Associations of socioeconomic status and healthy lifestyle with incident early-onset and late-onset dementia: a prospective cohort study

Rui Li, Ruyi Li*, Jinchi Xie, Junxiang Chen, Sen Liu, An Pan, Gang Liu*

Summary

Background Modifiable risk factor estimates are sparse for early-onset dementia incidence. This study aimed to estimate and compare the risk factor profiles of early-onset dementia and late-onset dementia, and to explore the complex relationships between socioeconomic status, lifestyles, and early-onset dementia risk.

Methods In this prospective cohort study, we used data from the UK Biobank for analysis of early-onset dementia and late-onset dementia. For early-onset dementia analyses, data were collected on those aged younger than 60 years without prevalent dementia at baseline. For late-onset dementia analyses, data were collected on those aged 65 years or older at the end of follow-up. Participants with missing information on socioeconomic factors were excluded. Two models were used to test associations between early-onset dementia incidence and socioeconomic status. The first model tested associations between socioeconomic status and early-onset and late-onset dementia incidence, adjusting for covariates. Participant socioeconomic status was defined using education level, income, and employment status via latent class analysis. The second model additionally included a healthy lifestyle score, which was constructed using data on smoking, alcohol consumption, physical activity, and the Healthy Diet Index. Incident early-onset dementia was defined as a dementia case diagnosed before 65 years of age. Multivariable-adjusted Cox proportional hazard regression models were used to estimate the hazard ratio (HR) for risk of dementia. We used multivariable-adjusted Cox proportional-hazard regression models to estimate the HR for risk of both early-onset dementia and late-onset dementia.

Findings Between 2007 and 2010, 257 345 individuals were included in the analysis of early-onset dementia, and 294 133 older individuals were included in the analysis of late-onset dementia. During a mean follow-up of 11·9–12·5 years, 502 early-onset dementia cases and 5768 late-onset dementia cases were documented. Risk factor profiles were typically dissimilar between early-onset dementia and late-onset dementia. For instance, the age and sex adjusted HR for low socioeconomic status (*vs* high) was 4·40 (95% CI 3·43–5·65) for early-onset dementia and 1·90 (1·74–2·07) for late-onset dementia, yielding a ratio of HRs of 2·32 (1·78–3·02). After adjusting for various risk factors, participants with low socioeconomic status (*vs* high) had increased risk for early-onset dementia (3·38, 2·61–4·37), and overall lifestyle mediated 3·2% (1·8–5·7) of the association. Individuals with both low socioeconomic status and unhealthy lifestyles had a higher risk of early-onset dementia (5·40, 3·66–7·97). No significant interaction was observed between lifestyle and socioeconomic status. The association between socioeconomic status and early-onset dementia seemed to be more pronounced in individuals with type 2 diabetes (HR 11·21, 95% CI 2·70–46·57).

Interpretation Early-onset dementia and late-onset dementia might have different risk factor profiles; although risk factors were similar, the magnitude of associations between risk factors and dementia incidence was greater for early-onset dementia. Only a small proportion of the socioeconomic inequity in dementia risk was mediated by healthy lifestyles, which indicates that measures other than healthy lifestyle promotion to improve social determinants of health are warranted.

Funding The National Key Research and Development Program of China, the National Natural Science Foundation of China, the Hubei Province Science Fund for Distinguished Young Scholars, and the Fundamental Research Funds for the Central Universities.

Lancet Healthy Longev 2023; 4: e693–702

See **Comment** page e660

*Contributed equally

Department of Nutrition and Food Hygiene, Hubei Key Laboratory of Food Nutrition and Safety, Ministry of Education Key Lab of Environment and Health, and State Key Laboratory of Environment Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (Rui Li MS, Ruy Li MBBS, S Liu MBBS, Prof G Liu PhD); **Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China** (J Xie MBBS, J Chen MBBS, Prof A Pan PhD)

Correspondence to: Prof Gang Liu, Department of Nutrition and Food Hygiene, Hubei Key Laboratory of Food Nutrition and Safety, Ministry of Education Key Lab of Environment and Health, and State Key Laboratory of Environment Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
liugang026@hust.edu.cn

Introduction

Early-onset dementia refers to the onset of dementia before 65 years of age.[1] Studies have estimated that 3·9 million people aged 30–64 years have early-onset dementia worldwide,[2] and 370 000 people are newly diagnosed with early-onset dementia each year.[3] Most studies primarily focus on late-onset dementia, which might marginalise the importance of dementia in younger people. Since the relative importance of risk factors might vary with age,[4–6] investigation of the risk

Research in context

Evidence before this study

We searched PubMed for studies published from database inception to April 8, 2023, using the combination of terms "socioeconomic status" or "social determinant" or "lifestyle" or "risk factor" or "dementia" or "early-onset dementia" or "young-onset dementia", without language restrictions. In addition, reference lists from Google Scholar were checked to identify relevant studies. Most studies primarily focused on late-onset dementia, which might suggest that the importance of dementia in younger people is largely overlooked. There are important gaps in our understanding of how risk factors contribute to early-onset dementia risk.

Added value of this study

We found that associations with socioeconomic status and healthy lifestyles were more pronounced for early-onset dementia risk than for late-onset dementia risk. Our study contributes to the field by comprehensively assessing early-onset dementia risk profiles and highlighting the differences between early-onset and late-onset dementia risk profiles. Compared with individuals with high socioeconomic status, those with low socioeconomic status had a more than three-times higher risk of early-onset dementia, and only a small proportion of these associations were mediated by overall lifestyle. The highest risk group for early-onset dementia were individuals of low socioeconomic status with unhealthy lifestyles, who had a 440% greater risk compared with individuals of high socioeconomic status with healthy lifestyles. Although the interaction is not statistically significant, the association between socioeconomic status and early-onset dementia appeared to be more pronounced in individuals with type 2 diabetes. To our knowledge, this study is the first to quantify the complex relationships between socioeconomic status, lifestyle factors, and early-onset dementia risk.

Implications of all the available evidence

Early-onset dementia and late-onset dementia might have varying magnitudes of associations with risk factor profiles. Although socioeconomic status and lifestyle are both important contributors to early-onset dementia and late-onset dementia risk, the magnitude of associations was greater for early-onset dementia. Our findings indicate that healthy lifestyle promotion alone might not substantially reduce the socioeconomic inequity in early-onset dementia and late-onset dementia risk. Therefore, other measures to improve social determinants of health are warranted. Further studies, especially in subgroups such as individuals with diabetes, are warranted to confirm and expand our findings.

factors for early-onset dementia is crucial, as has been done for late-onset dementia. Nonetheless, assessment of early-onset dementia risk profiles is insufficient,[7] even for factors with substantial implications for public health.

