JAMA Neurology | Original Investigation

Risk Factors for Young-Onset Dementia in the UK Biobank

Stevie Hendriks, PhD; Janice M. Ranson, PhD; Kirsten Peetoom, PhD; Ilianna Lourida, PhD; Xin You Tai, PhD; Marjolein de Vugt, PhD; David J. Llewellyn, PhD; Sebastian Köhler, PhD

IMPORTANCE There is limited information on modifiable risk factors for young-onset dementia (YOD).

OBJECTIVE To examine factors that are associated with the incidence of YOD.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study used data from the UK Biobank, with baseline assessment between 2006 and 2010 and follow-up until March 31, 2021, for England and Scotland, and February 28, 2018, for Wales. Participants younger than 65 years and without a dementia diagnosis at baseline assessment were included in this study. Participants who were 65 years and older and those with dementia at baseline were excluded. Data were analyzed from May 2022 to April 2023.

EXPOSURES A total of 39 potential risk factors were identified from systematic reviews of late-onset dementia and YOD risk factors and grouped into domains of sociodemographic factors (education, socioeconomic status, and sex), genetic factors (apolipoprotein E), lifestyle factors (physical activity, alcohol use, alcohol use disorder, smoking, diet, cognitive activity, social isolation, and marriage), environmental factors (nitrogen oxide, particulate matter, pesticide, and diesel), blood marker factors (vitamin D, C-reactive protein, estimated glomerular filtration rate function, and albumin), cardiometabolic factors (stroke, hypertension, diabetes, hypoglycemia, heart disease, atrial fibrillation, and aspirin use), psychiatric factors (depression, anxiety, benzodiazepine use, delirium, and sleep problems), and other factors (traumatic brain injury, rheumatoid arthritis, thyroid dysfunction, hearing impairment, and handgrip strength).

MAIN OUTCOME AND MEASURES Multivariable Cox proportional hazards regression was used to study the association between the risk factors and incidence of YOD. Factors were tested stepwise first within domains and then across domains.

RESULTS Of 356 052 included participants, 197 036 (55.3%) were women, and the mean (SD) age at baseline was 54.6 (7.0) years. During 2 891 409 person-years of follow-up, 485 incident YOD cases (251 of 485 men [51.8%]) were observed, yielding an incidence rate of 16.8 per 100 000 person-years (95% CI, 15.4-18.3). In the final model, 15 factors were significantly associated with a higher YOD risk, namely lower formal education, lower socioeconomic status, carrying 2 apolipoprotein ε4 allele, no alcohol use, alcohol use disorder, social isolation, vitamin D deficiency, high C-reactive protein levels, lower handgrip strength, hearing impairment, orthostatic hypotension, stroke, diabetes, heart disease, and depression.

CONCLUSIONS AND RELEVANCE In this study, several factors, mostly modifiable, were associated with a higher risk of YOD. These modifiable risk factors should be incorporated in future dementia prevention initiatives and raise new therapeutic possibilities for YOD.

JAMA Neurol. 2024;81(2):134-142. doi:10.1001/jamaneurol.2023.4929
Published online December 26, 2023.

Multimedia

Supplemental content

Author Affiliations: Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, Maastricht, the Netherlands (Hendriks, Peetoom, de Vugt, Köhler); University of Exeter Medical School, Exeter, United Kingdom (Ranson, Lourida, Llewellyn); Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom (Tai); Division of Clinical Neurology, John Radcliffe Hospital, Oxford University Hospitals Trust, Oxford, United Kingdom (Tai); Alan Turing Institute, London, United Kingdom (Llewellyn).

Corresponding Author: Stevie Hendriks, PhD, Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, PO Box 616 (DRT10), 6200 MD Maastricht, the Netherlands (stevie.hendriks@maastrichtuniversity.nl).

The global prevalence of dementia is expected to rise from 50 million in 2020 to 115 million in 2050.[1] Although prevalence is highest in older people (late-onset dementia [LOD]), dementia can also occur at a younger age. When the onset of dementia symptoms occurs before the age of 65 years, it is defined as young-onset dementia (YOD).[2] The estimated global prevalence of YOD is 3.9 million.[3] Although prevalence of YOD is low compared with LOD, the personal, societal, and economic impact of YOD is particularly high, with consequences related to employment, social life, and familial responsibilities.[4]

Identification of modifiable and nonmodifiable risk factors would aid in developing targeted interventions to prevent YOD and increase our understanding of underlying mechanisms. In YOD, previous research has largely focused on genetic factors, although genetic factors identified so far only account for 5% to 10% of all YOD cases.[5] Apolipoprotein E (*APOE*) is one of the major genetic risk factors in YOD, as it could increase the risk of Alzheimer dementia in younger persons.[6]

While modifiable risk factors for LOD have been studied extensively, little is known about factors increasing risk for YOD. The 2020 report of the Lancet Commission on Dementia Prevention, Intervention and Care suggests that by eliminating modifiable risk factors, the number of LOD cases could be reduced by as much as 40%.[7] Some well-established risk factors for LOD include smoking, high alcohol intake, cardiometabolic factors, and depression.[8] Protective factors for LOD are physical activity, healthy diet, and cognitive or social activity.[8] It is unclear whether these factors also apply to YOD. To our knowledge, the only systematic review on risk factors of YOD identified 14 studies investigating modifiable risk factors for YOD, with most studies focusing on a single factor and none examining interactions between factors.[9]

The aim of the present study is to use data from a large population-based cohort to examine a comprehensive set of factors in relation to the incidence of YOD.

