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Association of psychosocial state with subsequent risk of dementia: a prospective cohort study based on the UK Biobank

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Abstract

Background Multiple psychosocial factors have been associated with dementia, while the individual or joint effects of various psychosocial states on dementia remain unrevealed due to the complex interplay between those factors. Here, the authors examined the associations of psychosocial factors and patterns with subsequent risk of dementia, and if the associations could be modified by genetic susceptibility to dementia.

Methods UK Biobank dementia-free participants were followed from one year after recruitment (median date: 24 January, 2010) until 31 October, 2022. Psychosocial states were measured by 22 items related to five dimensions, including psychiatric history, recent stressful life events, current psychiatric symptoms, social contact, and individual socioeconomic state. We identified clusters of individuals with distinct psychosocial patterns using latent class analysis. Cox proportional hazards models were used to evaluate the association between psychosocial items, as well as psychosocial patterns, and risk of dementia. We further performed stratification analyses by apolipoprotein E (*APOE*) genotype, polygenic risk score (PRS) of dementia, and family history of dementia.

Results Of 497,787 included participants, 54.54% were female. During a median follow-up of 12.70 years, we identified 9,858 (1.98%) patients with newly diagnosed dementia. We identified seven clusters with distinct psychosocial patterns. Compared to individuals with a pattern of 'good state', individuals with other unfavorable patterns, featured by varying degrees of poor psychological state ('fair state' and 'mildly, moderately, and extremely poor psychological state'), low social contact or socioeconomic state ('living alone' and 'short education years'), were all at an increased risk of dementia (hazard ratios [HR] between 1.29 and 2.63). The observed associations showed no significant differences across individuals with varying *APOE* genotypes, levels of PRS, and family histories of dementia.

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Conclusion Unfavorable psychosocial patterns are associated with an increased risk of dementia, independent of genetic susceptibility. The findings highlight the importance of surveillance and prevention of cognitive decline among individuals with suboptimal psychosocial state.

Keywords Dementia, Alzheimer's disease, Psychosocial state, Genetic susceptibility

Background

Dementia is a group of diseases primarily affecting the brain, damaging memory, thinking and functional abilities for daily activities, affecting patients living with the disease, their families, and society [1]. The burden of this disease is increasing heavily over time, with the number of patients expected to increase from 50 million to 152 million by 2050 worldwide [1, 2]. Due to the absence of effective treatment, exploring the role of modifiable risk factors, in particular psychosocial state [3], in the development of dementia has become an important approach for establishing preventive strategies.

The psychosocial state represents a combined state of mental, emotional, social and spiritual health and is proposed to be an essential modifiable risk factor for the development and progression of dementia [1, 4]. Existing evidence has reported that several unfavorable psychosocial factors, including poor socioeconomic state (SES) (e.g., education, employment, household income) [5–8], stressful life events and traumatic experiences [9, 10], poor psychiatric state (e.g., depression, stress-related disorder) [11–13], and a lack of social health [14, 15], are positively associated with the risk of dementia. However, psychosocial factors are usually assessed with different definitions [16] and, importantly, are correlated with each other (e.g., individuals experiencing stressful life events are more likely to be in a poor psychiatric state) [17]. Previous studies indicated that identification of distinct psychosocial patterns was helpful to implement individualized mental health care programs [18–20], while no study to date has clustered these related factors in researching risk of dementia, using, i.e., latent class analysis. The coexistence of multiple psychosocial risk factors might even be more strongly related to the risk of dementia compared to a single risk factor, leaving the effect of multiple psychosocial factors, jointly or individually, on the risk of dementia unrevealed.

Evidence has been accumulated suggesting that the risk of dementia is clustered within families [21] and possibly determined by disease susceptibility of dementia [22]. For instance, the ε4 allele of the apolipoprotein E (*APOE*) gene is the most established genetic risk factor for sporadic Alzheimer's disease (AD) and other types of dementia [23]. The polygenic risk score (PRS) combining multiple risk genes for AD provides a quantitative measure of the genetic risk of dementia [24]. Thus, whether the association between psychosocial state and risk of dementia is modified by family history of dementia and associated genetic determinants has not been investigated.

Therefore, taking advantage of the community-based UK Biobank cohort with enriched records on psychosocial factors and individual-level genotype information, we aimed to group individuals according to exclusive psychosocial patterns after combining multiple psychosocial factors, and to investigate associations of different patterns with the risk of dementia. We further explored if the association would be modified by disease susceptibility of dementia.

Methods

Study design and participants

UK Biobank is a community-based prospective cohort that recruited 502,507 participants aged between 40 and 69 years from 2006 to 2010 [25]. This study included three steps: (1) association analysis of individual psychosocial items with risk of dementia; (2) identification of clusters of participants with distinct psychosocial patterns using items from step 1, and their relationships with risk of dementia; and (3) stratified analysis by disease susceptibility (Fig. 1). In step 1, we excluded individuals who withdrew from the UK Biobank (n=151), had a diagnosis of dementia at recruitment (n=267), had a history of traumatic brain injury that might have affected cognitive function (n=3,357), and lacked any data on 22 assessed psychosocial items (n=945), leaving 497,787 participants to be included. In step 2, because the identification of clusters requires complete information on all items, 366,493 participants were included. In step 3, we included 307,506 participants for stratified analyses by disease susceptibility, after excluding those who were non-Caucasian ancestry or without available genetic and family history data (n=58,987), to reduce genetic heterogeneity and enhance the statistical power to detect associations between genes and phenotypes [26]. The characteristics of the participants included in each step are shown in Supplementary Table 1. We followed all participants from one year after recruitment (median date: 24 January, 2010) until a clinical diagnosis of dementia, death, loss to follow-up or the end of study (31 October, 2022), whichever occurred first.

