BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-049918
Article Type:	Original research
Date Submitted by the Author:	06-Feb-2021
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Keywords:	Dementia < NEUROLOGY, PREVENTIVE MEDICINE, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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TITLE

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

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ABSTRACT

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

DESIGN: A cross-sectional study

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

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

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

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

- No other study investigating the association between a parental family history of dementia and modifiable risk factors for dementia used a wide range of the currently known modifiable risk factors for dementia.
- Our large study sample provided sufficient power to detect relevant associations independent of confounding factors.
- We used sophisticated statistical techniques to prevent selection bias and calculated odds ratios and regression coefficients with 95%-confidence intervals.
- Parental family history of dementia was based on self-reported questionnaires, which could have led to misclassification.
- Results were based on cross-sectional data in which previous health behaviours were not taken into account.

KEY WORDS:

- Dementia Risk Reduction
- Family History
- Modifiable Risk Factors
- Multiple Imputation
- Propensity Score Matching
- Middle Aged

INTRODUCTION

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

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

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

to 15-25% for individuals with a family history of dementia (17). This increased risk can be explained by both genetic and lifestyle factors (18–21), which are passed on from parents to offspring (20,22). The APOE ε4 allele is one of the genes to be consistently shown to increase the risk for dementia (23–25). Individuals with a PFH of dementia are more often carrier of this allele compared to individuals without a PFH of dementia (21,26–29). Nevertheless, several studies have shown that individuals with a PFH of dementia have an increased risk, independent of their genetic risk (18,27,28).

Although the role of APOE genotype on dementia risk has been well studied, the risk factor of a PFH remains rarely studied. Only a few studies investigated the association between family history of dementia and modifiable risk factors for dementia (28,30,31). They found that family history of dementia was associated with both higher diastolic (DBP) as systolic blood pressure (SBP) and depression (28,31), while it was not associated with Body Mass Index (BMI), serum lipid profiles (e.g. Total cholesterol, HDL, LDL), alcohol consumption and smoking behaviour (30). However, previous studies did not take all currently known modifiable risk factors for dementia into account and included a relatively small sample of participants. Moreover, these findings might be a result of confounding bias. Propensity score matching (PSM) is a sophisticated analysis technique that can reduce this bias by assembling a matched sample of people with and without a PFH of dementia, in which confounding factors are balanced between groups (32). By matching, a greater proportion of the systematic differences in characteristics of individuals with and without a PFH is eliminated compared to the commonly used regression adjustment (32).

Finding differences in modifiable risk factors for dementia among middle-aged individuals with and without a PFH of dementia, might help to identify individuals with an increased risk for dementia and subsequently offer them tailor-made interventions for DRR. Therefore, the aim of this study was to investigate the association between a PFH of dementia and modifiable risk factors for dementia among middle-aged individuals from the general population.

METHOD

Study population

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

Measurement of independent and dependent variables

Independent variable

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

Dependent variables

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

HbA1C, total cholesterol, HDL and serum creatinine) and questionnaires, including questions on demographic characteristics, health behaviours, (parental) health and medication use. Participants brought their medication to the research site, which was subsequently reported and categorized using the Anatomical Therapeutic Chemical (ATC) codes (35).

Hypertension

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

High cholesterol

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

Renal dysfunction

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

Obesity and overweight

BMI was calculated using measured body weight (in kg) and length (in cm) (BMI = weight/length^2). Subsequently, the presence or absence of overweight (BMI≥ 25.0) and obesity (BMI≥ 30.0) was determined (40,41).

Diabetes

Diabetes Mellitus was defined as: (i) glucose (fasting capillary blood) of 7.0 mmol/l or higher, or (ii) HbA1C levels higher than 53 mmol/mol, or (iii) using blood glucose lowering medication (ATC code A10 (drugs used in diabetes)) (35,42). In case glucose and HbA1c levels were missing and the participant did not use any glucose lowering medication, the presence of diabetes mellitus was based on the answer of the self-reported questionnaire (Do you have diabetes mellitus?).

Cardiovascular diseases

Participants reported whether they have suffered or still suffer from one of the following cardiovascular diseases (CVDs): myocardial infarction, stroke or peripheral arterial diseases. If at least one of these CVDs was indicated with 'yes' in the self-reported questionnaire, participants were known with CVDs.

Healthy diet

A quantitative Food Frequency Questionnaire (FFQ) was used to assess dietary intake over the previous month (43,44). The Mediterranean diet was associated with slower cognitive decline (45–47), however not all food groups of the Mediterranean diet were measured within the Lifelines population on baseline. Therefore, the Lifelines diet score (LLDS) was used to determine adherence to a healthy diet, which includes most food groups of the Mediterranean diet. The LLDS was based on the consumption of nine positive food groups (vegetables, fruit, whole grain products, legumes and nuts, fish, oils and soft margarines, unsweetened dairy, coffee and tea) and three negative food groups (red and processed meat, butter and hard margarines and sugar-sweetened beverages). The consumption of each food group was divided into quintiles to score an individual's consumption compared to the total Lifelines population. For each food group, the quintiles ranged from 0 to 4 points, using 4 points for the highest quintile of consumption for positive food groups and the lowest quintile for the negative food groups. The total LLDS ranges from 0 to 48, with a higher score indicating a healthier diet (48).

Alcohol consumption

Alcohol consumption is categorized into: (i) no alcohol consumption (0 alcohol units in the past month), (ii) low/moderate alcohol consumption (average ≤1 alcohol unit per day and no binge drinking) and (iii) excessive alcohol consumption (average >1 alcohol unit per day and/or binge drinking, which is defined as more than three alcohol units per occasion for females and more than four alcohol units per occasion for males).

Physical inactivity

Physical inactivity was measured with the Short Questionnaire to Assess Health enhancing physical activity (SQUASH) (49). The results are converted to minutes per week spent in physical activity of light intensity and physical activity of moderate to vigorous intensity (MVPA), based on Metabolic Equivalent Tasks (METs) derived from the Ainsworth's compendium of physical activity (50). Physical inactivity is defined as less than 150 minutes per week MVPA (51).

Smoking

Smoking behaviour was assessed with the self-reported questionnaire, including the following two questions: (i) 'Do you smoke now, or have you smoked in the past month?' and (ii) 'Have you ever smoked for a full year?'. Subsequently, smoking behaviour was categorized into: (i) non-smoker, (ii) ex-smoker and (iii) current smoker. Current smokers are defined as people who reported smoking in the past month. Ex-smokers reported smoking for at least one year, but did not smoke in the past month.

Social activity

Social activity was measured with the following question 'On average how many people did you have contact with in the past two weeks?'. Subsequently, social activity is categorized into low (contacts<4), moderate (contacts: 4-7) and high (contacts≥8) (52).

Depression

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

Stress

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

LIBRA score

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

INSERT TABLE 1 ABOUT HERE

Covariates

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

was based on the question 'What is your highest completed level of education?'. Highest level of education was categorized into: (i) elementary (no education or primary education), (ii) lower secondary (lower or preparatory vocational education or lower general secondary education), (iii) upper secondary (intermediate vocational education) and (iv) tertiary (higher general secondary education or pre-university secondary education, higher vocational education and university) (57).

Statistical methods

The baseline characteristics of the total study population were described and differences between participants with and without a PFH of dementia were calculated using Standardized Mean Differences (SMD). Five imputed datasets were generated to replace missing values, using Multiple Imputation using Chained Equations (MICE). In each imputed dataset, we assessed the association between PFH of dementia and each modifiable risk factor in two steps. First, to eliminate selection bias, PSM was used to match each individual with a PFH of dementia to an individual without a PFH of dementia (ratio 1:1) (caliper=0.2), based on the standard potential confounders age, sex and educational level (model 1) and other potential confounders (model 2) (see **Supplementary file 1**) (32). After PSM, we checked if the balance in the covariates was achieved (SMD < 0.2). Second, logistic (dichotomous outcomes), linear (continuous outcomes) and multinomial (categorical outcomes) regression analyses were used to examine the association between a PFH of dementia and each modifiable risk factor. These analyses were conducted for each imputed matched dataset to obtain the estimates, which were pooled using Rubin's rules (58). Since the LIBRA score is a composite score and includes all individual modifiable risk factors for dementia, this analysis is based on model 1 (only matched on sex, age and educational level). Results are presented as odds ratios (OR) or regression coefficients (RC) with 95% confidence intervals (95%-CI). Sensitivity analyses were conducted in which covariate adjustment is used instead of PSM. R statistical software environment version 1.3.383 was used (59). In particular, we used the 'MatchThem', 'tableone' and 'cobalt' package in R.

Patient and Public Involvement

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

RESULTS

Baseline characteristics

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

INSERT TABLE 2 ABOUT HERE

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

The results of the logistic, linear and multinomial regression analyses on the association between a PFH of dementia and modifiable risk factors for dementia are presented in **Table 3**. Individuals with a PFH of dementia had more often hypertension (OR=1.19, 95%-CI: 1.14,1.24), high cholesterol (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: 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 depressive symptoms (OR=1.23, 95%-CI: 1.08,1.41) compared to their peers without a PFH of dementia. Further, individuals with a PFH of dementia were more often current-smokers (OR=1.20,

95%-CI: 1.14,1.27) and ex-smokers (OR=1.21, 95%-CI:1.16,1.27), but were less often low/moderate alcohol consumers (OR=0.87, 95%-CI: 0.83,0.91), excessive alcohol consumers (OR=0.93, 95%-CI:0.89,0.98), physically inactive (OR=0.93, 95%-CI: 0.91,0.97) and had less often a low social activity (OR=0.84, 95%-CI:0.78,0.90). Finally, individuals with a PFH of dementia also had an overall higher risk to develop dementia (LIBRA score RC=0.15, 95%-CI: 0.11,0.19) compared to their peers without a PFH of dementia.