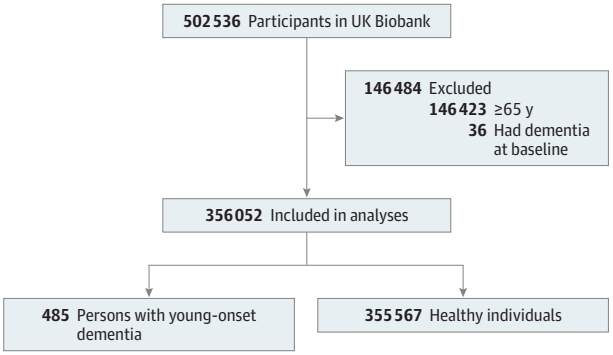
Key Points

Question Are there modifiable risk factors associated with young-onset dementia (YOD)?

Findings In this cohort study including more than 356 052 participants in the UK Biobank, there were multiple modifiable and nonmodifiable risk factors for YOD. Alcohol use, higher formal education, and lower physical frailty (higher handgrip strength) were associated with lower risk of incidence of YOD, whereas increased risk of YOD was associated with low socioeconomic status, apolipoprotein E status, alcohol use disorder, social isolation, vitamin D deficiency, high C-reactive protein levels, hearing impairment, orthostatic hypotension, stroke, diabetes, heart disease, and depression.

Meaning In this study, a wide range of risk factors were associated with YOD, and targeted interventions may prove effective for dementia prevention in middle-aged adults.

Figure 1. Flowchart of Included Participants



Methods

Study Design and Participants

We used data from the UK Biobank, an ongoing prospective cohort study in the UK consisting of more than 500 000 participants recruited between 2006 and 2010 aged 37 to 73 years at baseline. Participants were assessed in one of 22 centers across the UK and underwent a comprehensive baseline assessment.[10] They provided biological samples, completed touch-screen questionnaires, and underwent physical examination. All participants provided written informed consent, which was approved by the North West Multicenter Research Ethics Committee; because data were deidentified, this study did not require additional approval. The present study was conducted in all participants younger than 65 years and without a diagnosis of dementia at baseline (**Figure 1**). For the analyses, everyone was right-censored when they turned 65 years of age during follow-up. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Incident Dementia

Incident YOD cases were identified from hospital inpatient registers or death register linkage. A diagnosis of all-cause dementia was based on the *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *ICD-10* codes (eTable 1 in Supplement 1). Incident all-cause dementia was used as defined by the UK Biobank Outcome Adjudication Group.[11]

Risk Factors

A total of 39 potential risk factors were identified based on systematic reviews on factors having a potential association with either YOD or LOD (eTables 2 and 3 in Supplement 1). All factors available in UK Biobank were included for analysis using the baseline data (self-report and hospital records). We grouped them into domains of sociodemographic, genetic (*APOE* status), lifestyle, environmental, blood marker, cardiometabolic, psychiatric, and other factors. eTable 4 in Supplement 1 shows the factors available in the UK Biobank, including how they were operationalized for our analyses. Age, sex, education, socioeconomic status, and *APOE* status were included in all analyses. *APOE* status was extracted from blood assays in the UK Biobank. Two single-nucleotide variants, *rs429358* and *rs7412*, within the *APOE* gene define the 3 main *APOE* alleles (ε4, ε3, and ε2). These variants were genotyped, leading to 6

Table 1. Baseline Characteristics

Characteristic	No. (%)	
	Incident YOD (n = 485)	No YOD (n = 355 567)
Age, mean (SD), y	53.5 (5.2)	54.6 (7.0)
Sex		
Female	234 (48.2)	196 802 (55.3)
Male	251 (51.8)	158 765 (44.7)
APOE status[a]		
No ε4 allele	307 (63.3)	246 463 (69.3)
1 ε4 Allele	127 (26.2)	90 070 (25.3)
2 ε4 Alleles	30 (6.2)	8206 (2.3)
Level of education[b]		
Academic or other professional degree	299 (61.6)	176 245 (49.6)
Lower degree	166 (34.2)	172 547 (48.5)
Socioeconomic status[c]		
Quintile 1 (least deprived)	58 (12.0)	69 956 (19.7)
Quintiles 2-4	232 (47.8)	212 024 (59.6)
Quintile 5 (most deprived)	194 (40.0)	73 107 (20.6)
Lifestyle factors		
Regular physical activity	295 (60.8)	254 899 (71.7)
Moderate alcohol use	206 (42.5)	171 950 (48.4)
Heavy alcohol use	188 (38.8)	148 649 (41.8)
Alcohol use disorder	30 (6.2)	2126 (0.6)
Former smoker	133 (27.4)	114 950 (32.3)
Current smoker	110 (22.7)	39 985 (11.2)
Healthy diet	193 (39.8)	165 975 (46.7)
High level of cognitive activities	19 (3.9)	16 343 (4.6)
No social isolation	333 (68.7)	269 393 (75.8)
Married	274 (56.5)	256 970 (72.3)
Environmental factors		
Nitrogen oxide, mean (SD), μg/m^3	48.03 (15.20)	44.33 (15.62)
Particulate matter, mean (SD), μg/m^3	10.31 (1.14)	10.01 (1.06)
Pesticide exposure	0	1723 (0.1)
Diesel exposure	3 (0.6)	7332 (2.1)
Blood markers		
Vitamin D of 10-20 ng/mL	170 (35.1)	135 317 (38.1)
Vitamin D <10 ng/mL	107 (22.1)	54 787 (15.4)
eGFR function of 60-90 mL/min/1.73 m^2	153 (31.5)	112 632 (31.7)
eGFR function <60 mL/min/1.73 m^2	36 (7.4)	11 351 (3.2)
C-reactive protein >1 mg/dL	72 (14.8)	37 096 (10.4)
Microalbumin	30 (6.2)	13 301 (3.7)
Macroalbumin	7 (1.4)	1226 (0.3)
Cardiometabolic factors		
Stroke	29 (6.0)	4296 (1.2)
Hypertension	182 (37.5)	91 403 (25.7)
Diabetes	59 (12.2)	16 545 (4.7)
Hypoglycemia	3 (0.6)	246 (0.07)
Heart disease	46 (9.5)	11 727 (3.3)
Atrial fibrillation	6 (1.2)	3107 (0.9)
Aspirin use	91 (18.8)	39 766 (11.2)
Overweight (BMI of 25-30)	154 (31.8)	131 169 (36.9)
Obesity (BMI >30)	124 (25.6)	67 860 (19.1)
Orthostatic hypotension	3 (0.6)	181 (0.1)
Psychiatric factors		
Depression	34 (7.0)	3273 (0.9)
Anxiety	28 (5.8)	31 494 (8.9)
Benzodiazepine use	3 (0.6)	425 (0.1)
Delirium	1 (0.2)	33 (<0.1)
Sleep problems sometimes	191 (39.4)	168 667 (47.4)
Sleep problems usually	165 (34.0)	97 717 (27.5)
Other factors		
Traumatic brain injury	0	42 (<0.1)
Rheumatoid arthritis	2 (0.4)	546 (0.2)
Thyroid dysfunction	0	2 (<0.1)
High handgrip strength	159 (32.8)	157 859 (44.4)
Hearing impairment	151 (31.1)	78 927 (22.2)

