



Original Article

Socioeconomic disparities in modifiable risk burden and dementia prevention: A prospective cohort study

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ABSTRACT

Objectives: The Lancet Commission has recommended 14 modifiable risk factors for dementia, but their cumulative impacts and potential socioeconomic disparities remain underexplored. We aimed to investigate the association of individual risk factors and their weighted composite risk score with incident dementia in different socioeconomic status (SES).

Methods: This prospective cohort study included 344,793 participants without dementia at baseline (2006~2010) from the UK Biobank. A weighted composite dementia risk score (0–14) was developed by assigning distinct weights to binary risk factors using $\log(\text{relative risk}) \times (1 - \text{communality})$ from the Lancet study. Cox models and restricted cubic splines were used to examine associations of interest across SES tertiles.

Results: During a median 14.1-year follow-up, 5,515 individuals were diagnosed with dementia. Some risk factors showed SES-specific associations, e.g., hypertension was linked to dementia only in the low-SES group. The population attributable fraction (PAF) for all 14 risk factors was 40.70% (95% CI: 35.81%, 45.23%), with less education accounting for the largest preventable fraction in low- and medium-SES groups (24.6% and 18.3%) and smoking in the high-SES group (5.7%). Each 1-point increase in the composite risk score corresponded to a 19% (95% CI: 17%, 21%) higher risk of dementia, especially in early-onset cases, individuals younger at baseline, APOE $\epsilon 4$ non-carriers, and low-SES population.

Conclusion: Our findings highlight that a substantial proportion of dementia cases may be preventable by addressing modifiable risk factors, with potential effects varying by SES. Targeted modifiable interventions, especially in disadvantaged populations, are substantial to reducing dementia burden and socioeconomic inequalities.

1. Introduction

Dementia is an escalating global public health concern, particularly in socioeconomically disadvantaged regions. As populations age, the number of affected individuals is projected to rise from 57.4 million in 2019 to 152.8 million by 2050, with a disproportionate increase in low-socioeconomic regions (330%) compared to high-socioeconomic regions (140%) [1]. The lack of therapies and the 10–15-year prodromal phase of dementia underscore the urgent need for pre-symptomatic prevention through risk factor modification [2]. In 2024, the Lancet Commission recommended 14 modifiable risk factors, including less education, obesity, excessive alcohol consumption, smoking, physical inactivity,

social isolation, air pollution, hearing loss, traumatic brain injury (TBI), hypertension, diabetes, depression, untreated vision loss, and high low-density lipoprotein (LDL) cholesterol, which collectively explained 45% of global dementia burden [3].

Many studies have examined the association between individual modifiable risk factors and dementia [4,5]. Given that risk factors often co-occur, domain-based aggregation and count-based approaches were commonly used to assess their combined influence [6,7]. For example, one study used latent class analysis to group 12 risk factors into cardiometabolic, substance use-related, and low-risk profiles, and found a 44%–133% higher dementia risk in the first two profiles [8]. Another study found that each additional midlife factor among eight modifiable

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exposures increased dementia risk by 16% [9]. However, domain-based grouping may overlook individuals with multiple risk factors spanning different domains, while treating all factors equally in simple counts may obscure their heterogeneous impacts, leading to inaccurate risk estimation. Previous UK Biobank studies have also linked individual- and area-level socioeconomic deprivation to dementia [10,11]. However, these studies primarily treated socioeconomic deprivation as an independent exposure or potential mediator related to dementia [10–12], the potential socioeconomic disparities in the association between combined modifiable risk factor burden and dementia risk remain underexplored.

To fill the gaps, we aimed to investigate the associations between modifiable risk factors recommended by the Lancet Commission and risk of dementia, and to quantify their prevention potential across socioeconomic strata in the UK Biobank. Additionally, we developed a weighted composite risk score incorporating all these factors, and explored potential effect modifications by age, sex, and genetic susceptibility.

2. Methods

2.1. Study population

The UK Biobank is a population-based prospective cohort that includes 502,411 adults recruited across the United Kingdom between 2006 and 2010. During the baseline assessment, participants attended one of 22 dedicated centers located throughout England, Scotland, and Wales. They completed standardized touchscreen questionnaires, physical measurements, and provided biological samples for collection. All participants provided written informed consent for longitudinal linkage to national electronic health registries. Ethical oversight was ensured by the NHS National Research Ethics Service (11/NW/0382). Participants were excluded if they lacked data on any one of the 14 risk factors ($n = 156,188$), had a history of dementia at baseline ($n = 128$), or lacked available data on covariates ($n = 1302$). A total of 344,793 participants were included in the final analyses (Supplementary Fig. S1).