The UK Biobank has full ethical approval from the NHS National Research Ethics Service (reference number: 16/NW/0274), all participants completed informed consent prior to the initiation of any study procedures. This study was also approved by the biomedical research ethics

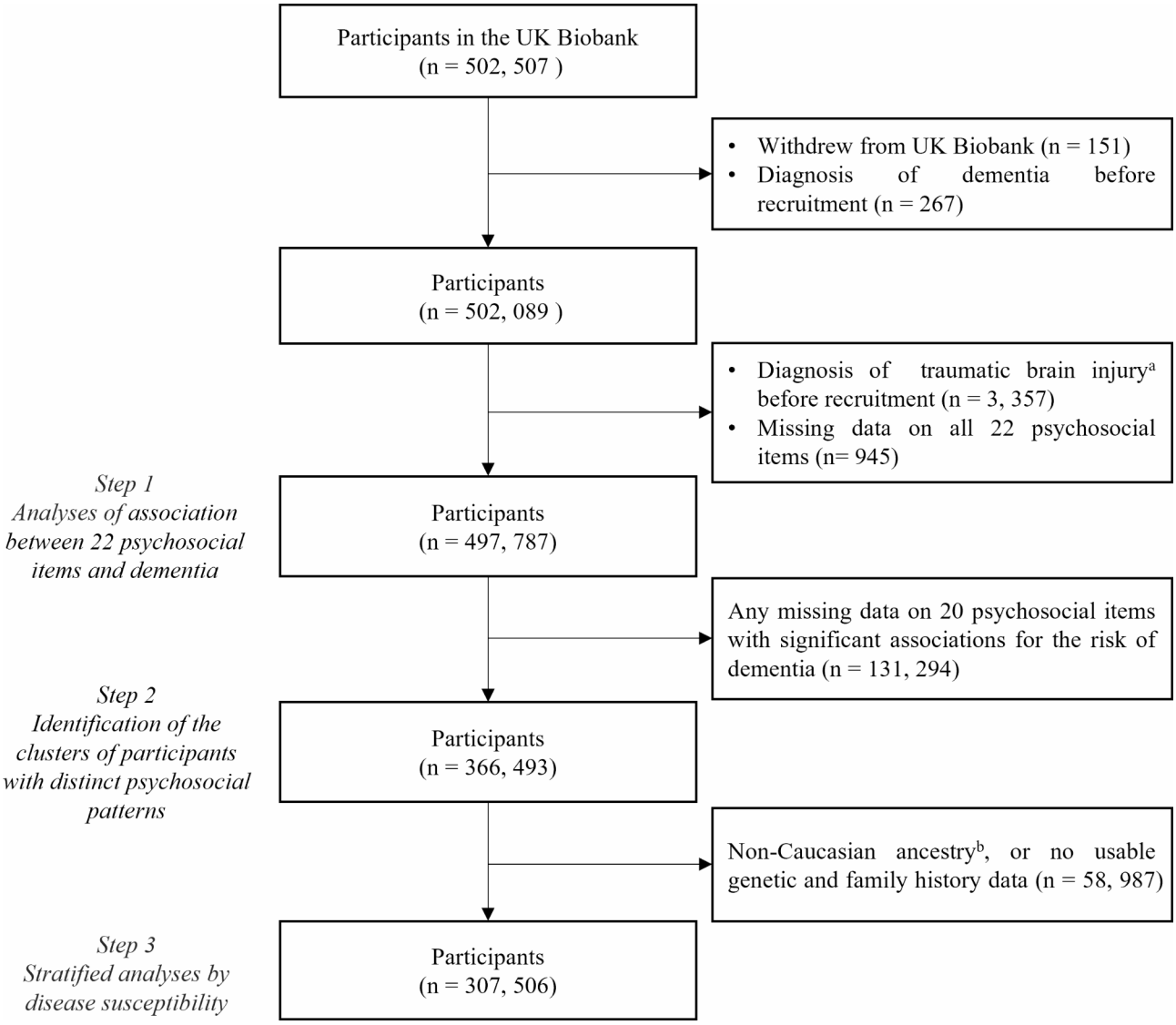


Fig. 1 Flowchart of the study. [a] Traumatic brain injury diagnoses before recruitment were identified according to the International Classification of Diseases-10 codes (S06, S02.0, S02.1, S02.7, S02.8, S02.9) using hospital inpatient records. [b] Caucasian ancestry refers to a genetic ethnic group, involving individuals who self-identified as White British and have very similar genetic ancestry based on a principal components analysis of the genotypes

committee of West China Hospital (reference number: 2019.1171) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Ascertainment of psychosocial state