Abbreviations: APOE, apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); YOD, young-onset dementia.

SI conversion factor: To convert vitamin D to nmol/L, multiply by 2.496; C-reactive protein to mg/L, multiply by 10.

[a] 21 Persons with YOD and 10 828 persons without YOD did not have *APOE* information.

[b] 20 Persons with YOD and 6775 persons without YOD did not have education information.

[c] 1 Person with YOD and 480 persons without YOD did not have socioeconomic status information.

possible alleles (ε4ε4, ε4ε3, ε4ε2, ε3ε3, ε2ε3, and ε2ε2). A 3-category variable was derived for *APOE* status; no ε4 alleles, 1 ε4 allele, or 2 ε4 alleles.

Statistical Analysis

Baseline characteristics were summarized for persons with and without YOD separately and are presented as percentages for categorical variables and means with SDs for normally distributed continuous variables. Incidence rates of YOD were analyzed for 5-year age bands starting at age 40 years (earliest recruitment age) and separately for men and women. We used Cox proportional hazards regression models to analyze the association between risk factors and incident YOD. Age was used as the timescale, starting at birth, with participants becoming at risk at their baseline assessments (between 2006 and 2010) and continued until whichever came first: incident dementia, loss to follow-up, death, end of follow-up (March 31, 2021, for England and Scotland and February 28, 2018, for Wales) or reaching the age of 65 years.

Risk factors were analyzed in a manual stepwise-forward manner. The correlation between factors was assessed with a correlation matrix. All 39 factors were first analyzed separately, adjusting for age, sex, education, socioeconomic status, and *APOE* status (model 1). Factors that were statistically significant in model 1 ($P < .05$), were analyzed in multivariable models together with other significant factors within the same domain (eTable 4 in Supplement 1) (model 2). Factors that remained significant within the domain-specific multivariable models were then analyzed together across domains. For this step, we started with the sociodemographic domain and added the other domains stepwise, first including lifestyle factors (model 3), then

Table 2. Incidence Rates of Young-Onset Dementia in the UK Biobank by 5-Year Age Bands and Sex

	Incidence per 100 000 person-years (95% CI)		
Age, y	Total	Among male participants	Among female participants
40-44.9	1.00 (0.14-7.11)	0	1.88 (0.26-13.33)
45-49.9	3.55 (2.06-6.12)	5.41 (2.81-10.39)	2.00 (0.75-5.34)
50-54.9	8.65 (6.66-11.24)	9.36 (6.42-13.64)	8.08 (5.62-11.63)
55-59.9	14.64 (12.22-17.55)	17.18 (13.34-22.12)	12.68 (9.79-16.43)
60-64.9	30.43 (27.17-34.09)	36.06 (30.81-42.21)	26.03 (22.10-30.67)
Total	16.77 (15.35-18.34)	19.60 (17.32-22.18)	14.53 (12.78-16.51)

environmental factors (model 4), followed by blood markers (model 5), cardiometabolic factors (model 6), psychiatric factors (model 7), and other factors (model 8). Model 8 was used for final inferences and interaction analyses with sex and *APOE* status. This approach allowed us to balance handling the number of candidate risk factors with a need for keeping control over mutual dependencies among variables, especially potential mediating effects.[12]

We conducted 3 different sensitivity analyses. Age of diagnosis was extended to 70 years to include cases with a diagnostic delay.[13] The sample size increased to 437 957 persons, and 1209 persons had a diagnosis of dementia. Second, to investigate possible reverse causation, the outcome variable was restricted to participants diagnosed with dementia 3 years or more after their baseline assessment. A total of 77 participants with a diagnosis within 3 years of their assessment were excluded. Third, to compare the risk factors from the final model between YOD and LOD, we also analyzed this model for persons 65 years or older. Here, 4957 persons had a dementia diagnosis over 2 402 206 person-years. Both stratified analyses and interaction analyses with age were performed.

The proportional hazard assumption was tested by Schoenfeld residuals[14] and was satisfied. All statistical analyses were performed with Stata version 17 (StataCorp). Statistical significance was set at an α of .05 in 2-sided tests.

Results

At baseline, 502 536 participants were assessed. After exclusion, 356 052 participants were included in the analysis (Figure 1). Baseline characteristics are provided in **Table 1**. Of 356 052 included participants, 197 036 (55.3%) were women, and the mean (SD) age was 54.6 (7.0) years. During 2 891 409 person-years (mean [SD] follow-up duration 8.12 [4.35] years; median [IQR] follow-up of 9.18 [4.05-12.09] years), 485 incident YOD cases were identified. Incidence rates increased with age in 5-year age bands and were higher in men compared with women (**Table 2**).

