BMJ Open

Association between dementia parental family history and mid-life modifiable risk factors for dementia: a cross-sectional study using propensity score matching within the Lifelines cohort

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To cite: Vrijsen J, Abu-Hanna A, de Rooij SE, *et al*. Association between dementia parental family history and mid-life modifiable risk factors for dementia: a cross-sectional study using propensity score matching within the Lifelines cohort. *BMJ Open* 2021;**11**:e049918. doi:10.1136/bmjopen-2021-049918

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-049918).

Received 06 February 2021
Accepted 19 November 2021

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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 (12.2%) had a PFH of dementia (mean (SD) age=52.95 (7.2)) and 36 389 (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=1.19; 95% CI 1.14 to 1.24), high cholesterol (OR=1.24; 95% CI 1.18 to 1.30), diabetes (OR=1.26; 95% CI 1.11 to 1.42), cardiovascular diseases (OR=1.49; 95% CI 1.18 to 1.88), depression (OR=1.23; 95% CI 1.08 to 1.41), obesity (OR=1.14; 95% CI 1.08 to 1.20) and overweight (OR=1.10; 95% CI 1.05 to 1.17), and were more often current smokers (OR=1.20; 95% CI 1.14 to 1.27) and ex-smokers (OR=1.21; 95% CI 1.16 to 1.27). However, they were less often low/moderate alcohol consumers (OR=0.87; 95% CI 0.83 to 0.91), excessive alcohol consumers (OR=0.93; 95% CI 0.89 to 0.98), socially inactive (OR=0.84; 95% CI 0.78 to 0.90) and physically inactive (OR=0.93; 95% CI 0.91 to 0.97). Having a PFH of dementia resulted in a higher LIBRA score (RC=0.15; 95% CI 0.11 to 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 ORs and regression coefficients with 95% CIs.
- ► 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.

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 1 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 10–20 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* found that 40% of the dementia cases are attributable to several lifestyle-related risk factors (ie, 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 multidomain 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 multidomain 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 Apolipoprotein E (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 with 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) and systolic blood pressure (SBP) and depression,[28 31] while it was not associated with body mass index (BMI), serum lipid profiles (eg, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (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 with 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 multidisciplinary 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, sociodemographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics.[33 34] The Lifelines Cohort Study was conducted according to the guidelines of the Declaration of Helsinki. All participants provided written informed consent. For the current study, we selected participants aged 35–65 years who 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 dichotomised (yes/no). Furthermore, participants reported whether parents were deceased and the year of birth and death of their father and/or mother if applicable. In case one of the parents was 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 the Statistical methods section).

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, TC, 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 categorised using the Anatomical Therapeutic Chemical (ATC) codes.[35]

Hypertension

Hypertension was defined as: (1) SBP >140 mm Hg, or (2) DBP >90 mm Hg, or (3) 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: (1) a ratio of TC and HDL higher than 5 mmol/L, or (2) 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 categorised into: (1) low dysfunction (estimated glomerular filtration rate (eGFR) >90 mL/min/1.73 m^2), (2) moderate dysfunction (eGFR 60–89 mL/min/1.73 m^2), and (3) high dysfunction (eGFR <60 mL/min/1.73 m^2).[37–39]

Obesity and overweight

BMI was calculated using measured body weight (in kilogram) and length (in centimetre) (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: (1) glucose (fasting capillary blood) of 7.0 mmol/L or higher, or (2) HbA1c levels higher than 53 mmol/mol, or (3) 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 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 with 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 categorised into: (1) no alcohol consumption (0 alcohol unit in the past month), (2) low/moderate alcohol consumption (average ≤1 alcohol unit per day and no binge drinking), and (3) excessive alcohol consumption (average >1 alcohol unit per day and/or binge drinking, which is defined as more than 3 alcohol units per occasion for females and more than 4 alcohol units per occasion for males).

Physical inactivity

Physical inactivity was measured with the Short Questionnaire to Assess Health-enhancing Physical Activity.[46] The results are converted to minutes/week spent in physical activity of light intensity and moderate to vigorous physical activity (MVPA) intensity, based on metabolic equivalent of tasks derived from the Ainsworth's compendium of physical activity.[47] Physical inactivity is defined as less than 150 min/week MVPA.[48]

Smoking

Smoking behaviour was assessed with the self-reported questionnaire, including the following two questions: (1) 'Do you smoke now, or have you smoked in the past month?' and (2) 'Have you ever smoked for a full year?' Subsequently, smoking behaviour was categorised into: (1) non-smoker, (2) ex-smoker, and (3) current smoker. Current smokers are defined as people who reported smoking in the past month. Ex-smokers reported smoking for at least 1 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 categorised 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.[50] Major depression was defined as having at least one key symptom of depression (eg, depressed mood or loss of interest) and four additional symptoms in the past month, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[51]

Stress

Chronic stress was measured by the Long-term Difficulties Inventory,[52 53] which consists of 12 items that refer to 12 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 12 months with regard to each aspect on a 3-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 12 protective (ie, Mediterranean diet, low/moderate alcohol consumption, high-cognitive activity) and risk factors (ie, 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*, 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.