Dementia risk has been associated with socioeconomic status,[8] and socioeconomic inequity has become more pronounced in developed countries.[9] Moreover, socioeconomic inequities in dementia risk might be alleviated by lifestyle factors, which are commonly viewed as mediators between socioeconomic status and dementia risk.[10,11] However, there are important gaps in our understanding of how risk factors contribute to early-onset dementia risk. First, we have sparse data on the extent to which various risk factors influence early-onset dementia risk, especially when compared with the expanse of data on risk factors in late-onset dementia. Second, the extent to which overall lifestyle mediates the association between socioeconomic status and early-onset dementia incidence is unclear.[11,12] Third, previous studies often used single variables (eg, income or education level) as indicators of socioeconomic status, but these variables cannot reflect overall socioeconomic status. Finally, the interaction and joint associations of socioeconomic status and overall lifestyle with early-onset dementia risk remain unknown.

Informing efforts to prevent or delay the emergence of early-onset dementia and late-onset dementia is of great public health importance. This study aimed to estimate and compare the risk factor profiles of early-onset dementia and late-onset dementia, and to investigate the complex relationships between socioeconomic status, lifestyle factors, and early-onset dementia risk.

For **UK Biobank** see www.ukbiobank.ac.uk

See Online for appendix

Methods

Study design and participants

The UK Biobank is a large population-based prospective cohort study; the details of the study protocol have been reported previously.[13] Briefly, the UK Biobank recruited over 500 000 participants aged 37–73 years from 22 assessment centres across England, Scotland, and Wales between 2006 and 2010. The end of follow-up was different by country: April 1, 2022, for England; March 1, 2022, for Scotland; and Oct 7, 2021, for Wales. The UK Biobank's website provides baseline summary characteristics of the cohort. We collected data on two groups: individuals aged younger than 60 years without prevalent dementia at baseline were included in the early-onset dementia analyses (appendix p 22), and individuals without prevalent dementia aged 65 years or older at the end of follow-up were included in the late-onset dementia analyses. Participants with missing information on socioeconomic factors were excluded.

The UK Biobank received ethical approval from the North West Multi-Centre Research Ethical Committee and participants provided written informed consent. This research was done under UK Biobank application number 68307.

Procedures

Data on socioeconomic status, lifestyle and other covariates were collected at baseline. Household income, highest education qualification, and employment status were used to construct an overall socioeconomic status variable using latent class analysis.[14] Education qualifications consisted of seven groups based on the UK qualification system: college or university degree; A levels, AS levels, or equivalent; O levels, GCSEs, or equivalent; CSEs or equivalent; NVQ, HND, HNC, or equivalent; other professional qualifications; or none of the above. Participants were classified into six groups according to average household income before tax: less than £18 000, £18 000–30 999, £31 000–51 999, £52 000–100 000, more than £100 000, and do not know. Employment status was divided into three groups: employed (ie, those in paid employment, self-employed, retired, doing unpaid or voluntary work, or who are full or part-time students), unemployed (ie, those unemployed, looking after home or family, or unable to work because of sickness or disability), and none of the above. Three latent classes were identified, representing high, medium, and low socioeconomic status according to the item-response probabilities (appendix pp 25–29).

We also constructed a healthy lifestyle score reflecting cigarette smoking, alcohol consumption, physical activity, and diet according to a previous study and recommendations from WHO (appendix pp 29–31).[14–16] The healthy lifestyle score was the sum of the points, 1 for each factor, and ranged between 0 and 4, with higher scores indicating healthier lifestyles.

Other covariates included age; sex; self-reported race; assessment centres; social isolation; sleep quality; depressive symptoms; presence of *APOE* ε4; body mass index (BMI); high-density lipoprotein cholesterol (HDL-C); low-density lipoprotein cholesterol (LDL-C); triglycerides; HbA_{1c}; prevalent comorbidities (ie, hearing difficulty, hypertension, and cardiovascular disease), and family history of dementia. There were 22 UK Biobank assessment centres across England, Scotland, and Wales. Data were collected and stored by trained staff when participants visited these centres. Assessment centre was included as a covariate based on previous studies, which indicated that centre might be a confounding factor.[14]

We produced two models. The first model tested associations between socioeconomic status and early-onset and late-onset dementia incidence, adjusting for all covariates. The second model additionally included the healthy lifestyle score as a covariate.

We also did a joint association analysis, which assessed the association between early-onset and late-onset dementia, socioeconomic status, and healthy lifestyle factors.

Outcomes

The outcomes of the analysis were incidence of early-onset dementia and of late-onset dementia. The data provided by UK Biobank were used to ascertain dementia cases via algorithms, which were generated based on electronic health records including hospital admissions and death registry, using International Classification of Diseases (ICD)-9 and ICD-10 codes (appendix p 4). Prevalent dementia cases at baseline were also identified using medical history information on dementia-specific prescriptions including memantine, donepezil, galantamine, and rivastigmine.[17] Early-onset dementia was defined as a dementia case diagnosed before 65 years of age, and late-onset dementia was defined as a dementia case diagnosed after 65 years of age.[4]

Statistical analysis

Baseline characteristics were presented as n (%) if categorical, mean (SD) if normally distributed, and median (IQR) if non-normally distributed. ANOVA and χ^2 tests were used to assess differences among groups, and the Kruskal-Wallis test was used if data were non-normally distributed. Cox proportional hazard regression models were used to estimate the hazard ratios (HR) and 95% CIs of outcomes associated with risk factors. Person-years were calculated from baseline until the date of death or diagnosis, or end of follow-up, whichever occurred first. To quantify the HR differences between early-onset dementia and late-onset dementia in each of the risk factors, we calculated a ratio of HRs as has been done in previous studies using the UK Biobank (appendix p 34).[18]

For model two, mediation proportions of the associations between socioeconomic status and early-onset dementia by the mediator (healthy lifestyle score) were calculated by SAS MEDIATE Macro.