Risk Factors of YOD

Of the 39 factors univariately analyzed in model 1, 30 had a significant association with YOD incidence (**Table 3**; eTable 5 in Supplement 1). These factors were combined in joined analyses, within domains, and across domains (Table 3; eTable 5 in Supplement 1). For the domain analyses, correlation matrixes were assessed, showing no highly correlated variables (eResults in Supplement 1). In the final model, associations between 15 factors and YOD incidence remained (Table 3; **Figure 2**).

For education, having an academic or other professional degree was associated with a lower risk of YOD compared with having a lower level of education. For socioeconomic status, persons with the lowest socioeconomic status showed a higher risk of YOD compared with persons with the highest socioeconomic status. Moderate or heavy alcohol use had a lower association with YOD compared with alcohol abstinence, while persons with a diagnosis of alcohol use disorder had a higher association with YOD. For social isolation, participants who visited friends or family once a month or less had a higher association with YOD than persons visiting friends or family more often. Vitamin D deficiency (less than 10 ng/mL; to convert to nanomoles per liter, multiply by 2.496) or a high C-reactive protein (CRP) level (more than 1 mg/dL; to convert to milligrams per liter, multiply by 10) was associated with YOD. Participants who had a handgrip strength (as a proxy for physical frailty) higher than the normative value (eTable 4 in Supplement 1) had a lower association with YOD compared with persons with a lower handgrip strength. Hearing impairment was associated with a higher incidence of YOD, as well as orthostatic hypotension, stroke, diabetes, heart disease, or depression. Persons with 2 *APOE* ε4 alleles had a higher association with YOD compared with those with no ε4 allele, while there was no association for those with 1 allele.

Interactions With Sex and *APOE* Status

Diabetes and CRP levels had a significant interaction with sex (eTable 6 in Supplement 1). Men with diabetes had a higher risk for YOD than men without diabetes, while there was no association with diabetes in women. Women with high CRP levels had higher risk of YOD compared with women with low CRP levels, while there was no association with CRP in men. There were no interactions between *APOE* status and the risk factors from the final model (eTable 6 in Supplement 1).

Sensitivity Analyses

The final analyses were repeated also including those diagnosed with dementia between ages 65 and 70 years. All risk factors remained significantly associated with YOD incidence (eTable 7 in Supplement 1). Observed associations were stronger for *APOE* status, stroke, diabetes, and heart disease. Associations for socioeconomic status, education, alcohol use disorder, hearing impairment, orthostatic hypotension, vitamin D, and depression slightly attenuated.

Table 3. Risk Factor Analyses

Risk factor	HR (95% CI)[a]				
	Model 1	Model 2	Model 3	Model 4	Model 8
Sociodemographic factors					
Formal education	0.60 (0.49-0.72)	0.60 (0.49-0.72)	0.60 (0.47-0.76)	0.61 (0.48-0.78)	0.63 (0.48-0.81)
Socioeconomic status[b]					
Middle deprivation (quintiles 2-4)	1.28 (0.95-1.72)	1.28 (0.95-1.72)	1.41 (0.97-2.05)	1.44 (0.97-2.14)	1.26 (0.85-1.88)
High deprivation (quintile 5)	3.01 (2.22-4.08)	3.01 (2.22-4.08)	2.45 (1.65-3.63)	2.37 (1.54-3.64)	1.82 (1.19-2.77)
Sex	1.29 (1.07-1.55)	1.29 (1.07-1.55)	1.36 (1.08-1.71)	1.32 (1.05-1.67)	NA
Genetic factor					
APOE status					
1 Allele	1.13 (0.92-1.39)	1.13 (0.92-1.39)	1.19 (0.93-1.53)	1.25 (0.97-1.61)	1.27 (0.97-1.65)
2 Alleles	2.92 (2.00-4.28)	2.92 (2.00-4.28)	2.18 (1.29-3.69)	2.18 (1.27-3.76)	1.87 (1.01-3.44)
Lifestyle factors					
Physical activity	0.71 (0.58-0.87)	0.73 (0.55-0.96)	0.78 (0.62-0.98)	0.79 (0.62-1.00)	NA
Alcohol use					
Moderate	0.57 (0.44-0.74)	0.61 (0.41-0.91)	0.55 (0.40-0.75)	0.55 (0.40-0.76)	0.72 (0.52-1.00)
Heavy	0.54 (0.42-0.71)	0.63 (0.43-0.93)	0.53 (0.39-0.73)	0.53 (0.39-0.73)	0.64 (0.46-0.90)
Alcohol use disorder	4.91 (3.20-7.53)	4.52 (2.26-9.05)	3.87 (2.37-6.33)	4.15 (2.50-6.88)	2.39 (1.37-4.15)
Smoking					
Former	0.95 (0.76-1.19)	0.86 (0.63-1.18)	NA	NA	NA
Current	1.73 (1.35-2.20)	1.12 (0.75-1.67)	NA	NA	NA
Diet	0.84 (0.70-1.02)	NA	NA	NA	NA
Cognitive activity	1.07 (0.67-1.73)	NA	NA	NA	NA
Social isolation	1.26 (1.02-1.55)	1.41 (1.05-1.89)	1.40 (1.10-1.79)	1.40 (1.09-1.81)	1.53 (1.18-1.98)
Marriage	1.38 (1.02-1.85)	1.18 (0.82-1.70)	NA	NA	NA
Environmental factors					
Nitrogen oxide	1.01 (1.00-1.02)	1.00 (0.99-1.01)	NA	NA	NA
Particulate matter	1.25 (1.16-1.36)	1.26 (1.09-1.46)	NA	1.08 (0.97-1.20)	NA
Pesticide	NA	NA	NA	NA	NA
Diesel					
Sometimes	0.89 (0.21-3.88)	NA	NA	NA	NA
Often	1.69 (0.22-12.92)	NA	NA	NA	NA
Blood markers					
Vitamin D					
10-20 ng/dL	1.13 (0.89-1.42)	0.93 (0.63-1.38)	NA	NA	1.10 (0.82-1.47)
<10 ng/mL	1.66 (1.28-2.16)	1.88 (1.26-2.80)	NA	NA	1.59 (1.15-2.18)
C-reactive protein >1 mg/dL	1.41 (1.06-1.88)	2.50 (1.58-3.95)	NA	NA	1.54 (1.03-2.30)
eGFR function					
60-90 mL/min/1.73 m^2	1.09 (0.89-1.34)	0.87 (0.61-1.24)	NA	NA	1.02 (0.78-1.32)
<60 mL/min/1.73 m^2	2.57 (1.79-3.69)	2.01 (1.15-3.50)	NA	NA	1.55 (0.99-2.44)
Albumin					
Microalbumin	1.29 (0.86-1.95)	1.07 (0.68-1.68)	NA	NA	NA
Macroalbumin	3.28 (1.53-7.04)	1.15 (0.36-3.73)	NA	NA	NA
Cardiometabolic factors					
Stroke	4.26 (2.86-6.35)	3.41 (2.23-5.21)	NA	NA	2.07 (1.26-3.41)
Hypertension	1.44 (1.18-1.76)	1.38 (1.07-1.77)	NA	NA	NA
Diabetes	2.27 (1.69-3.04)	1.97 (1.40-2.78)	NA	NA	1.65 (1.15-2.36)
Hypoglycemia	7.31 (2.34-22.80)	3.53 (1.10-11.34)	NA	NA	2.25 (0.54-9.36)
Heart disease	2.77 (2.05-3.76)	1.64 (1.11-2.43)	NA	NA	1.61 (1.10-2.36)
Atrial fibrillation	1.00 (0.42-2.45)	NA	NA	NA	NA
Aspirin use	1.69 (1.33-2.16)	1.03 (0.75-1.42)	NA	NA	NA
BMI					
Overweight (25-30)	0.81 (0.65-1.00)	0.74 (0.57-0.96)	NA	NA	NA
Obesity (>30)	1.11 (0.88-1.41)	0.99 (0.74-1.31)	NA	NA	NA
Orthostatic hypotension	8.76 (2.80-27.36)	6.72 (2.12-21.35)	NA	NA	4.20 (1.30-13.62)