INSERT TABLE 3 ABOUT HERE

DISCUSSION

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

In general, most findings are in line with our expectations, except that individuals with a PFH of dementia were less often physically and socially inactive, and less often low/moderate alcohol consumer and excessive alcohol consumer than no alcohol consumer. Since individuals with a PFH of dementia had more often cardiovascular risk factors, it might be that they did not consume alcohol due to health concerns or use of medication (60). Furthermore, in our study, PFH of dementia was determined by the first follow-up questionnaire. In case dementia was diagnosed before baseline assessment, individuals with a PFH of dementia could already have adjusted their lifestyle. Therefore,

these findings may reflect a reverse causality from having a parent with dementia to more physical and social activity. No data was available on the date of onset of dementia.

To our knowledge, this is the first study that investigated the association between having a PFH of dementia and currently known modifiable risk factors for dementia among middle-aged individuals using a large sample size and PSM. Only few studies have been conducted to test the differences in several modifiable risk factors of dementia between individuals with and without a family history of dementia (28,30,31). However, it is likely that these studies were hampered by small sample sizes of the study population. For instance, Luckhoff et al. (2016) did not find differences in BMI (objectively measured), total cholesterol, HDL, LDL, alcohol intake and smoking behaviour between middle-aged individuals with (n=75) and without (n=505) a self-reported family history of dementia ($p>0.05$)(30). Exel et al. (2009) found that middle-aged individuals with an objectively measured PFH of dementia (n=206) had more often hypertension and caregiver burden stress compared to their peers (n=200) ($p<0.05$)(28). However, no differences were found in high cholesterol, glucose levels and lifestyle-related risk factors such as smoking and physical activity ($p>0.05$) (61). La Rue et al. (2008) also showed that individuals with a PFH of dementia (n=623) had higher cholesterol levels, higher DBP and SBP and higher depression rates compared to individuals without a PFH of dementia (n=157) ($p<0.01$)(31). Although differences with the current study could be explained by the use of different statistical methods, sensitivity analyses in which covariate adjustment is used showed similar results when using PSM (see **Supplementary file 4**). A major advantage of PSM is that the balance in potential confounders can be inspected between individuals with and without a PFH of dementia before conducting the analyses. After PSM most potential confounders were balanced between participants with and without a PFH of dementia (SMD<0.2), except for the variable renal dysfunction (SMD=-0.207). Therefore, it is possible that the associations between having a PFH of dementia and lifestyle-related risk factors for dementia are slightly biased.

Strengths and limitations

Our large study sample provided sufficient power to detect relevant associations independent of confounding factors. In addition, no other study investigating the association between a PFH of dementia and modifiable risk factors for dementia used a wide range of the currently known modifiable risk factors for dementia. A large part of these modifiable risk factors (e.g., hypertension, high cholesterol, diabetes mellitus, obesity, overweight, renal dysfunction) were objectively measured through physical examination and fasting blood samples. Further, we used sophisticated statistical techniques to prevent selection bias. The potential confounders used in PSM were carefully chosen per outcome measure. Finally, in contrast to previous studies, we reported adjusted ORs and RCs with 95%-confidence intervals instead of p-values, which gives more information on the magnitude and direction of the association studied.

This study also had certain limitations. One drawback is that PFH of dementia was based on self-reported questionnaires and could have led to misclassification. Nonetheless, it is likely that the misclassification was non-differential and would have led to an underestimation of our results. Second, no data was available on the APOE genotype, which may be an important effect modifier (19). Previous literature showed that a healthy lifestyle might especially be beneficial for the cognition of APOE e4 carriers (19,62). Since individuals with a PFH of dementia are more often carrier of the APOE e4 allele, a healthy lifestyle might also be especially beneficial for individuals with a PFH of dementia. Therefore, absence of APOE genotype data could have led to an underestimation of the results for APOE e4 carriers with a PFH of dementia. Third, the results were based on cross-sectional data in which previous health behaviours were not taken into account. It might be possible that individuals with a PFH of dementia adopted a healthier lifestyle after their parent got diagnosed with dementia. In other words, our findings may reflect a reverse causality from PFH of dementia to health behaviour, indicating that our estimates may be underestimated. Finally, we imputed PFH of dementia of all participants without a PFH of dementia with at least one deceased parent. We did not distinguish in the age of death of deceased parents, since the incidence of dementia increases with age and the average age of onset of dementia differs between types of dementia (63). However, relatively young parents are less likely to develop dementia compared to older parents. Nevertheless, sensitivity

analyses in which individuals with deceased fathers who survived to at least the age of 70 or mothers who survived to at least the age of 75 were assigned to the group without having a PFH of dementia instead of PFH being imputed, showed similar results (31).

These findings support a high-risk prevention strategy for dementia by identifying the individuals with a PFH of dementia, screening them for modifiable risk factors for dementia, and implementing multi-domain interventions targeting these modifiable risk factors. Future studies should first explore the knowledge, beliefs and attitudes towards dementia (risk reduction) among middle-aged individuals with a PFH of dementia, and whether they are willing to assess their protective and risk factors for dementia and adopt a healthier lifestyle. Next, the effectiveness of these multi-domain interventions in changing health behaviour for DRR among middle-aged individuals with a PFH of dementia should be investigated.

CONCLUSION

We found that a PFH of dementia was associated with several modifiable risk factors for dementia independent of age, sex and educational level, including hypertension, high cholesterol, diabetes mellitus, CVDs, obesity, overweight and depression. This suggests that middle-aged individuals with a PFH of dementia are a group at risk for dementia and might benefit from DRR. Further research should examine knowledge, beliefs and attitudes towards DRR among middle-aged individuals with a PFH of dementia, and their willingness to address and tackle their personal risk factors for dementia in order to prevent of postpone dementia.

Acknowledgements: The Lifelines Biobank initiative has been made possible by subsidy from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University Medical Centre Groningen (UMCG the Netherlands), University Groningen and the Northern Provinces of the Netherlands.

Author contributions: JV, AAH, SR and NS were involved in the design of the study. JV conducted the analysis with support of AAH. JV wrote the manuscript and AAH, SR and NS revised the manuscript. All authors read and approved the final manuscript.

Funding: None declared.

Competing Interests: The authors declare that no conflict of interest exists.

Patient consent: Not applicable.

Data sharing statement: Lifelines is a facility that is open for all researchers (www.lifelines.net).

REFERENCES

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

Alzheimer Res. 2019;16(14):1254–68.

11. Schiepers OJG, Köhler S, Deckers K, Irving K, O'Donnell CA, van den Akker M, et al. Lifestyle for Brain Health (LIBRA): a new model for dementia prevention. Int J Geriatr Psychiatry. 2018 Feb 28;33:167–75.

12. Vos SJB, van Boxtel MPJ, Schiepers OJG, Deckers K, de Vugt M, Carri?re I, et al. Modifiable Risk Factors for Prevention of Dementia in Midlife, Late Life and the Oldest-Old: Validation of the LIBRA Index. J Alzheimer's Dis. 2017 May 11;58(2):537–47.

13. Deckers K, Köhler S, van Boxtel M, Verhey F, Brayne C, Fleming J, et al. Lack of associations between modifiable risk factors and dementia in the very old: findings from the Cambridge City over-75s cohort study. Aging Ment Health. 2017 Feb;1–7.

14. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015 Jun;385(9984):2255–63.

15. van Charante EPM, Richard E, Eurelings LS, van Dalen J-W, Ligthart SA, van Bussel EF, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. Lancet. 2016;388(10046):797–805.

16. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol. 2017 May 1;16(5):377–89.

17. Goldman JS, Hahn SE, Catania JW, LaRusse-Eckert S, Butson MB, Rumbaugh M, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. 2011 Jun;13(6):597–605.

18. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hyppönen E, Kuzma E, et al. Association of lifestyle and genetic risk with incidence of dementia. JAMA. 2019 Aug 6;322(5):430.

19. Kivipelto M, Rovio S, Ngandu T, Kåreholt I, Eskelinen M, Winblad B, et al. Apolipoprotein E

epsilon4 magnifies lifestyle risks for dementia: a population-based study. J Cell Mol Med. 2008 Dec;12(6B):2762–71.

20. Borenstein AR, Copenhaver CI, Mortimer JA. Early-Life Risk Factors for Alzheimer Disease. Alzheimer Dis Assoc Disord. 2006 Jan;20(1):63–72.

21. Donix M, Small GW, Bookheimer SY. Family History and APOE-4 Genetic Risk in Alzheimer's Disease. Neuropsychol Rev. 2012 Sep 23;22(3):298–309.

22. Muñoz M, Pong-Wong R, Canela-Xandri O, Rawlik K, Haley CS, Tenesa A. Evaluating the contribution of genetics and familial shared environment to common disease using the UK Biobank. Nat Genet. 2016 Jul 18;48(9):980–3.

23. Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet. 1994 Jun;7(2):180–4.

24. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease. JAMA. 1997 Oct 22;278(16):1349.

25. Choudhury P, Ramanan VK, Boeve BF. APOE ε 4 Allele Testing and Risk of Alzheimer Disease. JAMA. 2021 Jan 14;

26. Sager MA, Hermann B, La Rue A. Middle-aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer's Prevention. J Geriatr Psychiatry Neurol. 2005 Dec 29;18(4):245–9.

27. Scarabino D, Gambina G, Broggio E, Pelliccia F, Corbo RM. Influence of family history of dementia in the development and progression of late-onset Alzheimer's disease. Am J Med Genet Part B Neuropsychiatr Genet. 2016 Mar;171(2):250–6.

28. van Exel E, Eikelenboom P, Comijs H, Frölich M, Smit JH, Stek ML, et al. Vascular factors and markers of inflammation in offspring with a parental history of late-onset Alzheimer disease. Arch Gen Psychiatry. 2009 Nov 1;66(11):1263–70.

29. Johnson SC, Koscik RL, Jonaitis EM, Clark LR, Mueller KD, Berman SE, et al. The Wisconsin Registry for Alzheimer's Prevention: A review of findings and current directions.

Alzheimer's Dement (Amsterdam, Netherlands). 2018;10:130–42.

30. Lückhoff HK, Kidd M, van Rensburg SJ, van Velden DP, Kotze MJ. Apolipoprotein E genotyping and questionnaire-based assessment of lifestyle risk factors in dyslipidemic patients with a family history of Alzheimer's disease: test development for clinical application. Metab Brain Dis. 2016 Feb 20;31(1):213–24.