2.2. Modifiable risk factors and composite risk score for dementia

The 14 modifiable factors for dementia recommended by the Lancet Commission were assessed using self-report data, clinical assessment, linked inpatient records, and linked environmental exposure data (Supplementary Table S1). We developed a weighted composite risk score to reflect the differential impact of each risk factor on dementia. The original weight was calculated as $\log(\text{relative risk}) \times (1 - \text{communality})$ using values from the Lancet study to facilitate cross-study comparisons [3]. The term $(1 - \text{communality})$ accounts for each factor's unique contribution by reducing the influence of overlapping variance with other factors. These original weights were then standardized so that their sum equaled 1. For each individual, a composite risk score was calculated as the weighted sum of the binary risk factors (0 = absent, 1 = present) using the standardized weights. The total score was then multiplied by 14 to rescale it to a range of 0–14, with higher values indicating greater level of risk. Participants were subsequently categorized into three distinct risk groups based on tertiles of the score.

Composite risk score = $14 \times (\text{less education} \times 0.073 + \text{obesity} \times 0.0394 + \text{improper alcohol consumption} \times 0.0167 + \text{smoking} \times 0.0366 + \text{physical inactivity} \times 0.0314 + \text{social isolation} \times 0.1107 + \text{air pollution} \times 0.0251 + \text{hearing loss} \times 0.0520 + \text{TBI} \times 0.1216 + \text{hypertension} \times 0.0294 + \text{diabetes} \times 0.1071 + \text{depression} \times 0.1719 + \text{untreated vision loss} \times 0.0719 + \text{high LDL cholesterol} \times 0.0553)$

2.3. Covariates

Covariates in this study included age at baseline (in years), sex (female or male), ethnicity (White or non-White), and the Townsend deprivation index (TDI). Age, sex, and ethnicity were obtained from touchscreen questionnaires or verbal interviews. TDI is a composite indicator of unemployment, car ownership, house ownership, and household overcrowding, with higher values indicating lower socioeconomic status (SES) [13]. This index provides a dimension of SES that is distinct from education attainment.

2.4. Polygenic risk score and APOE genotyping for dementia

We utilized a pre-existing validated polygenic risk score (PRS) for dementia (Field ID: 26206) from the Standard PRS set in the UK Biobank [14]. This set was developed by a meta-analysis of multiple external genome-wide association study sources by Thompson et al. [14]. Participants were assigned to three polygenic risk groups based on tertiles of PRS. Genotyping and imputation were conducted by UK Biobank using the Affymetrix UK BiLEVE Axiom and UK Biobank Axiom arrays [15]. Participants were stratified into APOE $\epsilon 4$ carriers and non-carriers based on the presence or absence of at least one $\epsilon 4$ allele.

2.5. Ascertainment of dementia outcomes

The outcome of interest was incident all-cause dementia. Information on the date of dementia diagnosis was obtained from the 'first occurrences' in the UK Biobank (category ID 1712), which is a multisource dataset that integrates information from primary care data, hospital inpatient records, death registers, and self-reported medical conditions [16]. Dementia cases were defined as all-cause dementia in this study, containing Alzheimer's disease, vascular dementia, and other unspecified neurodegenerative dementias (ICD codes: F00–F03, G30). Previous research has demonstrated that routinely-collected healthcare data reliably identified dementia, with a positive predictive value of 80–87% [17]. Participants were followed from the date of baseline assessment until their first dementia diagnosis, death, loss to follow-up, or the end of follow-up (1 April 2023), whichever occurred first.

2.6. Statistical analysis

Baseline characteristics of the participants were described as means and standard deviations (SDs) for continuous variables, or as numbers and percentages for categorical variables. Cox proportional hazards models were performed to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for incident dementia associated with each individual modifiable risk factor and the composite risk score. Furthermore, restricted cubic spline was used to examine the dose-response relationship between the composite risk score and dementia. The reference values were set at the 1st percentile, and knots were located at the 5th, 35th, 65th and 95th percentiles of composite risk score. Departure from linearity was assessed by a Wald test. Two incremental models were constructed. Model 1 was adjusted for age and sex. Model 2 was further adjusted for ethnicity and TDI. For analyses of individual risk factors, Model 2 additionally included mutual adjustment for individual modifiable risk factors. We further examined the associations of each individual modifiable risk factor and the composite risk score with dementia, stratified by SES groups defined by tertiles of the TDI, and tested for multiplicative interaction. Kaplan-Meier plots stratified by tertiles of composite risk score were generated to illustrate the cumulative incidence of dementia, with age as time scale. Time-dependent receiver operating characteristic (ROC) analysis was used to assess the score's performance for predicting incident dementia over time. The PAFs quantify the theoretical proportion of dementia cases that could be prevented through the complete elimination of specific risk factors. All these analyses were also conducted across strata of SES

defined by tertiles of the TDI.

Subgroup analyses were performed for early-onset dementia (before 65 years) and late-onset dementia (after 65 years), and for Alzheimer's disease and vascular dementia. For early-onset dementia analyses, participants were further restricted to those aged younger than 60 years without prevalent dementia at baseline, while for late-onset dementia analyses, participants were restricted to those aged 65 years or older at the end of follow-up [18]. Stratified analyses were conducted according to age (≤ 60 and >60 years), sex (female and male), Apolipoprotein E (APOE) $\epsilon 4$ genotype (carrier and non-carrier), tertiles of PRS (low, moderate, and high), and tertiles of TDI (low SES, medium SES, and high SES). To assess whether the effect modification by SES was robust to the categorization of TDI, we additionally modelled TDI as a z-standardized continuous variable and tested its multiplicative interaction with the composite risk score. We investigated whether these factors modified the associations between the composite risk score and incident dementia. Wald tests were used to evaluate the significance of interaction terms.