(continued)

Table 3. Risk Factor Analyses (continued)

Risk factor	HR (95% CI)[a] Model 1	Model 2	Model 3	Model 4	Model 8
Psychiatric factors					
Depression	5.25 (3.63-7.59)	4.60 (3.15-6.72)	NA	NA	3.25 (2.08-5.09)
Anxiety	0.66 (0.44-0.98)	0.80 (0.52-1.21)	NA	NA	NA
Benzodiazepine use	4.22 (1.35-13.16)	2.57 (0.64-10.34)	NA	NA	NA
Delirium	18.83 (2.64-134.44)	9.80 (1.34-71.71)	NA	NA	NA
Sleep problems					
Sometimes	0.79 (0.62-0.99)	0.86 (0.62-1.18)	NA	NA	NA
Usually	1.12 (0.87-1.43)	1.16 (0.85-1.60)	NA	NA	NA
Other factors					
Traumatic brain injury	NA	NA	NA	NA	NA
Rheumatoid arthritis	2.20 (0.55-8.84)	NA	NA	NA	NA
Thyroid dysfunction	NA	NA	NA	NA	NA
Hearing impairment	1.55 (1.26-1.90)	1.58 (1.29-1.93)	NA	NA	1.56 (1.22-2.01)
Handgrip strength	0.62 (0.51-0.76)	0.58 (0.48-0.71)	NA	NA	0.58 (0.52-0.88)

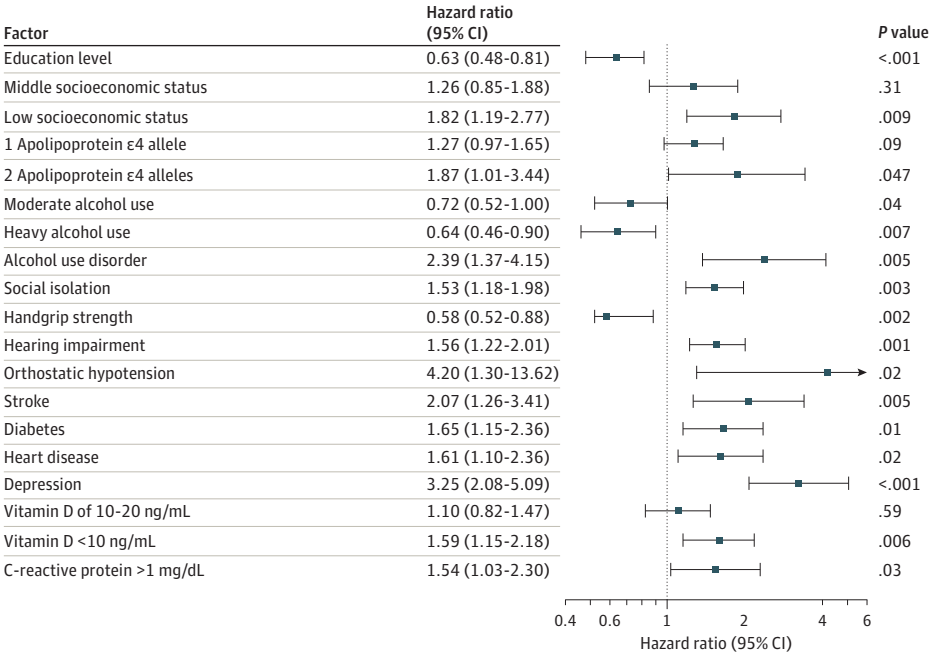
Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; YOD, young-onset dementia.