31. Rue A La, Hermann B, Jones JE, Johnson S, Asthana S, Sager MA. Effect of parental family history of Alzheimer's disease on serial position profiles. Alzheimer's Dement. 2008 Jul 1;4(4):285–90.

32. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011 May;46(3):399–424.

33. Scholtens S, Smidt N, Swertz MA, Bakker SJL, Dotinga A, Vonk JM, et al. Cohort Profile: LifeLines, a three-generation cohort study and biobank. Int J Epidemiol. 2015 Aug;44(4):1172–80.

34. Stolk RP, Rosmalen JGM, Postma DS, de Boer RA, Navis G, Slaets JPJ, et al. Universal risk factors for multifactorial diseases. Eur J Epidemiol. 2008 Jan 13;23(1):67–74.

35. World Health Organization. ATC/DDD Index 2020. Oslo, Norway; 2020.

36. van Dis SJ, Kromhout D, Geleijnse JM, Boer JMA, Verschuren WMM. Evaluation of cardiovascular risk predicted by different score equations: the Netherlands as an example. Eur J Cardiovasc Prev Rehabil. 2010;17:244–9.

37. De Grauw W, De Leest K, Schenk P, Scherpbier-De Haan N, Tjin-A-Ton J, Tuut M, et al. NHG-Standaard Chronische Nierschade. TPO - Prakt. 2018;13(5):26–9.

38. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.

39. Levey AS, Inker LA, Coresh J. GFR estimation: From physiology to public health. Am J Kidney Dis. 2014;63(5):820–34.

40. Centers for Disease Control and Prevention (CDC). Body Mass Index (BMI) [Internet]. [cited 2020 Sep 9]. Available from: https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html

41. World Health Organization (WHO). Body mass index (BMI) [Internet]. World Health Organization; [cited 2019 May 6]. Available from: http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi

42. Rutten G, De Grauw W, Nijpels G, Houweling S, Van de Laar F, Bilo H, et al. NHG-Standaard Diabetes mellitus type 2. 2013.

43. Molag ML, de Vries JHM, Duif N, Ocké MC, Dagnelie PC, Goldbohm RA, et al. Selecting informative food items for compiling food-frequency questionnaires: comparison of procedures. Br J Nutr. 2010 Aug 8;104(03):446–56.

44. Siebelink E, Geelen A, de Vries JHM. Self-reported energy intake by FFQ compared with actual energy intake to maintain body weight in 516 adults. Br J Nutr. 2011 Jul 22;106(02):274–81.

45. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimer's Dement. 2015 Sep;11(9):1007–14.

46. Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA, et al. MIND diet slows cognitive decline with aging. Alzheimer's Dement. 2015 Sep;11(9):1015–22.

47. Abbatecola AM, Russo M, Barbieri M. Dietary patterns and cognition in older persons. Curr Opin Clin Nutr Metab Care. 2018 Jan;21(1):10–3.

48. Vinke PC, Corpeleijn E, Dekker LH, Jacobs DR, Navis G, Kromhout D. Development of the food-based Lifelines Diet Score (LLDS) and its application in 129,369 Lifelines participants. Eur J Clin Nutr. 2018;72(8):1111–9.

49. Wendel-Vos G. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003 Dec;56(12):1163–9.

50. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011 Aug;43(8):1575–81.

51. Weggemans RM, Backx FJG, Borghouts L, Chinapaw M, Hopman MTE, Koster A, et al. The 2017 Dutch Physical Activity Guidelines. Int J Behav Nutr Phys Act. 2018 Jun 25;15(1):58.

52. Kuiper JS, Zuidersma M, Oude Voshaar RC, Zuidema SU, van den Heuvel ER, Stolk RP, et al. Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev. 2015 Jul 1;22:39–57.

53. Sheehan D V, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 2:22–33; quiz 34–57.

54. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). Fifth edit. Washington; 2013.

55. Rosmalen JGM, Bos EH, de Jonge P. Validation of the Long-term Difficulties Inventory (LDI) and the List of Threatening Experiences (LTE) as measures of stress in epidemiological population-based cohort studies. Psychol Med. 2012 Dec;42(12):2599–608.

56. Motrico E, Moreno-Küstner B, de Dios Luna J, Torres-González F, King M, Nazareth I, et al. Psychometric properties of the List of Threatening Experiences—LTE and its association with psychosocial factors and mental disorders according to different scoring methods. J Affect Disord. 2013;150(3):931–40.

57. Klijs B, Kibele EUB, Ellwardt L, Zuidersma M, Stolk RP, Wittek RPM, et al. Neighborhood income and major depressive disorder in a large Dutch population: results from the LifeLines Cohort study. BMC Public Health. 2016 Aug 11;16(1):773.

58. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011 Feb 20;30(4):377–99.

59. R Core team. R: A language and environment for statistical computing. Vienna, Austria; 2020.

60. Green CA, Polen MR. The health and health behaviors of people who do not drink alcohol. Am J Prev Med. 2001 Nov 1;21(4):298–305.

61. van Exel E, Eikelenboom P, Comijs H, Frölich M, Smit JH, Stek ML, et al. Vascular Factors and Markers of Inflammation in Offspring With a Parental History of Late-Onset Alzheimer Disease. Arch Gen Psychiatry. 2009 Nov 1;66(11):1263.

62. Dekhtyar S, Marseglia A, Xu W, Darin-Mattsson A, Wang HX, Fratiglioni L. Genetic risk of

dementia mitigated by cognitive reserve: A cohort study. Ann Neurol. 2019 Jul 1;86(1):68–78.

63. Ott A, Breteler MMB, Van Harskamp F, Stijnen T, Hofman A. Incidence and Risk of Dementia The Rotterdam Study. 1998;147(6).

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

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

	PFH+ (n=10,940)	PFH- (n=36,389)	Standardized mean differences
Age, mean(sd)	52.95 (7.2)	43.19 (5.5)	**1.534**
Sex, female	6606 (60.4)	21566 (59.3)	0.023
Education			**0.271**
Elementary	231 (2.1)	303 (0.8)	0.106
Lower secondary	3557 (32.5)	8068 (22.2)	**0.234**
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)	
Hypertension	4637 (42.4)	10201 (28.0)	**0.304**
unknown	0	0	
High cholesterol	3250 (29.7)	6722 (18.5)	**0.265**
unknown	1 (0.0)	9 (0.0)	
Diabetes	446 (4.1)	734 (2.0)	0.121
unknown	1 (0.0)	9 (0.0)	
Cardiovascular diseases	247 (2.3)	290 (0.8)	0.119
unknown	0	0	
Obesity	1772 (16.2)	5429 (14.9)	0.037
Overweight	6557 (59.9)	19789 (54.4)	0.113
unknown	4 (0.0)	7 (0.0)	
Renal dysfunction			**0.334**
No dysfunction	6216 (56.8)	26269 (74.5)	**0.325**
Moderate	4232 (38.7)	8883 (25.2)	**0.311**
High	97 (0.9)	99 (0.3)	0.081
unknown	395 (3.6)	1138 (3.1)	
Physical inactivity	3545 (32.4)	18038 (49.6)	**0.375**
unknown	717 (6.6)	2712 (7.5)	
Diet score, mean(sd)	25.61 (5.91)	23.97 (5.81)	**0.278**
unknown	1079 (9.9)	4903 (13.5)	
Alcohol consumption			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)	
Smoking			**0.333**
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)	
Social activity			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)	
Depression	207 (1.9)	639 (1.8)	0.045
unknown	164 (1.5)	756 (2.1)	
Stress, mean(sd)	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[1] (n=53,218)**	**Model 2 (n=53,644)**
Hypertension	**1.89 (1.81, 1.97)**	**1.82 (1.77, 1.88)**	**1.16 (1.12, 1.21)**	**1.19 (1.14, 1.24)** [2a]
High cholesterol	**1.87 (1.78, 1.96)**	**1.80 (1.74, 1.86)**	**1.16 (1.10, 1.22)**	**1.24 (1.18, 1.30)** [2a]
Diabetes Mellitus	**2.06 (1.83, 2.33)**	**2.07 (1.91, 2.26)**	**1.20 (1.07, 1.34)**	**1.26 (1.11, 1.42)** [2a]
CVD	**2.88 (2.42, 3.41)**	**2.93 (2.58, 3.33)**	**1.40 (1.17, 1.68)**	**1.49 (1.18, 1.88)** [2a]
Obesity	**1.10 (1.04, 1.17)**	**1.21 (1.17, 1.26)**	**1.14 (1.09, 1.20)**	**1.14 (1.08, 1.20)** [2a]
Overweight	**1.26 (1.20, 1.31)**	**1.31 (1.28, 1.35)**	**1.07 (1.02, 1.11)**	**1.10 (1.05, 1.17)** [2a]
Renal dysfunction (ref: no dysfunction)				
Moderate	**2.01 (1.92, 2.11)**	**1.79 (1.74, 1.84)**	1.02 (0.98, 1.06)	1.02 (0.97, 1.07) [2a]
High	**4.14 (3.13, 5.49)**	**4.10 (3.30, 5.09)**	1.32 (0.98, 1.79)	1.28 (0.96, 1.71) [2a]
Physical inactivity	**0.46 (0.44, 0.48)**	**0.55 (0.53, 0.56)**	**0.94 (0.93, 1.00)**	**0.93 (0.91, 0.97)** [2b]
Diet (RC; 95%-CI)	**1.63 (1.50, 1.76)**	**1.13 (1.05, 1.22)**	**0.27 (0.11, 0.43)**	-0.04 (-0.16, 0.09) [2b]
Alcohol (ref: no consumption)				
Low/Moderate	**1.14 (1.08, 1.21)**	1.02 (0.99, 1.06)	**0.87 (0.82, 0.92)**	**0.87 (0.83, 0.91)** [2b]
Excessive	**1.35 (1.27, 1.44)**	**1.18 (1.14, 1.23)**	**0.90 (0.84, 0.97)**	**0.93 (0.89, 0.98)** [2b]
Smoking (ref: never smoker)				
Ex-smoker	**2.04 (1.94, 2.14)**	**1.83 (1.77, 1.89)**	**1.19 (1.14, 1.24)**	**1.21 (1.16, 1.27)** [2b]
Current smoker	**1.13 (1.06, 1.20)**	**1.22 (1.18, 1.27)**	**1.16 (1.11, 1.22)**	**1.20 (1.14, 1.27)** [2b]
Social activity (ref: high activity)				
Moderate	1.05 (0.99, 1.11)	**0.89 (0.84, 0.95)**	0.97 (0.47, 0.90)	0.95 (0.87, 1.02) [2b]
Low	1.05 (0.96, 1.15)	**0.83 (0.78, 0.87)**	**0.88 (0.82, 0.95)**	**0.84 (0.78, 0.90)** [2b]
Depression	1.07 (0.92, 1.26)	**1.18 (1.07, 1.30)**	**1.24 (1.10, 1.40)**	**1.23 (1.08, 1.41)** [2c]
Stress (RC; 95%-CI)	**-0.41 (-0.46, -0.36)**	**-0.42 (-0.45, -0.39)**	0.03 (-0.02, 0.07)	0.03 (-0.13, 0.19) [2c]
LIBRA score (RC; 95%-CI)	n.a.	**0.49 (0.47, 0.51)**	**0.15 (0.11, 0.19)**	n.a.