Several sensitivity analyses were also performed to test the robustness of our results. First, we excluded participants who developed dementia within the first five years to further account for potential reverse causality. Second, we performed competing risk analyses by treating mortality from other causes as a competing event. Third, given the potential impact of missing data in covariates, we used multiple imputation methods and subsequently conducted analyses on the imputed datasets. Fourth, we additionally adjusted for APOE $\epsilon 4$ genotype as a covariate considering its impact on the risk of dementia. Fifth, we developed a weighted composite risk score based on β coefficients from the multivariate-adjusted Cox regression of single modifiable risk factors and repeated the primary analyses.

All the analyses were conducted using STATA 18 (Stata Corp LLP, college station, TX) and R software (version 4.2.2). The statistical significance was set as $P < 0.05$ (two-sided test).

3. Results

3.1. Participant characteristics

Baseline characteristics of 344,793 participants categorized by tertiles of composite risk score are presented in Table 1. The mean age was 56.2 years old (SD: 8.1 years) and 51.9% were female. The group with a higher composite risk score had a lower SES. The proportion of females was higher in the low-risk group.

3.2. Individual modifiable risk factors and dementia

During a median follow-up of 14.1 years, 5,515 participants were diagnosed with dementia. The most prevalent risk factors in the overall population were less education (64.1%), hypertension (48.4%), and smoking (45.0%, Table 1). Smoking, social isolation, air pollution, diabetes, and depression were more prevalent in lower SES groups (Supplementary Table S2). Significant associations were observed between most individual modifiable risk factors and incident all-cause dementia, except for obesity, air pollution, and high LDL cholesterol (Fig. 1 and Supplementary Table S4). The HRs for dementia ranged from 1.06 (95% CI: 1.00, 1.12) for improper alcohol consumption to 4.67 (95% CI: 3.42, 6.38) for TBI after adjusting for potential confounders. Several risk factors demonstrated SES-specific associations. The positive association between less education and dementia was weaker in higher SES groups. Hypertension was a significant dementia risk factor only in the low-SES group (HR: 1.22; 95% CI: 1.10, 1.35), whereas hearing loss was associated with dementia exclusively in the high-SES group (HR: 1.12; 95% CI: 1.02, 1.24). Depression and untreated vision loss showed no association with dementia in the high-SES group.

Table 1
Baseline characteristics by composite risk score for dementia.

Characteristics	Total, n	Composite risk score		
		Low	Middle	High
Total, n	3444,793	115,570	114,718	114,505
Dementia case, n	5,515	1,058	1,830	2,627
Age, Mean (SD)	56.2 (8.1)	54.1 (8.2)	56.8 (8.0)	57.8 (7.7)
TDI, Mean (SD)	-1.5 (3.0)	-2.0 (2.7)	-1.5 (2.9)	-0.9 (3.2)
Sex, n (%)				
Female	179,018 (51.9)	64,557 (55.9)	58,204 (50.7)	56,257 (49.1)
Male	165,775 (48.1)	51,013 (44.1)	56,514 (49.3)	58,248 (50.9)
Ethnicity, n (%)				
White	328,874 (95.4)	110,499 (95.6)	109,770 (95.7)	108,605 (94.8)
Non-White	15,919 (4.6)	5,071 (4.4)	4,948 (4.3)	5,900 (5.2)
Modifiable dementia risk factors, n (%)				
Less education	220,877 (64.1)	39,085 (33.8)	88,248 (76.9)	93,544 (81.7)
Obesity	79,382 (23.0)	9,132 (7.9)	25,901 (22.6)	44,349 (38.7)
Improper alcohol consumption	123,826 (35.9)	32,466 (28.1)	42,800 (37.3)	48,560 (42.4)
Smoking	155,184 (45.0)	28,553 (24.7)	56,649 (49.4)	69,982 (61.1)
Physical inactivity	63,269 (18.3)	12,644 (10.9)	19,953 (17.4)	30,672 (26.8)
Social isolation	29,253 (8.5)	421 (0.4)	4,670 (4.1)	24,162 (21.1)
Air pollution	118,688 (34.4)	29,063 (25.1)	42,128 (36.7)	47,497 (41.5)
Hearing loss	116,453 (33.8)	18,987 (16.4)	36,978 (32.2)	60,488 (52.8)
Traumatic brain injury	395 (0.1)	4 (0.0)	52 (0.0)	339 (0.3)
Hypertension	166,821 (48.4)	34,066 (29.5)	59,153 (51.6)	73,602 (64.3)
Diabetes	18,465 (5.4)	129 (0.1)	1,589 (1.4)	16,747 (14.6)
Depression	38,669 (11.2)	0 (0.0)	1,565 (1.4)	37,104 (32.4)
Untreated vision loss	22,051 (6.4)	1,405 (1.2)	5,059 (4.4)	15,587 (13.6)
High LDL cholesterol	82,641 (24.0)	11,263 (9.7)	31,139 (27.1)	40,239 (35.1)

LDL, low-density lipoprotein; SD, standard deviation; TDI, Townsend deprivation index.