SI conversion factor: To convert vitamin D to nmol/L, multiply by 2.496; C-reactive protein to mg/L, multiply by 10.

[a] Model 1 adjusted for sex and *APOE* status. Model 2 within-domain analysis adjusted for sex and *APOE* status. Model 3 adjusted for sociodemographic and lifestyle domain. Model 4 adjusted for model 3 and environmental factors. Model 8 adjusted for model 4, blood markers, cardiovascular disease, and psychiatric factors and other variables.

[b] Deprivation was measured using the Townsend deprivation index.

Figure 2. Risk Factors Associated With Incident Young-Onset Dementia in the Fully Adjusted Model



When the dementia outcome was restricted to participants diagnosed at least 3 years after their baseline assessment, *APOE* status, alcohol use disorder, CRP levels, and orthostatic hypotension ceased to be significantly associated with YOD incidence (eTable 8 in Supplement 1).

Stratified analyses comparing YOD and LOD showed that hearing impairment, orthostatic hypotension, and CRP levels were not associated with LOD. For education, *APOE* status, and hearing impairment, there was a significant interaction with age. For education and *APOE* status, the association was significantly higher for those with LOD compared with those with YOD; conversely, for hearing impairment, the association was significantly lower for those with LOD compared with those with YOD (eTable 9 in Supplement 1).

Discussion

We investigated the association of 39 risk factors with the incidence of YOD. We identified 15 factors robustly associated with YOD. Higher formal education, lower physical frailty (handgrip strength), and alcohol use (relative to abstinence) were associated with lower incidence of YOD, whereas having 2 *APOE* ε4 alleles, lower socioeconomic status, high CRP levels, orthostatic hypotension, stroke, diabetes, heart disease, depression, hearing impairment, vitamin D deficiency, alcohol use disorder, and social isolation were associated with an increased risk.

Two previous case-control studies[15,16] and 1 retrospective cohort study[17] have investigated multiple risk factors for YOD, with Nordström et al[17] including the most factors (18). Similar to our results, stroke, depression, and alcohol use disorder were found to be associated with incident YOD. Additionally, they found height, hypertension, dementia in the father, overall cognitive function, other drug use disorder, and neuroleptic use were associated with YOD. In contrast to our results, the study found an association for hypertension but no association for socioeconomic status (yearly income). In our study, the association of hypertension with YOD became nonsignificant when socioeconomic status was added to the model, suggesting confounding. The difference could be attributed to our use of the Townsend deprivation index for socioeconomic status, as opposed to yearly income in the study by Nordström et al.[17] In addition, their study was conducted in men only, yet this might not explain the differences observed since our interaction analysis did not suggest that these associations differ across sex.

In the present study, moderate to heavy alcohol use was associated with a lower incidence of YOD. For moderate alcohol use, this may be due to the healthy drinker effect, in which people who drink are healthier, while abstainers are more likely to not consume alcohol because of poor health or use of medication.[18] Our results showed alcohol use disorder is associated with higher risk of YOD, which aligns with results from previous studies,[17,18] although in our sensitivity analysis investigating reverse causation, the association ceased to be significant, indicating that impeding YOD might also cause alcohol use disorder due to excessive drinking. Our findings regarding heavy alcohol use are complex and should be interpreted with caution.

We found diabetes, stroke, heart disease, and depression were associated with increased YOD incidence. These results are supported by previous smaller studies.[17,19] In future studies, the difference of effect of recent depression (maybe a prodromal dementia symptom) and depression more than 5 years before diagnosis could be addressed. Interestingly, we found a significant interaction between sex and diabetes. One possible explanation might be that men with diabetes have more microvascular complications than women, which may lead to small-vessel disease and dementia.[20]

For socioeconomic status, conflicting results have been reported,[17,21] but measures and criteria of socioeconomic status differ across studies. We used the Townsend deprivation index, a widely used indicator for socioeconomic status. It is based on area-level scores and is highly correlated with deprivation measures at the individual level,[22] indicating this index is useful for measuring socioeconomic status.

Our study identified several risk factors for YOD that have not, to our knowledge, been studied or reported before, namely social isolation, orthostatic hypotension, vitamin D deficiency, and high CRP levels. Studies indicate social isolation is a risk factor for LOD,[23] and it was endorsed by the Lancet Commission on Dementia Prevention, Intervention and Care.[7] Social isolation is linked to depression, but depression did not mediate the association of social isolation with YOD in our analyses, suggesting that both directly contribute to dementia risk. It has been suggested that social isolation is a sociobehavioral proxy for cognitive reserve, a theory explaining individual differences in cognitive functioning in the light of similar neuropathological burden.[24]

Orthostatic hypotension was indicated as a risk factor for LOD in a recent umbrella review,[25] possibly through recurrent transient cerebral hypoperfusion leading to cerebral hypoxia,[26] ultimately leading to dementia. Additionally, orthostatic hypotension may also be an early sign of Parkinson dementia or Lewy body dementia, sometimes occurring years or decades before diagnosis,[27] explaining the reverse causality we found in our sensitivity analysis.

We found both vitamin D deficiency and high CRP levels were associated with increased risk of YOD. It has been suggested that vitamin D acts as a neurosteroid that protects against neurodegenerative processes.[28] Notably, CRP was only significantly associated with YOD when vitamin D was included in the model. Furthermore, CRP levels are significantly higher in women, and higher CRP levels are believed to be a risk factor for cardiovascular complications.[29] These in turn could then increase the risk of dementia. Interestingly, CRP ceased to be significant in our additional analyses, suggesting reverse causation. Further investigation is warranted to understand the underlying mechanisms.