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

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

SUPPLEMENTARY FILES

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

Supplementary file 2: Flowchart of participant selection

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

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

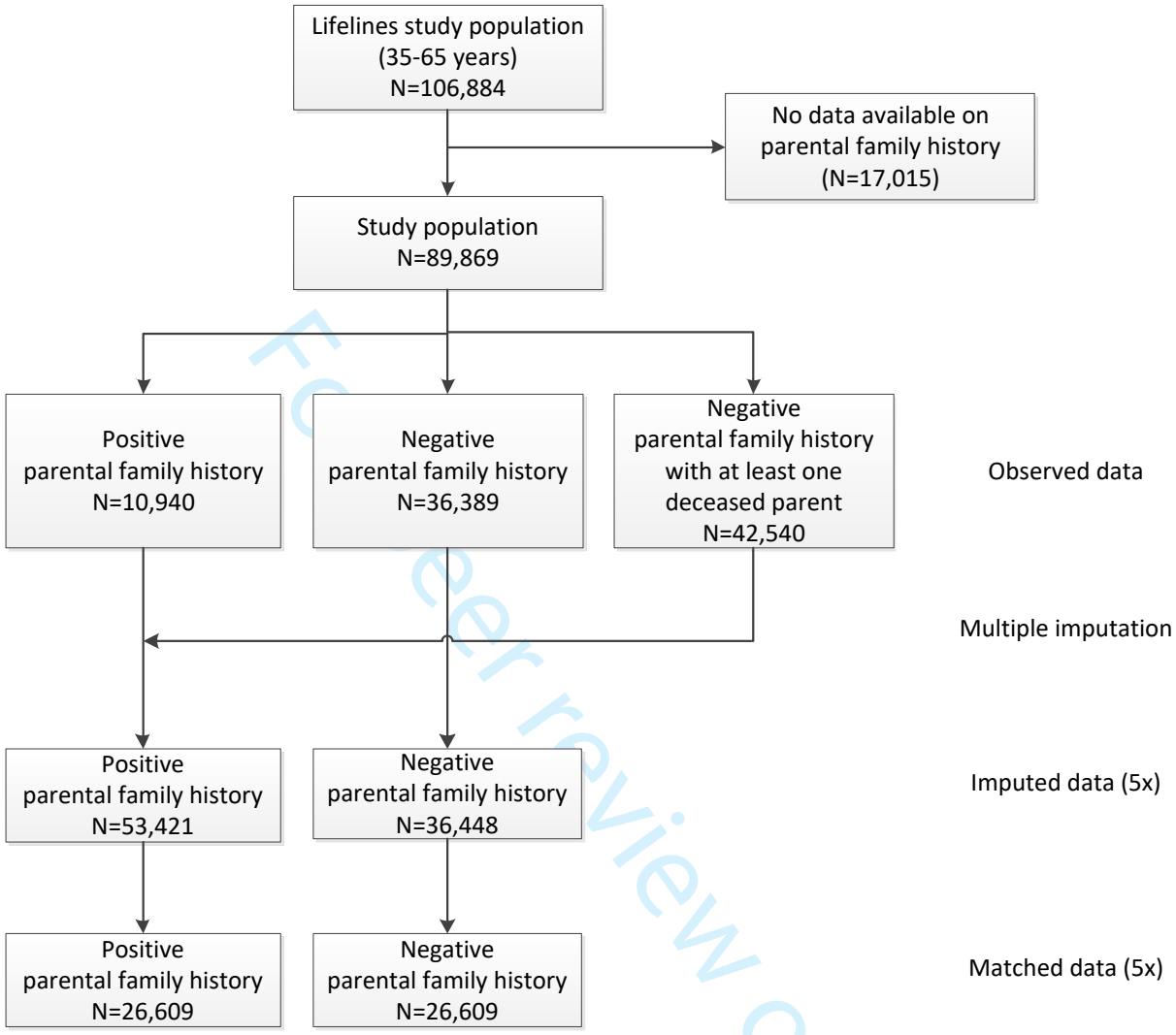
Supplementary file 1. Models for the association between parental family history of dementia and the modifiable risk factors for dementia

	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[1] (n=53,218)**	**Model 2[2#] (n=53,644)**
Age	**1.534**	**1.209**	0.133	0.170
Sex, female	0.023	0.005	0.091	0.017
Education				
Elementary	0.106	0.123	0.048	0.062
Lower secondary	**0.234**	**0.274**	0.035	0.020
Upper secondary	0.170	0.141	-0.172	-0.035
Tertiary	0.078	0.154	0.133	-0.005
Hypertension	**0.304**	**0.286**	0.066	0.041
High cholesterol	**0.265**	**0.248**	**0.231**	0.038
Diabetes	0.121	0.125	-0.025	0.018
Cardiovascular diseases	0.119	0.122	**0.261**	0.007
Obesity	0.037	0.070	0.052	0.055
Overweight	0.113	0.134	0.102	0.103
Renal dysfunction				
No dysfunction	**0.325**	**0.278**	**-0.206**	**-0.207**
Moderate	**0.311**	**0.264**	0.193	0.027
High	0.081	0.087	0.078	0.004
Physical inactivity	**0.375**	**0.300**	**0.278**	0.012
Diet score	**0.278**	0.194	0.160	0.051
Alcohol consumption				
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
Smoking				
Never smoker	0.105	**0.228**	-0.193	-0.167
Ex-smoker	0.066	**0.259**	**0.218**	0.039
Current smoker	0.059	0.024	-0.021	0.008
Social activity				
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
Depression	0.045	0.023	0.018	0.024
Stress	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[1]**	**Adjusted model 2[2]**
Hypertension	**1.82 (1.77, 1.88)**	**1.12 (1.09, 1.16)**	**1.12 (1.08, 1.16)**
High cholesterol	**1.80 (1.74, 1.86)**	**1.20 (1.55, 1.24)**	**1.17 (1.13, 1.22)**
Diabetes Mellitus	**2.07 (1.91, 2.26)**	**1.12 (1.02, 1.24)**	1.09 (0.99, 1.21)
CVD	**2.93 (2.58, 3.33)**	**1.34 (1.16, 1.56)**	**1.29 (1.12, 1.50)**
Obesity	**1.21 (1.17, 1.26)**	**1.13 (1.08, 1.18)**	**1.12 (1.07, 1.17)**
Overweight	**1.31 (1.28, 1.35)**	**1.09 (1.06, 1.13)**	**1.08 (1.05, 1.12)**
Renal dysfunction (ref: no dysfunction)			
Moderate	**1.79 (1.74, 1.84)**	**0.92 (0.89, 0.95)**	**0.93 (0.89, 0.96)**
High	**4.10 (3.30, 5.09)**	0.95 (0.74, 1.20)	0.96 (0.75, 1.24)
Physical inactivity	**0.55 (0.53, 0.56)**	1.02 (0.99, 1.06)	0.99 (0.95, 1.02)
Diet (RC; 95%-CI)	**1.13 (1.05, 1.22)**	-0.04 (-0.12, 0.05)	-0.02 (-0.11, 0.07)
Alcohol (ref: no consumption)			
Low/Moderate	1.02 (0.99, 1.06)	0.90 (0.86, 0.94)	**0.91 (0.88, 0.95)**
Excessive	**1.18 (1.14, 1.23)**	0.98 (0.93, 1.03)	0.99 (0.94, 1.04)
Smoking (ref: never smoker)			
Ex-smoker	**1.83 (1.77, 1.89)**	**1.16 (1.12, 1.20)**	**1.15 (1.11, 1.19)**
Current smoker	**1.22 (1.18, 1.27)**	**1.21 (1.16, 1.26)**	**1.18 (1.14, 1.24)**
Social activity (ref: high activity)			
Moderate	**0.89 (0.84, 0.95)**	0.98 (0.91, 1.05)	0.98 (0.91, 1.05)
Low	**0.83 (0.78, 0.87)**	0.88 (0.82, 0.94)	**0.88 (0.83, 0.94)**
Depression	**1.18 (1.07, 1.30)**	**1.25 (1.12, 1.40)**	**1.23 (1.10, 1.38)**
Stress (RC; 95%-CI)	**-0.42 (-0.45, -0.39)**	**0.09 (0.05, 0.12)**	**0.08 (0.04, 0.11)**

*** 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
Title and abstract	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
Introduction			
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
Methods			
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
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(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
Discussion			
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
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	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.

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:	*BMJ Open*
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
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	Dementia < NEUROLOGY, PREVENTIVE MEDICINE, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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TITLE

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

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ABSTRACT

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

DESIGN: A cross-sectional study

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

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

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

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

- No other study investigating the association between a parental family history of dementia and modifiable risk factors for dementia used a wide range of the currently known modifiable risk factors for dementia.
- Our large study sample provided sufficient power to detect relevant associations independent of confounding factors.
- We used sophisticated statistical techniques to prevent selection bias and calculated odds ratios and regression coefficients with 95%-confidence intervals.
- Parental family history of dementia was based on self-reported questionnaires, which could have led to misclassification.
- Results were based on cross-sectional data in which previous health behaviours were not taken into account.