3.3. PAFs of modifiable risk factors

Regarding PAF calculations, 40.70% (95% CI: 35.81%, 45.23%) of dementia cases could potentially be prevented by eliminating all 14 identified risk factors, with the proportion slightly higher in lower SES groups (43.98% in low-, 39.73% in medium-, and 37.58% in high-SES groups) (Fig. 2 and Supplementary Table S5). In the overall population, less education (15.84%), hypertension (8.32%), and diabetes (7.23%) contributed most to the preventable cases. The PAFs of risk factors varied across different SES groups. Specifically, the PAFs for smoking (9.25%), and social isolation (4.96%) were significantly higher in the low-SES group. Less education was the leading contributor in the low- and medium-SES groups (24.58% and 18.27%, respectively), whereas smoking accounted for the largest proportion in the high-SES group (5.72%). For most modifiable factors, the PAF decreased with higher SES. For example, the PAF for diabetes ranged from 9.98% (95% CI: 7.81%, 12.09%) in the lowest SES group to 5.22% (95% CI: 3.51%, 6.90%) in the highest SES group.

3.4. Composite risk score for dementia

The predictive performance of the composite risk score were 0.821

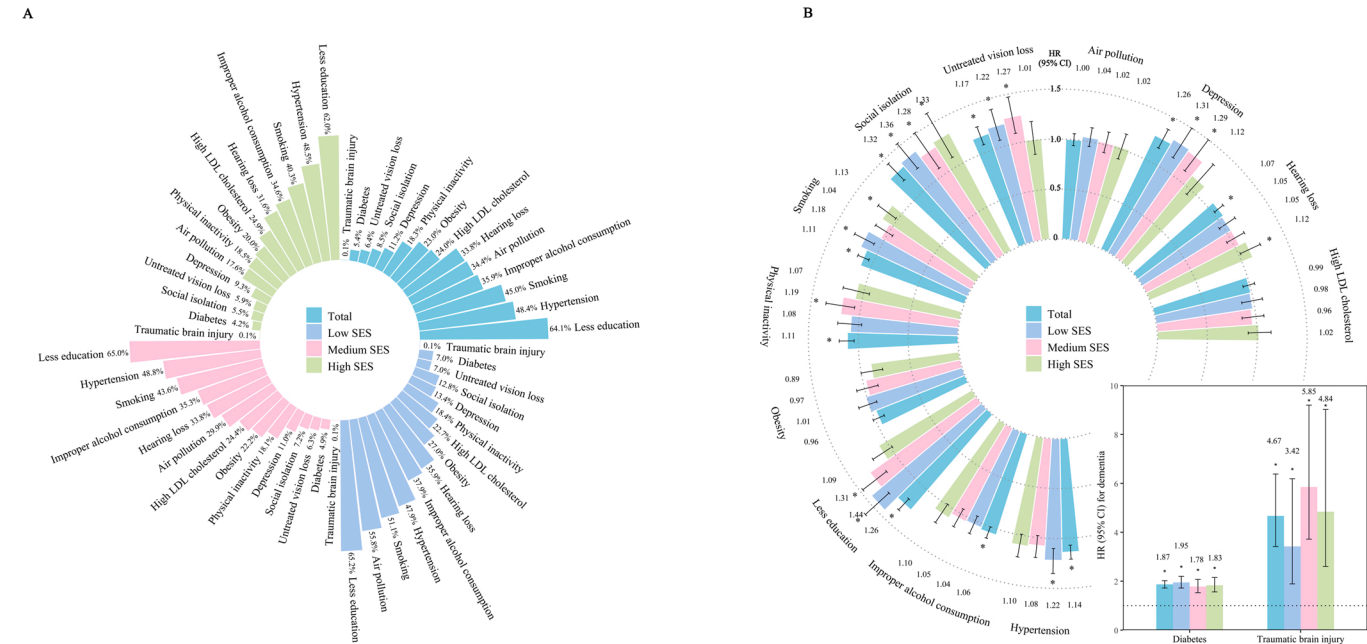


Fig. 1. Prevalence and hazard ratios of 14 modifiable risk factors for dementia. HRs, hazard ratios; LDL, low-density lipoprotein; SES, socioeconomic status. Modifiable risk factors included less education, obesity, improper alcohol consumption, smoking, physical inactivity, social isolation, air pollution, hearing loss, traumatic brain injury, hypertension, diabetes, depression, untreated vision loss, and high LDL cholesterol. Prevalence of 14 modifiable risk factors for dementia (A). HRs of 14 modifiable risk factors for dementia (B). HRs and 95% CIs were calculated in Cox proportional hazard models after adjusting for age (years), sex (female or male), ethnicity (White or non-White), and mutually adjusting for individual modifiable risk factors. * $P < 0.05$.