Several notable differences exist among known risk factors for LOD and the risk factors for YOD found in this study. Only a limited number of lifestyle-related factors (alcohol use, vitamin D deficiency, and social isolation) were significantly associated with the risk of YOD, while more lifestyle factors have been reported in LOD.[7,8] In our analyses, physical activity, diet, and smoking ceased to be statistically significant when either sociodemographic or other lifestyle factors were added to the analyses, suggesting confounding. Also, our analyses showed having cardiovascular diseases was a risk factor for YOD. Lifestyle factors may thus indirectly be associated with risk of YOD. However, the direct association of lifestyle factors with YOD may indeed be lower compared with LOD since people are still relatively young, and the relative effects of lifestyle factors may have had less time to contribute to the underlying dementia-related pathologies.

Finally, we included *APOE* status as a risk factor for YOD. *APOE* carries the largest genetic risk for sporadic LOD and therefore was included in our study on YOD. While *APOE* is not the only genetic factor in YOD, it still increases the risk of typical Alzheimer dementia in young persons.[6]

Strengths and Limitations

The strengths of this study include the large population-based sample size of the UK Biobank cohort, which allowed us to study the incidence of YOD prospectively, and the comprehensive number of risk factors from different domains. The data were analyzed in a manual stepwise-forward manner, using different domains of factors. This diminished the risk of overadjustment and allowed for careful distinction between mediators from confounders.[12]

Several limitations should also be considered. The study is observational and does not attempt to infer causality. However, we have tried to assess potential risk of reverse causality, although dementia pathology may start years or decades before the onset of clinical symptoms, so some of the associations we found may still be first symptoms of YOD rather than risk factors for YOD. Moreover, some factors may also directly reflect the underlying dementia etiology, for instance, dementia due to stroke. Next, several factors were based on self-reported data, which might be a source of response bias. In prospective studies, such bias is likely nondifferential and, thus, likely affected participants who developed YOD and those who did not equally, leading to dilution of the strength of associations. There may also be factors that were not considered in this study that may have driven or confounded the associations found in our analyses. Examples may be family history of dementia, drug use disorder other than alcohol, or neuroleptic use, which have previously been found to be associated with YOD,[16] which were unavailable for analysis in the current sample. For some factors, there were few exposed cases, leading to a decreased power to detect associations and wider confidence intervals (eg, orthostatic hypotension). Additionally, we did not statistically correct for multiple comparison, giving the chance of a type I error. Future research should validate our findings, preferably with more exposed cases to increase reliability of the results. Also, not all cases of YOD may have been captured by the hospital or death records. The incidence rates of YOD from our study were lower than the incidence rates observed in a 2022 meta-analysis.[30] Consequently, this may have led to outcome misclassification and dilution of associations by including cases in the nondementia group. The UK Biobank is also overrepresented by healthy and White persons, making the results of this study not generalizable to other racial and ethnic groups. Our analyses only focused on all-cause dementia, but since YOD is caused by a broad range of subtypes, it is possible that different factors are associated with different subtypes of dementia. Therefore, future studies should aim to identify factors that are associated with specific subtypes of dementia.

Conclusions

Our study identified 15 lifestyle and health-related factors that were associated with YOD incidence in this study. Most factors are potentially modifiable and overlap with known risk and protective factors for LOD. With external validation of our results, more risk factors for YOD could be incorporated in the prevention strategy communicated from the Lancet Commission.[8] While further exploration of these risk factors is necessary to identify potential underlying mechanisms, addressing these modifiable factors may prove effective in mitigating the risk of developing YOD and can be readily integrated in current dementia prevention initiatives.

ARTICLE INFORMATION

Accepted for Publication: October 30, 2023.

Published Online: December 26, 2023. doi:10.1001/jamaneurol.2023.4929

Author Contributions: Drs Hendriks and Köhler had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Llewellyn and Köhler contributed equally.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Hendriks, Ranson, Lourida, Tai, Llewellyn, Köhler.
Drafting of the manuscript: Hendriks, Peetoom, Tai, Llewellyn.
Critical review of the manuscript for important intellectual content: Ranson, Peetoom, Lourida, de Vugt, Llewellyn, Köhler.
Statistical analysis: Hendriks, Tai, Köhler.
Obtained funding: Hendriks, de Vugt, Llewellyn.
Administrative, technical, or material support: Ranson, Lourida, Tai.
Supervision: Peetoom, de Vugt, Llewellyn, Köhler.

Conflict of Interest Disclosures: Drs Ranson and Llewellyn reported grants from Alzheimer's Research UK and the Alan Turing Institute/Engineering and Physical Sciences Research Council. Dr de Vugt reported grants from Alzheimer Nederland and Gieskes Strijbis Fonds during the conduct of the study. Dr Llewellyn reported funding from the Medical Research Council, National Institute for Health Research Applied Research Collaboration South West Peninsula, National Health and Medical Research Council, and National Institute on Aging. No other disclosures were reported.

Funding/Support: This research was supported by Alzheimer Netherlands. Dr Lourida received support from the NIHR Applied Research Collaboration South West Peninsula (PenARC) and Alzheimer's Society and was funded through a postdoctoral Fellowship.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed are those of the authors and not necessarily those of the funders, National Health Service, or Department of Health and Social Care.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement*. 2013;9(1):63-75.e2. doi:10.1016/j.jalz.2012.11.007

2. van de Veen D, Bakker C, Peetoom K, et al; PRECODE study group. Provisional consensus on the nomenclature and operational definition of dementia at a young age, a Delphi study. *Int J Geriatr Psychiatry*. 2022;37(3). doi:10.1002/gps.5691

3. Hendriks S, Peetoom K, Bakker C, et al; Young-Onset Dementia Epidemiology Study Group. Global prevalence of young-onset dementia: a systematic review and meta-analysis. *JAMA Neurol*. 2021;78(9):1080-1090. doi:10.1001/jamaneurol.2021.2161