Based on previous studies [1, 4, 16], we ascertained psychosocial state as a profile consisting of five dimensions, including history of psychiatric disorder, recent stressful life events, current psychiatric symptoms, social contact, and individual SES. History of psychiatric disorder included four items, each coded as yes or no to diagnoses of anxiety, depression, stress-related disorder, and substance misuse, by using International Classification of Diseases (ICD)-10 codes from hospital inpatients, primary care, and self-reported data to those occurring before recruitment. Information on recent stressful life events was ascertained from baseline self-report questionnaires, collected as yes or no to those that happened in the past two years, including traumatic event occurred to yourself, traumatic event occurred to a close relative, death of a close relative, death of a spouse/partner, marital separation, and financial difficulties. Current psychiatric symptoms were ascertained from self-report questionnaires at recruitment, reported as a frequency (nearly every day, more than half the days, several days, and not at all) during the past two weeks to each item involving depression, unenthusiasm, tenseness, and tiredness. Social contact was collected at baseline as yes or no to living alone, low frequency of friends/family

visit, low frequency of leisure/social activities, loneliness, and not able to confide, according to cut-offs defined previously [14, 15]. Self-reported individual SES was collected at recruitment as education years (<10 years, 10–13 years, 13–15 years, 15–20 years, ≥20 years), calculated using the age completed full time education and qualifications [27], annual household income (low [less than £18, 000], low-moderate [£18, 000–30, 999], moderate [£31, 000–51, 999], moderate-high [£52, 000-100, 000], and high [greater than £100, 000]), and employment state (unemployed and employed). The details for ICD-10 codes, field codes, and cut-offs of psychosocial items are available in Supplementary Table 2.

Ascertainment of dementia

The outcome was the first-ever diagnosis of dementia, including AD, vascular dementia (VD), other dementia and unspecified dementia, ascertained through data from hospital inpatients, primary care, death registers, and self-reported data at subsequent assessment center visits using ICD-10 codes (Supplementary Table 3).

Covariates

Data on demographics (age, gender, ethnicity), lifestyle factors (e.g., smoking, alcohol drinking, hours of sleep [28]), and hearing loss state [29] were collected at baseline using self-report questionnaires. Physical activity was evaluated by the International Physical Activity Questionnaire score summarizing the metabolic equivalent task (MET)-weighted time spent in vigorous, moderate, and walking activity. The body mass index (BMI) was constructed from height and weight measured at the initial visit to the assessment center. The Charlson comorbidity index (CCI) was calculated by summarizing the presence of multiple medical conditions according to inpatient hospitals, primary care and self-reported records [30], except for dementia (ICD-10 codes in Supplementary Table 3). A history of hypertension and hyperlipidaemia was identified through inpatient hospital and primary care data (Supplementary Table 3). Grip strength, measured at the initial visit to the assessment center by adjusting for sex and BMI, was used as an index of physical frailty [31]. The *APOE* ε4 genotype was determined by *APOE* SNVs rs429358 and rs7412, where individuals with 1 or 2 ε4 alleles were considered to be *APOE* ε4 carriers and the others to be *APOE* ε4 non-carriers [32–34]. We used calculated standard PRS for AD as an index of genetic risk of dementia, the process of generating PRS including methodologies pertaining to genotyping, imputation, and quality control within the UK Biobank, and the validation of this PRS has been documented previously [24, 35, 36]. Higher scores indicate an increased genetic predisposition to dementia. A family history of dementia was defined as dementia for any first-degree relatives (father, mother, and siblings) according to baseline self-report questionnaires.

Statistical analysis

The incidence rate (IR) was calculated as the total number of patients with dementia divided by the accumulated person-time at risk. In step 1, we assessed the associations between individual psychosocial items and incident dementia using conditional Cox proportional hazards regression models, represented as hazard ratios (HRs) with 95% CIs, attained age was used as the time scale. The estimates were adjusted for gender (female or male), ethnicity (non-Caucasian or Caucasian), smoking (never, previous, current, or unknown), alcohol drinking (never, previous, current, or unknown), hours of sleep (normal [7–9 h], long or short sleep [>9 h or <7 h], or unknown), physical activity (low, moderate, high, or unknown), BMI (<25 kg/m², 25–30 kg/m², ≥30 kg/m², or unknown), grip strength (normal, low, or unknown), CCI (0, or ≥1), history of hypertension (no or yes), and history of hyperlipidemia (no or yes). We adjusted the P values using the false discovery rate (FDR) to correct for multiple testing, with an FDR threshold of 0.05 chosen to balance Type I and Type II errors [37].

In step 2, we used latent class analysis (LCA) to identify the clusters of participants with distinct psychosocial patterns, by taking into account the contributions from the correlations between the items with significant associations with the risk of dementia (Supplementary Method) [38]. The optimal number of clusters was selected by comparing the performance and interpretability of LCA models with different numbers of clusters (selection criteria in Supplementary Table 6) [39]. To validate the robustness and generalizability of these clusters, we further randomly divided participants into two validation datasets and identified clusters in each validation dataset. Using the most favorable patten (i.e., good state) as the reference, we estimated the association between unfavorable psychosocial patterns and the risk of dementia. We further performed stratified analyses by age at recruitment (≤65 years or >65 years) and gender (female or male). In step 3, we conducted stratified analyses according to the *APOE* ε4 genotype (non-carrier or carrier), PRS for dementia (grouped as low, or high genetic risk by terciles), and family history of dementia (without or with).

