.who.int/en/health-](http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi)  
6  
7 548 [topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi](http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi)  
8  
9 549 42. Rutten G, De Grauw W, Nijpels G, Houweling S, Van de Laar F, Bilo H, et al. NHG-Standaard  
10  
11 550 Diabetes mellitus type 2. 2013.  
12  
13 551 43. Molag ML, de Vries JHM, Duif N, Ocké MC, Dagnelie PC, Goldbohm RA, et al. Selecting  
14  
15 552 informative food items for compiling food-frequency questionnaires: comparison of  
16  
17 553 procedures. *Br J Nutr*. 2010 Aug 8;104(03):446–56.  
18  
19 554 44. Siebelink E, Geelen A, de Vries JHM. Self-reported energy intake by FFQ compared with  
20  
21 555 actual energy intake to maintain body weight in 516 adults. *Br J Nutr*. 2011 Jul  
22  
23 556 22;106(02):274–81.  
24  
25 557 45. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet  
26  
27 558 associated with reduced incidence of Alzheimer’s disease. *Alzheimer’s Dement*. 2015  
28  
29 559 Sep;11(9):1007–14.  
30  
31 560 46. Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA, et al. MIND diet slows  
32  
33 561 cognitive decline with aging. *Alzheimer’s Dement*. 2015 Sep;11(9):1015–22.  
34  
35 562 47. Abbatecola AM, Russo M, Barbieri M. Dietary patterns and cognition in older persons. *Curr*  
36  
37 563 *Opin Clin Nutr Metab Care*. 2018 Jan;21(1):10–3.  
38  
39 564 48. Vinke PC, Corpeleijn E, Dekker LH, Jacobs DR, Navis G, Kromhout D. Development of the  
40  
41 565 food-based Lifelines Diet Score (LLDS) and its application in 129,369 Lifelines participants.  
42  
43 566 *Eur J Clin Nutr*. 2018;72(8):1111–9.  
44  
45 567 49. Wendel-Vos G. Reproducibility and relative validity of the short questionnaire to assess health-  
46  
47 568 enhancing physical activity. *J Clin Epidemiol*. 2003 Dec;56(12):1163–9.  
48  
49 569 50. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, et al. 2011  
50  
51 570 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci*  
52  
53 571 *Sports Exerc*. 2011 Aug;43(8):1575–81.  
54  
55 572 51. Weggemans RM, Backx FJG, Borghouts L, Chinapaw M, Hopman MTE, Koster A, et al. The  
56  
57 573 2017 Dutch Physical Activity Guidelines. *Int J Behav Nutr Phys Act*. 2018 Jun 25;15(1):58.

- 1  
2  
3 574 52. Kuiper JS, Zuidersma M, Oude Voshaar RC, Zuidema SU, van den Heuvel ER, Stolk RP, et al.  
4  
5 575 Social relationships and risk of dementia: A systematic review and meta-analysis of  
6  
7 576 longitudinal cohort studies. *Ageing Res Rev.* 2015 Jul 1;22:39–57.  
8  
9 577 53. Sheehan D V, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-  
10  
11 578 International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a  
12  
13 579 structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.*  
14  
15 580 1998;59 Suppl 2:22–33; quiz 34–57.  
16  
17 581 54. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*  
18  
19 582 (DSM-5®). Fifth edit. Washington; 2013.  
20  
21 583 55. Rosmalen JGM, Bos EH, de Jonge P. Validation of the Long-term Difficulties Inventory (LDI)  
22  
23 584 and the List of Threatening Experiences (LTE) as measures of stress in epidemiological  
24  
25 585 population-based cohort studies. *Psychol Med.* 2012 Dec;42(12):2599–608.  
26  
27 586 56. Motrico E, Moreno-Küstner B, de Dios Luna J, Torres-González F, King M, Nazareth I, et al.  
28  
29 587 Psychometric properties of the List of Threatening Experiences—LTE and its association with  
30  
31 588 psychosocial factors and mental disorders according to different scoring methods. *J Affect*  
32  
33 589 *Disord.* 2013;150(3):931–40.  
34  
35 590 57. Klijs B, Kibele EUB, Ellwardt L, Zuidersma M, Stolk RP, Wittek RPM, et al. Neighborhood  
36  
37 591 income and major depressive disorder in a large Dutch population: results from the LifeLines  
38  
39 592 Cohort study. *BMC Public Health.* 2016 Aug 11;16(1):773.  
40  
41 593 58. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and  
42  
43 594 guidance for practice. *Stat Med.* 2011 Feb 20;30(4):377–99.  
44  
45 595 59. R Core team. *R: A language and environment for statistical computing.* Vienna, Austria; 2020.  
46  
47 596 60. Green CA, Polen MR. The health and health behaviors of people who do not drink alcohol. *Am*  
48  
49 597 *J Prev Med.* 2001 Nov 1;21(4):298–305.  
50  
51 598 61. van Exel E, Eikelenboom P, Comijs H, Frölich M, Smit JH, Stek ML, et al. Vascular Factors  
52  
53 599 and Markers of Inflammation in Offspring With a Parental History of Late-Onset Alzheimer  
54  
55 600 Disease. *Arch Gen Psychiatry.* 2009 Nov 1;66(11):1263.  
56  
57 601 62. Dekhtyar S, Marseglia A, Xu W, Darin-Mattsson A, Wang HX, Fratiglioni L. Genetic risk of

- 1  
2  
3 602 dementia mitigated by cognitive reserve: A cohort study. *Ann Neurol.* 2019 Jul 1;86(1):68–78.  
4  
5 603 63. Ott A, Breteler MMB, Van Harskamp F, Stijnen T, Hofman A. Incidence and Risk of  
6  
7 604 Dementia The Rotterdam Study. 1998;147(6).  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

**Table 1.** Definition of risk and protective factors in the LIBRA score and corresponding scores

Modifiable risk factors	Definition	Score	
<b>Protective factors</b>			
<b>1</b>	Healthy diet	LLDS $\geq$ 5 <sup>th</sup> quintile (score of 30 and higher)	-1.7
<b>2</b>	No to low/moderate alcohol consumption	Average number of alcohol units per day $\leq$ 1 without binge drinking (i.e., > 3 units per day for women; > 4 units per day for men)	-1.0
<b>Risk factors</b>			
<b>3</b>	Cardiovascular diseases	The presence of at least one cardiovascular disease (myocardial infarction, stroke or peripheral arterial diseases)	+1.0
<b>4</b>	Physical inactivity	Not fulfilling the Dutch Norm for Physical activity (i.e., $\geq$ 150 min/week physical activity of moderate to vigorous intensity, measured with the SQUASH questionnaire)	+1.1
<b>5</b>	Renal dysfunction	eGFR < 60 ml/min/1.73 m <sup>2</sup>	+1.1
<b>6</b>	Diabetes	Glucose (capillary blood) $\geq$ 7.0 mmol/L or HbA1c > 53 mmol/mol	+1.3
<b>7</b>	High cholesterol	TC/HDL > 5	+1.4
<b>8</b>	Smoking	Current smoker	+1.5
<b>9</b>	Obesity	BMI $\geq$ 30	+1.6
<b>10</b>	Hypertension	SBP > 140 mmHg or DBP > 90 mmHg	+1.6
<b>11</b>	Depression	At least 1 key symptom and 4 additional symptoms measured with the MINI	+2.1

*LLDS* Lifelines diet score, *eGFR* estimated glomerular filtration rate, *LDL* low-density lipoproteins, *TC* total cholesterol, *HDL* high-density lipoproteins, *SQUASH* Short Questionnaire to Assess Health-enhancing physical activity, *BMI* Body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MINI* Mini-International Neuropsychiatric Interview

**Table 2.** Differences in characteristics between participants with and without a parental family history \*

	<b>PFH+ (n=10,940)</b>	<b>PFH- (n=36,389)</b>	<b>Standardized mean differences</b>
<b>Age, mean(sd)</b>	52.95 (7.2)	43.19 (5.5)	<b>1.534</b>
<b>Sex, female</b>	6606 (60.4)	21566 (59.3)	0.023
<b>Education</b>			<b>0.271</b>
Elementary	231 (2.1)	303 (0.8)	0.106
Lower secondary	3557 (32.5)	8068 (22.2)	<b>0.234</b>
Upper secondary	3729 (34.1)	15395 (42.3)	0.170
Tertiary	3183 (29.1)	11902 (32.7)	0.078
unknown	240 (2.2)	721 (2.0)	
<b>Hypertension</b>	4637 (42.4)	10201 (28.0)	<b>0.304</b>
unknown	0	0	
<b>High cholesterol</b>	3250 (29.7)	6722 (18.5)	<b>0.265</b>
unknown	1 (0.0)	9 (0.0)	
<b>Diabetes</b>	446 (4.1)	734 (2.0)	0.121
unknown	1 (0.0)	9 (0.0)	
<b>Cardiovascular diseases</b>	247 (2.3)	290 (0.8)	0.119
unknown	0	0	
<b>Obesity</b>	1772 (16.2)	5429 (14.9)	0.037
<b>Overweight</b>	6557 (59.9)	19789 (54.4)	0.113
unknown	4 (0.0)	7 (0.0)	
<b>Renal dysfunction</b>			<b>0.334</b>
No dysfunction	6216 (56.8)	26269 (74.5)	<b>0.325</b>
Moderate	4232 (38.7)	8883 (25.2)	<b>0.311</b>
High	97 (0.9)	99 (0.3)	0.081
unknown	395 (3.6)	1138 (3.1)	
<b>Physical inactivity</b>	3545 (32.4)	18038 (49.6)	<b>0.375</b>
unknown	717 (6.6)	2712 (7.5)	
<b>Diet score, mean(sd)</b>	25.61 (5.91)	23.97 (5.81)	<b>0.278</b>
unknown	1079 (9.9)	4903 (13.5)	
<b>Alcohol consumption</b>			0.147
No drinking	2086 (19.1)	7904 (21.7)	0.066
Moderate	4771 (43.6)	15892 (43.7)	0.001
Excessive	3548 (32.4)	9947 (27.3)	0.112
unknown	535 (4.9)	2646 (7.3)	
<b>Smoking</b>			<b>0.333</b>
Never smoker	4048 (37.0)	17535 (48.2)	0.105
Ex-smoker	4677 (42.8)	9928 (27.3)	0.066
Current smoker	1823 (16.7)	6988 (19.2)	0.059
unknown	392 (3.6)	1938 (5.3)	
<b>Social activity</b>			0.026
Low	684 (6.3)	2181 (6.0)	0.011
Moderate	1944 (17.8)	6243 (17.2)	0.016
High	8180 (75.7)	27452 (75.4)	0.015
unknown	1049 (1.3)	513 (1.4)	
<b>Depression</b>	207 (1.9)	639 (1.8)	0.045
unknown	164 (1.5)	756 (2.1)	
<b>Stress, mean(sd)</b>	2.19 (2.24)	2.42 (2.33)	0.027
unknown	256 (1.5)	1066 (2.0)	

\*N (%) noted unless indicated otherwise

**Table 3.** Results of logistic, linear and multinomial regression models assessing the association between parental family history of dementia and each modifiable risk factor for dementia