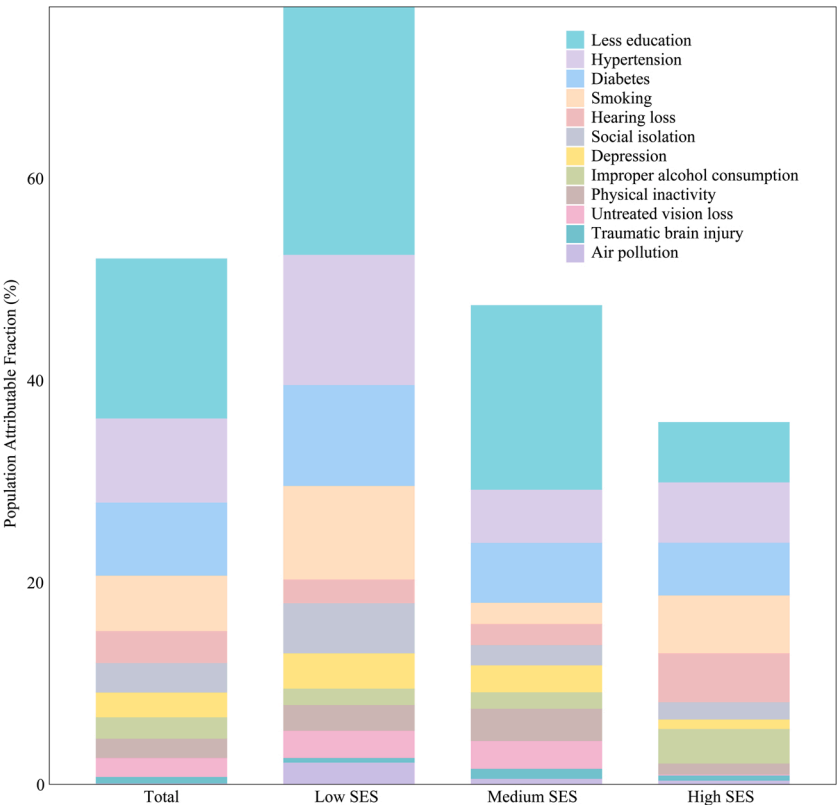


Fig. 2. Population-attributable fractions of 14 modifiable risk factors for dementia. LDL, low-density lipoprotein; PAFs, population-attributable fractions; SES, socioeconomic status. Modifiable risk factors included less education, obesity, improper alcohol consumption, smoking, physical inactivity, social isolation, air pollution, hearing loss, traumatic brain injury, hypertension, diabetes, depression, untreated vision loss, and high LDL cholesterol. PAFs were adjusted for age (years), sex (female or male), ethnicity (White or non-White), and mutually adjusted for individual modifiable risk factors.

and 0.828 at 5 and 10 years, respectively (Fig. 3). The areas under the ROC curves were 0.836, 0.827 and 0.819 at 10 years in low-SES, medium-SES and high-SES group, respectively (Supplementary Fig. S2). A linear increase in dementia risk was observed with higher composite risk scores (19% per 1-point increase), with steeper risk gradients in the low-SES (23%) and medium-SES (18%) groups compared to the high-SES group (13%) (Fig. 3, Supplementary Fig. S3, Supplementary Table S6, and Supplementary Table S7). The lifetime risk of dementia increased with age in all tertiles of the score, with group differences widening over time and reaching 6.08%, 7.30%, and 9.54% at age 85 in the low-, medium-, and high-risk groups, respectively (Fig. 3). The corresponding results by SES were presented in Supplementary Figure S4. Specifically, the high-risk group in the low-SES group reached a lifetime risk of 11.66%, whereas in the medium- and high-SES cohorts, the risk was lower, at 8.67% and 8.76%, respectively.

3.5. Stratified analyses

This association between the composite risk score and dementia risk was stronger for early-onset dementia (40%) than late-onset dementia (18%), and for vascular dementia (36%) than Alzheimer's dementia (13%) (Table 2). Stratified analyses identified significant interactions between the composite risk score and age, APOE ϵ 4 genotype, PRS, and SES (P for interaction < 0.05 , Supplementary Table S6). Stronger associations were observed among individuals aged ≤ 60 years at baseline (39% vs. 17%), APOE ϵ 4 non-carriers (24% vs. 13%), individuals with lower PRS (26% vs. 21% vs. 15%), and those with lower SES (23% vs. 18% vs. 13%) compared to their counterparts.

3.6. Sensitivity analyses

The results remained largely consistent with the primary analyses under various sensitivity analyses (Supplementary Table S8), including the exclusion of participants diagnosed with dementia within the first five years, treating mortality from other causes as a competing event, imputing missing covariates, and adjusting for the APOE ϵ 4 genotype. Notably, the positive association between the weighted score based on 10 modifiable risk factors and dementia risk appeared more pronounced (41% per 1-point increase).