KEY WORDS:

- Dementia Risk Reduction
- Family History
- Modifiable Risk Factors
- Multiple Imputation
- Propensity Score Matching
- Middle Aged

INTRODUCTION

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

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

Several multi-domain interventions to reduce dementia risk and prevent cognitive decline among older individuals were conducted, however only small or non-significant effects on cognition were found (14–16). These multi-domain interventions may be more effective among cognitively healthy middle-aged individuals with a higher risk for developing dementia, for instance individuals with a parental family history (PFH) of dementia. The average lifetime risk of developing dementia is 10-12% and increases to 15-25% for individuals with a family history of dementia (17). This increased risk can be explained by both genetic and lifestyle factors (18–21), which are passed on from parents to offspring (20,22). The APOE ε4 allele is one of the genes to be consistently shown to increase the risk for dementia (23–25). Individuals with a PFH of dementia are more often carrier of this allele compared

to individuals without a PFH of dementia (21,26–29). Nevertheless, several studies have shown that individuals with a PFH of dementia have an increased risk, independent of their genetic risk (18,27,28).

Although the role of APOE genotype on dementia risk has been well studied, the risk factor of a PFH remains rarely studied. Only a few studies investigated the association between family history of dementia and modifiable risk factors for dementia (28,30,31). They found that family history of dementia was associated with both higher diastolic (DBP) as systolic blood pressure (SBP) and depression (28,31), while it was not associated with Body Mass Index (BMI), serum lipid profiles (e.g. Total cholesterol, HDL, LDL), alcohol consumption and smoking behaviour (30). However, previous studies did not take all currently known modifiable risk factors for dementia into account and included a relatively small sample of participants. Moreover, these findings might be a result of confounding bias. Since age is an important risk factor for dementia, individuals with a PFH of dementia are often older and could therefore have more often modifiable risk factors for dementia, such as hypertension and high cholesterol levels (9). By using covariate adjustment, there is the threat that this confounding bias is not tackled sufficiently. Propensity score matching (PSM) is a sophisticated analysis technique that can reduce this bias by assembling a matched sample of people with and without a PFH of dementia, in which confounding factors are balanced between groups (32). By matching, a greater proportion of the systematic differences in characteristics of individuals with and without a PFH is eliminated compared to the commonly used covariate adjustment (32).

Finding differences in modifiable risk factors for dementia among middle-aged individuals with and without a PFH of dementia, might help to identify individuals with an increased risk for dementia and subsequently offer them tailor-made interventions for DRR. Therefore, the aim of this study was to investigate the association between a PFH of dementia and modifiable risk factors for dementia among middle-aged individuals from the general population.

METHOD

Study population

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

Measurement of independent and dependent variables

Independent variable

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

Dependent variables

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

demographic characteristics, health behaviours, (parental) health and medication use. Participants brought their medication to the research site, which was subsequently reported and categorized using the Anatomical Therapeutic Chemical (ATC) codes (35).

Hypertension

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

High cholesterol

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

Renal dysfunction

Renal dysfunction is categorized into: (i) low dysfunction (eGFR>90 ml/min/1.73 m^2), (ii) moderate dysfunction (eGFR:60-89 ml/min/1.73 m^2) and (iii) high dysfunction (eGFR<60 ml/min/1.73 m^2) (37–39).

Obesity and overweight

BMI was calculated using measured body weight (in kg) and length (in cm) (BMI = weight/length^2). Subsequently, the presence or absence of overweight (BMI≥ 25.0) and obesity (BMI≥ 30.0) was determined (40,41).

Diabetes

Diabetes Mellitus was defined as: (i) glucose (fasting capillary blood) of 7.0 mmol/l or higher, or (ii) HbA1C levels higher than 53 mmol/mol, or (iii) using blood glucose lowering medication (ATC code A10 (drugs used in diabetes)) (35,42). In case glucose and HbA1c levels were missing and the participant did not use any glucose lowering medication, the presence of diabetes mellitus was based on the answer of the self-reported questionnaire (Do you have diabetes mellitus?).

Cardiovascular diseases

Participants reported whether they have suffered or still suffer from one of the following cardiovascular diseases (CVDs): myocardial infarction, stroke or peripheral arterial diseases. If at least one of these CVDs was indicated with 'yes' in the self-reported questionnaire, participants were known with CVDs.

Healthy diet

A quantitative Food Frequency Questionnaire (FFQ) was used to assess dietary intake over the previous month (43,44). Subsequently, the Lifelines diet score (LLDS) was used to determine adherence to a healthy diet, which is based on the consumption of nine positive food groups (vegetables, fruit, whole grain products, legumes and nuts, fish, oils and soft margarines, unsweetened dairy, coffee and tea) and three negative food groups (red and processed meat, butter and hard margarines and sugar-sweetened beverages). The consumption of each food group was divided into quintiles to score an individual's consumption compared to the total Lifelines population. For each food group, the quintiles ranged from 0 to 4 points, using 4 points for the highest quintile of consumption for positive food groups and the lowest quintile for the negative food groups. The total LLDS ranges from 0 to 48, with a higher score indicating a healthier diet (45).

Alcohol consumption

Alcohol consumption is categorized into: (i) no alcohol consumption (0 alcohol units in the past month), (ii) low/moderate alcohol consumption (average ≤1 alcohol unit per day and no binge drinking) and (iii) excessive alcohol consumption (average >1 alcohol unit per day and/or binge drinking, which is defined as more than three alcohol units per occasion for females and more than four alcohol units per occasion for males).

Physical inactivity

Physical inactivity was measured with the Short Questionnaire to Assess Health enhancing physical activity (SQUASH) (46). The results are converted to minutes per week spent in physical activity of light intensity and physical activity of moderate to vigorous intensity (MVPA), based on Metabolic Equivalent Tasks (METs) derived from the Ainsworth's compendium of physical activity (47). Physical inactivity is defined as less than 150 minutes per week MVPA (48).

Smoking

Smoking behaviour was assessed with the self-reported questionnaire, including the following two questions: (i) 'Do you smoke now, or have you smoked in the past month?' and (ii) 'Have you ever smoked for a full year?'. Subsequently, smoking behaviour was categorized into: (i) non-smoker, (ii) ex-smoker and (iii) current smoker. Current smokers are defined as people who reported smoking in the past month. Ex-smokers reported smoking for at least one year, but did not smoke in the past month.

Social activity

Social activity was measured with the following question 'On average how many people did you have contact with in the past two weeks?'. Subsequently, social activity is categorized into low (contacts<4), moderate (contacts: 4-7) and high (contacts≥8) (49).

Depression

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

Stress

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

LIBRA score

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

INSERT TABLE 1 ABOUT HERE

Covariates

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

was based on the question 'What is your highest completed level of education?'. Highest level of education was categorized into: (i) elementary (no education or primary education), (ii) lower secondary (lower or preparatory vocational education or lower general secondary education), (iii) upper secondary (intermediate vocational education) and (iv) tertiary (higher general secondary education or pre-university secondary education, higher vocational education and university) (54).

Statistical methods

The baseline characteristics of the total study population were described and differences between participants with and without a PFH of dementia were calculated using Standardized Mean Differences (SMD). Five imputed datasets were generated to replace missing values, using the Multiple Imputation using Chained Equations (MICE) approach. Specifically, we used predictive mean matching (ppm) for continuous data, logistic regression imputation (logreg) for binary data, polytomous regression imputation (polyreg) for unordered categorical data and proportional odds model (polr) for ordered categorical data. In each imputed dataset, we assessed the association between PFH of dementia and each modifiable risk factor in two steps. First, to eliminate selection bias, PSM was used to match each individual with a PFH of dementia to an individual without a PFH of dementia (ratio 1:1) (caliper=0.2), based on the standard potential confounders age, sex and educational level (model 1) and other potential confounders (model 2) (see **Supplementary file 1**) (32). The other potential confounders were a-priori carefully selected per outcome measure in a consensus meeting, in which each potential confounder had to be associated with both the independent and the dependent variables. After PSM, we checked if the balance in the covariates was achieved (SMD < 0.2). Second, logistic (dichotomous outcomes), linear (continuous outcomes) and multinomial (categorical outcomes) regression analyses were used to examine the association between a PFH of dementia and each modifiable risk factor. These analyses were conducted for each imputed matched dataset to obtain the estimates, which were pooled using Rubin's rules (55). Since the LIBRA score is a composite score and includes all individual modifiable risk factors for dementia, this analysis is based on model 1 (only matched on sex, age and educational level). Results are presented as odds ratios (OR) or regression coefficients (RC) with 95% confidence intervals (95%-CI). Sensitivity

analyses were conducted in which covariate adjustment is used instead of PSM. R statistical software environment version 1.3.383 was used (56). In particular, we used the 'MatchThem', 'tableone' and 'cobalt' package in R.

Patient and Public Involvement

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

RESULTS

Baseline characteristics

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

INSERT TABLE 2 ABOUT HERE

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

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

PFH of dementia had more often hypertension (OR=1.19, 95%-CI: 1.14,1.24), high cholesterol (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: 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 depressive symptoms (OR=1.23, 95%-CI: 1.08,1.41) compared to their peers without a PFH of dementia. Further, individuals with a PFH of dementia were more often current-smokers (OR=1.20, 95%-CI: 1.14,1.27) and ex-smokers (OR=1.21, 95%-CI:1.16,1.27), but were less often low/moderate alcohol consumers (OR=0.87, 95%-CI: 0.83,0.91), excessive alcohol consumers (OR=0.93, 95%-CI:0.89,0.98), physically inactive (OR=0.93, 95%-CI: 0.91,0.97) and had less often a low social activity (OR=0.84, 95%-CI:0.78,0.90). Finally, individuals with a PFH of dementia also had an overall higher risk to develop dementia (LIBRA score RC=0.15, 95%-CI: 0.11,0.19) compared to their peers without a PFH of dementia.