In the joint association analysis, we further classified participants into nine groups according to socioeconomic status (low, medium, and high) and healthy lifestyle score (score of 0 or 1; 2; and 3 or 4) and estimated the HRs of incident early-onset and late-onset dementia in different socioeconomic groups, compared with those with high socioeconomic status, and a healthy lifestyle score of 3–4. Stratified analyses were done to investigate the association of the lifestyle score with early-onset and late-onset dementia incidence by socioeconomic status. Healthy lifestyle scores were grouped to increase statistical power, with individuals scoring 0 and 1 grouped together (unhealthy lifestyle) and those scoring 3 and 4 grouped together (healthy lifestyle). The unhealthy lifestyle group was used as the reference group. We used the relative excess risk due to interaction and attributable proportion due to interaction with corresponding 95% CIs as the measure of interaction on the additive scale. To test the robustness and potential variations in different subgroups, we repeated all analyses stratified by sex, race, presence of *APOE* ε4, family history of dementia, hearing difficulty, hypertension, type 2 diabetes, and air pollution scores for their home town.

We did several sensitivity analyses. First, we repeated all analyses by substituting overall socioeconomic status

	Total population (n=257 345)	High socioeconomic status (n=90 950)	Medium socioeconomic status (n=81 579)	Low socioeconomic status (n=84 816)	p value
Age (years)	51·00 (46·00–56·00)	50·00 (45·00–55·00)	51·00 (46·00–55·00)	52·00 (47·00–56·00)	<0·0001
Sex	..	..	..	..	<0·0001
Male	115 570 (44·9%)	42 895 (47·2%)	37 065 (45·4%)	35 610 (42·0%)	..
Female	141 775 (55·1%)	48 055 (52·8%)	44 514 (54·6%)	49 206 (58·0%)	..
Ethnicity	..	..	..	..	<0·0001
White	239 467 (93·1%)	86 199 (94·8%)	77 296 (94·8%)	75 972 (89·6%)	..
Mixed	2051 (0·8%)	695 (0·8%)	556 (0·7%)	800 (0·9%)	..
Asian	5708 (2·2%)	1594 (1·8%)	1328 (1·6%)	2786 (3·3%)	..
Black	5497 (2·1%)	1119 (1·2%)	1377 (1·7%)	3001 (3·5%)	..
Chinese	1015 (0·4%)	400 (0·4%)	241 (0·3%)	374 (0·4%)	..
Other	2923 (1·1%)	773 (0·9%)	616 (0·8%)	1534 (1·8%)	..
Unknown	684 (0·3%)	170 (0·2%)	165 (0·2%)	349 (0·4%)	..
Education levels	..	..	..	..	<0·0001
High qualifications	99 660 (38·7%)	76 543 (84·2%)	14 128 (17·3%)	8989 (10·6%)	..
Intermediate qualifications	134 104 (52·1%)	14 407 (15·8%)	65 440 (80·2%)	54 257 (64·0%)	..
Low qualifications	23 581 (9·2%)	0	2011 (2·5%)	21 570 (25·4%)	..
Occupation	..	..	..	..	<0·0001
Employed	228 002 (88·6%)	87 578 (96·3%)	73 297 (89·9%)	67 127 (79·1%)	..
Unemployed	27 944 (10·9%)	3241 (3·6%)	7811 (9·6%)	16 892 (19·9%)	..
None of the above	1399 (0·5%)	131 (0·1%)	471 (0·6%)	797 (0·9%)	..
Household income, GBP	..	..	..	..	<0·0001
<18 000	36 798 (14·3%)	0	0	36 798 (43·4%)	..
18 000–51 999	124 610 (48·4%)	25 546 (28·1%)	60 197 (73·8%)	38 867 (45·8%)	..
>52 000	87 233 (33·9%)	65 404 (71·9%)	21 382 (26·2%)	447 (0·5%)	..
Do not know	8704 (3·4%)	0	0	8704 (10·3%)	..
Never smoking	148 732 (57·8%)	57 775 (63·5%)	47 146 (57·8%)	43 811 (51·7%)	<0·0001
No excessive alcohol consumption	179 528 (69·8%)	67 604 (74·3%)	57 554 (70·6%)	54 370 (64·1%)	<0·0001
Physical activity	197 835 (76·9%)	72 600 (79·8%)	63 509 (77·9%)	61 726 (72·8%)	<0·0001
Healthy diet	131 566 (51·1%)	48 438 (53·3%)	40 938 (50·2%)	42 190 (49·7%)	<0·0001
Social isolation	123 819 (48·1%)	37 243 (41·0%)	36 118 (44·3%)	50 458 (59·5%)	<0·0001
Quality sleep	162 842 (63·3%)	63 290 (69·6%)	52 455 (64·3%)	47 097 (55·5%)	<0·0001
Depressive symptoms	17 463 (6·8%)	3214 (3·5%)	4527 (5·6%)	9722 (11·5%)	<0·0001
APOE ε4 carriers	65 742 (25·6%)	21 541 (23·7%)	23 404 (28·7%)	20 797 (24·5%)	0·57
Air pollution in participant's local town	..	..	..	..	<0·0001
High levels	79 787 (31·0%)	26 333 (29·0%)	22 244 (27·3%)	31 210 (36·8%)	..
Medium levels	75 639 (29·4%)	23 835 (26·2%)	25 913 (31·8%)	25 891 (30·5%)	..
Low levels	101 919 (39·6%)	40 782 (44·8%)	33 422 (41·0%)	27 715 (32·7%)	..
BMI (kg/m^2)	..	..	..	..	<0·0001
<18·5 or ≥30·0	62 626 (24·3%)	16 623 (18·3%)	20 620 (25·3%)	25 383 (29·9%)	..
18·5–24·9	89 696 (34·9%)	37 293 (41·0%)	26 422 (32·4%)	25 981 (30·6%)	..
25·0–29·9	103 747 (40·3%)	36 738 (40·4%)	34 237 (42·0%)	32 772 (38·6%)	..
HbA_{1c} (mmol/mol)	34·40 (32·10–37·00)	34·00 (31·60–36·30)	34·30 (32·00–36·80)	35·10 (32·60–37·80)	<0·0001
High-density lipoprotein cholesterol (mmol/L)	1·39 (1·17–1·66)	1·43 (1·20–1·70)	1·38 (1·16–1·65)	1·36 (1·14–1·63)	<0·0001
Low-density lipoprotein cholesterol (mmol/L)	3·51 (2·97–4·08)	3·48 (2·96–4·05)	3·53 (3·00–4·10)	3·51 (2·96–4·10)	<0·0001

(Table 1 continues on next page)