We performed several sensitivity analyses. First, we stratified the association by baseline cognitive function among a sample of 364,422 participants with available data on reaction time at baseline (grouped as high [reaction time<1st tertile] or low [reaction time>2nd tertile]). Reaction time is an index validated to represent cognitive functioning, with a higher score representing a poorer level of cognitive function [40, 41]. Second,

because the *APOE* ε4 genotype and PRS represent the genetic determinants of AD, we repeated the stratified analyses between patterns and risk of AD. Third, to test the robustness of our results to the concern of reverse causality, we repeated the association by applying 5- and 10 year lag times.

All data analyses were completed using R software (version 4.0). A two-tailed test with $P<0.05$ was considered statistically significant. The proportional hazards assumptions for Cox regression were held in all models by using a Schoenfeld residual plot.

Results

The median age of the participants at recruitment was 58.00 years, and 54.54% were female (Supplementary Table 1). During a median follow-up of 12.70 years, we identified 9,858 (1.98%) patients with newly diagnosed dementia, among whom 3,383 had AD, 1,529 had VD, 1,799 had other subtypes of dementia and 3,147 had unspecified dementia (Supplementary Table 4).

The associations of psychosocial items and dementia risk

In step 1, compared with individuals belonging to the favorable psychosocial categories, those who reported unfavorable levels of psychosocial items had a higher risk of dementia (Fig. 2, Supplementary Table 5). The strongest association was observed for low household income (HR 2.05, 95% CI 1.70 to 2.47). Traumatic event occurred to a close relative was inversely associated with an individuals' risk of dementia (HR 0.86, 95% CI 0.80 to 0.92), while the association for death of a close relative or spouse/partner was not statistically significant.The identification of clusters of participants with distinct psychosocial patterns.

In step 2, with the inclusion of 20 psychosocial items with a significant association with the risk of dementia, we identified seven clusters with distinct psychosocial patterns (Supplementary Table 6). We then named the seven clusters according to their most featured psychosocial profile (Fig. 3A and B; Table 1). Briefly, the pattern of 'good state' was characterized by lower possibilities of suffering all psychosocial abnormalities than the total population level (n=136,060). Patterns of 'short education years' (n=81,767) and 'living alone' (n=47,987) were merely featured by higher possibilities of short education years and social isolation, respectively. In addition, we observed 4 clusters of participants with similar psychosocial patterns but varying degrees of poor psychological state: 'fair state' (n=56,765), 'mildly poor psychological state' (n=28,402), 'moderately poor psychological state' (n=8,688) and 'extremely poor psychological state' (n=6,824). Similar seven clusters with distinct psychosocial patterns were also identified in two validation datasets (Supplementary Table 7).

The associations of psychosocial patterns with dementia risk

Compared with individuals belonging to the 'good state', individuals with other patterns were all at increased risk of dementia (HRs ranged from 1.29 to 2.63), with the strongest association for 'extremely poor psychological state' (HR 2.63, 95% CI 2.23 to 3.11) (Fig. 3C). Similar associations were observed for subtypes of dementia (Supplementary Table 8). Similar associations were noted across different age groups (Supplementary Table 9) and by gender (Supplementary Table 10).

In sensitivity analyses, although largely similar, we observed stronger associations with the risk of dementia among individuals with low cognitive function, for patterns of 'fair state' (Supplementary Table 11). We found largely similar associations between psychosocial patterns and risk of any dementia when applying a 5- and 10 years lag times (Supplementary Table 12).

Disease susceptibility of dementia

The associations between psychosocial patterns and risk of dementia were not modified by the *APOE* genotype, levels of PRS of dementia, or family history of dementia (Fig. 4), although no significant association was observed for individuals with patterns of 'fair state' or with family history of dementia. The results were largely similar when restricting dementia to AD (Supplementary Tables 13 and 14).

Discussion

In this prospective cohort study based on the UK Biobank, we identified and validated seven clusters of participants with exclusive psychosocial patterns. Compared with the pattern 'good state', we found an increased risk of dementia for individuals with other patterns, with the strongest association noted for 'extremely poor psychological state'. The association was largely independent of the disease susceptibility of dementia, i.e., the *APOE* genotype, PRS, and family history of dementia. Our findings demonstrate the contribution of combined psychosocial factors to the development of dementia in addition to genetic determinants, and call for increased awareness to integrate various psychosocial dimensions for the surveillance of high-risk groups for dementia.

Although evidence has reported some specific psychosocial patterns associated with the risk of dementia, these studies often used various psychosocial assessments [16], evaluated single psychosocial factors [42, 43], and focused on selected populations [6]. In this study, we included five dimensions consisting of 20 factors that were mostly reported to be associated with the risk of dementia [1, 4, 16], and identified seven psychosocial patterns that optimally