4. van Vliet D, de Vugt ME, Bakker C, Koopmans RTCM, Verhey FRJ. Impact of early onset dementia on caregivers: a review. *Int J Geriatr Psychiatry*. 2010;25(11):1091-1100. doi:10.1002/gps.2439

5. Jarmolowicz AI, Chen HY, Panegyres PK. The patterns of inheritance in early-onset dementia: Alzheimer's disease and frontotemporal dementia. *Am J Alzheimers Dis Other Demen*. 2015;30(3):299-306. doi:10.1177/1533317514545825

6. van der Flier WM, Pijnenburg YA, Fox NC, Scheltens P. Early-onset versus late-onset Alzheimer's disease: the case of the missing *APOE* ε4 allele. *Lancet Neurol*. 2011;10(3):280-288. doi:10.1016/S1474-4422(10)70306-9

7. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020

report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6

8. Deckers K, van Boxtel MPJ, Schiepers OJG, 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;30(3):234-246. doi:10.1002/gps.4245

9. Cations M, Withall A, Low LF, Draper B. What is the role of modifiable environmental and lifestyle risk factors in young onset dementia? *Eur J Epidemiol*. 2016;31(2):107-124. doi:10.1007/s10654-015-0103-9

10. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779. doi:10.1371/journal.pmed.1001779

11. Wilkinson T, Schnier C, Bush K, et al; Dementias Platform UK and UK Biobank. Identifying dementia outcomes in UK Biobank: a validation study of primary care, hospital admissions and mortality data. *Eur J Epidemiol*. 2019;34(6):557-565. doi:10.1007/s10654-019-00499-1

12. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology*. 2009;20(4):488-495. doi:10.1097/EDE.0b013e3181a819a1

13. van Vliet D, de Vugt ME, Bakker C, et al. Time to diagnosis in young-onset dementia as compared with late-onset dementia. *Psychol Med*. 2013;43(2):423-432. doi:10.1017/S0033291712001122

14. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69(1):239-241. doi:10.1093/biomet/69.1.239

15. Cations M, Draper B, Low LF, et al. Non-genetic risk factors for degenerative and vascular young onset dementia: results from the INSPIRED and KGOW studies. *J Alzheimers Dis*. 2018;62(4):1747-1758. doi:10.3233/JAD-171027

16. Chen Y, Sillaire AR, Dallongeville J, et al; Lille YOD Study Group. Low prevalence and clinical effect of vascular risk factors in early-onset Alzheimer's disease. *J Alzheimers Dis*. 2017;60(3):1045-1054. doi:10.3233/JAD-170367

17. Nordström P, Nordström A, Eriksson M, Wahlund LO, Gustafson Y. Risk factors in late adolescence for young-onset dementia in men: a nationwide cohort study. *JAMA Intern Med*. 2013;173(17):1612-1618. doi:10.1001/jamainternmed.2013.9079

18. Wiegmann C, Mick I, Brandl EJ, Heinz A, Gutwinski S. Alcohol and dementia—what is the link? a systematic review. *Neuropsychiatr Dis Treat*. 2020;16:87-99. doi:10.2147/NDT.S198772

19. Heath CA, Mercer SW, Guthrie B. Vascular comorbidities in younger people with dementia: a cross-sectional population-based study of 616 245 middle-aged people in Scotland. *J Neurol Neurosurg Psychiatry*. 2015;86(9):959-964. doi:10.1136/jnnp-2014-309033

20. Maric-Bilkan C. Sex differences in micro- and macro-vascular complications of diabetes mellitus. *Clin Sci (Lond)*. 2017;131(9):833-846. doi:10.1042/CS20160998

21. Whalley LJ, Thomas BM, Starr JM. Epidemiology of presenile Alzheimer's disease in Scotland (1974-88) II. exposures to possible risk factors. *Br J Psychiatry*. 1995;167(6):732-738. doi:10.1192/bjp.167.6.732

22. Adams J, Ryan V, White M. How accurate are Townsend Deprivation Scores as predictors of self-reported health? a comparison with individual level data. *J Public Health (Oxf)*. 2005;27(1):101-106. doi:10.1093/pubmed/fdh193

23. Kuiper JS, Zuidersma M, Oude Voshaar RC, et al. Social relationships and risk of dementia: a systematic review and meta-analysis of longitudinal cohort studies. *Ageing Res Rev*. 2015;22:39-57. doi:10.1016/j.arr.2015.04.006

24. Stern Y. What is cognitive reserve? theory and research application of the reserve concept. *J Int Neuropsychol Soc*. 2002;8(3):448-460. doi:10.1017/S1355617702813248

25. Zhang YR, Xu W, Zhang W, et al. Modifiable risk factors for incident dementia and cognitive impairment: an umbrella review of evidence. *J Affect Disord*. 2022;314:160-167. doi:10.1016/j.jad.2022.07.008

26. Raz L, Knoefel J, Bhaskar K. The neuropathology and cerebrovascular mechanisms of dementia. *J Cereb Blood Flow Metab*. 2016;36(1):172-186. doi:10.1038/jcbfm.2015.164

27. Freeman R. Neurogenic orthostatic hypotension. *N Engl J Med*. 2008;358(6):615-624. doi:10.1056/NEJMcp074189

28. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 α-hydroxylase in human brain. *J Chem Neuroanat*. 2005;29(1):21-30. doi:10.1016/j.jchemneu.2004.08.006

29. Khera A, McGuire DK, Murphy SA, et al. Race and gender differences in C-reactive protein levels. *J Am Coll Cardiol*. 2005;46(3):464-469. doi:10.1016/j.jacc.2005.04.051

30. Hendriks S, Peetoom K, Bakker C, et al; Young-Onset Dementia Epidemiology Study Group. Global incidence of young-onset dementia: a systematic review and meta-analysis. *Alzheimers Dement*. 2022;19(3):831-843. doi:10.1002/alz.12695