	Total population (n=257 345)	High socioeconomic status (n=90 950)	Medium socioeconomic status (n=81 579)	Low socioeconomic status (n=84 816)	p value
(Continued from previous page)					
Triglycerides (mmol/L)	1·41 (0·98–2·10)	1·32 (0·93–1·96)	1·44 (1·00–2·14)	1·49 (1·03–2·20)	<0·0001
Family history of dementia	23 346 (9·1%)	8632 (9·5%)	7124 (8·7%)	7590 (9·0%)	<0·0001
Medical history					
Hearing difficulty	93 936 (36·5%)	31 216 (34·3%)	29 304 (35·9%)	33 416 (39·4%)	<0·0001
Hypertension	116 434 (45·2%)	35 623 (39·2%)	37 298 (45·7%)	43 513 (51·3%)	<0·0001
Type 2 diabetes	11 440 (4·5%)	2557 (2·8%)	3143 (3·9%)	5740 (6·8%)	<0·0001
Cardiovascular diseases	12 292 (4·8%)	2823 (3·1%)	3401 (4·2%)	6068 (7·2%)	<0·0001

Data are median (IQR) or n (%). Early-onset dementia was defined as dementia diagnosed before 65 years of age, and the analyses were conducted among participants aged younger than 60 years at baseline. p values were calculated using analysis of variance for continuous variables and χ^2 tests for categorical variables.

Table 1: **Baseline characteristics of participants in the analysis of associations of socioeconomic status and healthy lifestyle score with incident early-onset dementia according to socioeconomic status**

with each socioeconomic factor (ie, family average income, employment status, and education level), and these factors were mutually adjusted in the models. We also used the individual lifestyle factors to evaluate whether the estimated mediation proportion was similar to that of the main analysis. Second, a weighted healthy lifestyle score was constructed to account for varied magnitudes of the associations between different lifestyle factors and outcomes. Third, we excluded individuals with prevalent Parkinson's disease or stroke as patients with these two diseases were more likely to develop dementia.[4] Fourth, we excluded events that occurred within the first 3 years of follow-up to reduce potential reverse causation. Fifth, we further included the Townsend deprivation index, a variable reflecting county-level socioeconomic status. Sixth, instead of the latent class-derived socioeconomic status variable, a socioeconomic score (range 0–6) was computed by assigning 0, 1, and 2 points to each low-level, medium-level, and high-level socioeconomic factor. Finally, missing data on socioeconomic status were imputed (appendix p 34) to examine how missing data might affect our findings. All analyses were done in SAS (version 9.4).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the 502 492 participants initially enrolled in the UK Biobank, 443 627 participants were included in these analyses (appendix p 22), after excluding those who dropped out of the project (n=125), those without information on socioeconomic factors (n=58 519), or those diagnosed with dementia at baseline (n=221). Among the included participants, 257 345 individuals aged younger than 60 years at baseline were included in the analysis of incident early-onset dementia and 294 133 participants aged 65 years or older at the end of follow-up were included in the analysis of incident late-onset dementia. For the analysis of early-onset dementia, 502 (0·2%) incident early-onset dementia cases were recorded (median length of follow-up 11·9 years, IQR 9·0–12·9), 9298 individuals (3·6%) died during follow-up, 810 participants (0·3%) were lost to follow-up, and 246 735 participants (95·9%) completed follow-up without developing early-onset dementia. For the analysis of late-onset dementia, 5768 (1·96%) incident late-onset dementia cases were recorded (median length of follow-up 12·5 years, IQR 11·7–13·3), 21 661 individuals (7·4%) died during follow-up, 261 participants (0·1%) were lost to follow-up, and 266 443 participants (90·6%) completed follow-up without developing late-onset dementia. Individuals who died or were lost to follow-up were included in the analyses. Participants excluded from the analysis due to missing data were more likely to be of lower socioeconomic status (appendix pp 7–9).

Among participants for early-onset dementia analysis, 90 950 (35·3%) were of high socioeconomic status, 81 579 (31·7%) of medium socioeconomic status, and 84 816 (33·0%) of low socioeconomic status (table 1). Among participants for late-onset dementia analysis, 66 182 (22·5%) were of high socioeconomic status, 72 143 (24·5%) of medium socioeconomic status, and 155 808 (53·0%) of low socioeconomic status (appendix pp 5–6).

For the comparison of early-onset dementia and late-onset dementia incidence, the direction of association was the same in both outcomes for socioeconomic status, healthy lifestyle score, and all other factors (figure 1). Low socioeconomic status, low healthy lifestyle scores, being male, experiencing social isolation, having prevalent diseases, and being *APOE* ε4 carriers were associated with elevated rates of early-onset dementia and late-onset dementia incidence. Some heterogeneity existed between early-onset dementia and late-onset dementia incidence