INSERT TABLE 3 ABOUT HERE

DISCUSSION

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

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

dementia had more often cardiovascular risk factors, it might be that they did not consume alcohol due to health concerns or use of medication (57). Furthermore, in our study, PFH of dementia was determined by the first follow-up questionnaire. In case dementia was diagnosed before baseline assessment, individuals with a PFH of dementia could already have adjusted their lifestyle. Therefore, these findings may reflect a reverse causality from having a parent with dementia to more physical and social activity. No data was available on the date of onset of dementia.

To our knowledge, this is the first study that investigated the association between having a PFH of dementia and currently known modifiable risk factors for dementia among middle-aged individuals using a large sample size and PSM. Only few studies have been conducted to test the differences in several modifiable risk factors of dementia between individuals with and without a family history of dementia (28,30,31). However, it is likely that these studies were hampered by small sample sizes of the study population. For instance, Luckhoff et al. (2016) did not find differences in BMI (objectively measured), total cholesterol, HDL, LDL, alcohol intake and smoking behaviour between middle-aged individuals with (n=75) and without (n=505) a self-reported family history of dementia ($p>0.05$)(30). Exel et al. (2009) found that middle-aged individuals with an objectively measured PFH of dementia (n=206) had more often hypertension and caregiver burden stress compared to their peers (n=200) ($p<0.05$)(28). However, no differences were found in high cholesterol, glucose levels and lifestyle-related risk factors such as smoking and physical activity ($p>0.05$) (58). La Rue et al. (2008) also showed that individuals with a PFH of dementia (n=623) had higher cholesterol levels, higher DBP and SBP and higher depression rates compared to individuals without a PFH of dementia (n=157) ($p<0.01$)(31). Although differences with the current study could be explained by the use of different statistical methods, sensitivity analyses in which covariate adjustment is used showed similar results when using PSM (see **Supplementary file 4**). In comparison to the main analyses, the estimates for physical inactivity and social activity are slightly smaller in the sensitivity results. This could be explained by the smaller sample size in the main results (n=53,644 versus n=89,869). Due to one-to-one matching, a relatively high number of healthy living individuals with a PFH of dementia could not be matched and therefore not included in the main analyses. A major advantage of PSM is that the

balance in potential confounders can be inspected between individuals with and without a PFH of dementia before conducting the analyses. After PSM most potential confounders were balanced between participants with and without a PFH of dementia (SMD<0.2), except for the variable renal dysfunction (SMD=-0.207). Therefore, it is possible that the associations between having a PFH of dementia and lifestyle-related risk factors for dementia are slightly biased.

Strengths and limitations

Our large study sample provided sufficient power to detect relevant associations independent of confounding factors. In addition, no other study investigating the association between a PFH of dementia and modifiable risk factors for dementia used a wide range of the currently known modifiable risk factors for dementia. A large part of these modifiable risk factors (e.g., hypertension, high cholesterol, diabetes mellitus, obesity, overweight, renal dysfunction) were objectively measured through physical examination and fasting blood samples. Further, we used sophisticated statistical techniques to prevent selection bias. The potential confounders used in PSM were carefully chosen per outcome measure. Finally, in contrast to previous studies, we reported adjusted ORs and RCs with 95%-confidence intervals instead of p-values, which gives more information on the magnitude and direction of the association studied.

This study also had certain limitations. One drawback is that PFH of dementia was based on self-reported questionnaires and could have led to misclassification. Nonetheless, it is likely that the misclassification was non-differential and would have led to an underestimation of our results. Second, no data was available on the APOE genotype, which may be an important effect modifier (19). Previous literature showed that a healthy lifestyle might especially be beneficial for the cognition of APOE e4 carriers (19,59). Since individuals with a PFH of dementia are more often carrier of the APOE e4 allele, a healthy lifestyle might also be especially beneficial for individuals with a PFH of dementia. Therefore, absence of APOE genotype data could have led to an underestimation of the results for APOE e4 carriers with a PFH of dementia. Third, the results were based on cross-sectional data in which previous health behaviours were not taken into account. It might be possible that

individuals with a PFH of dementia adopted a healthier lifestyle after their parent got diagnosed with dementia. In other words, our findings may reflect a reverse causality from PFH of dementia to health behaviour, indicating that our estimates may be underestimated. Finally, we imputed PFH of dementia of all participants without a PFH of dementia with at least one deceased parent. We did not distinguish in the age of death of deceased parents, since the incidence of dementia increases with age and the average age of onset of dementia differs between types of dementia (60). However, relatively young parents are less likely to develop dementia compared to older parents. Nevertheless, sensitivity analyses in which individuals with deceased fathers who survived to at least the age of 70 or mothers who survived to at least the age of 75 were assigned to the group without having a PFH of dementia instead of PFH being imputed, showed similar results (31). Also, we did not take into account the age of onset of dementia of the parent(s), since the average age of onset of dementia differs between types of dementia (60). However, this might be an important effect modifier as early onset dementia may have a stronger genetic basis. Therefore, these results could be an underestimation of the results for individuals with a parents diagnosed at an older age. Nevertheless, after excluding individuals with a parent diagnosed before the age of 70 years, the results were similar.

These findings support a high-risk prevention strategy for dementia by identifying the individuals with a PFH of dementia, screening them for modifiable risk factors for dementia, and implementing multi-domain interventions targeting these modifiable risk factors. Future studies should first explore the knowledge, beliefs and attitudes towards dementia (risk reduction) among middle-aged individuals with a PFH of dementia, and whether they are willing to assess their protective and risk factors for dementia and adopt a healthier lifestyle. Next, the effectiveness of these multi-domain interventions in changing health behaviour for DRR among middle-aged individuals with a PFH of dementia should be investigated.

CONCLUSION

We found that a PFH of dementia was associated with several modifiable risk factors for dementia independent of age, sex and educational level, including hypertension, high cholesterol, diabetes

mellitus, CVDs, obesity, overweight and depression. This suggests that middle-aged individuals with a PFH of dementia are a group at risk for dementia and might benefit from DRR. Further research should examine knowledge, beliefs and attitudes towards DRR among middle-aged individuals with a PFH of dementia, and their willingness to address and tackle their personal risk factors for dementia in order to prevent of postpone dementia.

Acknowledgements: The Lifelines Biobank initiative has been made possible by subsidy from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University Medical Centre Groningen (UMCG the Netherlands), University Groningen and the Northern Provinces of the Netherlands.

Author contributions: JV, AAH, SR and NS were involved in the design of the study. JV conducted the analysis with support of AAH. JV wrote the manuscript and AAH, SR and NS revised the manuscript. All authors read and approved the final manuscript.

Funding: None declared.

Competing Interests: The authors declare that no conflict of interest exists.

Patient consent: Not applicable.

Data sharing statement: Lifelines is a facility that is open for all researchers (www.lifelines.net).

Ethics statement: The Lifelines Cohort Study was approved by the Medical Ethical Commission (METC) of the University Medical Center Groningen (Reference number-2007/152). All subjects signed written informed consent and all methods were carried out in accordance with relevant guidelines and regulations for human subjects.

REFERENCES

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

Alzheimer Res. 2019;16(14):1254–68.

11. Schiepers OJG, Köhler S, Deckers K, Irving K, O'Donnell CA, van den Akker M, et al. Lifestyle for Brain Health (LIBRA): a new model for dementia prevention. Int J Geriatr Psychiatry. 2018 Feb 28;33:167–75.

12. Vos SJB, van Boxtel MPJ, Schiepers OJG, Deckers K, de Vugt M, Carri?re I, et al. Modifiable Risk Factors for Prevention of Dementia in Midlife, Late Life and the Oldest-Old: Validation of the LIBRA Index. J Alzheimer's Dis. 2017 May 11;58(2):537–47.

13. Deckers K, Köhler S, van Boxtel M, Verhey F, Brayne C, Fleming J, et al. Lack of associations between modifiable risk factors and dementia in the very old: findings from the Cambridge City over-75s cohort study. Aging Ment Health. 2017 Feb;1–7.

14. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015 Jun;385(9984):2255–63.

15. van Charante EPM, Richard E, Eurelings LS, van Dalen J-W, Ligthart SA, van Bussel EF, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. Lancet. 2016;388(10046):797–805.

16. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol. 2017 May 1;16(5):377–89.

17. Goldman JS, Hahn SE, Catania JW, LaRusse-Eckert S, Butson MB, Rumbaugh M, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. 2011 Jun;13(6):597–605.

18. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hyppönen E, Kuzma E, et al. Association of lifestyle and genetic risk with incidence of dementia. JAMA. 2019 Aug 6;322(5):430.

19. Kivipelto M, Rovio S, Ngandu T, Kåreholt I, Eskelinen M, Winblad B, et al. Apolipoprotein E

epsilon4 magnifies lifestyle risks for dementia: a population-based study. J Cell Mol Med. 2008 Dec;12(6B):2762–71.

20. Borenstein AR, Copenhaver CI, Mortimer JA. Early-Life Risk Factors for Alzheimer Disease. Alzheimer Dis Assoc Disord. 2006 Jan;20(1):63–72.

21. Donix M, Small GW, Bookheimer SY. Family History and APOE-4 Genetic Risk in Alzheimer's Disease. Neuropsychol Rev. 2012 Sep 23;22(3):298–309.

22. Muñoz M, Pong-Wong R, Canela-Xandri O, Rawlik K, Haley CS, Tenesa A. Evaluating the contribution of genetics and familial shared environment to common disease using the UK Biobank. Nat Genet. 2016 Jul 18;48(9):980–3.

23. Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet. 1994 Jun;7(2):180–4.

24. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease. JAMA. 1997 Oct 22;278(16):1349.

25. Choudhury P, Ramanan VK, Boeve BF. APOE ε 4 Allele Testing and Risk of Alzheimer Disease. JAMA. 2021 Jan 14;

26. Sager MA, Hermann B, La Rue A. Middle-aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer's Prevention. J Geriatr Psychiatry Neurol. 2005 Dec 29;18(4):245–9.

27. Scarabino D, Gambina G, Broggio E, Pelliccia F, Corbo RM. Influence of family history of dementia in the development and progression of late-onset Alzheimer's disease. Am J Med Genet Part B Neuropsychiatr Genet. 2016 Mar;171(2):250–6.