	Without PSM OR (95%-CI)		with PSM OR (95%-CI)	
	Observed data (n=47,329)	Imputed data (n=89,869)	Model 1 <sup>1</sup> (n=53,218)	Model 2 (n=53,644)
<b>Hypertension</b>	<b>1.89 (1.81, 1.97)</b>	<b>1.82 (1.77, 1.88)</b>	<b>1.16 (1.12, 1.21)</b>	<b>1.19 (1.14, 1.24)</b> <sup>2a</sup>
<b>High cholesterol</b>	<b>1.87 (1.78, 1.96)</b>	<b>1.80 (1.74, 1.86)</b>	<b>1.16 (1.10, 1.22)</b>	<b>1.24 (1.18, 1.30)</b> <sup>2a</sup>
<b>Diabetes Mellitus</b>	<b>2.06 (1.83, 2.33)</b>	<b>2.07 (1.91, 2.26)</b>	<b>1.20 (1.07, 1.34)</b>	<b>1.26 (1.11, 1.42)</b> <sup>2a</sup>
<b>CVD</b>	<b>2.88 (2.42, 3.41)</b>	<b>2.93 (2.58, 3.33)</b>	<b>1.40 (1.17, 1.68)</b>	<b>1.49 (1.18, 1.88)</b> <sup>2a</sup>
<b>Obesity</b>	<b>1.10 (1.04, 1.17)</b>	<b>1.21 (1.17, 1.26)</b>	<b>1.14 (1.09, 1.20)</b>	<b>1.14 (1.08, 1.20)</b> <sup>2a</sup>
<b>Overweight</b>	<b>1.26 (1.20, 1.31)</b>	<b>1.31 (1.28, 1.35)</b>	<b>1.07 (1.02, 1.11)</b>	<b>1.10 (1.05, 1.17)</b> <sup>2a</sup>
<b>Renal dysfunction</b> (ref: no dysfunction)				
Moderate	<b>2.01 (1.92, 2.11)</b>	<b>1.79 (1.74, 1.84)</b>	1.02 (0.98, 1.06)	1.02 (0.97, 1.07) <sup>2a</sup>
High	<b>4.14 (3.13, 5.49)</b>	<b>4.10 (3.30, 5.09)</b>	1.32 (0.98, 1.79)	1.28 (0.96, 1.71) <sup>2a</sup>
<b>Physical inactivity</b>	<b>0.46 (0.44, 0.48)</b>	<b>0.55 (0.53, 0.56)</b>	<b>0.94 (0.93, 1.00)</b>	<b>0.93 (0.91, 0.97)</b> <sup>2b</sup>
<b>Diet (RC; 95%-CI)</b>	<b>1.63 (1.50, 1.76)</b>	<b>1.13 (1.05, 1.22)</b>	<b>0.27 (0.11, 0.43)</b>	-0.04 (-0.16, 0.09) <sup>2b</sup>
<b>Alcohol</b> (ref: no consumption)				
Low/Moderate	<b>1.14 (1.08, 1.21)</b>	1.02 (0.99, 1.06)	<b>0.87 (0.82, 0.92)</b>	<b>0.87 (0.83, 0.91)</b> <sup>2b</sup>
Excessive	<b>1.35 (1.27, 1.44)</b>	<b>1.18 (1.14, 1.23)</b>	<b>0.90 (0.84, 0.97)</b>	<b>0.93 (0.89, 0.98)</b> <sup>2b</sup>
<b>Smoking</b> (ref: never smoker)				
Ex-smoker	<b>2.04 (1.94, 2.14)</b>	<b>1.83 (1.77, 1.89)</b>	<b>1.19 (1.14, 1.24)</b>	<b>1.21 (1.16, 1.27)</b> <sup>2b</sup>
Current smoker	<b>1.13 (1.06, 1.20)</b>	<b>1.22 (1.18, 1.27)</b>	<b>1.16 (1.11, 1.22)</b>	<b>1.20 (1.14, 1.27)</b> <sup>2b</sup>
<b>Social activity</b> (ref: high activity)				
Moderate	1.05 (0.99, 1.11)	<b>0.89 (0.84, 0.95)</b>	0.97 (0.47, 0.90)	0.95 (0.87, 1.02) <sup>2b</sup>
Low	1.05 (0.96, 1.15)	<b>0.83 (0.78, 0.87)</b>	<b>0.88 (0.82, 0.95)</b>	<b>0.84 (0.78, 0.90)</b> <sup>2b</sup>
<b>Depression</b>	1.07 (0.92, 1.26)	<b>1.18 (1.07, 1.30)</b>	<b>1.24 (1.10, 1.40)</b>	<b>1.23 (1.08, 1.41)</b> <sup>2c</sup>
<b>Stress (RC; 95%-CI)</b>	<b>-0.41 (-0.46, -0.36)</b>	<b>-0.42 (-0.45, -0.39)</b>	0.03 (-0.02, 0.07)	0.03 (-0.13, 0.19) <sup>2c</sup>
<b>LIBRA score (RC; 95%-CI)</b>	n.a.	<b>0.49 (0.47, 0.51)</b>	<b>0.15 (0.11, 0.19)</b>	n.a.

\* Odds ratios with 95% confidence intervals are reported, unless stated otherwise; significant associations are shown in bold.

<sup>1</sup>: matched on age, sex and education level; <sup>2a</sup>: additionally matched on physical inactivity, diet, alcohol consumption, smoking, stress and depression; <sup>2b</sup>: additionally matched on stress, social activity, cardiovascular diseases, diabetes, high cholesterol, hypertension and renal dysfunction; <sup>2c</sup>: additionally matched on physical inactivity, diet, stress and social activity.

1  
2  
3 I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work  
4 (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for  
5 contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY  
6 licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government  
7 officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable,  
8 royalty-free basis to BMJ Publishing Group Ltd (“BMJ”) its licensees and where the relevant  
9 Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in BMJ Open  
10 and any other BMJ products and to exploit all rights, as set out in our [licence](#).  
11

12 The Submitting Author accepts and understands that any supply made under these terms is  
13 made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your  
14 employer or a postgraduate student of an affiliated institution which is paying any applicable  
15 article publishing charge (“APC”) for Open Access articles. Where the Submitting Author wishes  
16 to make the Work available on an Open Access basis (and intends to pay the relevant APC), the  
17 terms of reuse of such Open Access shall be governed by a Creative Commons licence – details  
18 of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our  
19 licence referred to above.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



1  
2  
3 **SUPPLEMENTARY FILES**  
4

5 **Supplementary file 1:** Models for the association between a PFH of dementia and the modifiable risk factors for dementia  
6

7 **Supplementary file 2:** Flowchart of participant selection  
8

9 **Supplementary file 3:** Standardized mean differences to identify imbalances between participants with and without a PFH of dementia without (with and  
10 without data imputation) and with PSM  
11  
12

13 **Supplementary file 4:** Sensitivity analyses with covariate adjustment to examine the association between having a PFH of dementia and modifiable risk  
14 factors for dementia  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

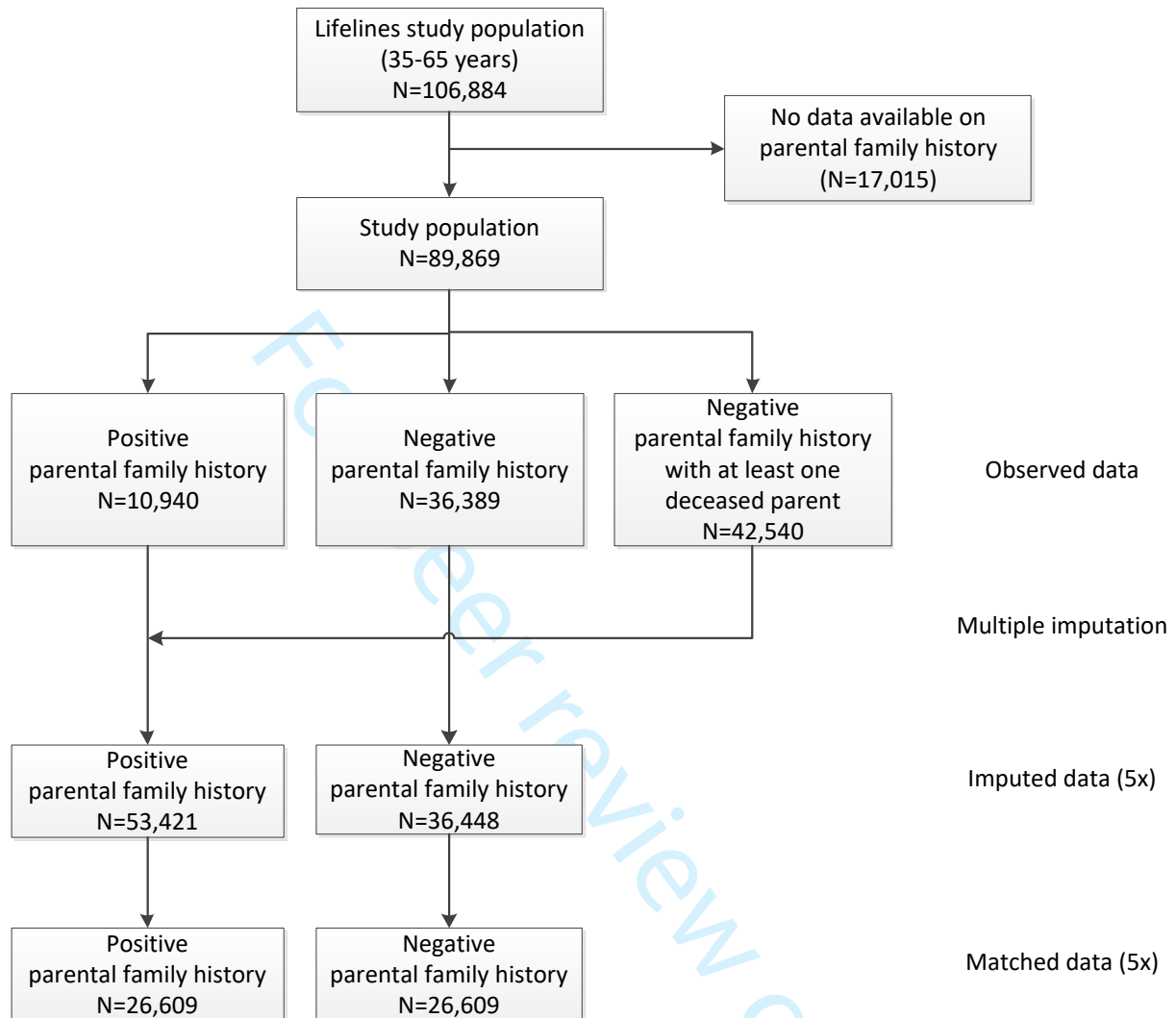
**Supplementary file 1.** Models for the association between parental family history of dementia and the modifiable risk factors for dementia

	Without PSM	With PSM	
Outcome measures	Imputed data Determinant	Model 1 Demographic confounders *	Model 2 Other potential confounders, including model 1*
Hypertension High Cholesterol Diabetes Mellitus CVD Obesity Overweight Renal dysfunction	Parental family history of dementia	Age Sex Education	Physical activity Diet Alcohol Smoking Stress Depression
Physical activity Diet Alcohol Smoking Social activity	Parental family history of dementia	Age Sex Education	Stress Social activity CVD Diabetes Cholesterol Hypertension Renal dysfunction
Depression Stress	Parental family history of dementia	Age Sex Education	Physical activity Diet Stress Social activity
LIBRA score	Parental family history of dementia	Age Sex Education	not applicable

\*Adjustment through matching on propensity score which is based on these potential confounders

Abbreviations: CVD Cardiovascular diseases, LIBRA Lifestyle for Brain Health

## Supplementary file 2. Flowchart of participant selection



**Supplementary file 3.** Standardized mean differences to identify imbalances between participants with and without a parental family history of dementia without (with and without data imputation) and with PSM\*

	Without PSM (SMD)		With PSM (SMD)	
	Observed data (n=47,329)	Imputed data (n=89,869)	Model 1 <sup>1</sup> (n=53,218)	Model 2 <sup>2#</sup> (n=53,644)
<b>Age</b>	<b>1.534</b>	<b>1.209</b>	0.133	0.170
<b>Sex, female</b>	0.023	0.005	0.091	0.017
<b>Education</b>				
Elementary	0.106	0.123	0.048	0.062
Lower secondary	<b>0.234</b>	<b>0.274</b>	0.035	0.020
Upper secondary	0.170	0.141	-0.172	-0.035
Tertiary	0.078	0.154	0.133	-0.005
<b>Hypertension</b>	<b>0.304</b>	<b>0.286</b>	0.066	0.041
<b>High cholesterol</b>	<b>0.265</b>	<b>0.248</b>	<b>0.231</b>	0.038
<b>Diabetes</b>	0.121	0.125	-0.025	0.018
<b>Cardiovascular diseases</b>	0.119	0.122	<b>0.261</b>	0.007
<b>Obesity</b>	0.037	0.070	0.052	0.055
<b>Overweight</b>	0.113	0.134	0.102	0.103
<b>Renal dysfunction</b>				
No dysfunction	<b>0.325</b>	<b>0.278</b>	<b>-0.206</b>	<b>-0.207</b>
Moderate	<b>0.311</b>	<b>0.264</b>	0.193	0.027
High	0.081	0.087	0.078	0.004
<b>Physical inactivity</b>	<b>0.375</b>	<b>0.300</b>	<b>0.278</b>	0.012
<b>Diet score</b>	<b>0.278</b>	0.194	0.160	0.051
<b>Alcohol consumption</b>				
No drinking	0.066	<0.001	-0.024	-0.039
Moderate	0.001	0.010	-0.036	-0.039
Excessive	0.112	0.072	0.059	-0.001
<b>Smoking</b>				
Never smoker	0.105	<b>0.228</b>	-0.193	-0.167
Ex-smoker	0.066	<b>0.259</b>	<b>0.218</b>	0.039
Current smoker	0.059	0.024	-0.021	0.008
<b>Social activity</b>				
Low (<4)	0.011	0.044	0.026	0.021
Moderate (4-7)	0.016	0.023	0.018	-0.036
High (≥8)	0.015	0.046	-0.031	-0.032
<b>Depression</b>	0.045	0.023	0.018	0.024
<b>Stress</b>	0.027	0.183	-0.162	0.028

\* SMDs higher than 0.2 are shown in bold

# The highest SMDs are shown for model 2

1 : matched on age, sex and education level

2: additionally matched on physical inactivity, diet, alcohol consumption, smoking, stress, depression, social activity, cardiovascular diseases, diabetes, high cholesterol, hypertension and renal dysfunction, depending on outcome measure (see **Supplementary file 1**)

**Supplementary file 4.** Sensitivity analyses with covariate adjustment to examine the association between having a PFH of dementia and modifiable risk factors for dementia