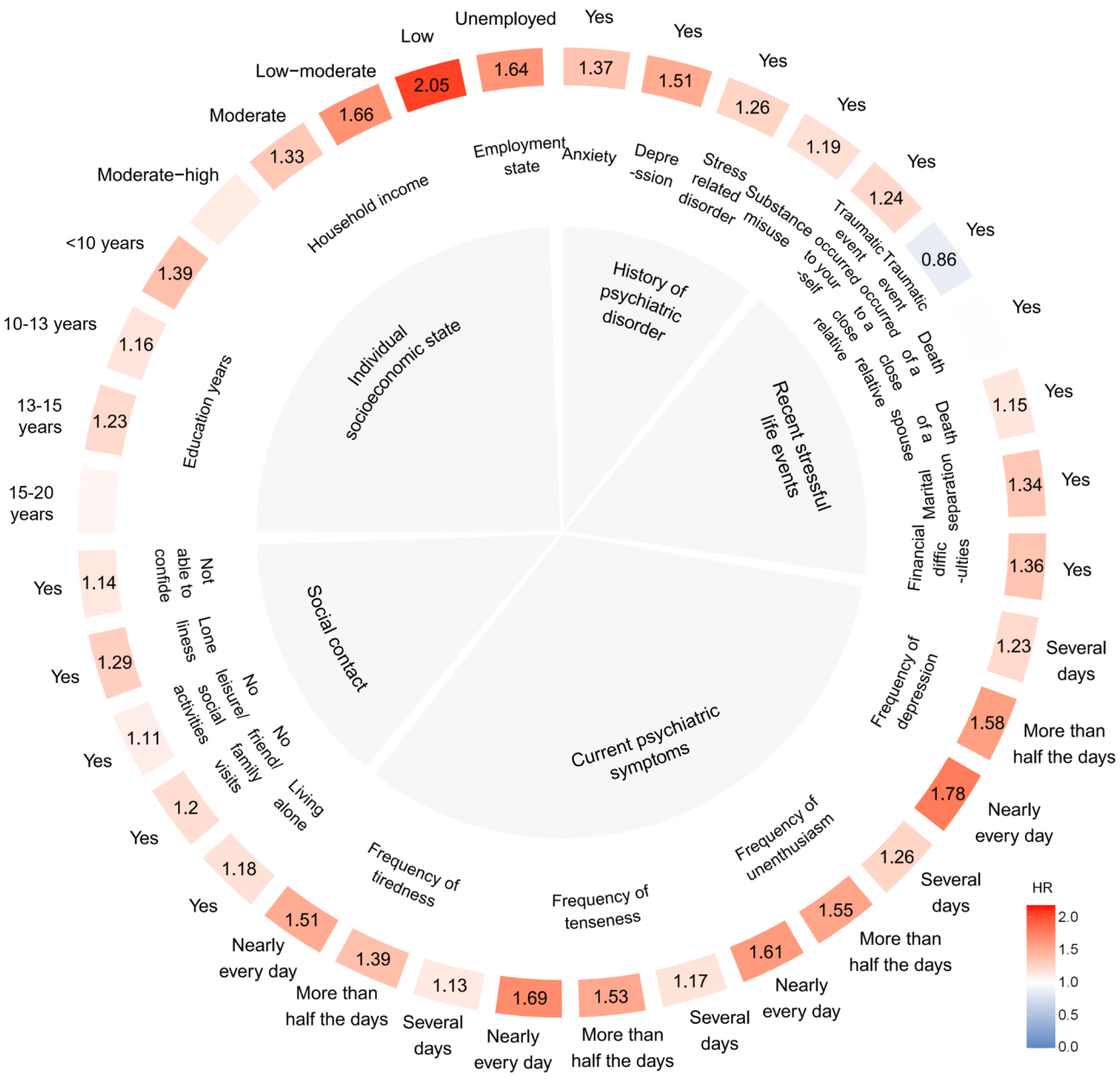
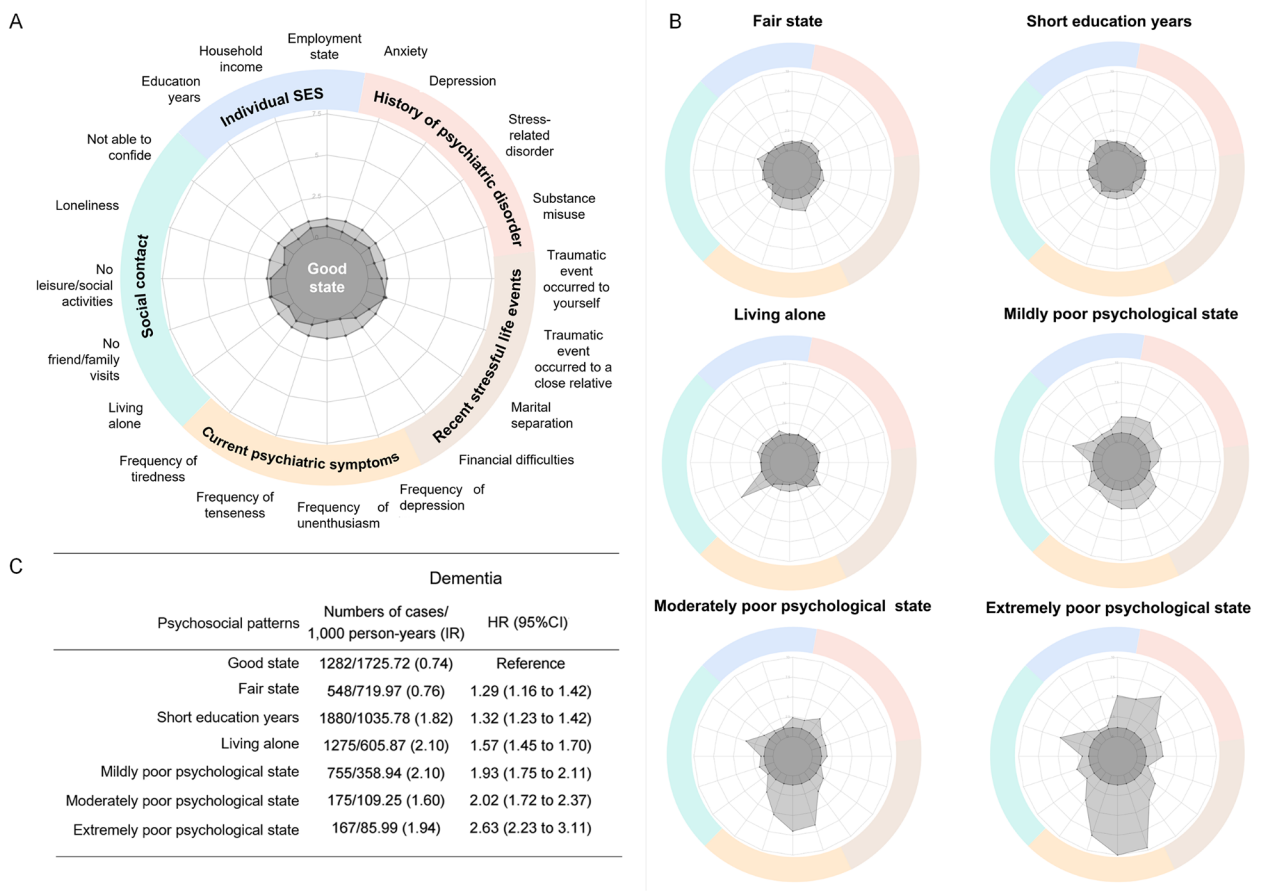