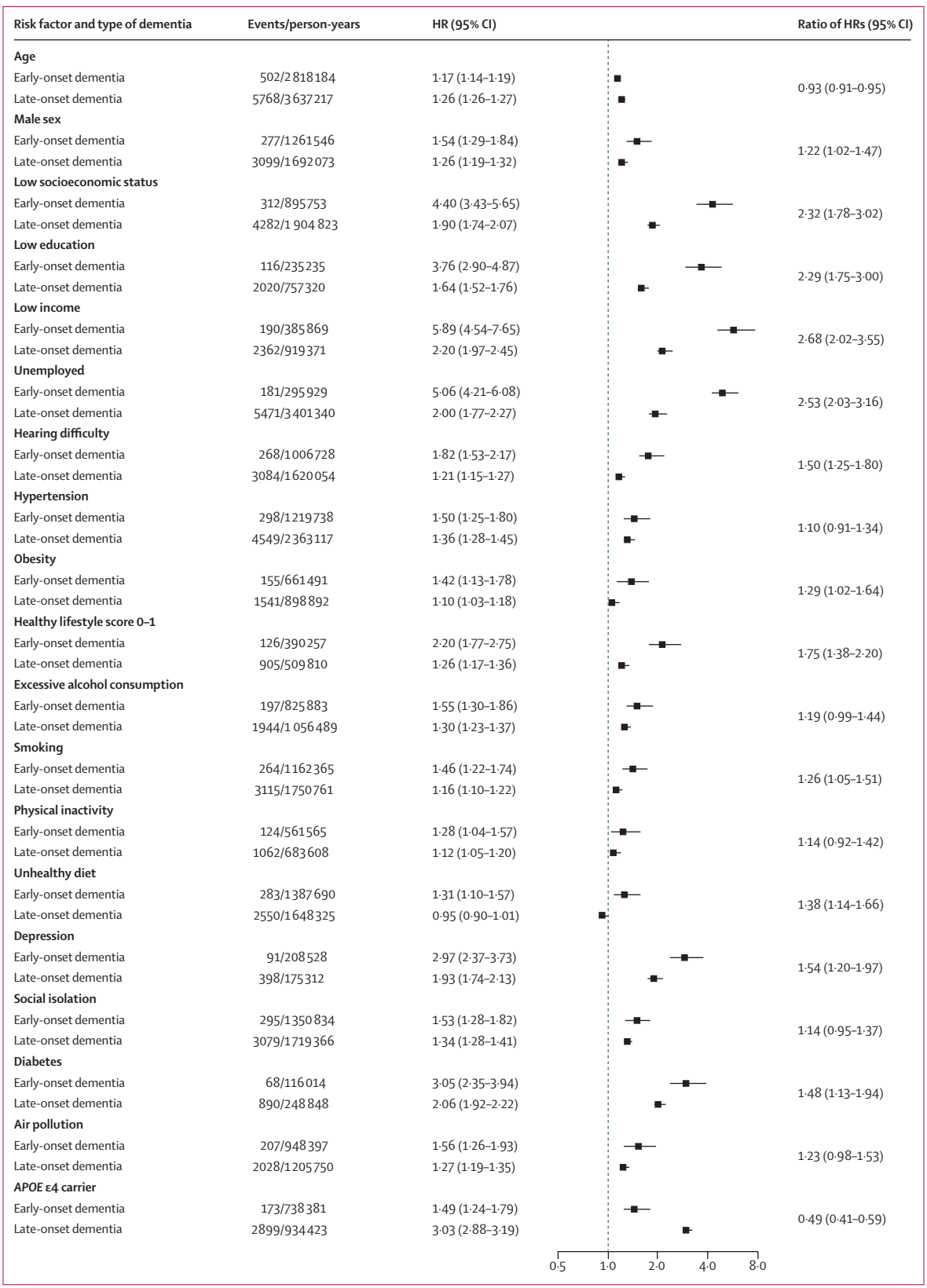

Figure 1: **Associations of risk factors with incident early-onset dementia and late-onset dementia**

Early-onset dementia was defined as dementia diagnosed before 65 years of age, and the analyses were conducted among participants aged younger than 60 years at baseline. Late-onset dementia was defined as dementia diagnosed at 65 years or older, and the analyses were conducted among individuals aged 65 years or older at the end of follow-up. HRs were adjusted for age (continuous) and sex (male or female), with the exception of individual effects for age and sex, which were mutually adjusted. HR=hazard ratio.

in the magnitude of these associations, such that HRs were typically higher for early-onset dementia incidence. For example, for low socioeconomic status (*vs* high), the HR was higher for early-onset dementia risk (HR 4·40, 95% CI 3·43–5·65) than for late-onset dementia risk (1·90, 1·74–2·07), yielding a ratio of HRs greater than 1 (2·32, 1·78–3·02). Conversely, for *APOE* ε4 carriers (*vs* non-carriers), the HR was lower for early-onset dementia (1·49, 1·24–1·79) than for late-onset dementia (3·03, 2·88–3·19), with a ratio of HRs of 0·49 (95% CI 0·41–0·59).

After adjusting for lifestyle score and other covariates, the HR for individuals with low socioeconomic status compared with high socioeconomic status was 3·38 (95% CI 2·61–4·37) for incident early-onset dementia (table 2). Healthy lifestyle (*vs* unhealthy lifestyle) was associated with a 23–51% lower risk in incident early-onset dementia (appendix p 10). The lifestyle score mediated 3·2% (1·8–5·7) of the association between low socioeconomic status and incident early-onset dementia (table 2). Each individual socioeconomic factor (low socioeconomic factor *vs* high socioeconomic factor) was associated with higher risk of early-onset dementia incidence, and the HRs ranged from 1·46 to 2·89 (appendix p 11). The proportion of these associations that was mediated by lifestyles ranged from 1·0% for household income to 9·4% for education level. The results were largely unchanged in the sensitivity analyses (appendix pp 12–13).

In the joint association analysis, we found that participants with low socioeconomic status and 0–1 healthy lifestyle score had a 440% greater risk of early-onset dementia (HR 5·40, 95% CI 3·66–7·97) than participants with high socioeconomic status and 3–4 healthy lifestyle score (figure 2), even though no significant interaction (multiplicative or additive) between socioeconomic status or lifestyle and early-onset dementia were found (appendix pp 23–24). In the stratified analysis, a higher healthy lifestyle score was associated with lower risks of early-onset dementia among individuals of high and low socioeconomic status subgroups and the associations were stronger among those in the high socioeconomic status subgroup (appendix pp 23–24).

Results were not substantially different in the subgroup analyses (p>0·05 for all; appendix pp 14–15). The proportions of socioeconomic inequity in health mediated by lifestyle were all modest and similar to those of the main analyses. Importantly, despite the small sample size, individuals with type 2 diabetes with low (*vs* high) socioeconomic status had a HR of 11·21 (95% CI 2·70–46·57) for early-onset dementia.

For late-onset dementia, the HR for low socioeconomic status was 1·16 (95% CI 1·05–1·29) and for medium socioeconomic status was 1·70 (1·55–1·86) compared with high socioeconomic status, and the proportion mediated by lifestyle was 1·5% for low and 1·9% for medium socioeconomic status (appendix pp 16–17). In the joint associations and stratified analyses of healthy lifestyle score and socioeconomic status, associations with incident late-onset dementia were weaker than incident early-onset dementia (appendix pp 18–19). In the joint association analysis, the HR for individuals with low socioeconomic status and a healthy lifestyle score of 0–1 was 1·97 (95% CI 1·73–2·24) for incident late-onset dementia, compared with those with high socioeconomic status and a healthy lifestyle score of 3–4. In the stratified analysis, a higher healthy lifestyle score was associated with lower risks of late-onset dementia among individuals of low socioeconomic status (0·83, 0·76–0·90). The results remained similar in all sensitivity analyses (appendix pp 20–21).

	n (%)	Events/ person-years	HR (95% CI)		Mediation proportion (%; 95% CI)
			Unadjusted for healthy lifestyle score	Adjusted for healthy lifestyle score	
High socioeconomic status	90 950 (35·3%)	77/1 018 452	1 (Ref)	1 (Ref)	..
Medium socioeconomic status	81 579 (31·7%)	113/903 980	1·54 (1·15–2·06)	1·51 (1·13–2·02)	4·0 (1·3–11·7)
Low socioeconomic status	84 816 (33·0%)	312/895 753	3·50 (2·70–4·53)	3·38 (2·61–4·37)	3·2 (1·8–5·7)

Early-onset dementia was defined as dementia diagnosed before 65 years of age, and the analyses were conducted among participants aged younger than 60 years at baseline. All models included age (continuous), sex (male or female), self-reported race (White or non-White), study centre (England, Wales, or Scotland), social isolation (yes or no), sleep quality (good quality or poor quality), depressive symptoms (yes or no), *APOE* ε4 carrier status (yes or no), body mass index (continuous), high-density lipoprotein cholesterol (continuous), low-density lipoprotein cholesterol (continuous), triglycerides (continuous), HbA_{1c} (continuous), prevalent comorbidities (ie, hearing difficulty, hypertension, and cardiovascular disease with a yes or no), and family history of dementia (yes or no).