	OR (95%-CI)		
	Imputed data (n=89,869)		
	Crude model	Adjusted model 1 <sup>1</sup>	Adjusted model 2 <sup>2</sup>
<b>Hypertension</b>	<b>1.82 (1.77, 1.88)</b>	<b>1.12 (1.09, 1.16)</b>	<b>1.12 (1.08, 1.16)</b>
<b>High cholesterol</b>	<b>1.80 (1.74, 1.86)</b>	<b>1.20 (1.55, 1.24)</b>	<b>1.17 (1.13, 1.22)</b>
<b>Diabetes Mellitus</b>	<b>2.07 (1.91, 2.26)</b>	<b>1.12 (1.02, 1.24)</b>	1.09 (0.99, 1.21)
<b>CVD</b>	<b>2.93 (2.58, 3.33)</b>	<b>1.34 (1.16, 1.56)</b>	<b>1.29 (1.12, 1.50)</b>
<b>Obesity</b>	<b>1.21 (1.17, 1.26)</b>	<b>1.13 (1.08, 1.18)</b>	<b>1.12 (1.07, 1.17)</b>
<b>Overweight</b>	<b>1.31 (1.28, 1.35)</b>	<b>1.09 (1.06, 1.13)</b>	<b>1.08 (1.05, 1.12)</b>
<b>Renal dysfunction</b> (ref: no dysfunction)			
Moderate	<b>1.79 (1.74, 1.84)</b>	<b>0.92 (0.89, 0.95)</b>	<b>0.93 (0.89, 0.96)</b>
High	<b>4.10 (3.30, 5.09)</b>	0.95 (0.74, 1.20)	0.96 (0.75, 1.24)
<b>Physical inactivity</b>	<b>0.55 (0.53, 0.56)</b>	1.02 (0.99, 1.06)	0.99 (0.95, 1.02)
<b>Diet (RC; 95%-CI)</b>	<b>1.13 (1.05, 1.22)</b>	-0.04 (-0.12, 0.05)	-0.02 (-0.11, 0.07)
<b>Alcohol</b> (ref: no consumption)			
Low/Moderate	1.02 (0.99, 1.06)	0.90 (0.86, 0.94)	<b>0.91 (0.88, 0.95)</b>
Excessive	<b>1.18 (1.14, 1.23)</b>	0.98 (0.93, 1.03)	0.99 (0.94, 1.04)
<b>Smoking</b> (ref: never smoker)			
Ex-smoker	<b>1.83 (1.77, 1.89)</b>	<b>1.16 (1.12, 1.20)</b>	<b>1.15 (1.11, 1.19)</b>
Current smoker	<b>1.22 (1.18, 1.27)</b>	<b>1.21 (1.16, 1.26)</b>	<b>1.18 (1.14, 1.24)</b>
<b>Social activity</b> (ref: high activity)			
Moderate	<b>0.89 (0.84, 0.95)</b>	0.98 (0.91, 1.05)	0.98 (0.91, 1.05)
Low	<b>0.83 (0.78, 0.87)</b>	0.88 (0.82, 0.94)	<b>0.88 (0.83, 0.94)</b>
<b>Depression</b>	<b>1.18 (1.07, 1.30)</b>	<b>1.25 (1.12, 1.40)</b>	<b>1.23 (1.10, 1.38)</b>
<b>Stress (RC; 95%-CI)</b>	<b>-0.42 (-0.45, -0.39)</b>	<b>0.09 (0.05, 0.12)</b>	<b>0.08 (0.04, 0.11)</b>

\* Odds ratios with 95% confidence intervals are reported, unless stated otherwise; significant associations are shown in bold

1: adjusted for age, sex and education level

2: additionally adjusted for on physical inactivity, diet, alcohol consumption, smoking, stress, depression, social activity, cardiovascular diseases, diabetes, high cholesterol, hypertension and renal dysfunction, depending on outcome measure (see **Supplementary file 1**)

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-12
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	7-8
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	12
		(b) Describe any methods used to examine subgroups and interactions	12
		(c) Explain how missing data were addressed	12
		(d) If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(e) Describe any sensitivity analyses	12
<b>Results</b>			
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
		(b) Give reasons for non-participation at each stage	12
		(c) Consider use of a flow diagram	30
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	13
Outcome data	15*	Report numbers of outcome events or summary measures	13
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	13

		(b) Report category boundaries when continuous variables were categorized	8-10
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
<b>Other information</b>			
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	17

\*Give information separately for exposed and unexposed groups.

**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](http://www.strobe-statement.org).

# BMJ Open

**The association between dementia parental family history and midlife modifiable risk factors for dementia: a cross-sectional study using propensity score matching within the Lifelines cohort**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-049918.R1
Article Type:	Original research
Date Submitted by the Author:	13-Sep-2021
Complete List of Authors:	Vrijsen, Joyce; University of Groningen, Epidemiology Abu-Hanna, Ameen; University of Amsterdam, Amsterdam UMC, Medical Informatics de Rooij, Sophia; Medical Spectrum Twente, Medical School Twente Smidt, Nynke; University of Groningen, Epidemiology
<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	Dementia < NEUROLOGY, PREVENTIVE MEDICINE, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™  
Manuscripts





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1  
2  
3 1 **TITLE**  
4

5 2 The association between dementia parental family history and midlife modifiable risk factors for  
6  
7 3 dementia: a cross-sectional study using propensity score matching within the Lifelines cohort  
8

9 4  
10  
11 5 **AUTHORS**  
12

13 6 J. Vrijsen<sup>1\*</sup>, A. Abu-Hanna<sup>2</sup>, S.E. de Rooij<sup>3</sup>, N. Smidt<sup>1</sup>  
14

15 7 <sup>1</sup> University of Groningen, University Medical Centre Groningen, Department of Epidemiology,  
16  
17 Groningen, the Netherlands  
18

19 9 <sup>2</sup> University of Amsterdam, Amsterdam UMC, Department of Medical Informatics, Amsterdam Public  
20  
21 Health research institute, Amsterdam, the Netherlands  
22

23 10  
24 11 <sup>3</sup> Medical Spectrum Twente, Medical School Twente, Enschede, the Netherlands  
25

26 12  
27  
28 13 \*Corresponding author. University Medical Centre Groningen, Department of Epidemiology,  
29

30 14 Hanzeplein 1, PO Box 30 001, FA40, 9700 RB Groningen, the Netherlands. E-mail:  
31

32 15 j.vrijsen@umcg.nl; Tel: 06-55257250  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 17 **ABSTRACT**  
4

5 18 **OBJECTIVE:** Individuals with a parental family history (PFH) of dementia have an increased risk to  
6  
7 19 develop dementia, regardless of genetic risks. The aim of this study is to investigate the association  
8  
9 20 between a PFH of dementia and currently known modifiable risk factors for dementia among middle-  
10  
11 21 aged individuals, using propensity score matching (PSM).  
12

13  
14 22 **DESIGN:** A cross-sectional study

15  
16 23 **SETTING AND PARTICIPANTS:** A subsample of Lifelines (35-65 years), a prospective  
17  
18 24 population-based cohort study in the Netherlands was used.

19  
20 25 **OUTCOME MEASURES:** Fourteen modifiable risk factors for dementia and the overall Lifestyle  
21  
22 26 for Brain Health (LIBRA) score, indicating someone's potential for dementia risk reduction (DRR).  
23

24 27 **RESULTS:** The study population included 89,869 participants of which 10,940 participants (12.2%)  
25  
26 28 with a PFH of dementia (mean(SD) age=52.95(7.2)) and 36,389 participants (40.5%) without a PFH of  
27  
28 29 dementia (mean(SD) age=43.19(5.5)). Of 42,540 participants (47.3%) PFH of dementia was imputed.  
29  
30 30 After PSM, potential confounding variables were balanced between individuals with and without PFH  
31  
32 31 of dementia. Individuals with a PFH of dementia had more often hypertension (OR; 95%-CI)=1.19;  
33  
34 32 1.14-1.24), high cholesterol (OR=1.24; 1.18-1.30), diabetes (OR=1.26; 1.11-1.42), CVDs (OR=1.49;  
35  
36 33 1.18-1.88)), depression (OR=1.23; 1.08-1.41), obesity (OR=1.14; 1.08-1.20), overweight (OR=1.10;  
37  
38 34 1.05-1.17) and were more often current-smokers (OR=1.20; 1.14-1.27) and ex-smokers (OR=1.21;  
39  
40 35 1.16-1.27). However, they were less often low/moderate alcohol consumers (OR=0.87; 0.83-0.91),  
41  
42 36 excessive alcohol consumers (OR=0.93; 0.89-0.98)), socially inactive (OR=0.84; 0.78-0.90) and  
43  
44 37 physically inactive (OR=0.93; 0.91-0.97). Having a PFH of dementia resulted in a higher LIBRA  
45  
46 38 score (RC=0.15; 0.11-0.19).  
47  
48

49 39 **CONCLUSION:** We found that having a PFH of dementia was associated with several modifiable  
50  
51 40 risk factors. This suggests that middle-aged individuals with a PFH of dementia are a group at risk and  
52  
53 41 could benefit from DRR. Further research should explore their knowledge, beliefs and attitudes  
54  
55 42 towards DRR, and whether they are willing to assess their risk and change their lifestyle to reduce  
56  
57 43 dementia risk.  
58  
59  
60

1  
2  
3 45 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
4

- 5 46 • No other study investigating the association between a parental family history of dementia and  
6  
7 47 modifiable risk factors for dementia used a wide range of the currently known modifiable risk  
8  
9 48 factors for dementia.  
10  
11 49 • Our large study sample provided sufficient power to detect relevant associations independent  
12  
13 50 of confounding factors.  
14  
15 51 • We used sophisticated statistical techniques to prevent selection bias and calculated odds  
16  
17 52 ratios and regression coefficients with 95%-confidence intervals.  
18  
19 53 • Parental family history of dementia was based on self-reported questionnaires, which could  
20  
21 54 have led to misclassification.  
22  
23 55 • Results were based on cross-sectional data in which previous health behaviours were not taken  
24  
25 56 into account.  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

58 **KEY WORDS:**

- 59 • Dementia Risk Reduction
- 60 • Family History
- 61 • Modifiable Risk Factors
- 62 • Multiple Imputation
- 63 • Propensity Score Matching
- 64 • Middle Aged

For peer review only

## 66 INTRODUCTION

67 Since the world's population is ageing, the total number of people with dementia will increase (1). In  
68 2019, around 50 million people were living with dementia worldwide and the number of people with  
69 dementia is expected to increase to 152 million by 2050 (2). Since treatment options for curing  
70 dementia are unavailable to date, prevention of dementia is the key in decreasing the burden of  
71 dementia. It is estimated that delaying dementia onset by one year would reduce the total worldwide  
72 number of people with dementia over 60 years old in 2050 by 11.8% (3).

73  
74 Accumulating evidence shows that the development of dementia is a long-term pathological process  
75 that starts approximately ten to twenty years before dementia is clinically diagnosed (4–6). The  
76 evidence of modifiable risk factors influencing this process has been mounting (1,7,8). Livingston et  
77 al. (2020) found that 40% of the dementia cases is attributable to several lifestyle-related risk factors  
78 (i.e. less education, hypertension, hearing impairment, smoking, obesity, depression, physical  
79 inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury and air  
80 pollution) (9). Also support for several other factors was found, such as hyperlipidaemia, coronary  
81 heart disease, renal dysfunction, Mediterranean diet, cognitive activity and stress (8,10). The majority  
82 of these risk factors were combined in the Lifestyle for Brain Health (LIBRA) score, reflecting  
83 someone's potential for dementia risk reduction (DRR) (8,11–13).

84  
85 Several multi-domain interventions to reduce dementia risk and prevent cognitive decline among older  
86 individuals were conducted, however only small or non-significant effects on cognition were found  
87 (14–16). These multi-domain interventions may be more effective among cognitively healthy middle-  
88 aged individuals with a higher risk for developing dementia, for instance individuals with a parental  
89 family history (PFH) of dementia. The average lifetime risk of developing dementia is 10-12% and  
90 increases to 15-25% for individuals with a family history of dementia (17). This increased risk can be  
91 explained by both genetic and lifestyle factors (18–21), which are passed on from parents to offspring  
92 (20,22). The APOE  $\epsilon$ 4 allele is one of the genes to be consistently shown to increase the risk for  
93 dementia (23–25). Individuals with a PFH of dementia are more often carrier of this allele compared

1  
2  
3 94 to individuals without a PFH of dementia (21,26–29). Nevertheless, several studies have shown that  
4  
5 95 individuals with a PFH of dementia have an increased risk, independent of their genetic risk  
6  
7 96 (18,27,28).  
8

9  
10 97  
11 98 Although the role of APOE genotype on dementia risk has been well studied, the risk factor of a PFH  
12  
13 99 remains rarely studied. Only a few studies investigated the association between family history of  
14  
15 100 dementia and modifiable risk factors for dementia (28,30,31). They found that family history of  
16  
17 101 dementia was associated with both higher diastolic (DBP) as systolic blood pressure (SBP) and  
18  
19 102 depression (28,31), while it was not associated with Body Mass Index (BMI), serum lipid profiles (e.g.  
20  
21 103 Total cholesterol, HDL, LDL), alcohol consumption and smoking behaviour (30). However, previous  
22  
23 104 studies did not take all currently known modifiable risk factors for dementia into account and included  
24  
25 105 a relatively small sample of participants. Moreover, these findings might be a result of confounding  
26  
27 106 bias. Since age is an important risk factor for dementia, individuals with a PFH of dementia are often  
28  
29 107 older and could therefore have more often modifiable risk factors for dementia, such as hypertension  
30  
31 108 and high cholesterol levels (9). By using covariate adjustment, there is the threat that this confounding  
32  
33 109 bias is not tackled sufficiently. Propensity score matching (PSM) is a sophisticated analysis technique  
34  
35 110 that can reduce this bias by assembling a matched sample of people with and without a PFH of  
36  
37 111 dementia, in which confounding factors are balanced between groups (32). By matching, a greater  
38  
39 112 proportion of the systematic differences in characteristics of individuals with and without a PFH is  
40  
41 113 eliminated compared to the commonly used covariate adjustment (32).  
42  
43  
44

45 114  
46  
47 115 Finding differences in modifiable risk factors for dementia among middle-aged individuals with and  
48  
49 116 without a PFH of dementia, might help to identify individuals with an increased risk for dementia and  
50  
51 117 subsequently offer them tailor-made interventions for DRR. Therefore, the aim of this study was to  
52  
53 118 investigate the association between a PFH of dementia and modifiable risk factors for dementia among  
54  
55 119 middle-aged individuals from the general population.  
56  
57

58 120

## 59 121 **METHOD**

## 122 **Study population**

123 The Lifelines Cohort Study is a multi-disciplinary prospective population-based cohort study  
124 examining, in a unique three-generation design, the health and health-related behaviours of 167,729  
125 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in  
126 assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which  
127 contribute to the health and disease of the general population, with a special focus on multi-morbidity  
128 and complex genetics (33,34). The Lifelines Cohort study was conducted according to the guidelines  
129 in the Declaration of Helsinki, and approved by the Medical Ethics Committee of the University  
130 Medical Centre Groningen. All participants provided written informed consent. For the current study,  
131 we selected participants aged 35 to 65 years that participated in the baseline assessment and the first  
132 follow-up questionnaire.