Fig. 2 Hazard ratios for the associations between five psychosocial dimensions with 22 specific items and risk of any dementia. The rings represent the HRs for the associations between 22 psychosocial items and risk of any dementia. The point estimates of statistically significant HRs after correction for multiple testing (i.e., false discovery rate-adjusted P value < 0.05) are shown as numbers. HRs were derived from Cox regression models, adjusted for gender, ethnicity, smoking, alcohol drinking, hours of sleep, physical activities, body mass index, Charlson comorbidity index, history of hypertension and hyperlipidemia, grip strength, and hearing loss state. Abbreviations: HR, hazard ratio

characterized this study population. In compliment to the influence of a single factor, we found persons with these psychosocial patterns were at increased risk of dementia. Consistent with previous literature [44, 45], the most pronounced risk was observed for 'extremely poor psychological state' (i.e., history of psychiatric disorder, recent stressful life events, current psychiatric symptoms, loneliness as well as unemployment), indicating the importance of considering the interplay and complicity of multiple psychosocial factors on the risk prediction of dementia. Further, our findings that the observed associations are mostly independent of disease susceptibility to dementia, highlight the possible opportunity and importance of intervening with modifiable factors for the prevention of dementia.

More specifically, we observed a dose-response relationship between varying degrees of psychological states and dementia risk, representing a gradient risk elevation that was noted for individuals with 'fair state' and 'mildly, moderately, and extremely



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	Dementia	
Psychosocial patterns	Numbers of cases/ 1,000 person-years (IR)	HR (95%CI)
Good state	1282/1725.72 (0.74)	Reference
Fair state	548/719.97 (0.76)	1.29 (1.16 to 1.42)
Short education years	1880/1035.78 (1.82)	1.32 (1.23 to 1.42)
Living alone	1275/605.87 (2.10)	1.57 (1.45 to 1.70)
Mildly poor psychological state	755/358.94 (2.10)	1.93 (1.75 to 2.11)
Moderately poor psychological state	175/109.25 (1.60)	2.02 (1.72 to 2.37)
Extremely poor psychological state	167/85.99 (1.94)	2.63 (2.23 to 3.11)

Fig. 3 The radar charts of seven psychosocial patterns and association between seven psychosocial patterns and risk of any dementia. (**A, B**) The radar charts of seven psychosocial patterns. (**C**) Association between seven psychosocial patterns and risk of any dementia. In radar charts, a graduated scale along each radial axis indicates the deviations of each psychosocial item in relation to the total population level. Lines connect the values for each item and form a closed polygon, which allows visual comparison of different psychosocial patterns. HRs and 95% CIs were derived from Cox regression models, adjusted for gender, ethnicity, smoking, alcohol drinking, hours of sleep, physical activities, body mass index, Charlson comorbidity index, history of hypertension and hyperlipidemia, grip strength, and hearing loss state. Abbreviations: SES, individual socioeconomic state; HR, hazard ratio; CI, confidence interval

poor psychological state'. Additionally, the patterns featured by merely 'living alone' and 'short education years' were also associated with the risk of dementia, independent of the influence of other psychological factors. Future risk assessment and disease surveillance studies shall consider placing more resources on the groups with these features. Because genetic background is often considered as an important risk factor for the onset of dementia, our study thereby demonstrate that future surveillance should not only focus on individuals with family history or inherited risk genes of dementia, but also those who belong to high-risk psychosocial patterns independent of family history or risk genes. An increased risk of dementia was also observed for persons featured by 'fair state', and was largely attributed to the group with low cognitive performance (Supplementary Table 10). It was likely that this group captured the subclinical stage of dementia with cognitive decline.