Table 2: **Associations of socioeconomic status with incident early-onset dementia and mediation proportion of socioeconomic inequity in early-onset dementia risk attributed to lifestyle**

Discussion

In this prospective cohort study, associations between socioeconomic status and healthy lifestyles with dementia incidence were more pronounced in early-onset dementia risk relative to late-onset dementia risk. Compared with individuals with high socioeconomic status, individuals with low socioeconomic status were associated with more than three-times higher risk of early-onset dementia, and only 1·3–11·7% of the associations were mediated by overall lifestyle. The highest risk group for early-onset dementia were individuals of low socioeconomic status with unhealthy lifestyles, who had a 440% higher risk compared with individuals of high socioeconomic status with healthy lifestyles.

There has been growing interest in identifying disparities in risk factors between early-onset dementia and late-onset dementia.[4,6,19] Most epidemiological studies of dementia set inclusion criteria greater than 65 years or

Risk factor and type of dementia	n/N (%)	Events/person-years	HR (95% CI)	p value
High socioeconomic status				
Healthy lifestyle score 3–4	56 433/90 950 (62·1%)	40/635 616	1 (ref)	..
Healthy lifestyle score 2	24 524/90 950 (27·0%)	19/272 964	1·01 (0·59–1·75)	0·96
Healthy lifestyle score 0–1	9993/90 950 (11·0%)	18/109 871	2·19 (1·25–3·83)	0·0059
Medium socioeconomic status				
Healthy lifestyle score 3–4	45 829/81 579 (56·2%)	55/510 202	1·62 (1·08–2·44)	0·020
Healthy lifestyle score 2	24 302/81 579 (29·8%)	33/268 091	1·68 (1·06–2·68)	0·028
Healthy lifestyle score 0–1	11 448/81 579 (14·0%)	25/125 686	2·50 (1·51–4·13)	0·0004
Low socioeconomic status				
Healthy lifestyle score 3–4	42 776/84 816 (50·4%)	122/453 665	3·41 (2·38–4·91)	<0·0001
Healthy lifestyle score 2	27 203/84 816 (32·1%)	107/287 388	4·23 (2·92–6·14)	<0·0001
Healthy lifestyle score 0–1	14 837/84 816 (17·5%)	83/154 699	5·40 (3·66–7·97)	<0·0001

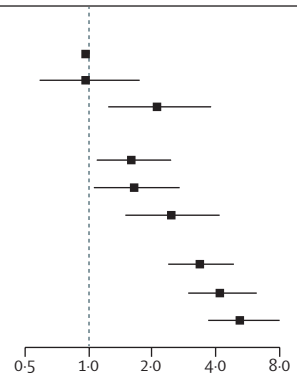

Figure 2: **Joint associations of healthy lifestyle score and socioeconomic status with incident early-onset dementia**
Early-onset dementia was defined as dementia diagnosed before 65 years of age, and the analyses were conducted among participants aged younger than 60 years at baseline. HRs were adjusted for age (continuous), sex (male or female), self-reported race (White or non-White), study centre (England, Wales, or Scotland), social isolation (yes or no), sleep quality (good or poor), depressive symptoms (yes or no), *APOE* ε4 carrier status (yes or no), BMI (continuous), high-density lipoprotein cholesterol (continuous), low-density lipoprotein cholesterol (continuous), triglycerides (continuous), HbA_{1c} (continuous), prevalent comorbidities (ie, hearing difficulty, hypertension, or cardiovascular disease with a yes or no), and family history of dementia (yes or no). HR=hazard ratio.

60 years, considering age-related heterogeneity in diagnostic, recruitment, and genetic factors.[12] Consequently, the importance of dementia in younger people has been largely overlooked. However, understanding the risk profile, pathogenesis, and management of early-onset dementia has recently been attracting considerable attention.[20] A wide range of chronic diseases are more predictive of early-onset dementia than of late-onset dementia, though *APOE* ε4 is more predictive of late-onset dementia.[4] Aside from risk factors, differences in mediators between early-onset dementia and late-onset dementia have also been identified.[5] Specifically, the sex disparity in incident dementia has been shown to be mediated by multimorbidity risk and lifestyle factors; multimorbidity risk was a stronger mediator for the association between sex and incident dementia for late-onset dementia, while lifestyle factors were stronger mediators for the association between sex and incident dementia for early-onset dementia.[5] Collectively, previous studies indicate that early-onset dementia and late-onset dementia might have different risk profiles and pathways. Our study provides additional information to research gaps from a public health perspective as we found that socioeconomic status and lifestyle factors, two paramount modifiable factors, had stronger associations with early-onset dementia risk compared with late-onset dementia risk. These findings need to be confirmed in future studies.

Socioeconomic status, commonly measured by educational level, income level, and occupation, has been used to study socioeconomic inequity in epidemiology. Several previous studies discussed socioeconomic inequity in dementia risk.[8,21,22] In the English Longitudinal Study of Ageing,[23] researchers found that low socioeconomic status, defined by wealth, was associated with a 68% higher risk of dementia in people aged 65 years and older, indicating that the incidence of dementia appeared to be socioeconomically driven primarily by the level of wealth. Similar results were also observed in other studies,[11,21] which support the hypothesis that individual-level and area-level socioeconomic deprivation are associated with increased dementia risk. Moreover, socioeconomic inequity has a far-reaching effect on dementia diagnosis.[24] In Denmark, older adults with higher incomes seem to receive an earlier diagnosis at a less severe dementia stage, which could continuously widen socioeconomic inequity in dementia incidence.[24] By contrast, relatively little is known about early-onset dementia risk and socioeconomic inequity. In a cross-sectional study, individuals with early-onset dementia had an average of 2 years less of formal education than individuals without dementia.[25] Using various factors to represent individual socioeconomic status, our analyses suggest that early-onset dementia risk was more strongly associated with social inequity compared with late-onset dementia risk. The associations were independent of traditional risk factors, such as hypertension and BMI, and genetic risk. Therefore, exploration of possible methods to reduce socioeconomic inequity in early-onset dementia is urgently needed.