## 134 **Measurement of independent and dependent variables**

### 135 **Independent variable**

136 Family history of dementia was assessed during the first follow-up questionnaire, on average 1.5 years  
137 after baseline measurement with the question 'Does your biological father and/or mother have or had  
138 one of the following diseases?'. Participants could indicate whether their father and/or mother had  
139 dementia. This variable was dichotomized [yes/no]. Furthermore, participants reported whether  
140 parents deceased and the year of birth and death of their father and/or mother if applicable. In case one  
141 of the parents deceased and no information was given about whether at least one parent had dementia,  
142 the PFH of dementia was recoded as missing. In these cases, dementia symptoms might not have been  
143 revealed yet. Therefore, it is unclear whether they would have developed dementia if they would still  
144 be alive. We attended to this by the use of multiple imputation (see Statistical analyses).

### 146 **Dependent variables**

147 Dependent variables are risk and protective factors for dementia and are based on data collection  
148 during physical examination (SBP, DBP, body weight and length), a fasting blood sample (glucose,  
149 HbA1C, total cholesterol, HDL and serum creatinine) and questionnaires, including questions on



1  
2  
3 150 demographic characteristics, health behaviours, (parental) health and medication use. Participants  
4  
5 151 brought their medication to the research site, which was subsequently reported and categorized using  
6  
7 152 the Anatomical Therapeutic Chemical (ATC) codes (35).  
8

9 153

### 11 154 *Hypertension*

13 155 Hypertension was defined as: (i) SBP > 140 mmHg, or (ii) DBP > 90 mmHg, or (iii) using blood  
14  
15 156 pressure lowering medication, which was based on the following ATC codes: C02 (antihypertensives),  
16  
17 157 C03 (diuretics), C07 ( $\beta$ -blocking agents), C08 (calcium channel blockers) and C09 (agents acting on  
18  
19 158 renin-angiotensin system) (35,36). In case the recorded SBP and DBP were missing and the participant  
20  
21 159 did not use blood pressure lowering medication, the presence of hypertension was based on the answer  
22  
23 160 of the self-reported questionnaire (Do you have hypertension?).  
24  
25

26 161

### 28 162 *High cholesterol*

30 163 High cholesterol was defined as: (i) a ratio of total cholesterol (TC) and High Density Lipoprotein  
31  
32 164 (HDL) higher than 5 mmol/l, or (ii) use of lipid lowering medication (ATC code C10 (lipid modifying  
33  
34 165 agents)) (35,36). If TC and HDL levels were missing and the participant did not use any lipid lowering  
35  
36 166 medication, high cholesterol was based on the answer of the self-reported questionnaire (Have you  
37  
38 167 ever been diagnosed with high cholesterol?).  
39  
40

41 168

### 43 169 *Renal dysfunction*

45 170 Renal dysfunction is categorized into: (i) low dysfunction (eGFR > 90 ml/min/1.73 m<sup>2</sup>), (ii) moderate  
46  
47 171 dysfunction (eGFR: 60-89 ml/min/1.73 m<sup>2</sup>) and (iii) high dysfunction (eGFR < 60 ml/min/1.73 m<sup>2</sup>) (37-  
48  
49 172 39).  
50

51 173

### 53 174 *Obesity and overweight*

55 175 BMI was calculated using measured body weight (in kg) and length (in cm) (BMI = weight/length<sup>2</sup>).  
56  
57 176 Subsequently, the presence or absence of overweight (BMI  $\geq$  25.0) and obesity (BMI  $\geq$  30.0) was  
58  
59 177 determined (40,41).  
60

1  
2  
3 1784  
5 179 ***Diabetes***

6  
7 180 Diabetes Mellitus was defined as: (i) glucose (fasting capillary blood) of 7.0 mmol/l or higher, or (ii)  
8  
9 181 HbA1C levels higher than 53 mmol/mol, or (iii) using blood glucose lowering medication (ATC code  
10  
11 182 A10 (drugs used in diabetes)) (35,42). In case glucose and HbA1c levels were missing and the  
12  
13 183 participant did not use any glucose lowering medication, the presence of diabetes mellitus was based  
14  
15 184 on the answer of the self-reported questionnaire (Do you have diabetes mellitus?).  
16  
17

18 185

19  
20 186 ***Cardiovascular diseases***

21  
22 187 Participants reported whether they have suffered or still suffer from one of the following  
23  
24 188 cardiovascular diseases (CVDs): myocardial infarction, stroke or peripheral arterial diseases. If at least  
25  
26 189 one of these CVDs was indicated with 'yes' in the self-reported questionnaire, participants were  
27  
28 190 known with CVDs.  
29

30 191

31  
32 192 ***Healthy diet***

33  
34 193 A quantitative Food Frequency Questionnaire (FFQ) was used to assess dietary intake over the  
35  
36 194 previous month (43,44). Subsequently, the Lifelines diet score (LLDS) was used to determine  
37  
38 195 adherence to a healthy diet, which is based on the consumption of nine positive food groups  
39  
40 196 (vegetables, fruit, whole grain products, legumes and nuts, fish, oils and soft margarines, unsweetened  
41  
42 197 dairy, coffee and tea) and three negative food groups (red and processed meat, butter and hard  
43  
44 198 margarines and sugar-sweetened beverages). The consumption of each food group was divided into  
45  
46 199 quintiles to score an individual's consumption compared to the total Lifelines population. For each  
47  
48 200 food group, the quintiles ranged from 0 to 4 points, using 4 points for the highest quintile of  
49  
50 201 consumption for positive food groups and the lowest quintile for the negative food groups. The total  
51  
52 202 LLDS ranges from 0 to 48, with a higher score indicating a healthier diet (45).  
53  
54

55 203

56  
57 204 ***Alcohol consumption***58  
59  
60

1  
2  
3 205 Alcohol consumption is categorized into: (i) no alcohol consumption (0 alcohol units in the past  
4  
5 206 month), (ii) low/moderate alcohol consumption (average  $\leq 1$  alcohol unit per day and no binge  
6  
7 207 drinking) and (iii) excessive alcohol consumption (average  $> 1$  alcohol unit per day and/or binge  
8  
9 208 drinking, which is defined as more than three alcohol units per occasion for females and more than  
10  
11 209 four alcohol units per occasion for males).

12  
13  
14 210

### 15 211 *Physical inactivity*

16  
17  
18 212 Physical inactivity was measured with the Short Questionnaire to Assess Health enhancing physical  
19  
20 213 activity (SQUASH) (46). The results are converted to minutes per week spent in physical activity of  
21  
22 214 light intensity and physical activity of moderate to vigorous intensity (MVPA), based on Metabolic  
23  
24 215 Equivalent Tasks (METs) derived from the Ainsworth's compendium of physical activity (47).  
25  
26 216 Physical inactivity is defined as less than 150 minutes per week MVPA (48).

27  
28  
29 217

### 30 218 *Smoking*

31  
32  
33 219 Smoking behaviour was assessed with the self-reported questionnaire, including the following two  
34  
35 220 questions: (i) 'Do you smoke now, or have you smoked in the past month?' and (ii) 'Have you ever  
36  
37 221 smoked for a full year?'. Subsequently, smoking behaviour was categorized into: (i) non-smoker, (ii)  
38  
39 222 ex-smoker and (iii) current smoker. Current smokers are defined as people who reported smoking in  
40  
41 223 the past month. Ex-smokers reported smoking for at least one year, but did not smoke in the past  
42  
43 224 month.

44  
45 225

### 46 47 226 *Social activity*

48  
49 227 Social activity was measured with the following question 'On average how many people did you have  
50  
51 228 contact with in the past two weeks?'. Subsequently, social activity is categorized into low  
52  
53 229 (contacts $<4$ ), moderate (contacts: 4-7) and high (contacts $\geq 8$ ) (49).

54  
55  
56 230

### 57 58 231 *Depression*

1  
2  
3 232 The presence of a major depression was measured with the Mini International Neuropsychiatric  
4  
5 233 Interview (MINI) (50). Major depression was defined as having at least one key symptom of  
6  
7 234 depression (e.g. depressed mood or loss of interest) and four additional symptoms in the past month,  
8  
9 235 according the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) (51).

236

### 237 *Stress*

238 Chronic stress was measured by the Long-term Difficulties Inventory (LDI) (52,53), which consists of  
239 twelve items that refer to twelve stressful life events, with regard to housing, work, social  
240 relationships, free time, finances, health, school/study and religion. Participants indicated how much  
241 stress they experienced over the past twelve months with regard to each aspect on a three-point scale  
242 (0=not stressful; 1=slightly stressful; 2=very stressful). Total scores range from 0 (no stress) to 24  
243 (very stressful).

244

### 245 *LIBRA score*

246 The LIBRA score reflects an individual's potential to reduce their risk on developing dementia and is  
247 based on a total of twelve protective (i.e. Mediterranean diet, low/moderate alcohol consumption, high  
248 cognitive activity) and risk factors (i.e. physical inactivity, smoking, CVDs, hypertension, high  
249 cholesterol, diabetes mellitus, obesity, renal dysfunction, depression) for dementia (8,11–13). Using  
250 the relative risks derived from the systematic review of Deckers et al. (2015), the LIBRA score was  
251 calculated (8). Since cognitive activities were not measured in Lifelines, LIBRA scores could range  
252 from -2.7 (low risk for dementia) to 12.7 (high risk for dementia). In **Table 1** the definitions and  
253 corresponding scores for each protective and risk factor for dementia are presented.

254

255 **INSERT TABLE 1 ABOUT HERE**

256

### 257 *Covariates*

258 The demographic factors such as age, sex and education were measured at baseline. Age (in years) is  
259 included as a continuous variable. Sex is included as a dichotomous variable (male/female). Education

1  
2  
3 260 was based on the question ‘What is your highest completed level of education?’. Highest level of  
4  
5 261 education was categorized into: (i) elementary (no education or primary education), (ii) lower  
6  
7 262 secondary (lower or preparatory vocational education or lower general secondary education), (iii)  
8  
9 263 upper secondary (intermediate vocational education) and (iv) tertiary (higher general secondary  
10  
11 264 education or pre-university secondary education, higher vocational education and university) (54).

13 265

## 15 266 **Statistical methods**

17 267 The baseline characteristics of the total study population were described and differences between  
18  
19 268 participants with and without a PFH of dementia were calculated using Standardized Mean  
20  
21 269 Differences (SMD). Five imputed datasets were generated to replace missing values, using the  
22  
23 270 Multiple Imputation using Chained Equations (MICE) approach. Specifically, we used predictive  
24  
25 271 mean matching (ppm) for continuous data, logistic regression imputation (logreg) for binary data,  
26  
27 272 polytomous regression imputation (polyreg) for unordered categorical data and proportional odds  
28  
29 273 model (polr) for ordered categorical data. In each imputed dataset, we assessed the association  
30  
31 274 between PFH of dementia and each modifiable risk factor in two steps. First, to eliminate selection  
32  
33 275 bias, PSM was used to match each individual with a PFH of dementia to an individual without a PFH  
34  
35 276 of dementia (ratio 1:1) (caliper=0.2), based on the standard potential confounders age, sex and  
36  
37 277 educational level (model 1) and other potential confounders (model 2) (see **Supplementary file 1**)  
38  
39 278 (32). The other potential confounders were a-priori carefully selected per outcome measure in a  
40  
41 279 consensus meeting, in which each potential confounder had to be associated with both the independent  
42  
43 280 and the dependent variables. After PSM, we checked if the balance in the covariates was achieved  
44  
45 281 (SMD < 0.2). Second, logistic (dichotomous outcomes), linear (continuous outcomes) and multinomial  
46  
47 282 (categorical outcomes) regression analyses were used to examine the association between a PFH of  
48  
49 283 dementia and each modifiable risk factor. These analyses were conducted for each imputed matched  
50  
51 284 dataset to obtain the estimates, which were pooled using Rubin’s rules (55). Since the LIBRA score is  
52  
53 285 a composite score and includes all individual modifiable risk factors for dementia, this analysis is  
54  
55 286 based on model 1 (only matched on sex, age and educational level). Results are presented as odds  
56  
57 287 ratios (OR) or regression coefficients (RC) with 95% confidence intervals (95%-CI). Sensitivity

1  
2  
3 288 analyses were conducted in which covariate adjustment is used instead of PSM. R statistical software  
4  
5 289 environment version 1.3.383 was used (56). In particular, we used the ‘MatchThem’, ‘tableone’ and  
6  
7 290 ‘cobalt’ package in R.  
8