Although the underlying mechanisms between psychosocial factors and the risk of dementia are widely discussed, the combined contribution of multiple psychosocial factors to the development of dementia is less clear. It is often the approach to exclusively adopt a single factor when studying its influence on the risk of dementia. However, psychosocial risk factors usually tend to cluster together. Psychosocial adversity, i.e., loss of income and traumatic experience, can be life stressors causing mental stress and stress reaction, which is often linked with prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis, hippocampal damage, and dysregulation of the immune system [46, 47], these are likely to be associated with the incidence of dementia. In addition, psychosocial adversity may indirectly foster unhealthy lifestyles, e.g., smoking, heavy drinking and physical inactivity, which are associated with an increased risk of dementia [48]. This indicates that lifestyle factors

Table 1 Characteristics of study participants by seven identified psychosocial patterns, among 336,493 participants free of dementia at baseline from the UK Biobank

Characteristics	No. (%)						
	Good state	Fair state	Short education	Living alone	Mildly poor psychological state	Moderately poor psychological state	Extremely poor psychological state
No. of participants	136,060	56,765	81,767	47,987	28,402	8,688	6,824
Follow up, y, median (IQR)	12.70 (1.38)	12.70 (1.39)	12.80 (1.36)	12.70 (1.41)	12.70 (1.42)	12.70 (1.42)	12.70 (1.46)
Age at baseline, y, median (IQR)	55.00 (13.00)	53.00 (12.00)	61.00 (10.00)	61.00 (11.00)	58.00 (13.00)	54.00 (13.00)	53.00 (12.00)
Sex							
Female	66,319 (48.74)	31,167 (54.91)	40,607 (49.66)	28,290 (58.95)	17,051 (60.03)	4,948 (56.95)	3,905 (57.22)
Male	69,741 (51.26)	25,598 (45.09)	41,160 (50.34)	19,697 (41.05)	11,351 (39.97)	3,740 (43.05)	2,919 (42.78)
Ethnicity [a]							
Non-Caucasian	22,728 (16.70)	9,710 (17.11)	9,463 (11.57)	8,279 (17.25)	4,934 (17.37)	2,285 (26.30)	1,530 (22.42)
Caucasian	113,332 (83.30)	47,055 (82.89)	72,304 (88.43)	39,708 (82.75)	23,468 (82.63)	6,403 (73.70)	5,294 (77.58)
Smoking status							
Never	82,666 (60.76)	31,720 (55.88)	40,732 (49.81)	24,626 (51.32)	12,247 (43.12)	4,506 (51.86)	2,984 (43.73)
Previous	44,829 (32.95)	19,374 (34.13)	32,695 (39.99)	17,032 (35.49)	10,139 (35.70)	2,635 (30.33)	2,032 (29.78)
Current	8,421 (6.19)	5,605 (9.87)	8,107 (9.91)	6,189 (12.90)	5,943 (20.92)	1,531 (17.62)	1,785 (26.16)
Unknown	144 (0.11)	66 (0.12)	233 (0.28)	140 (0.29)	73 (0.26)	16 (0.18)	23 (0.34)
Drinking status							
Never	3,151 (2.32)	1,313 (2.31)	3,449 (4.22)	2,377 (4.95)	1,382 (4.87)	546 (6.28)	463 (6.78)
Previous	2,644 (1.94)	1,506 (2.65)	2,704 (3.31)	2,232 (4.65)	1,942 (6.84)	512 (5.89)	711 (10.42)
Current	130,245 (95.73)	53,938 (95.02)	75,595 (92.45)	43,354 (90.35)	25,050 (88.20)	7,617 (87.67)	5,633 (82.55)
Unknown	20 (0.01)	8 (0.01)	19 (0.02)	24 (0.05)	28 (0.10)	13 (0.15)	17 (0.25)
Hours of sleep [b]							
Normal	109,417 (80.42)	40,336 (71.06)	62,894 (76.92)	34,782 (72.48)	17,498 (61.61)	5,014 (57.71)	3,149 (46.15)
Long or short sleep	26,643 (19.58)	16,429 (28.94)	18,873 (23.08)	13,205 (27.52)	10,904 (38.39)	3,674 (42.29)	3,675 (53.85)
Physical activity [c]							
Low	21,510 (15.81)	11,166 (19.67)	10,923 (13.36)	6,612 (13.78)	5,277 (18.58)	1,846 (21.25)	1,904 (27.90)
Moderate	52,308 (38.44)	21,229 (37.40)	25,546 (31.24)	16,642 (34.68)	9,179 (32.32)	2,733 (31.46)	1,936 (28.37)
High	47,927 (35.22)	17,499 (30.83)	30,934 (37.83)	17,388 (36.23)	8,715 (30.68)	2,572 (29.60)	1,633 (23.93)
Unknown	14,315 (10.52)	6,871 (12.10)	14,364 (17.57)	7,345 (15.31)	5,231 (18.42)	1,537 (17.69)	1,351 (19.80)
Body mass index, kg/m^2							
< 25	51,847 (38.11)	19,576 (34.49)	22,487 (27.50)	15,996 (33.33)	8,090 (28.48)	2,424 (27.90)	1,769 (25.92)
25–30	59,030 (43.39)	23,559 (41.50)	37,568 (45.95)	19,361 (40.35)	10,907 (38.40)	3,313 (38.13)	2,387 (34.98)
≥ 30	24,785 (18.22)	13,428 (23.66)	21,415 (26.19)	12,362 (25.76)	9,191 (32.36)	2,870 (33.03)	2,588 (37.92)
Unknown	398 (0.29)	202 (0.36)	297 (0.36)	268 (0.56)	214 (0.75)	81 (0.93)	80 (1.17)
Charlson comorbidity index							
0	112,095 (82.39)	45,069 (79.40)	63,561 (77.73)	36,740 (76.56)	19,590 (68.97)	6,283 (72.32)	4,446 (65.15)
≥ 1	23,965 (17.61)	11,696 (20.60)	18,206 (22.27)	11,247 (23.44)	8,812 (31.03)	2,405 (27.68)	2,378 (34.85)
History of hypertension							
No	123,935 (91.09)	51,183 (90.17)	67,868 (83.00)	40,285 (83.95)	22,995 (80.96)	7,293 (83.94)	5,543 (81.23)
Yes	12,125 (8.91)	5,582 (9.83)	13,899 (17.00)	7,702 (16.05)	5,407 (19.04)	1,395 (16.06)	1,281 (18.77)
History of hyperlipidemia							
No	132,547 (97.42)	55,300 (97.42)	78,178 (95.61)	46,040 (95.94)	27,027 (95.16)	8,321 (95.78)	6,487 (95.06)
Yes	3,513 (2.58)	1,465 (2.58)	3,589 (4.39)	1,947 (4.06)	1,375 (4.84)	367 (4.22)	337 (4.94)
Grip strength							
Normal	118,539 (87.12)	47,747 (84.11)	63,916 (78.17)	35,899 (74.81)	19,894 (70.04)	6,262 (72.08)	4,481 (65.67)
Low	16,711 (12.28)	8,611 (15.17)	17,162 (20.99)	11,548 (24.06)	8,073 (28.42)	2,290 (26.36)	2,203 (32.28)
Unknown	810 (0.60)	407 (0.72)	689 (0.84)	540 (1.13)	435 (1.53)	136 (1.57)	140 (2.05)
Hearing loss state [d]							
No	103,608 (76.15)	40,316 (71.02)	57,663 (70.52)	34,968 (72.87)	18,462 (65.00)	5,788 (66.62)	4,187 (61.36)