Existing evidence indicates causal relationships between socioeconomic status and dementia incidence[11,12] and that socioeconomic status could affect protective factors, such as healthy lifestyle.[11,26] Several studies have investigated the contribution of health behaviours to socioeconomic inequity in the risk of late-onset dementia among older adults, with the mediation proportion varying with different study designs and populations.[10] A 2022 study[10] reported that a combination of lifestyle and social support factors explained about 25% of the total effect of socioeconomic status on late-onset dementia risk among individuals aged 60 years or older at baseline,

although the findings were not significant in each income group separately. Additionally, other studies have indicated that the associations between socioeconomic status and late-onset dementia risk or cognitive functioning are modestly mediated by lifestyle factors.[27] Regarding early-onset dementia risk, lifestyle factors were also identified as the most important factors by Shang and colleagues,[5] and were found to significantly mediate the sex disparity in early-onset dementia.[5] However, to our knowledge, no previous study has explored the pathway between socioeconomic status and early-onset dementia risk in people younger than 60 years. Our study is therefore among the first to use a prospective cohort to examine the mediating proportion of healthy lifestyle factors in socioeconomic status and early-onset dementia risk. Our study found that only up to 11·7% of the association between socioeconomic status and early-onset dementia was explained by lifestyle factors, and our results are in line with results of previous studies done in various populations.

Although healthy lifestyle is considered one of the most impactful factors for preventing dementia,[28] two previous trials[29,30] found that multidomain interventions including lifestyle interventions did not prevent incident dementia in people aged 70 years or older. As there is no specific approach to stop the progression of dementia, identifying modifiable factors in the younger population and informing efforts to prevent or delay the emergence of early-onset dementia are of great public health importance. We confirmed that healthy lifestyles were associated with lower early-onset dementia risk. Our research of early-onset dementia incidence builds on previous research, which primarily focused on late-onset dementia and healthy lifestyles and highlighted the necessity of lifestyle modification to prevent or delay the onset of dementia, regardless of socioeconomic status or genetic risk.[16,31] The investigation of vascular, inflammatory, oxidative stress, neurotoxic, and psychosocial processes contributing to cognitive impairment or dementia is ongoing,[32] but the mechanisms that underlie the relationships between lifestyle factors, socioeconomic inequity, and dementia,[28] especially early-onset dementia, are not yet appropriately prioritised.

Our study was among the first to examine the complex relationships of lifestyles and socioeconomic status with early-onset dementia risk in people aged 37–60 years. We constructed a composite socioeconomic status variable and healthy lifestyle score to encompass the combinations of various factors. The large sample size allowed us to perform joint association and stratified analyses with sufficient statistical power. Nevertheless, we also acknowledge several limitations. First, considering that the presenting symptoms of early-onset dementia are more variable than the initial symptoms seen in late-onset dementia,[33] the subtypes of early-onset dementia cannot be accurately classified, and delayed diagnosis or undiagnosed cases of early-onset dementia are inevitable. Although we used validated algorithms to identify incident dementia cases, misclassification might still exist. Second, information on socioeconomic status and lifestyle was mainly self-reported and was only measured at baseline, thus measurement errors were inevitable. Future studies with repeated measurements are preferred. Third, the lifestyle score was derived from a sum of healthy lifestyle factors and therefore assumed factors had equal weighting, which might not be true. Although we constructed a weighted lifestyle score in the sensitivity analysis and found similar results, the weighted score still cannot fully account for the complex interactions between different lifestyle factors, and the weights were study-specific. Fourth, this sample was limited in terms of ethnic diversity (>85% of European ancestry) and, therefore, further research is required to assess the generalisability of these findings to other populations. Fifth, those excluded from the analysis because of missing covariates were more likely to be of lower socioeconomic status (appendix pp 7–9); therefore, the socioeconomic inequity in health outcomes might be underestimated in our study. Nevertheless, the results remained similar after imputation for missing covariates. Sixth, although we controlled for key personal characteristics and comorbidities, residual confounding was still possible due to imprecise data on some confounding variables (such as depressive symptoms and other genetic factors associated with early-onset dementia). Finally, causal inference cannot be made due to the nature of observational research and the use of HRs with a built-in selection bias.[34]

In conclusion, early-onset dementia and late-onset dementia might have different risk factor profiles; the association between low socioeconomic status and risk of dementia incidence was found to be greater for early-onset dementia, compared with late-onset dementia, and the associations were minimally mediated by lifestyle factors. Therefore, relying solely on promoting healthy lifestyles might not substantially reduce the socioeconomic inequity in early-onset dementia and late-onset dementia risk without considering other social determinants of health. Our findings argue for social and fiscal policies that reduce socioeconomic inequity.[35] Nevertheless, individuals with disadvantaged socioeconomic status and unhealthy lifestyles had the highest risks of early-onset dementia, which highlights the importance of public health and promoting individual-level healthy lifestyles in reducing disease burden of dementia, especially for those of low socioeconomic status.

Contributors

RuiL, RuyL, JX, and GL planned and designed the study. RuiL and RuyL accessed and verified the data, did the statistical analysis, and drafted the manuscript. RuiL, JC, and SL checked the accuracy of the statistical analysis. All authors participated in the interpretation of the results and critical revision of the manuscript. All authors had full access to all the data in the study, have seen and approved the final manuscript, and had

final responsibility for the decision to submit it for publication. GL and AP obtained funding for the study. GL was the guarantor of this work, as such, had final responsibility for the integrity of the data, and the accuracy of the data analysis.

Declaration of interests

GL has received research funding from the National Natural Science Foundation of China, the Hubei Province Science Fund for Distinguished Young Scholars, and the Fundamental Research Funds for the Central Universities. AP has received research funding from the National Natural Science Foundation of China, and the Fundamental Research Funds for the Central Universities. All other authors declare no competing interests.

Data sharing

UK Biobank data are available to all researchers for health-related research and public interest through registration on the UK Biobank (www.ukbiobank.ac.uk).

Acknowledgments

This study was supported by the National Key Research and Development Program of China (2022YFC3600600), the National Natural Science Foundation of China (grant numbers 82273623, 82073554, 81930124, and 82021005), the Hubei Province Science Fund for Distinguished Young Scholars (2021CFA048), and the Fundamental Research Funds for the Central Universities (2021GCRC076, and 2021GCRC075).