9 291

## 11 292 **Patient and Public Involvement**

13 293 Participants of the Lifelines Cohort study were not involved in the design, conduct reporting or  
14  
15 294 dissemination plans of our research.  
16

17 295

## 20 296 **RESULTS**

### 22 297 **Baseline characteristics**

23  
24 298 A total of 106,884 Lifelines participants aged 35-65 years at baseline completed the baseline  
25  
26 299 assessment. For 17,015 participants no data was available on PFH of dementia, since they did not  
27  
28 300 participate in the first follow-up questionnaire and were therefore excluded from the analyses. This  
29  
30 301 resulted in 89,869 participants of which 10,940 participants (12.2%) with a PFH of dementia and  
31  
32 302 36,389 participants (40.5%) without a PFH of dementia. Of 42,540 participants (47.3%) PFH of  
33  
34 303 dementia was recoded as missing, since at least one parent was deceased (see flowchart in  
35  
36 304 **Supplementary file 2**). **Table 2** presents the characteristics of participants with and without a PFH of  
37  
38 305 dementia. In the observed data, we found an imbalance in age (SMD=1.534), education (SMD=0.271),  
39  
40 306 hypertension (SMD=0.304), high cholesterol (SMD=0.265), renal dysfunction (SMD=0.334), physical  
41  
42 307 inactivity (SMD=0.375), diet (SMD=0.278) and smoking (SMD=0.333). After PSM on potential  
43  
44 308 confounders, the balance in confounding variables was improved (see **Supplementary file 3**). We  
45  
46 309 focused further on the results of the final model (model 2).  
47  
48 310

49 310

51 311 **INSERT TABLE 2 ABOUT HERE**

52 312

### 55 313 **The association between a PFH of dementia and modifiable risk factors for dementia**

56  
57 314 The results of the logistic, linear and multinomial regression analyses on the association between a  
58  
59 315 PFH of dementia and modifiable risk factors for dementia are presented in **Table 3**. Individuals with a

1  
2  
3 316 PFH of dementia had more often hypertension (OR=1.19, 95%-CI: 1.14,1.24), high cholesterol  
4  
5 317 (OR=1.24, 95%-CI: 1.18,1.30), diabetes (OR=1.26, 95%-CI: 1.11,1.42), CVDs (OR=1.49, 95%-CI:  
6  
7 318 1.18,1.88), obesity (OR=1.14, 95%-CI: 1.08,1.20), overweight (OR=1.10, 95%-CI: 1.05,1.17), and  
8  
9 319 depressive symptoms (OR=1.23, 95%-CI: 1.08,1.41) compared to their peers without a PFH of  
10  
11 320 dementia. Further, individuals with a PFH of dementia were more often current-smokers (OR=1.20,  
12  
13 321 95%-CI: 1.14,1.27) and ex-smokers (OR=1.21, 95%-CI:1.16,1.27), but were less often low/moderate  
14  
15 322 alcohol consumers (OR=0.87, 95%-CI: 0.83,0.91), excessive alcohol consumers (OR=0.93, 95%-  
16  
17 323 CI:0.89,0.98), physically inactive (OR=0.93, 95%-CI: 0.91,0.97) and had less often a low social  
18  
19 324 activity (OR=0.84, 95%-CI:0.78,0.90). Finally, individuals with a PFH of dementia also had an overall  
20  
21 325 higher risk to develop dementia (LIBRA score RC=0.15, 95%-CI: 0.11,0.19) compared to their peers  
22  
23 326 without a PFH of dementia.  
24  
25  
26  
27

28 328 **INSERT TABLE 3 ABOUT HERE**

## 329 330 **DISCUSSION**

331 In this study, we investigated the association between having a PFH of dementia and fourteen  
332 modifiable risk factors for dementia among middle-aged individuals from the general population. We  
333 found that several modifiable risk factors for dementia were more common in individuals with a PFH  
334 of dementia independent of their age, sex and educational level. They had more often hypertension,  
335 high cholesterol, diabetes, CVDs, obesity, overweight, depression and were also more often ex-smoker  
336 and current smoker than never smoker. However, they were more often non-alcohol consumers,  
337 physically active and socially active compared to their peers without a PFH of dementia. Overall,  
338 individuals with a PFH of dementia had a higher risk of developing dementia, based on the LIBRA  
339 score, which suggests that they are a group at risk for dementia.

340

341 In general, most findings are in line with our expectations, except that individuals with a PFH of  
342 dementia were less often physically and socially inactive, and less often low/moderate alcohol  
343 consumer and excessive alcohol consumer than no alcohol consumer. Since individuals with a PFH of

1  
2  
3 344 dementia had more often cardiovascular risk factors, it might be that they did not consume alcohol due  
4  
5 345 to health concerns or use of medication (57). Furthermore, in our study, PFH of dementia was  
6  
7 346 determined by the first follow-up questionnaire. In case dementia was diagnosed before baseline  
8  
9 347 assessment, individuals with a PFH of dementia could already have adjusted their lifestyle. Therefore,  
10  
11 348 these findings may reflect a reverse causality from having a parent with dementia to more physical and  
12  
13 349 social activity. No data was available on the date of onset of dementia.  
14

15  
16 350

17  
18 351 To our knowledge, this is the first study that investigated the association between having a PFH of  
19  
20 352 dementia and currently known modifiable risk factors for dementia among middle-aged individuals  
21  
22 353 using a large sample size and PSM. Only few studies have been conducted to test the differences in  
23  
24 354 several modifiable risk factors of dementia between individuals with and without a family history of  
25  
26 355 dementia (28,30,31). However, it is likely that these studies were hampered by small sample sizes of  
27  
28 356 the study population. For instance, Luckhoff et al. (2016) did not find differences in BMI (objectively  
29  
30 357 measured), total cholesterol, HDL, LDL, alcohol intake and smoking behaviour between middle-aged  
31  
32 358 individuals with (n=75) and without (n=505) a self-reported family history of dementia ( $p>0.05$ )(30).  
33  
34 359 Exel et al. (2009) found that middle-aged individuals with an objectively measured PFH of dementia  
35  
36 360 (n=206) had more often hypertension and caregiver burden stress compared to their peers (n=200)  
37  
38 361 ( $p<0.05$ )(28). However, no differences were found in high cholesterol, glucose levels and lifestyle-  
39  
40 362 related risk factors such as smoking and physical activity ( $p>0.05$ ) (58). La Rue et al. (2008) also  
41  
42 363 showed that individuals with a PFH of dementia (n=623) had higher cholesterol levels, higher DBP  
43  
44 364 and SBP and higher depression rates compared to individuals without a PFH of dementia (n=157)  
45  
46 365 ( $p<0.01$ )(31). Although differences with the current study could be explained by the use of different  
47  
48 366 statistical methods, sensitivity analyses in which covariate adjustment is used showed similar results  
49  
50 367 when using PSM (see **Supplementary file 4**). In comparison to the main analyses, the estimates for  
51  
52 368 physical inactivity and social activity are slightly smaller in the sensitivity results. This could be  
53  
54 369 explained by the smaller sample size in the main results (n=53,644 versus n=89,869). Due to one-to-  
55  
56 370 one matching, a relatively high number of healthy living individuals with a PFH of dementia could not  
57  
58 371 be matched and therefore not included in the main analyses. A major advantage of PSM is that the  
59  
60



1  
2  
3 372 balance in potential confounders can be inspected between individuals with and without a PFH of  
4  
5 373 dementia before conducting the analyses. After PSM most potential confounders were balanced  
6  
7 374 between participants with and without a PFH of dementia (SMD<0.2), except for the variable renal  
8  
9 375 dysfunction (SMD=-0.207). Therefore, it is possible that the associations between having a PFH of  
10  
11 376 dementia and lifestyle-related risk factors for dementia are slightly biased.

12  
13  
14 377

### 15 378 **Strengths and limitations**

16  
17 379 Our large study sample provided sufficient power to detect relevant associations independent of  
18  
19 380 confounding factors. In addition, no other study investigating the association between a PFH of  
20  
21 381 dementia and modifiable risk factors for dementia used a wide range of the currently known  
22  
23 382 modifiable risk factors for dementia. A large part of these modifiable risk factors (e.g., hypertension,  
24  
25 383 high cholesterol, diabetes mellitus, obesity, overweight, renal dysfunction) were objectively measured  
26  
27 384 through physical examination and fasting blood samples. Further, we used sophisticated statistical  
28  
29 385 techniques to prevent selection bias. The potential confounders used in PSM were carefully chosen per  
30  
31 386 outcome measure. Finally, in contrast to previous studies, we reported adjusted ORs and RCs with  
32  
33 387 95%-confidence intervals instead of p-values, which gives more information on the magnitude and  
34  
35 388 direction of the association studied.

36  
37  
38  
39 389

40  
41 390 This study also had certain limitations. One drawback is that PFH of dementia was based on self-  
42  
43 391 reported questionnaires and could have led to misclassification. Nonetheless, it is likely that the  
44  
45 392 misclassification was non-differential and would have led to an underestimation of our results.  
46  
47 393 Second, no data was available on the APOE genotype, which may be an important effect modifier  
48  
49 394 (19). Previous literature showed that a healthy lifestyle might especially be beneficial for the cognition  
50  
51 395 of APOE e4 carriers (19,59). Since individuals with a PFH of dementia are more often carrier of the  
52  
53 396 APOE e4 allele, a healthy lifestyle might also be especially beneficial for individuals with a PFH of  
54  
55 397 dementia. Therefore, absence of APOE genotype data could have led to an underestimation of the  
56  
57 398 results for APOE e4 carriers with a PFH of dementia. Third, the results were based on cross-sectional  
58  
59 399 data in which previous health behaviours were not taken into account. It might be possible that

1  
2  
3 400 individuals with a PFH of dementia adopted a healthier lifestyle after their parent got diagnosed with  
4  
5 401 dementia. In other words, our findings may reflect a reverse causality from PFH of dementia to health  
6  
7 402 behaviour, indicating that our estimates may be underestimated. Finally, we imputed PFH of dementia  
8  
9 403 of all participants without a PFH of dementia with at least one deceased parent. We did not distinguish  
10  
11 404 in the age of death of deceased parents, since the incidence of dementia increases with age and the  
12  
13 405 average age of onset of dementia differs between types of dementia (60). However, relatively young  
14  
15 406 parents are less likely to develop dementia compared to older parents. Nevertheless, sensitivity  
16  
17 407 analyses in which individuals with deceased fathers who survived to at least the age of 70 or mothers  
18  
19 408 who survived to at least the age of 75 were assigned to the group without having a PFH of dementia  
20  
21 409 instead of PFH being imputed, showed similar results (31). Also, we did not take into account the age  
22  
23 410 of onset of dementia of the parent(s), since the average age of onset of dementia differs between types  
24  
25 411 of dementia (60). However, this might be an important effect modifier as early onset dementia may  
26  
27 412 have a stronger genetic basis. Therefore, these results could be an underestimation of the results for  
28  
29 413 individuals with a parents diagnosed at an older age. Nevertheless, after excluding individuals with a  
30  
31 414 parent diagnosed before the age of 70 years, the results were similar.  
32  
33  
34  
35  
36

37 416 These findings support a high-risk prevention strategy for dementia by identifying the individuals with  
38  
39 417 a PFH of dementia, screening them for modifiable risk factors for dementia, and implementing multi-  
40  
41 418 domain interventions targeting these modifiable risk factors. Future studies should first explore the  
42  
43 419 knowledge, beliefs and attitudes towards dementia (risk reduction) among middle-aged individuals  
44  
45 420 with a PFH of dementia, and whether they are willing to assess their protective and risk factors for  
46  
47 421 dementia and adopt a healthier lifestyle. Next, the effectiveness of these multi-domain interventions in  
48  
49 422 changing health behaviour for DRR among middle-aged individuals with a PFH of dementia should be  
50  
51 423 investigated.  
52  
53  
54

## 55 425 **CONCLUSION**

56 426 We found that a PFH of dementia was associated with several modifiable risk factors for dementia  
57  
58 427 independent of age, sex and educational level, including hypertension, high cholesterol, diabetes  
59  
60

1  
2  
3 428 mellitus, CVDs, obesity, overweight and depression. This suggests that middle-aged individuals with a  
4  
5 429 PFH of dementia are a group at risk for dementia and might benefit from DRR. Further research  
6  
7 430 should examine knowledge, beliefs and attitudes towards DRR among middle-aged individuals with a  
8  
9 431 PFH of dementia, and their willingness to address and tackle their personal risk factors for dementia in  
10  
11 432 order to prevent of postpone dementia.  
12

13  
14 433

15 434 **Acknowledgements:** The Lifelines Biobank initiative has been made possible by subsidy from the  
16  
17 435 Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University  
18  
19 436 Medical Centre Groningen (UMCG the Netherlands), University Groningen and the Northern  
20  
21 437 Provinces of the Netherlands.  
22

23  
24 438 **Author contributions:** JV, AAH, SR and NS were involved in the design of the study. JV conducted  
25  
26 439 the analysis with support of AAH. JV wrote the manuscript and AAH, SR and NS revised the  
27  
28 440 manuscript. All authors read and approved the final manuscript.  
29

30 441 **Funding:** None declared.  
31

32 442 **Competing Interests:** The authors declare that no conflict of interest exists.  
33

34 443 **Patient consent:** Not applicable.  
35

36 444 **Data sharing statement:** Lifelines is a facility that is open for all researchers ([www.lifelines.net](http://www.lifelines.net)).  
37