28. van Exel E, Eikelenboom P, Comijs H, Frölich M, Smit JH, Stek ML, et al. Vascular factors and markers of inflammation in offspring with a parental history of late-onset Alzheimer disease. Arch Gen Psychiatry. 2009 Nov 1;66(11):1263–70.

29. Johnson SC, Koscik RL, Jonaitis EM, Clark LR, Mueller KD, Berman SE, et al. The Wisconsin Registry for Alzheimer's Prevention: A review of findings and current directions.

Alzheimer's Dement (Amsterdam, Netherlands). 2018;10:130–42.

30. Lückhoff HK, Kidd M, van Rensburg SJ, van Velden DP, Kotze MJ. Apolipoprotein E genotyping and questionnaire-based assessment of lifestyle risk factors in dyslipidemic patients with a family history of Alzheimer's disease: test development for clinical application. Metab Brain Dis. 2016 Feb 20;31(1):213–24.

31. Rue A La, Hermann B, Jones JE, Johnson S, Asthana S, Sager MA. Effect of parental family history of Alzheimer's disease on serial position profiles. Alzheimer's Dement. 2008 Jul 1;4(4):285–90.

32. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011 May;46(3):399–424.

33. Scholtens S, Smidt N, Swertz MA, Bakker SJL, Dotinga A, Vonk JM, et al. Cohort Profile: LifeLines, a three-generation cohort study and biobank. Int J Epidemiol. 2015 Aug;44(4):1172–80.

34. Stolk RP, Rosmalen JGM, Postma DS, de Boer RA, Navis G, Slaets JPJ, et al. Universal risk factors for multifactorial diseases. Eur J Epidemiol. 2008 Jan 13;23(1):67–74.

35. World Health Organization. ATC/DDD Index 2020. Oslo, Norway; 2020.

36. van Dis SJ, Kromhout D, Geleijnse JM, Boer JMA, Verschuren WMM. Evaluation of cardiovascular risk predicted by different score equations: the Netherlands as an example. Eur J Cardiovasc Prev Rehabil. 2010;17:244–9.

37. De Grauw W, De Leest K, Schenk P, Scherpbier-De Haan N, Tjin-A-Ton J, Tuut M, et al. NHG-Standaard Chronische Nierschade. TPO - Prakt. 2018;13(5):26–9.

38. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.

39. Levey AS, Inker LA, Coresh J. GFR estimation: From physiology to public health. Am J Kidney Dis. 2014;63(5):820–34.

40. Centers for Disease Control and Prevention (CDC). Body Mass Index (BMI) [Internet]. [cited 2020 Sep 9]. Available from: https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html

41. World Health Organization (WHO). Body mass index (BMI) [Internet]. World Health Organization; [cited 2019 May 6]. Available from: http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi

42. Rutten G, De Grauw W, Nijpels G, Houweling S, Van de Laar F, Bilo H, et al. NHG-Standaard Diabetes mellitus type 2. 2013.

43. Molag ML, de Vries JHM, Duif N, Ocké MC, Dagnelie PC, Goldbohm RA, et al. Selecting informative food items for compiling food-frequency questionnaires: comparison of procedures. Br J Nutr. 2010 Aug 8;104(03):446–56.

44. Siebelink E, Geelen A, de Vries JHM. Self-reported energy intake by FFQ compared with actual energy intake to maintain body weight in 516 adults. Br J Nutr. 2011 Jul 22;106(02):274–81.

45. Vinke PC, Corpeleijn E, Dekker LH, Jacobs DR, Navis G, Kromhout D. Development of the food-based Lifelines Diet Score (LLDS) and its application in 129,369 Lifelines participants. Eur J Clin Nutr. 2018;72(8):1111–9.

46. Wendel-Vos G. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003 Dec;56(12):1163–9.

47. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011 Aug;43(8):1575–81.

48. Weggemans RM, Backx FJG, Borghouts L, Chinapaw M, Hopman MTE, Koster A, et al. The 2017 Dutch Physical Activity Guidelines. Int J Behav Nutr Phys Act. 2018 Jun 25;15(1):58.

49. Kuiper JS, Zuidersma M, Oude Voshaar RC, Zuidema SU, van den Heuvel ER, Stolk RP, et al. Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev. 2015 Jul 1;22:39–57.

50. Sheehan D V, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 2:22–33; quiz 34–57.

51. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). Fifth edit. Washington; 2013.

52. Rosmalen JGM, Bos EH, de Jonge P. Validation of the Long-term Difficulties Inventory (LDI) and the List of Threatening Experiences (LTE) as measures of stress in epidemiological population-based cohort studies. Psychol Med. 2012 Dec;42(12):2599–608.

53. Motrico E, Moreno-Küstner B, de Dios Luna J, Torres-González F, King M, Nazareth I, et al. Psychometric properties of the List of Threatening Experiences—LTE and its association with psychosocial factors and mental disorders according to different scoring methods. J Affect Disord. 2013;150(3):931–40.

54. Klijs B, Kibele EUB, Ellwardt L, Zuidersma M, Stolk RP, Wittek RPM, et al. Neighborhood income and major depressive disorder in a large Dutch population: results from the LifeLines Cohort study. BMC Public Health. 2016 Aug 11;16(1):773.

55. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011 Feb 20;30(4):377–99.

56. R Core team. R: A language and environment for statistical computing. Vienna, Austria; 2020.

57. Green CA, Polen MR. The health and health behaviors of people who do not drink alcohol. Am J Prev Med. 2001 Nov 1;21(4):298–305.

58. van Exel E, Eikelenboom P, Comijs H, Frölich M, Smit JH, Stek ML, et al. Vascular Factors and Markers of Inflammation in Offspring With a Parental History of Late-Onset Alzheimer Disease. Arch Gen Psychiatry. 2009 Nov 1;66(11):1263.

59. Dekhtyar S, Marseglia A, Xu W, Darin-Mattsson A, Wang HX, Fratiglioni L. Genetic risk of dementia mitigated by cognitive reserve: A cohort study. Ann Neurol. 2019 Jul 1;86(1):68–78.

60. Ott A, Breteler MMB, Van Harskamp F, Stijnen T, Hofman A. Incidence and Risk of Dementia The Rotterdam Study. 1998;147(6).

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

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

	PFH+ (n=10,940)	PFH- (n=36,389)	Standardized mean differences
Age, mean(sd)	52.95 (7.2)	43.19 (5.5)	**1.534**
Sex, female	6606 (60.4)	21566 (59.3)	0.023
Education			**0.271**
Elementary	231 (2.1)	303 (0.8)	0.106
Lower secondary	3557 (32.5)	8068 (22.2)	**0.234**
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)	
Hypertension	4637 (42.4)	10201 (28.0)	**0.304**
unknown	0	0	
High cholesterol	3250 (29.7)	6722 (18.5)	**0.265**
unknown	1 (0.0)	9 (0.0)	
Diabetes	446 (4.1)	734 (2.0)	0.121
unknown	1 (0.0)	9 (0.0)	
Cardiovascular diseases	247 (2.3)	290 (0.8)	0.119
unknown	0	0	
Obesity	1772 (16.2)	5429 (14.9)	0.037
Overweight	6557 (59.9)	19789 (54.4)	0.113
unknown	4 (0.0)	7 (0.0)	
Renal dysfunction			**0.334**
No dysfunction	6216 (56.8)	26269 (74.5)	**0.325**
Moderate	4232 (38.7)	8883 (25.2)	**0.311**
High	97 (0.9)	99 (0.3)	0.081
unknown	395 (3.6)	1138 (3.1)	
Physical inactivity	3545 (32.4)	18038 (49.6)	**0.375**
unknown	717 (6.6)	2712 (7.5)	
Diet score, mean(sd)	25.61 (5.91)	23.97 (5.81)	**0.278**
unknown	1079 (9.9)	4903 (13.5)	
Alcohol consumption			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)	
Smoking			**0.333**
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)	
Social activity			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)	
Depression	207 (1.9)	639 (1.8)	0.045
unknown	164 (1.5)	756 (2.1)	
Stress, mean(sd)	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[1] (n=53,218)**	**Model 2 (n=53,644)**
Hypertension	**1.89 (1.81, 1.97)**	**1.82 (1.77, 1.88)**	**1.16 (1.12, 1.21)**	**1.19 (1.14, 1.24)** [2a]
High cholesterol	**1.87 (1.78, 1.96)**	**1.80 (1.74, 1.86)**	**1.16 (1.10, 1.22)**	**1.24 (1.18, 1.30)** [2a]
Diabetes Mellitus	**2.06 (1.83, 2.33)**	**2.07 (1.91, 2.26)**	**1.20 (1.07, 1.34)**	**1.26 (1.11, 1.42)** [2a]
CVD	**2.88 (2.42, 3.41)**	**2.93 (2.58, 3.33)**	**1.40 (1.17, 1.68)**	**1.49 (1.18, 1.88)** [2a]
Obesity	**1.10 (1.04, 1.17)**	**1.21 (1.17, 1.26)**	**1.14 (1.09, 1.20)**	**1.14 (1.08, 1.20)** [2a]
Overweight	**1.26 (1.20, 1.31)**	**1.31 (1.28, 1.35)**	**1.07 (1.02, 1.11)**	**1.10 (1.05, 1.17)** [2a]
Renal dysfunction (ref: no dysfunction)				
Moderate	**2.01 (1.92, 2.11)**	**1.79 (1.74, 1.84)**	1.02 (0.98, 1.06)	1.02 (0.97, 1.07) [2a]
High	**4.14 (3.13, 5.49)**	**4.10 (3.30, 5.09)**	1.32 (0.98, 1.79)	1.28 (0.96, 1.71) [2a]
Physical inactivity	**0.46 (0.44, 0.48)**	**0.55 (0.53, 0.56)**	**0.94 (0.93, 1.00)**	**0.93 (0.91, 0.97)** [2b]
Diet (RC; 95%-CI)	**1.63 (1.50, 1.76)**	**1.13 (1.05, 1.22)**	**0.27 (0.11, 0.43)**	-0.04 (-0.16, 0.09) [2b]
Alcohol (ref: no consumption)				
Low/Moderate	**1.14 (1.08, 1.21)**	1.02 (0.99, 1.06)	**0.87 (0.82, 0.92)**	**0.87 (0.83, 0.91)** [2b]
Excessive	**1.35 (1.27, 1.44)**	**1.18 (1.14, 1.23)**	**0.90 (0.84, 0.97)**	**0.93 (0.89, 0.98)** [2b]
Smoking (ref: never smoker)				
Ex-smoker	**2.04 (1.94, 2.14)**	**1.83 (1.77, 1.89)**	**1.19 (1.14, 1.24)**	**1.21 (1.16, 1.27)** [2b]
Current smoker	**1.13 (1.06, 1.20)**	**1.22 (1.18, 1.27)**	**1.16 (1.11, 1.22)**	**1.20 (1.14, 1.27)** [2b]
Social activity (ref: high activity)				
Moderate	1.05 (0.99, 1.11)	**0.89 (0.84, 0.95)**	0.97 (0.47, 0.90)	0.95 (0.87, 1.02) [2b]
Low	1.05 (0.96, 1.15)	**0.83 (0.78, 0.87)**	**0.88 (0.82, 0.95)**	**0.84 (0.78, 0.90)** [2b]
Depression	1.07 (0.92, 1.26)	**1.18 (1.07, 1.30)**	**1.24 (1.10, 1.40)**	**1.23 (1.08, 1.41)** [2c]
Stress (RC; 95%-CI)	**-0.41 (-0.46, -0.36)**	**-0.42 (-0.45, -0.39)**	0.03 (-0.02, 0.07)	0.03 (-0.13, 0.19) [2c]
LIBRA score (RC; 95%-CI)	n.a.	**0.49 (0.47, 0.51)**	**0.15 (0.11, 0.19)**	n.a.