References

1 Rossor MN, Fox NC, Mummery CJ, Schott JM, Warren JD. The diagnosis of young-onset dementia. *Lancet Neurol* 2010; **9:** 793–806.

2 Hendriks S, Peetoom K, Bakker C, et al. Global prevalence of young-onset dementia: a systematic review and meta-analysis. *JAMA Neurol* 2021; **78:** 1080–90.

3 Hendriks S, Peetoom K, Bakker C, et al. Global incidence of young-onset dementia: a systematic review and meta-analysis. *Alzheimers Dement* 2022; published online June 17. https://doi.org/10.1002/alz.12695.

4 Shang X, Zhu Z, Zhang X, et al. Association of a wide range of chronic diseases and apolipoprotein E_4 genotype with subsequent risk of dementia in community-dwelling adults: a retrospective cohort study. *EClinicalMedicine* 2022; **45:** 101335.

5 Shang X, Roccati E, Zhu Z, et al. Leading mediators of sex differences in the incidence of dementia in community-dwelling adults in the UK Biobank: a retrospective cohort study. *Alzheimers Res Ther* 2023; **15:** 7.

6 Kim J, Woo S-Y, Kim S, et al. Differential effects of risk factors on the cognitive trajectory of early- and late-onset Alzheimer's disease. *Alzheimers Res Ther* 2021; **13:** 113.

7 Nordström P, Nordström A, Eriksson M, Wahlund L-O, Gustafson Y. Risk factors in late adolescence for young-onset dementia in men: a nationwide cohort study. *JAMA Intern Med* 2013; **173:** 1612–18.

8 Kivimäki M, Batty GD, Pentti J, et al. Association between socioeconomic status and the development of mental and physical health conditions in adulthood: a multi-cohort study. *Lancet Public Health* 2020; **5:** e140–49.

9 Chetty R, Stepner M, Abraham S, et al. The association between income and life expectancy in the United States, 2001–2014. *JAMA* 2016; **315:** 1750–66.

10 Beydoun MA, Beydoun HA, Banerjee S, Weiss J, Evans MK, Zonderman AB. Pathways explaining racial/ethnic and socio-economic disparities in incident all-cause dementia among older US adults across income groups. *Transl Psychiatry* 2022; **12:** 478.

11 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:** 107–24.

12 Cations M, Withall A, Draper B. Modifiable risk factors for young onset dementia. *Curr Opin Psychiatry* 2019; **32:** 138–43.

13 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:** e1001779.

14 Zhang Y-B, Chen C, Pan X-F, et al. Associations of healthy lifestyle and socioeconomic status with mortality and incident cardiovascular disease: two prospective cohort studies. *BMJ* 2021; **373:** n604.

15 WHO. Tackling NCDs: 'best buys' and other recommended interventions for the prevention and control of noncommunicable diseases. Geneva: World Health Organization, 2017.

16 Lourida I, Hannon E, Littlejohns TJ, et al. Association of lifestyle and genetic risk with incidence of dementia. *JAMA* 2019; **322:** 430–37.

17 Zheng B, Su B, Price G, Tzoulaki I, Ahmadi-Abhari S, Middleton L. Glycemic control, diabetic complications, and risk of dementia in patients with diabetes: results from a large UK cohort study. *Diabetes Care* 2021; **44:** 1556–63.

18 Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. *BMJ* 2020; **368:** m131.

19 Cations M, Draper B, Low L-F, 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:** 1747–58.

20 Loi SM, Cations M, Velakoulis D. Young-onset dementia diagnosis, management and care: a narrative review. *Med J Aust* 2023; **218:** 182–89.

21 Marden JR, Tchetgen Tchetgen EJ, Kawachi I, Glymour MM. Contribution of socioeconomic status at 3 life-course periods to late-life memory function and decline: early and late predictors of dementia risk. *Am J Epidemiol* 2017; **186:** 805–14.

22 Hunt JFV, Buckingham W, Kim AJ, et al. Association of neighborhood-level disadvantage with cerebral and hippocampal volume. *JAMA Neurol* 2020; **77:** 451–60.

23 Cadar D, Lassale C, Davies H, Llewellyn DJ, Batty GD, Steptoe A. Individual and area-based socioeconomic factors associated with dementia incidence in England: evidence from a 12-year follow-up in the English Longitudinal Study of Ageing. *JAMA Psychiatry* 2018; **75:** 723–32.

24 Petersen JD, Wehberg S, Packness A, et al. Association of socioeconomic status with dementia diagnosis among older adults in Denmark. *JAMA Netw Open* 2021; **4:** e2110432.

25 Chen Y, Sillaire AR, Dallongeville J, et al. Low prevalence and clinical effect of vascular risk factors in early-onset Alzheimer's disease. *J Alzheimers Dis* 2017; **60:** 1045–54.

26 Nagasu M, Kogi K, Yamamoto I. Association of socioeconomic and lifestyle-related risk factors with mental health conditions: a cross-sectional study. *BMC Public Health* 2019; **19:** 1759.

27 Röhr S, Pabst A, Baber R, et al. Socioeconomic inequalities in cognitive functioning only to a small extent attributable to modifiable health and lifestyle factors in individuals without dementia. *J Alzheimers Dis* 2022; **90:** 1523–34.

28 Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. *Nat Rev Neurol* 2018; **14:** 653–66.

29 Hafdi M, Hoevenaar-Blom MP, Richard E. Multi-domain interventions for the prevention of dementia and cognitive decline. *Cochrane Database Syst Rev* 2021; **11:** CD013572.

30 Moll van Charante EP, Richard E, Eurelings LS, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet* 2016; **388:** 797–805.

31 Dhana K, Franco OH, Ritz EM, et al. Healthy lifestyle and life expectancy with and without Alzheimer's dementia: population based cohort study. *BMJ* 2022; **377:** e068390.

32 Tom D, Alan T, Robert S, John-Paul T. Oxford textbook of old age psychiatry. Oxford: Oxford University Press, 2020.

33 Grayson L, Thomas A. A systematic review comparing clinical features in early age at onset and late age at onset late-life depression. *J Affect Disord* 2013; **150:** 161–70.

34 Hernán MA. The hazards of hazard ratios. *Epidemiology* 2010; **21:** 13–15.

35 Foster HME, Celis-Morales CA, Nicholl BI, et al. The effect of socioeconomic deprivation on the association between an extended measurement of unhealthy lifestyle factors and health outcomes: a prospective analysis of the UK Biobank cohort. *Lancet Public Health* 2018; **3:** e576–85.