38 445 **Ethics statement:** The Lifelines Cohort Study was approved by the Medical Ethical Commission  
39  
40 446 (METC) of the University Medical Center Groningen (Reference number-2007/152). All subjects  
41  
42 447 signed written informed consent and all methods were carried out in accordance with relevant  
43  
44 448 guidelines and regulations for human subjects.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

450 **REFERENCES**

- 451 1. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. The Lancet  
452 Commissions Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673–  
453 734.
- 454 2. World Health Organization. Dementia [Internet]. 2019. Available from:  
455 <https://www.who.int/news-room/fact-sheets/detail/dementia>
- 456 3. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of  
457 Alzheimer's disease. *Alzheimer's Dement*. 2007 Jul;3(3):186–91.
- 458 4. Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, et al. Timing of  
459 onset of cognitive decline: results from Whitehall II prospective cohort study. *BMJ*. 2012 Jan  
460 5;344:d7622.
- 461 5. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining  
462 the preclinical stages of Alzheimer's disease: recommendations from the National Institute on  
463 Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.  
464 *Alzheimers Dement*. 2011 May;7(3):280–92.
- 465 6. Rajan KB, Wilson RS, Weuve J, Barnes LL, Evans DA. Cognitive impairment 18 years before  
466 clinical diagnosis of Alzheimer disease dementia. *Neurology*. 2015 Sep 8;85(10):898–904.
- 467 7. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C, Ministers GH and S, et al. Potential  
468 for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet*  
469 *Neurol*. 2014 Aug;13(8):788–94.
- 470 8. Deckers K, van Boxtel MPJ, Schiepers OJG, de Vugt M, Muñoz Sánchez JL, Anstey KJ, et al.  
471 Target risk factors for dementia prevention: a systematic review and Delphi consensus study on  
472 the evidence from observational studies. *Int J Geriatr Psychiatry*. 2015 Mar;30(3):234–46.
- 473 9. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia  
474 prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*.  
475 2020;396(10248):413–46.
- 476 10. Li X-Y, Zhang M, Xu W, Li J-Q, Cao X-P, Yu J-T, et al. Midlife Modifiable Risk Factors for  
477 Dementia: A Systematic Review and Meta-analysis of 34 Prospective Cohort Studies. *Curr*

- 1  
2  
3 478 Alzheimer Res. 2019;16(14):1254–68.  
4  
5 479 11. Schiepers OJG, Köhler S, Deckers K, Irving K, O'Donnell CA, van den Akker M, et al.  
6  
7 480 Lifestyle for Brain Health (LIBRA): a new model for dementia prevention. *Int J Geriatr*  
8  
9 481 *Psychiatry*. 2018 Feb 28;33:167–75.  
10  
11 482 12. Vos SJB, van Boxtel MPJ, Schiepers OJG, Deckers K, de Vugt M, Carrière I, et al. Modifiable  
12  
13 483 Risk Factors for Prevention of Dementia in Midlife, Late Life and the Oldest-Old: Validation  
14  
15 484 of the LIBRA Index. *J Alzheimer's Dis*. 2017 May 11;58(2):537–47.  
16  
17 485 13. Deckers K, Köhler S, van Boxtel M, Verhey F, Brayne C, Fleming J, et al. Lack of associations  
18  
19 486 between modifiable risk factors and dementia in the very old: findings from the Cambridge  
20  
21 487 City over-75s cohort study. *Aging Ment Health*. 2017 Feb;1–7.  
22  
23 488 14. Ngandu T, Lehtisalo J, Solomon A, Levälähti E, Ahtiluoto S, Antikainen R, et al. A 2 year  
24  
25 489 multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring  
26  
27 490 versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised  
28  
29 491 controlled trial. *Lancet*. 2015 Jun;385(9984):2255–63.  
30  
31 492 15. van Charante EPM, Richard E, Eurelings LS, van Dalen J-W, Ligthart SA, van Bussel EF, et  
32  
33 493 al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia  
34  
35 494 (preDIVA): a cluster-randomised controlled trial. *Lancet*. 2016;388(10046):797–805.  
36  
37 495 16. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term  
38  
39 496 omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention  
40  
41 497 on cognitive function in elderly adults with memory complaints (MAPT): a randomised,  
42  
43 498 placebo-controlled trial. *Lancet Neurol*. 2017 May 1;16(5):377–89.  
44  
45 499 17. Goldman JS, Hahn SE, Catania JW, LaRusse-Eckert S, Butson MB, Rumbaugh M, et al.  
46  
47 500 Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American  
48  
49 501 College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med*. 2011  
50  
51 502 Jun;13(6):597–605.  
52  
53 503 18. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hyppönen E, Kuzma E, et al. Association of  
54  
55 504 lifestyle and genetic risk with incidence of dementia. *JAMA*. 2019 Aug 6;322(5):430.  
56  
57 505 19. Kivipelto M, Rovio S, Ngandu T, Kåreholt I, Eskelinen M, Winblad B, et al. Apolipoprotein E

- 1  
2  
3 506 epsilon4 magnifies lifestyle risks for dementia: a population-based study. *J Cell Mol Med.*  
4  
5 507 2008 Dec;12(6B):2762–71.  
6  
7 508 20. Borenstein AR, Copenhaver CI, Mortimer JA. Early-Life Risk Factors for Alzheimer Disease.  
8  
9 509 *Alzheimer Dis Assoc Disord.* 2006 Jan;20(1):63–72.  
10  
11 510 21. Donix M, Small GW, Bookheimer SY. Family History and APOE-4 Genetic Risk in  
12  
13 511 *Alzheimer’s Disease.* *Neuropsychol Rev.* 2012 Sep 23;22(3):298–309.  
14  
15 512 22. Muñoz M, Pong-Wong R, Canela-Xandri O, Rawlik K, Haley CS, Tenesa A. Evaluating the  
16  
17 513 contribution of genetics and familial shared environment to common disease using the UK  
18  
19 514 Biobank. *Nat Genet.* 2016 Jul 18;48(9):980–3.  
20  
21  
22 515 23. Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC, et al.  
23  
24 516 Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat Genet.*  
25  
26 517 1994 Jun;7(2):180–4.  
27  
28 518 24. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of Age,  
29  
30 519 Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer  
31  
32 520 Disease. *JAMA.* 1997 Oct 22;278(16):1349.  
33  
34  
35 521 25. Choudhury P, Ramanan VK, Boeve BF. APOE ε 4 Allele Testing and Risk of Alzheimer  
36  
37 522 Disease. *JAMA.* 2021 Jan 14;  
38  
39 523 26. Sager MA, Hermann B, La Rue A. Middle-aged children of persons with Alzheimer’s disease:  
40  
41 524 APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer’s Prevention.  
42  
43 525 *J Geriatr Psychiatry Neurol.* 2005 Dec 29;18(4):245–9.  
44  
45 526 27. Scarabino D, Gambina G, Broggio E, Pelliccia F, Corbo RM. Influence of family history of  
46  
47 527 dementia in the development and progression of late-onset Alzheimer’s disease. *Am J Med*  
48  
49 528 *Genet Part B Neuropsychiatr Genet.* 2016 Mar;171(2):250–6.  
50  
51 529 28. van Exel E, Eikelenboom P, Comijs H, Frölich M, Smit JH, Stek ML, et al. Vascular factors  
52  
53 530 and markers of inflammation in offspring with a parental history of late-onset Alzheimer  
54  
55 531 disease. *Arch Gen Psychiatry.* 2009 Nov 1;66(11):1263–70.  
56  
57  
58 532 29. Johnson SC, Kosciak RL, Jonaitis EM, Clark LR, Mueller KD, Berman SE, et al. The  
59  
60 533 Wisconsin Registry for Alzheimer’s Prevention: A review of findings and current directions.

- 1  
2  
3 534 Alzheimer's Dement (Amsterdam, Netherlands). 2018;10:130–42.  
4  
5 535 30. Lückhoff HK, Kidd M, van Rensburg SJ, van Velden DP, Kotze MJ. Apolipoprotein E  
6  
7 536 genotyping and questionnaire-based assessment of lifestyle risk factors in dyslipidemic patients  
8  
9 537 with a family history of Alzheimer's disease: test development for clinical application. *Metab*  
10  
11 538 *Brain Dis*. 2016 Feb 20;31(1):213–24.  
12  
13 539 31. Rue A La, Hermann B, Jones JE, Johnson S, Asthana S, Sager MA. Effect of parental family  
14  
15 540 history of Alzheimer's disease on serial position profiles. *Alzheimer's Dement*. 2008 Jul  
16  
17 541 1;4(4):285–90.  
18  
19 542 32. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of  
20  
21 543 Confounding in Observational Studies. *Multivariate Behav Res*. 2011 May;46(3):399–424.  
22  
23 544 33. Scholtens S, Smidt N, Swertz MA, Bakker SJL, Dotinga A, Vonk JM, et al. Cohort Profile:  
24  
25 545 LifeLines, a three-generation cohort study and biobank. *Int J Epidemiol*. 2015  
26  
27 546 Aug;44(4):1172–80.  
28  
29 547 34. Stolk RP, Rosmalen JGM, Postma DS, de Boer RA, Navis G, Slaets JPJ, et al. Universal risk  
30  
31 548 factors for multifactorial diseases. *Eur J Epidemiol*. 2008 Jan 13;23(1):67–74.  
32  
33 549 35. World Health Organization. ATC/DDD Index 2020. Oslo, Norway; 2020.  
34  
35 550 36. van Dis SJ, Kromhout D, Geleijnse JM, Boer JMA, Verschuren WMM. Evaluation of  
36  
37 551 cardiovascular risk predicted by different score equations: the Netherlands as an example. *Eur J*  
38  
39 552 *Cardiovasc Prev Rehabil*. 2010;17:244–9.  
40  
41 553 37. De Grauw W, De Leest K, Schenk P, Scherpbier-De Haan N, Tjin-A-Ton J, Tuut M, et al.  
42  
43 554 NHG-Standaard Chronische Nierschade. *TPO - Prakt*. 2018;13(5):26–9.  
44  
45 555 38. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation  
46  
47 556 to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–12.  
48  
49 557 39. Levey AS, Inker LA, Coresh J. GFR estimation: From physiology to public health. *Am J*  
50  
51 558 *Kidney Dis*. 2014;63(5):820–34.  
52  
53 559 40. Centers for Disease Control and Prevention (CDC). Body Mass Index (BMI) [Internet]. [cited  
54  
55 560 2020 Sep 9]. Available from:  
56  
57 561 [https://www.cdc.gov/healthyweight/assessing/bmi/adult\\_bmi/index.html](https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html)

- 1  
2  
3 562 41. World Health Organization (WHO). Body mass index (BMI) [Internet]. World Health  
4 563 Organization; [cited 2019 May 6]. Available from: [http://www.euro.who.int/en/health-](http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi)  
5 564 [topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi](http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi)  
6  
7  
8  
9 565 42. Rutten G, De Grauw W, Nijpels G, Houweling S, Van de Laar F, Bilo H, et al. NHG-Standaard  
10 566 Diabetes mellitus type 2. 2013.
- 11  
12  
13 567 43. Molag ML, de Vries JHM, Duif N, Ocké MC, Dagnelie PC, Goldbohm RA, et al. Selecting  
14 568 informative food items for compiling food-frequency questionnaires: comparison of  
15  
16 569 procedures. *Br J Nutr*. 2010 Aug 8;104(03):446–56.
- 17  
18  
19 570 44. Siebelink E, Geelen A, de Vries JHM. Self-reported energy intake by FFQ compared with  
20 571 actual energy intake to maintain body weight in 516 adults. *Br J Nutr*. 2011 Jul  
21  
22 572 22;106(02):274–81.
- 23  
24  
25 573 45. Vinke PC, Corpeleijn E, Dekker LH, Jacobs DR, Navis G, Kromhout D. Development of the  
26 574 food-based Lifelines Diet Score (LLDS) and its application in 129,369 Lifelines participants.  
27  
28 575 *Eur J Clin Nutr*. 2018;72(8):1111–9.
- 29  
30  
31 576 46. Wendel-Vos G. Reproducibility and relative validity of the short questionnaire to assess health-  
32 577 enhancing physical activity. *J Clin Epidemiol*. 2003 Dec;56(12):1163–9.
- 33  
34  
35 578 47. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, et al. 2011  
36 579 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci*  
37 580 *Sports Exerc*. 2011 Aug;43(8):1575–81.
- 38  
39  
40 581 48. Weggemans RM, Backx FJG, Borghouts L, Chinapaw M, Hopman MTE, Koster A, et al. The  
41 582 2017 Dutch Physical Activity Guidelines. *Int J Behav Nutr Phys Act*. 2018 Jun 25;15(1):58.
- 42  
43  
44 583 49. Kuiper JS, Zuidersma M, Oude Voshaar RC, Zuidema SU, van den Heuvel ER, Stolk RP, et al.  
45 584 Social relationships and risk of dementia: A systematic review and meta-analysis of  
46 585 longitudinal cohort studies. *Ageing Res Rev*. 2015 Jul 1;22:39–57.
- 47  
48  
49 586 50. Sheehan D V, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-  
50 587 International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a  
51 588 structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*.  
52 589 1998;59 Suppl 2:22–33; quiz 34–57.