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 categorised into: (1) elementary (no education or primary education), (2) lower secondary (lower or preparatory vocational education or lower general secondary education), (3) upper secondary (intermediate vocational education), and (4) tertiary (higher general secondary education or preuniversity 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 standardised mean differences (SMD). Five imputed data

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 (ie, >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 (ie, ≥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 mm Hg or DBP >90 mm Hg	+1.6
11	Depression	At least 1 key symptom and 4 additional symptoms measured with the MINI	+2.1

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LIBRA, Lifestyle for Brain Health; LLDS, Lifelines Diet Score; MINI, Mini-International Neuropsychiatric Interview; SBP, systolic blood pressure; SQUASH, Short Questionnaire to Assess Health-enhancing Physical Activity; TC, total cholesterol.

sets were generated to replace missing values using the multiple imputation using chained equations 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 data set, 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) (calliper=0.2), based on the standard potential confounders age, sex and educational level (model 1) and other potential confounders (model 2) (see online supplemental 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 data set 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 ORs or regression coefficients (RC) with 95% CIs. Sensitivity analyses were conducted in which covariate adjustment is used instead of PSM. R statistical software environment V.1.3.383 was used.[56] In particular, we used the 'MatchThem', 'tableone' and 'cobalt' packages 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 were 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 (12.2%) had a PFH of dementia and 36 389 (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 the flow chart in online supplemental 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 online supplemental file 3). We focused further on the results of the final model (model 2).

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 to 1.24), high cholesterol (OR=1.24; 95% CI 1.18 to 1.30), diabetes (OR=1.26; 95% CI 1.11 to 1.42), CVDs (OR=1.49; 95% CI 1.18 to 1.88), obesity (OR=1.14; 95% CI 1.08 to 1.20), overweight (OR=1.10; 95% CI 1.05 to 1.17) and depressive symptoms (OR=1.23; 95% CI 1.08 to 1.41), compared with 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 to 1.27) and ex-smokers (OR=1.21; 95% CI 1.16 to 1.27), but were less often low/moderate alcohol consumers (OR=0.87; 95% CI 0.83 to 0.91), excessive alcohol consumers (OR=0.93; 95% CI 0.89 to 0.98), physically inactive (OR=0.93; 95% CI 0.91 to 0.97) and had less often a low social activity (OR=0.84; 95% CI 0.78 to 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 to 0.19) compared with their peers without a PFH of dementia.

DISCUSSION

In this study, we investigated the association between having a PFH of dementia and 14 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 and depression, and were also more often ex-smokers and current smokers than never smokers. However, they were more often non-alcohol consumers, physically active and socially active compared with 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 consumers and excessive alcohol consumers than no alcohol

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

	PFH+ (n=10 940)	PFH− (n=36 389)	Standardised mean differences
Age, mean (SD)	52.95 (7.2)	43.19 (5.5)	**1.534**
Sex, female	6606 (60.4)	21 566 (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)	15 395 (42.3)	0.170
Tertiary	3183 (29.1)	11 902 (32.7)	0.078
Unknown	240 (2.2)	721 (2.0)	
Hypertension	4637 (42.4)	10 201 (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)	19 789 (54.4)	0.113
Unknown	4 (0.0)	7 (0.0)	
Renal dysfunction			**0.334**
No dysfunction	6216 (56.8)	26 269 (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)	18 038 (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)	15 892 (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)	17 535 (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)	27 452 (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

Continued

Table 2 Continued

	PFH+ (n=10 940)	PFH− (n=36 389)	Standardised mean differences
Unknown	256 (1.5)	1066 (2.0)	

Standardised mean differences higher than 0.2 are shown in bold.
*n (%) noted unless indicated otherwise.
PFH, parental family history.

consumers. 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 were available on the date of onset of dementia.