4. Discussion

In this large prospective cohort study from the UK, we found that both the prevalence and HRs of 14 modifiable risk factors recommended by the Lancet Commission for dementia were higher among socioeconomically disadvantaged groups, leading to greater prevention potential in these populations. Furthermore, we developed a weighted composite risk score based on these modifiable risk factors, with a higher score linked to increased dementia risk, regardless of SES or genetic susceptibility, indicating its value in identifying high-risk individuals.

4.1. SES-specific risk patterns for dementia

The PAF for all risk factors in our study was comparable to that reported in the Lancet Commission study (40.7% vs. 45%) [3]. Moreover, we observed higher PAFs among low-SES individuals within the UK, consistent with findings from another UK study and from China [19,20]. Similar patterns were also reported across countries with varying income levels [4]. Given that PAFs rest on causal assumptions and reflect both the magnitude of association (HRs) and the prevalence of risk factors, the interpretation requires examining all three components.

In our study, social isolation (HR = 1.32), diabetes (1.87), and TBI (4.67) were significantly associated with dementia. The magnitudes were comparable to that in prior studies. For example, meta-analyses have shown that loneliness was associated with an increased risk of dementia (HR = 1.31), and diabetes was linked to a 43% higher risk [21, 22]. In a Swedish nationwide cohort, the odds ratio for dementia following TBI declined from 3.52 in the first year to 1.25 after more than 30 years [23]. These epidemiological associations were further supported by evidence from Mendelian randomization (MR) and mechanistic studies, reinforcing their role as universal targets for prevention [24–26]. In contrast, factors such as improper alcohol consumption, air pollution, and high LDL cholesterol were not associated with dementia in any SES stratum, suggesting limited relevance in this context and the need for further research.

Some risk factors exhibited SES-specific associations. For example, less education and hypertension were associated with dementia only among individuals in the low- and medium-SES groups, despite strong MR-based evidence of causality [25,27]. This may be attributable to

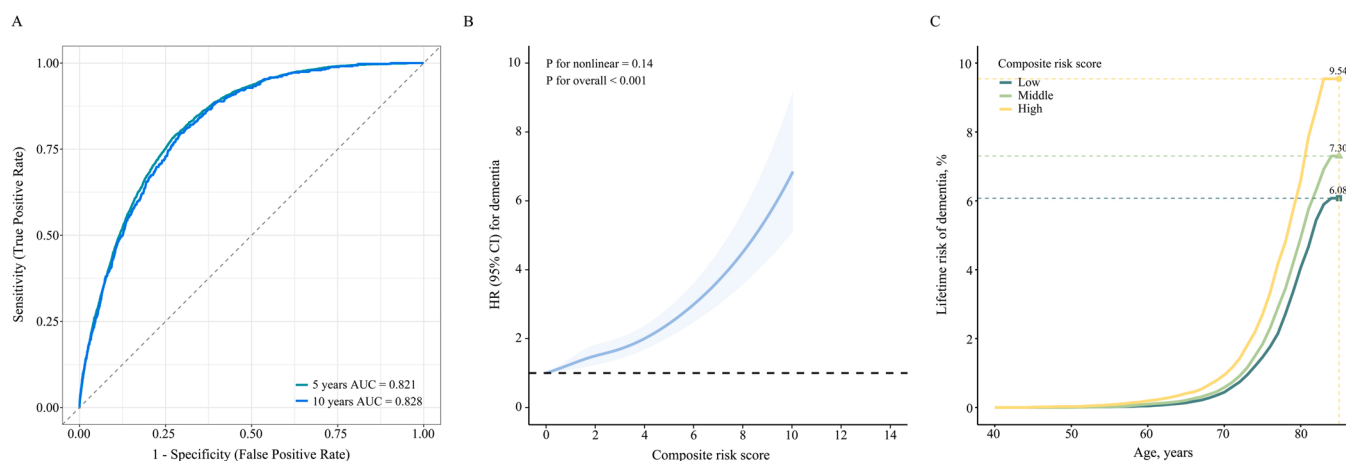


Fig. 3. Predictive performance of composite risk score, dose-response associations, and lifetime risk of dementia. HRs, hazard ratios; CI, confidence interval.

The composite risk score was constructed based on 14 modifiable factors: less education, obesity, improper alcohol consumption, smoking, physical inactivity, social isolation, air pollution, hearing loss, traumatic brain injury, hypertension, diabetes, depression, untreated vision loss, and high LDL cholesterol. Predictive performance of composite risk score for incident dementia (A). The green color shows the predictive accuracy of dementia for 5 years and blue color shows for 10 years. The dose-response associations between composite risk score and risk of dementia (B). Restricted cubic spline was constructed with four knots located at the 5th, 35th, 65th and 95th percentiles of composite risk score. The lifetime risk of dementia, stratified by composite risk score of 14 modifiable risk factors (C). The yellow color shows the low-risk group, light green shows the middle-risk group and the dark green shows the high-risk group. All adjusted for age (years), sex (female or male), ethnicity (White or non-White), and Townsend deprivation index.

Table 2
Composite risk score and incident dementia, subgroup analyses.