- 1  
2  
3 590 51. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders  
4  
5 591 (DSM-5®). Fifth edit. Washington; 2013.  
6  
7 592 52. Rosmalen JGM, Bos EH, de Jonge P. Validation of the Long-term Difficulties Inventory (LDI)  
8  
9 593 and the List of Threatening Experiences (LTE) as measures of stress in epidemiological  
10  
11 594 population-based cohort studies. *Psychol Med*. 2012 Dec;42(12):2599–608.  
12  
13 595 53. Motrico E, Moreno-Küstner B, de Dios Luna J, Torres-González F, King M, Nazareth I, et al.  
14  
15 596 Psychometric properties of the List of Threatening Experiences—LTE and its association with  
16  
17 597 psychosocial factors and mental disorders according to different scoring methods. *J Affect*  
18  
19 598 *Disord*. 2013;150(3):931–40.  
20  
21 599 54. Klijs B, Kibele EUB, Ellwardt L, Zuidersma M, Stolk RP, Wittek RPM, et al. Neighborhood  
22  
23 600 income and major depressive disorder in a large Dutch population: results from the LifeLines  
24  
25 601 Cohort study. *BMC Public Health*. 2016 Aug 11;16(1):773.  
26  
27 602 55. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and  
28  
29 603 guidance for practice. *Stat Med*. 2011 Feb 20;30(4):377–99.  
30  
31 604 56. R Core team. R: A language and environment for statistical computing. Vienna, Austria; 2020.  
32  
33 605 57. Green CA, Polen MR. The health and health behaviors of people who do not drink alcohol. *Am*  
34  
35 606 *J Prev Med*. 2001 Nov 1;21(4):298–305.  
36  
37 607 58. van Exel E, Eikelenboom P, Comijs H, Frölich M, Smit JH, Stek ML, et al. Vascular Factors  
38  
39 608 and Markers of Inflammation in Offspring With a Parental History of Late-Onset Alzheimer  
40  
41 609 Disease. *Arch Gen Psychiatry*. 2009 Nov 1;66(11):1263.  
42  
43 610 59. Dekhtyar S, Marseglia A, Xu W, Darin-Mattsson A, Wang HX, Fratiglioni L. Genetic risk of  
44  
45 611 dementia mitigated by cognitive reserve: A cohort study. *Ann Neurol*. 2019 Jul 1;86(1):68–78.  
46  
47 612 60. Ott A, Breteler MMB, Van Harskamp F, Stijnen T, Hofman A. Incidence and Risk of  
48  
49 613 Dementia The Rotterdam Study. 1998;147(6).  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Table 1.** Definition of risk and protective factors in the LIBRA score and corresponding scores

Modifiable risk factors	Definition	Score	
<b>Protective factors</b>			
<b>1</b>	Healthy diet	LLDS $\geq$ 5 <sup>th</sup> quintile (score of 30 and higher)	-1.7
<b>2</b>	No to low/moderate alcohol consumption	Average number of alcohol units per day $\leq$ 1 without binge drinking (i.e., > 3 units per day for women; > 4 units per day for men)	-1.0
<b>Risk factors</b>			
<b>3</b>	Cardiovascular diseases	The presence of at least one cardiovascular disease (myocardial infarction, stroke or peripheral arterial diseases)	+1.0
<b>4</b>	Physical inactivity	Not fulfilling the Dutch Norm for Physical activity (i.e., $\geq$ 150 min/week physical activity of moderate to vigorous intensity, measured with the SQUASH questionnaire)	+1.1
<b>5</b>	Renal dysfunction	eGFR < 60 ml/min/1.73 m <sup>2</sup>	+1.1
<b>6</b>	Diabetes	Glucose (capillary blood) $\geq$ 7.0 mmol/L or HbA1c > 53 mmol/mol	+1.3
<b>7</b>	High cholesterol	TC/HDL > 5	+1.4
<b>8</b>	Smoking	Current smoker	+1.5
<b>9</b>	Obesity	BMI $\geq$ 30	+1.6
<b>10</b>	Hypertension	SBP > 140 mmHg or DBP > 90 mmHg	+1.6
<b>11</b>	Depression	At least 1 key symptom and 4 additional symptoms measured with the MINI	+2.1

LLDS Lifelines diet score, eGFR estimated glomerular filtration rate, LDL low-density lipoproteins, TC total cholesterol, HDL high-density lipoproteins, SQUASH Short Questionnaire to Assess Health-enhancing physical activity, BMI Body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, MINI Mini-International Neuropsychiatric Interview

**Table 2.** Differences in characteristics between participants with and without a parental family history \*

	<b>PFH+ (n=10,940)</b>	<b>PFH- (n=36,389)</b>	<b>Standardized mean differences</b>
<b>Age, mean(sd)</b>	52.95 (7.2)	43.19 (5.5)	<b>1.534</b>
<b>Sex, female</b>	6606 (60.4)	21566 (59.3)	0.023
<b>Education</b>			<b>0.271</b>
Elementary	231 (2.1)	303 (0.8)	0.106
Lower secondary	3557 (32.5)	8068 (22.2)	<b>0.234</b>
Upper secondary	3729 (34.1)	15395 (42.3)	0.170
Tertiary	3183 (29.1)	11902 (32.7)	0.078
unknown	240 (2.2)	721 (2.0)	
<b>Hypertension</b>	4637 (42.4)	10201 (28.0)	<b>0.304</b>
unknown	0	0	
<b>High cholesterol</b>	3250 (29.7)	6722 (18.5)	<b>0.265</b>
unknown	1 (0.0)	9 (0.0)	
<b>Diabetes</b>	446 (4.1)	734 (2.0)	0.121
unknown	1 (0.0)	9 (0.0)	
<b>Cardiovascular diseases</b>	247 (2.3)	290 (0.8)	0.119
unknown	0	0	
<b>Obesity</b>	1772 (16.2)	5429 (14.9)	0.037
<b>Overweight</b>	6557 (59.9)	19789 (54.4)	0.113
unknown	4 (0.0)	7 (0.0)	
<b>Renal dysfunction</b>			<b>0.334</b>
No dysfunction	6216 (56.8)	26269 (74.5)	<b>0.325</b>
Moderate	4232 (38.7)	8883 (25.2)	<b>0.311</b>
High	97 (0.9)	99 (0.3)	0.081
unknown	395 (3.6)	1138 (3.1)	
<b>Physical inactivity</b>	3545 (32.4)	18038 (49.6)	<b>0.375</b>
unknown	717 (6.6)	2712 (7.5)	
<b>Diet score, mean(sd)</b>	25.61 (5.91)	23.97 (5.81)	<b>0.278</b>
unknown	1079 (9.9)	4903 (13.5)	
<b>Alcohol consumption</b>			0.147
No drinking	2086 (19.1)	7904 (21.7)	0.066
Moderate	4771 (43.6)	15892 (43.7)	0.001
Excessive	3548 (32.4)	9947 (27.3)	0.112
unknown	535 (4.9)	2646 (7.3)	
<b>Smoking</b>			<b>0.333</b>
Never smoker	4048 (37.0)	17535 (48.2)	0.105
Ex-smoker	4677 (42.8)	9928 (27.3)	0.066
Current smoker	1823 (16.7)	6988 (19.2)	0.059
unknown	392 (3.6)	1938 (5.3)	
<b>Social activity</b>			0.026
Low	684 (6.3)	2181 (6.0)	0.011
Moderate	1944 (17.8)	6243 (17.2)	0.016
High	8180 (75.7)	27452 (75.4)	0.015
unknown	1049 (1.3)	513 (1.4)	
<b>Depression</b>	207 (1.9)	639 (1.8)	0.045
unknown	164 (1.5)	756 (2.1)	
<b>Stress, mean(sd)</b>	2.19 (2.24)	2.42 (2.33)	0.027
unknown	256 (1.5)	1066 (2.0)	

\*N (%) noted unless indicated otherwise

**Table 3.** Results of logistic, linear and multinomial regression models assessing the association between parental family history of dementia and each modifiable risk factor for dementia

	Without PSM OR (95%-CI)		with PSM OR (95%-CI)	
	Observed data (n=47,329)	Imputed data (n=89,869)	Model 1 <sup>1</sup> (n=53,218)	Model 2 (n=53,644)
<b>Hypertension</b>	<b>1.89 (1.81, 1.97)</b>	<b>1.82 (1.77, 1.88)</b>	<b>1.16 (1.12, 1.21)</b>	<b>1.19 (1.14, 1.24)</b> <sup>2a</sup>
<b>High cholesterol</b>	<b>1.87 (1.78, 1.96)</b>	<b>1.80 (1.74, 1.86)</b>	<b>1.16 (1.10, 1.22)</b>	<b>1.24 (1.18, 1.30)</b> <sup>2a</sup>
<b>Diabetes Mellitus</b>	<b>2.06 (1.83, 2.33)</b>	<b>2.07 (1.91, 2.26)</b>	<b>1.20 (1.07, 1.34)</b>	<b>1.26 (1.11, 1.42)</b> <sup>2a</sup>
<b>CVD</b>	<b>2.88 (2.42, 3.41)</b>	<b>2.93 (2.58, 3.33)</b>	<b>1.40 (1.17, 1.68)</b>	<b>1.49 (1.18, 1.88)</b> <sup>2a</sup>
<b>Obesity</b>	<b>1.10 (1.04, 1.17)</b>	<b>1.21 (1.17, 1.26)</b>	<b>1.14 (1.09, 1.20)</b>	<b>1.14 (1.08, 1.20)</b> <sup>2a</sup>
<b>Overweight</b>	<b>1.26 (1.20, 1.31)</b>	<b>1.31 (1.28, 1.35)</b>	<b>1.07 (1.02, 1.11)</b>	<b>1.10 (1.05, 1.17)</b> <sup>2a</sup>
<b>Renal dysfunction</b> (ref: no dysfunction)				
Moderate	<b>2.01 (1.92, 2.11)</b>	<b>1.79 (1.74, 1.84)</b>	1.02 (0.98, 1.06)	1.02 (0.97, 1.07) <sup>2a</sup>
High	<b>4.14 (3.13, 5.49)</b>	<b>4.10 (3.30, 5.09)</b>	1.32 (0.98, 1.79)	1.28 (0.96, 1.71) <sup>2a</sup>
<b>Physical inactivity</b>	<b>0.46 (0.44, 0.48)</b>	<b>0.55 (0.53, 0.56)</b>	<b>0.94 (0.93, 1.00)</b>	<b>0.93 (0.91, 0.97)</b> <sup>2b</sup>
<b>Diet (RC; 95%-CI)</b>	<b>1.63 (1.50, 1.76)</b>	<b>1.13 (1.05, 1.22)</b>	<b>0.27 (0.11, 0.43)</b>	-0.04 (-0.16, 0.09) <sup>2b</sup>
<b>Alcohol</b> (ref: no consumption)				
Low/Moderate	<b>1.14 (1.08, 1.21)</b>	1.02 (0.99, 1.06)	<b>0.87 (0.82, 0.92)</b>	<b>0.87 (0.83, 0.91)</b> <sup>2b</sup>
Excessive	<b>1.35 (1.27, 1.44)</b>	<b>1.18 (1.14, 1.23)</b>	<b>0.90 (0.84, 0.97)</b>	<b>0.93 (0.89, 0.98)</b> <sup>2b</sup>
<b>Smoking</b> (ref: never smoker)				
Ex-smoker	<b>2.04 (1.94, 2.14)</b>	<b>1.83 (1.77, 1.89)</b>	<b>1.19 (1.14, 1.24)</b>	<b>1.21 (1.16, 1.27)</b> <sup>2b</sup>
Current smoker	<b>1.13 (1.06, 1.20)</b>	<b>1.22 (1.18, 1.27)</b>	<b>1.16 (1.11, 1.22)</b>	<b>1.20 (1.14, 1.27)</b> <sup>2b</sup>
<b>Social activity</b> (ref: high activity)				
Moderate	1.05 (0.99, 1.11)	<b>0.89 (0.84, 0.95)</b>	0.97 (0.47, 0.90)	0.95 (0.87, 1.02) <sup>2b</sup>
Low	1.05 (0.96, 1.15)	<b>0.83 (0.78, 0.87)</b>	<b>0.88 (0.82, 0.95)</b>	<b>0.84 (0.78, 0.90)</b> <sup>2b</sup>
<b>Depression</b>	1.07 (0.92, 1.26)	<b>1.18 (1.07, 1.30)</b>	<b>1.24 (1.10, 1.40)</b>	<b>1.23 (1.08, 1.41)</b> <sup>2c</sup>
<b>Stress (RC; 95%-CI)</b>	<b>-0.41 (-0.46, -0.36)</b>	<b>-0.42 (-0.45, -0.39)</b>	0.03 (-0.02, 0.07)	0.03 (-0.13, 0.19) <sup>2c</sup>
<b>LIBRA score (RC; 95%-CI)</b>	n.a.	<b>0.49 (0.47, 0.51)</b>	<b>0.15 (0.11, 0.19)</b>	n.a.

\* Odds ratios with 95% confidence intervals are reported, unless stated otherwise; significant associations are shown in bold.

<sup>1</sup>: matched on age, sex and education level; <sup>2a</sup>: additionally matched on physical inactivity, diet, alcohol consumption, smoking, stress and depression; <sup>2b</sup>: additionally matched on stress, social activity, cardiovascular diseases, diabetes, high cholesterol, hypertension and renal dysfunction; <sup>2c</sup>: additionally matched on physical inactivity, diet, stress and social activity.

1  
2  
3 I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work  
4 (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for  
5 contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY  
6 licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government  
7 officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable,  
8 royalty-free basis to BMJ Publishing Group Ltd (“BMJ”) its licensees and where the relevant  
9 Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in BMJ Open  
10 and any other BMJ products and to exploit all rights, as set out in our [licence](#).