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* (n=53 218)	Model 2 (n=53 644)
Hypertension	**1.89 (1.81 to 1.97)**	**1.82 (1.77 to 1.88)**	**1.16 (1.12 to 1.21)**	**1.19 (1.14 to 1.24)**†
High cholesterol	**1.87 (1.78 to 1.96)**	**1.80 (1.74 to 1.86)**	**1.16 (1.10 to 1.22)**	**1.24 (1.18 to 1.30)**†
Diabetes mellitus	**2.06 (1.83 to 2.33)**	**2.07 (1.91 to 2.26)**	**1.20 (1.07 to 1.34)**	**1.26 (1.11 to 1.42)**†
CVD	**2.88 (2.42 to 3.41)**	**2.93 (2.58 to 3.33)**	**1.40 (1.17 to 1.68)**	**1.49 (1.18 to 1.88)**†
Obesity	**1.10 (1.04 to 1.17)**	**1.21 (1.17 to 1.26)**	**1.14 (1.09 to 1.20)**	**1.14 (1.08 to 1.20)**†
Overweight	**1.26 (1.20 to 1.31)**	**1.31 (1.28 to 1.35)**	**1.07 (1.02 to 1.11)**	**1.10 (1.05 to 1.17)**†
Renal dysfunction (ref: no dysfunction)				
Moderate	**2.01 (1.92 to 2.11)**	**1.79 (1.74 to 1.84)**	1.02 (0.98 to 1.06)	1.02 (0.97 to 1.07)†
High	**4.14 (3.13 to 5.49)**	**4.10 (3.30 to 5.09)**	1.32 (0.98 to 1.79)	1.28 (0.96 to 1.71)†
Physical inactivity	**0.46 (0.44 to 0.48)**	**0.55 (0.53 to 0.56)**	**0.94 (0.93 to 1.00)**	**0.93 (0.91 to 0.97)**‡
Diet (RC; 95% CI)	**1.63 (1.50 to 1.76)**	**1.13 (1.05 to 1.22)**	**0.27 (0.11 to 0.43)**	−0.04 (−0.16 to 0.09)‡
Alcohol (ref: no consumption)				
Low/moderate	**1.14 (1.08 to 1.21)**	1.02 (0.99 to 1.06)	**0.87 (0.82 to 0.92)**	**0.87 (0.83 to 0.91)**‡
Excessive	**1.35 (1.27 to 1.44)**	**1.18 (1.14 to 1.23)**	**0.90 (0.84 to 0.97)**	**0.93 (0.89 to 0.98)**‡
Smoking (ref: never smoker)				
Ex-smoker	**2.04 (1.94 to 2.14)**	**1.83 (1.77 to 1.89)**	**1.19 (1.14 to 1.24)**	**1.21 (1.16 to 1.27)**‡
Current smoker	**1.13 (1.06 to 1.20)**	**1.22 (1.18 to 1.27)**	**1.16 (1.11 to 1.22)**	**1.20 (1.14 to 1.27)**‡
Social activity (ref: high activity)				
Moderate	1.05 (0.99 to 1.11)	**0.89 (0.84 to 0.95)**	0.97 (0.47 to 0.90)	0.95 (0.87 to 1.02)‡
Low	1.05 (0.96 to 1.15)	**0.83 (0.78 to 0.87)**	**0.88 (0.82 to 0.95)**	**0.84 (0.78 to 0.90)**‡
Depression	1.07 (0.92 to 1.26)	**1.18 (1.07 to 1.30)**	**1.24 (1.10 to 1.40)**	**1.23 (1.08 to 1.41)**§
Stress (RC; 95% CI)	**−0.41 (−0.46 to −0.36)**	**−0.42 (−0.45 to −0.39)**	0.03 (−0.02 to 0.07)	0.03 (−0.13 to 0.19)§
LIBRA score (RC; 95% CI)	n.a.	**0.49 (0.47 to 0.51)**	**0.15 (0.11 to 0.19)**	n.a.

ORs with 95% CIs are reported, unless stated otherwise; significant associations are shown in bold.
*Matched on age, sex and education level.
†Additionally matched on physical inactivity, diet, alcohol consumption, smoking, stress and depression.
‡Additionally matched on stress, social activity, cardiovascular diseases, diabetes, high cholesterol, hypertension and renal dysfunction.
§Additionally matched on physical inactivity, diet, stress and social activity.
CVD, cardiovascular disease; LIBRA, Lifestyle for Brain Health; n.a., not available; PSM, propensity score matching; RC, regression coefficient.

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, Lückhoff *et al* did not find differences in BMI (objectively measured), TC, 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] van Exel *et al* found that middle-aged individuals with an objectively measured PFH of dementia (n=206) had more often hypertension and caregiver burden stress compared with 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).[28] La Rue *et al* also showed that individuals with a PFH of dementia (n=623) had higher cholesterol levels, higher DBP and SBP and higher depression rates compared with 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 online supplemental 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 vs 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 (eg, 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% CIs 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 were 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 58] Since individuals with a PFH of dementia are more often carriers 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.[59] However, relatively young parents are less likely to develop dementia compared with 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.[59] 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 parent 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 multidomain 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 multidomain 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 or 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), the University of Groningen and the Northern Provinces of the Netherlands.

Contributors JV, AA-H, SEdR and NS were involved in the design of the study. JV conducted the analysis with support from AA-H. JV wrote the manuscript and is guarantor. AA-H, SEdR and NS revised the manuscript. All authors read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Lifelines Cohort Study was approved by the Medical Ethical Commission (METC) of the University Medical Centre Groningen (Reference number: METc2007/152). All subjects signed written informed consent and all methods were carried out in accordance with relevant guidelines and regulations for human subjects.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. Lifelines is a facility that is open for all researchers (www.lifelines.net).

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