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

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

SUPPLEMENTARY FILES

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

Supplementary file 2: Flowchart of participant selection

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

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

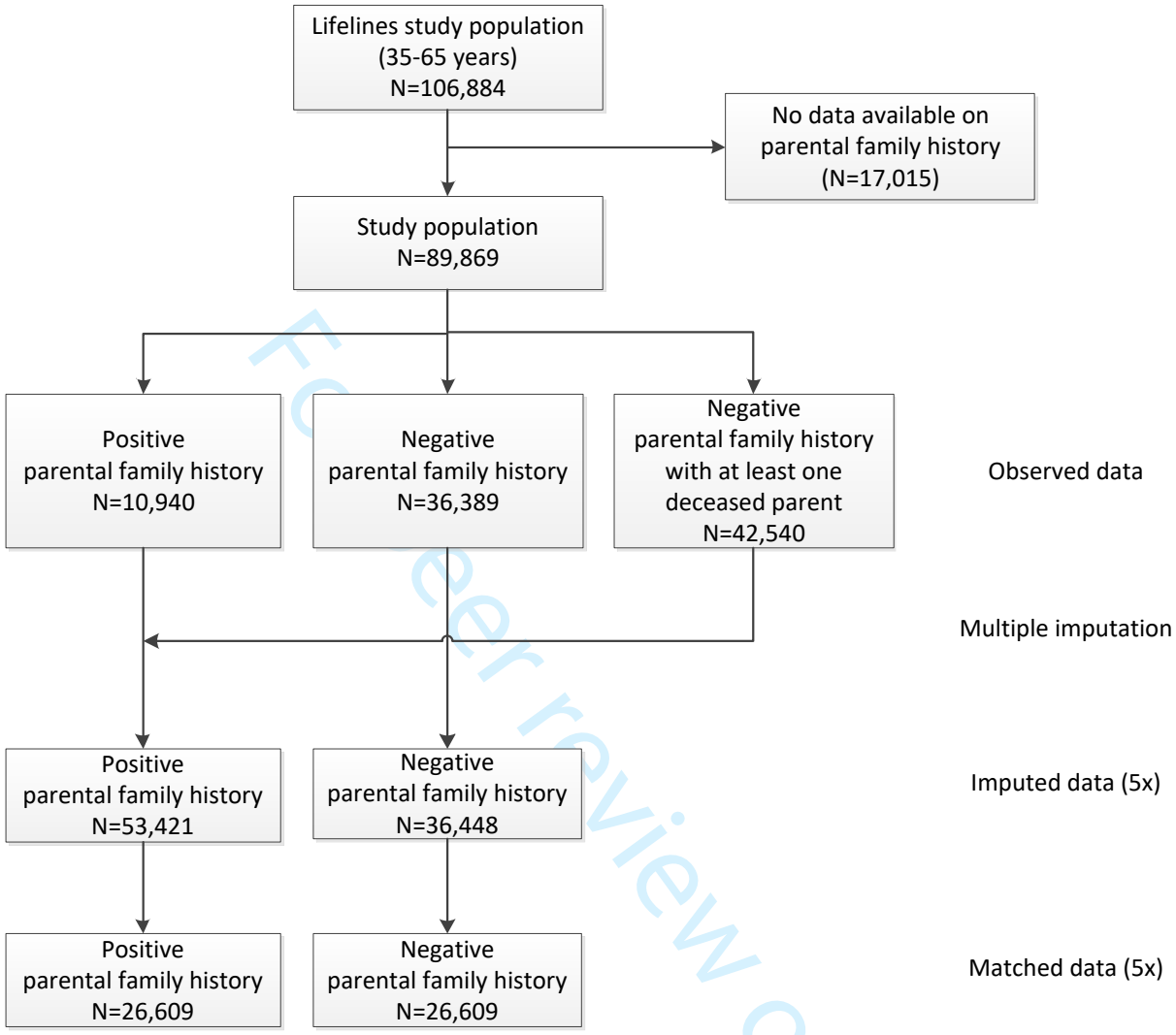
Supplementary file 1. Models for the association between parental family history of dementia and the modifiable risk factors for dementia

	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[1] (n=53,218)**	**Model 2[2#] (n=53,644)**
Age	**1.534**	**1.209**	0.133	0.170
Sex, female	0.023	0.005	0.091	0.017
Education				
Elementary	0.106	0.123	0.048	0.062
Lower secondary	**0.234**	**0.274**	0.035	0.020
Upper secondary	0.170	0.141	-0.172	-0.035
Tertiary	0.078	0.154	0.133	-0.005
Hypertension	**0.304**	**0.286**	0.066	0.041
High cholesterol	**0.265**	**0.248**	**0.231**	0.038
Diabetes	0.121	0.125	-0.025	0.018
Cardiovascular diseases	0.119	0.122	**0.261**	0.007
Obesity	0.037	0.070	0.052	0.055
Overweight	0.113	0.134	0.102	0.103
Renal dysfunction				
No dysfunction	**0.325**	**0.278**	**-0.206**	**-0.207**
Moderate	**0.311**	**0.264**	0.193	0.027
High	0.081	0.087	0.078	0.004
Physical inactivity	**0.375**	**0.300**	**0.278**	0.012
Diet score	**0.278**	0.194	0.160	0.051
Alcohol consumption				
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
Smoking				
Never smoker	0.105	**0.228**	-0.193	-0.167
Ex-smoker	0.066	**0.259**	**0.218**	0.039
Current smoker	0.059	0.024	-0.021	0.008
Social activity				
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
Depression	0.045	0.023	0.018	0.024
Stress	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[1]**	**Adjusted model 2[2]**
Hypertension	**1.82 (1.77, 1.88)**	**1.12 (1.09, 1.16)**	**1.12 (1.08, 1.16)**
High cholesterol	**1.80 (1.74, 1.86)**	**1.20 (1.55, 1.24)**	**1.17 (1.13, 1.22)**
Diabetes Mellitus	**2.07 (1.91, 2.26)**	**1.12 (1.02, 1.24)**	1.09 (0.99, 1.21)
CVD	**2.93 (2.58, 3.33)**	**1.34 (1.16, 1.56)**	**1.29 (1.12, 1.50)**
Obesity	**1.21 (1.17, 1.26)**	**1.13 (1.08, 1.18)**	**1.12 (1.07, 1.17)**
Overweight	**1.31 (1.28, 1.35)**	**1.09 (1.06, 1.13)**	**1.08 (1.05, 1.12)**
Renal dysfunction (ref: no dysfunction)			
Moderate	**1.79 (1.74, 1.84)**	**0.92 (0.89, 0.95)**	**0.93 (0.89, 0.96)**
High	**4.10 (3.30, 5.09)**	0.95 (0.74, 1.20)	0.96 (0.75, 1.24)
Physical inactivity	**0.55 (0.53, 0.56)**	1.02 (0.99, 1.06)	0.99 (0.95, 1.02)
Diet (RC; 95%-CI)	**1.13 (1.05, 1.22)**	-0.04 (-0.12, 0.05)	-0.02 (-0.11, 0.07)
Alcohol (ref: no consumption)			
Low/Moderate	1.02 (0.99, 1.06)	0.90 (0.86, 0.94)	**0.91 (0.88, 0.95)**
Excessive	**1.18 (1.14, 1.23)**	0.98 (0.93, 1.03)	0.99 (0.94, 1.04)
Smoking (ref: never smoker)			
Ex-smoker	**1.83 (1.77, 1.89)**	**1.16 (1.12, 1.20)**	**1.15 (1.11, 1.19)**
Current smoker	**1.22 (1.18, 1.27)**	**1.21 (1.16, 1.26)**	**1.18 (1.14, 1.24)**
Social activity (ref: high activity)			
Moderate	**0.89 (0.84, 0.95)**	0.98 (0.91, 1.05)	0.98 (0.91, 1.05)
Low	**0.83 (0.78, 0.87)**	0.88 (0.82, 0.94)	**0.88 (0.83, 0.94)**
Depression	**1.18 (1.07, 1.30)**	**1.25 (1.12, 1.40)**	**1.23 (1.10, 1.38)**
Stress (RC; 95%-CI)	**-0.42 (-0.45, -0.39)**	**0.09 (0.05, 0.12)**	**0.08 (0.04, 0.11)**

*** 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
Title and abstract	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
Introduction			
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
Methods			
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
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(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
Discussion			
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
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	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.