11  
12 The Submitting Author accepts and understands that any supply made under these terms is  
13 made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your  
14 employer or a postgraduate student of an affiliated institution which is paying any applicable  
15 article publishing charge (“APC”) for Open Access articles. Where the Submitting Author wishes  
16 to make the Work available on an Open Access basis (and intends to pay the relevant APC), the  
17 terms of reuse of such Open Access shall be governed by a Creative Commons licence – details  
18 of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our  
19 licence referred to above.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3 **SUPPLEMENTARY FILES**  
4

5 **Supplementary file 1:** Models for the association between a PFH of dementia and the modifiable risk factors for dementia  
6

7 **Supplementary file 2:** Flowchart of participant selection  
8

9 **Supplementary file 3:** Standardized mean differences to identify imbalances between participants with and without a PFH of dementia without (with and  
10 without data imputation) and with PSM  
11  
12

13 **Supplementary file 4:** Sensitivity analyses with covariate adjustment to examine the association between having a PFH of dementia and modifiable risk  
14 factors for dementia  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

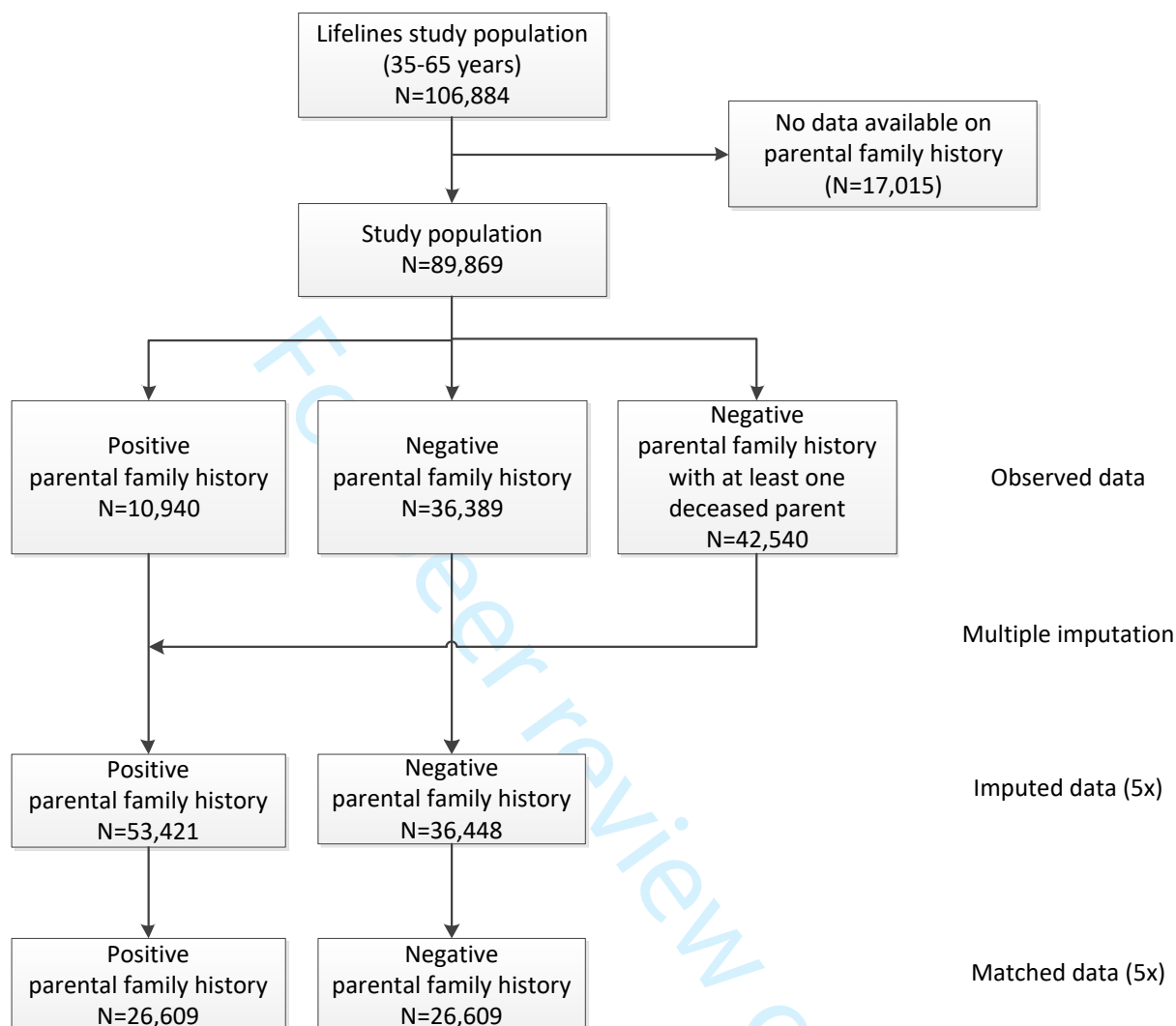
**Supplementary file 1.** Models for the association between parental family history of dementia and the modifiable risk factors for dementia

	<b>Without PSM</b>	<b>With PSM</b>	
<b>Outcome measures</b>	<b>Imputed data Determinant</b>	<b>Model 1 Demographic confounders *</b>	<b>Model 2 Other potential confounders, including model 1*</b>
Hypertension High Cholesterol Diabetes Mellitus CVD Obesity Overweight Renal dysfunction	Parental family history of dementia	Age Sex Education	Physical activity Diet Alcohol Smoking Stress Depression
Physical activity Diet Alcohol Smoking Social activity	Parental family history of dementia	Age Sex Education	Stress Social activity CVD Diabetes Cholesterol Hypertension Renal dysfunction
Depression Stress	Parental family history of dementia	Age Sex Education	Physical activity Diet Stress Social activity
LIBRA score	Parental family history of dementia	Age Sex Education	not applicable

*\*Adjustment through matching on propensity score which is based on these potential confounders*

*Abbreviations: CVD Cardiovascular diseases, LIBRA Lifestyle for Brain Health*

Supplementary file 2. Flowchart of participant selection





**Supplementary file 3.** Standardized mean differences to identify imbalances between participants with and without a parental family history of dementia without (with and without data imputation) and with PSM\*

	Without PSM (SMD)		With PSM (SMD)	
	Observed data (n=47,329)	Imputed data (n=89,869)	Model 1 <sup>1</sup> (n=53,218)	Model 2 <sup>2#</sup> (n=53,644)
<b>Age</b>	<b>1.534</b>	<b>1.209</b>	0.133	0.170
<b>Sex, female</b>	0.023	0.005	0.091	0.017
<b>Education</b>				
Elementary	0.106	0.123	0.048	0.062
Lower secondary	<b>0.234</b>	<b>0.274</b>	0.035	0.020
Upper secondary	0.170	0.141	-0.172	-0.035
Tertiary	0.078	0.154	0.133	-0.005
<b>Hypertension</b>	<b>0.304</b>	<b>0.286</b>	0.066	0.041
<b>High cholesterol</b>	<b>0.265</b>	<b>0.248</b>	<b>0.231</b>	0.038
<b>Diabetes</b>	0.121	0.125	-0.025	0.018
<b>Cardiovascular diseases</b>	0.119	0.122	<b>0.261</b>	0.007
<b>Obesity</b>	0.037	0.070	0.052	0.055
<b>Overweight</b>	0.113	0.134	0.102	0.103
<b>Renal dysfunction</b>				
No dysfunction	<b>0.325</b>	<b>0.278</b>	<b>-0.206</b>	<b>-0.207</b>
Moderate	<b>0.311</b>	<b>0.264</b>	0.193	0.027
High	0.081	0.087	0.078	0.004
<b>Physical inactivity</b>	<b>0.375</b>	<b>0.300</b>	<b>0.278</b>	0.012
<b>Diet score</b>	<b>0.278</b>	0.194	0.160	0.051
<b>Alcohol consumption</b>				
No drinking	0.066	<0.001	-0.024	-0.039
Moderate	0.001	0.010	-0.036	-0.039
Excessive	0.112	0.072	0.059	-0.001
<b>Smoking</b>				
Never smoker	0.105	<b>0.228</b>	-0.193	-0.167
Ex-smoker	0.066	<b>0.259</b>	<b>0.218</b>	0.039
Current smoker	0.059	0.024	-0.021	0.008
<b>Social activity</b>				
Low (<4)	0.011	0.044	0.026	0.021
Moderate (4-7)	0.016	0.023	0.018	-0.036
High (≥8)	0.015	0.046	-0.031	-0.032
<b>Depression</b>	0.045	0.023	0.018	0.024
<b>Stress</b>	0.027	0.183	-0.162	0.028

\* SMDs higher than 0.2 are shown in bold

# The highest SMDs are shown for model 2

1 : matched on age, sex and education level

2: additionally matched on physical inactivity, diet, alcohol consumption, smoking, stress, depression, social activity, cardiovascular diseases, diabetes, high cholesterol, hypertension and renal dysfunction, depending on outcome measure (see **Supplementary file 1**)

**Supplementary file 4.** Sensitivity analyses with covariate adjustment to examine the association between having a PFH of dementia and modifiable risk factors for dementia

	OR (95%-CI)		
	Imputed data (n=89,869)		
	Crude model	Adjusted model 1 <sup>1</sup>	Adjusted model 2 <sup>2</sup>
<b>Hypertension</b>	<b>1.82 (1.77, 1.88)</b>	<b>1.12 (1.09, 1.16)</b>	<b>1.12 (1.08, 1.16)</b>
<b>High cholesterol</b>	<b>1.80 (1.74, 1.86)</b>	<b>1.20 (1.55, 1.24)</b>	<b>1.17 (1.13, 1.22)</b>
<b>Diabetes Mellitus</b>	<b>2.07 (1.91, 2.26)</b>	<b>1.12 (1.02, 1.24)</b>	1.09 (0.99, 1.21)
<b>CVD</b>	<b>2.93 (2.58, 3.33)</b>	<b>1.34 (1.16, 1.56)</b>	<b>1.29 (1.12, 1.50)</b>
<b>Obesity</b>	<b>1.21 (1.17, 1.26)</b>	<b>1.13 (1.08, 1.18)</b>	<b>1.12 (1.07, 1.17)</b>
<b>Overweight</b>	<b>1.31 (1.28, 1.35)</b>	<b>1.09 (1.06, 1.13)</b>	<b>1.08 (1.05, 1.12)</b>
<b>Renal dysfunction</b> (ref: no dysfunction)			
Moderate	<b>1.79 (1.74, 1.84)</b>	<b>0.92 (0.89, 0.95)</b>	<b>0.93 (0.89, 0.96)</b>
High	<b>4.10 (3.30, 5.09)</b>	0.95 (0.74, 1.20)	0.96 (0.75, 1.24)
<b>Physical inactivity</b>	<b>0.55 (0.53, 0.56)</b>	1.02 (0.99, 1.06)	0.99 (0.95, 1.02)
<b>Diet (RC; 95%-CI)</b>	<b>1.13 (1.05, 1.22)</b>	-0.04 (-0.12, 0.05)	-0.02 (-0.11, 0.07)
<b>Alcohol</b> (ref: no consumption)			
Low/Moderate	1.02 (0.99, 1.06)	0.90 (0.86, 0.94)	<b>0.91 (0.88, 0.95)</b>
Excessive	<b>1.18 (1.14, 1.23)</b>	0.98 (0.93, 1.03)	0.99 (0.94, 1.04)
<b>Smoking</b> (ref: never smoker)			
Ex-smoker	<b>1.83 (1.77, 1.89)</b>	<b>1.16 (1.12, 1.20)</b>	<b>1.15 (1.11, 1.19)</b>
Current smoker	<b>1.22 (1.18, 1.27)</b>	<b>1.21 (1.16, 1.26)</b>	<b>1.18 (1.14, 1.24)</b>
<b>Social activity</b> (ref: high activity)			
Moderate	<b>0.89 (0.84, 0.95)</b>	0.98 (0.91, 1.05)	0.98 (0.91, 1.05)
Low	<b>0.83 (0.78, 0.87)</b>	0.88 (0.82, 0.94)	<b>0.88 (0.83, 0.94)</b>
<b>Depression</b>	<b>1.18 (1.07, 1.30)</b>	<b>1.25 (1.12, 1.40)</b>	<b>1.23 (1.10, 1.38)</b>
<b>Stress (RC; 95%-CI)</b>	<b>-0.42 (-0.45, -0.39)</b>	<b>0.09 (0.05, 0.12)</b>	<b>0.08 (0.04, 0.11)</b>

\* Odds ratios with 95% confidence intervals are reported, unless stated otherwise; significant associations are shown in bold

1: adjusted for age, sex and education level

2: additionally adjusted for on physical inactivity, diet, alcohol consumption, smoking, stress, depression, social activity, cardiovascular diseases, diabetes, high cholesterol, hypertension and renal dysfunction, depending on outcome measure (see **Supplementary file 1**)

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-12
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	7-8
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	12
		(b) Describe any methods used to examine subgroups and interactions	12
		(c) Explain how missing data were addressed	12
		(d) If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(e) Describe any sensitivity analyses	12
<b>Results</b>			
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
		(b) Give reasons for non-participation at each stage	12
		(c) Consider use of a flow diagram	30
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	13
Outcome data	15*	Report numbers of outcome events or summary measures	13
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	13

		(b) Report category boundaries when continuous variables were categorized	8-10
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
<b>Other information</b>			
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	17

\*Give information separately for exposed and unexposed groups.

**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](http://www.strobe-statement.org).