	Events/ Total, n	Score (per point increment)	Composite risk score		
			Low	Middle	High
All-cause dementia			1,058/ 115,570	1,830/ 114,718	2,627/ 114,505
Model 1	5,515/ 344,793	1.21 (1.19, 1.23)	1.00 (Reference)	1.24 (1.15, 1.34)	1.73 (1.61, 1.85)
Model 2	5,515/ 344,793	1.19 (1.17, 1.21)	1.00 (Reference)	1.20 (1.12, 1.30)	1.62 (1.51, 1.74)
Early-onset dementia			59/79,513	78/ 63,129	147/ 57,752
Model 1	284/ 200,394	1.45 (1.36, 1.55)	1.00 (Reference)	1.54 (1.10, 2.16)	3.13 (2.31, 4.25)
Model 2	284/ 200,394	1.40 (1.31, 1.49)	1.00 (Reference)	1.44 (1.02, 2.02)	2.71 (1.99, 3.70)
Late-onset dementia			922/70,590	1,738/ 84,147	2,459/ 87,750
Model 1	5,189/ 242,487	1.19 (1.17, 1.22)	1.00 (Reference)	1.22 (1.12, 1.31)	1.67 (1.55, 1.80)
Model 2	5,189/ 242,487	1.18 (1.15, 1.20)	1.00 (Reference)	1.19 (1.10, 1.28)	1.58 (1.46, 1.70)
Alzheimer's dementia			523/ 115,570	951/ 114,718	1,159/ 114,505
Model 1	2,633/ 344,793	1.15 (1.12, 1.18)	1.00 (Reference)	1.30 (1.17, 1.45)	1.56 (1.41, 1.73)
Model 2	2,633/ 344,793	1.13 (1.10, 1.17)	1.00 (Reference)	1.27 (1.14, 1.41)	1.48 (1.33, 1.64)
Vascular dementia			184/ 115,570	389/ 114,718	728/ 114,505
Model 1	1,301/ 344,793	1.39 (1.34, 1.43)	1.00 (Reference)	1.49 (1.25, 1.77)	2.70 (2.29, 3.17)
Model 2	1,301/ 344,793	1.36 (1.31, 1.41)	1.00 (Reference)	1.43 (1.20, 1.71)	2.49 (2.11, 2.94)

The composite risk score was constructed based on 14 modifiable factors: less education, obesity, improper alcohol consumption, smoking, physical inactivity, social isolation, air pollution, hearing loss, traumatic brain injury, hypertension, diabetes, depression, untreated vision loss, and high LDL cholesterol. Model 1 was adjusted for age (years) and sex (female or male). Model 2 was adjusted for age (years), sex (female or male), ethnicity (White or non-White), and Townsend deprivation index.

ceiling effects or mitigating influences linked to greater resources in high-SES populations [28]. Other factors like smoking and physical inactivity exhibited inconsistent associations across SES strata and MR studies, implying possible confounding or context-specific influences shaped by factors such as access to healthcare and lifestyle patterns [25]. These findings highlight the importance of considering SES as an effect modifier.

Moreover, similar HRs may still yield divergent PAFs due to differences in the prevalence of risk factors. For instance, in our study, social isolation had comparable HRs across SES strata but much higher prevalence in the low-SES group, leading to a larger PAF and greater prevention potential in this population. Thus, both causality and population distribution must be jointly considered when identifying and prioritizing risk factors for dementia prevention. While MR studies provide valuable causal evidence, they may overlook SES-specific effect modifications, underscoring the complementary role of randomized trials and mechanistic research.

4.2. Weighted composite risk score for dementia

Modifiable risk factors for dementia often co-occur in individuals (Supplementary Figure S5), underscoring the need for integrated risk assessment. Accumulating evidence indicated a dose-response relationship between the number of risk factors and the incidence of dementia [7]. A Japanese cohort found that compared to those with no risk factors, the age- and sex-adjusted HRs for dementia were 1.25 for one risk factor, 1.59 for two, and 2.21 for three or more [29]. However, simply counting risk factors assumes equal weighting, which may reduce the accuracy of risk estimation, as factors with stronger associations likely exert greater influence. To address this, we developed a weighted composite risk score based on estimates from the Lancet Commission report, which exhibited a positive linear association with dementia risk. Our study revealed that the risk of dementia increased significantly with both higher composite risk scores and lower SES. Prior studies have linked SES or individual modifiable risk factor to dementia [10–12]. Our study further extends this evidence by examining whether SES modifies the association between the burden of multiple modifiable risk factors and incident dementia. These results emphasize the importance of integrating various dimensions and considering socioeconomic status when developing personalized prevention strategies for dementia.

4.3. Potential effect modifications

We observed significant age-specific effect modification in the association between the composite risk score and dementia risk, consistent with previous findings [30,31]. The stronger association among younger participants may reflect their longer cumulative exposure to modifiable risk factors over time [32]. Furthermore, we found that the association was even stronger among APOE $\epsilon 4$ non-carriers and participants in the low PRS groups. This finding aligned with a study showing stronger associations between metabolic syndrome and dementia risk in APOE $\epsilon 4$ non-carriers [33]. While APOE $\epsilon 4$ is recognized as the most potent genetic risk factor for dementia, it may overshadow the contributions of modifiable risk factors. In contrast, some studies have reported a higher risk of dementia among APOE $\epsilon 4$ carriers with unfavorable cardiovascular health [34]. These divergent findings may reflect the complex interplay of genetic and environmental factors in shaping dementia risk [35]. Given that most of the population are APOE $\epsilon 4$ non-carriers, population-wide mitigation of modifiable risk factors remains a cost-effective strategy for dementia prevention.

4.4. Potential mechanisms between risk factors and dementia

The mechanisms underlying these associations may involve reduced cognitive reserve, vascular dysfunction, neuroinflammation, and pathological protein aggregation. For example, lower education may reduce cognitive reserve, increasing vulnerability to neuropathological insults [36]. Hypertension and type 2 diabetes can impair cerebral perfusion and promote neuroinflammation through vascular injury and blood–brain barrier disruption [37,38]. TBI induces axonal damage and persistent immune activation, facilitating amyloid and tau pathology [39]. Social isolation may exacerbate hypothalamic-pituitary-adrenal axis dysregulation and chronic inflammation, impairing synaptic plasticity and accelerating cognitive decline [40]. These mechanisms suggest common biological pathways that could be targeted to prevent or delay dementia.

4.5. Global and national efforts toward dementia prevention

In response to the rising burden of dementia, international organizations and national governments have launched strategic plans. The World Health Organization (WHO) introduced the Global Action Plan on the Public Health Response to Dementia 2017–2025, which outlines seven priority areas and aims for 75% of countries to establish or update

national dementia policies by 2025 [41]. Many of these plans emphasize reducing dementia risk by addressing modifiable factors—for example, the National Alzheimer's Project Act in the United States and the National Action Plan to Address Senile Dementia in China [42].

In parallel, both observational studies and clinical trials have shown that reducing modifiable risk factors—either individually or through multidomain interventions—can lead to improved cognitive outcomes or lower dementia risk [43]. For example, the Framingham study reported a decline in dementia incidence following reductions in the PAFs for low education and smoking [44], while the FINGER trial demonstrated that combined lifestyle interventions (diet, exercise, cognitive training, and vascular risk monitoring) could help preserve cognitive function in at-risk older adults [45]. Adaptations of this model in other countries (e.g., U.S. POINTER, the multinational WW-FINGERS network) highlight growing global interest in population-based prevention strategies [46,47].

However, these initiatives also underscore persistent challenges, including scalability, long-term adherence, and the need to tailor interventions to diverse cultural and socioeconomic contexts. Moreover, although our study revealed a higher prevention potential among lower socioeconomic groups, global policy responses remain uneven. Among the 50 member states that have developed national dementia plans under the Global Dementia Observatory, 65% are high-income countries [48]. This imbalance reflects structural inequities in policy prioritization and resource allocation, which may hinder effective dementia prevention in lower-resource settings.

4.6. Strengths and limitations

Strengths of this study include the large sample size, long-term follow-up, and the stratified analysis by SES, which provided insight into how risk factors and prevention potential vary across SES groups. In addition, we developed a weighted composite score, allowing a more nuanced assessment of cumulative dementia risk than traditional unweighted approaches. However, several important limitations should be noted. First, while our study observed robust associations, these findings do not necessarily imply causation due to the inherent limitations of observational research designs. To address potential reverse causality, we excluded participants who developed dementia within the first five years of follow-up. Second, the UK Biobank may not be representative of the general population, as participants tend to be healthier and the cohort was predominantly White. This may attenuate the observed associations and limit the generalizability of findings to more diverse racial and ethnic groups. Further studies involving more diverse populations across wider geographical areas are needed to corroborate these findings. Third, dementia ascertainment via medical records could introduce bias and may underestimate incident dementia. However, the use of a multisource dataset in our study helped to capture the full spectrum of cases, potentially minimizing bias. Finally, the PRS examined was constructed specifically for Alzheimer's disease, limiting our ability to explore genetic risk associations for other dementia subtypes.

5. Conclusion

In this prospective cohort study of UK Biobank participants, we found socioeconomic disparities in the association between modifiable risk factors raised by the Lancet Commission and the risk of all-cause dementia, and we developed a weighted composite score to quantify individual risk. These findings highlight the need for tailored prevention strategies across socioeconomic contexts and support the use of a person-centered weighted risk score to identify individuals at elevated risk of dementia.

Authors' contributions

CX, ZC and XW were involved in the conception, design, and

interpretation of the results. XZ and KS wrote the first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript. XZ and KS analyzed the data and interpreted the results. NC, ZC, XW and CX have made critical revision of the manuscript for important intellectual content. CX had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Patient consent for publication

Not applicable.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. The studies involving human participants were reviewed and approved by NHS National Research Ethics Service (NW/0382). Patients/participants provided their written informed consent to participate in this study.

Declaration of Generative AI and AI-assisted technologies in the writing process

Not applicable.

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Data availability

The data that we used in this study can be accessed by researchers on application. Requests for data access should be made directly to the UK Biobank.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jnha.2026.100909>.

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