Table 1 (continued)

Characteristics	No. (%)						
	Good state	Fair state	Short education	Living alone	Mildly poor psychological state	Moderately poor psychological state	Extremely poor psychological state
Yes	29,011 (21.32)	14,375 (25.32)	21,607 (26.43)	11,493 (23.95)	8,620 (30.35)	2,502 (28.80)	2,282 (33.44)
Unknown	3,441 (2.53)	2,074 (3.65)	2,497 (3.05)	1,526 (3.18)	1,320 (4.65)	398 (4.58)	355 (5.20)

[a] Ethnicity was collected via a self-report questionnaire, Caucasian ancestry refers to a genetic ethnic group, involving individuals who self-identified as White British and have very similar genetic ancestry based on a principal components analysis of the genotypes

[b] Hours of sleep were categorized as normal (7–9 h), long or short sleep (>9 h or <7 h), and unknown

[c] Physical activity was evaluated by the International Physical Activity Questionnaire score summarizing the metabolic equivalent task (MET)-weighted time spent in vigorous, moderate, and walking activity

[d] Hearing loss state was collected via a self-report question: 'Do you have any difficulty with your hearing?' and was categorized as without hearing loss ('no' responses), with hearing loss ('yes' or 'I am completely deaf' responses), and unknown

may mediate the association, although the difference in the risk of dementia was not pronounced across socioeconomic groups [49]. Other modifiable risk factors, such as sleep deprivation [50], have also been reported for dementia. The resulting metabolic and molecular alterations that presumably inhibit inflammation and oxidative stress may otherwise accelerate dementia pathogenesis [51, 52], although the specific pathways are not fully understood. Furthermore, psychosocial adversity is linked with multiple risk factors for dementia, including depression and cardiovascular disease [53]. Finally, our findings reinforce the importance of being involved in social contact and obtaining high cognitive reserve, since living alone and having few years of education may directly influence the incidence of dementia [34, 54, 55].

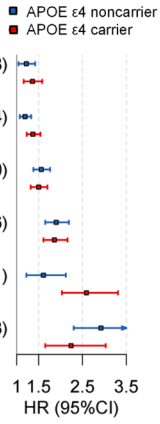
The main strength of our study is the use of the UK Biobank cohort, with large sample size, prospective and independent data collection and a long follow-up on dementia occurrence, enabling us to perform detailed subgroup and sensitivity analyses. We use the LCA method to identify the optimal psychosocial patterns in the study population, which allows the simultaneous consideration of multiple psychosocial factors. Further, we take into account the impact of disease susceptibility to dementia according to *APOE* genotype, PRS and family history of dementia, reassuring the importance of psychosocial patterns on the risk of dementia independent of its genetic determinants.

There are limitations to be acknowledged. First, psychosocial data were collected at recruitment, which might potentially be influenced by recall bias and not reflect longitudinal changes. In addition, we used history of psychiatric diagnoses and self-reported current symptoms as proxies for mental health, which may not be accurate to reflect real mental status. The impact of treatments for mental illnesses, such as the use of antidepressants, can influence psychiatric symptoms, which was not considered in this study. Second, although impact from lifestyle factors has been adjusted, a detailed classification on lifestyle factors, such as the amounts/frequencies of smoking and alcohol drinking, was not considered. Third, reverse causality can be a potential issue, because the disease may already progress due to the often delayed diagnosis of dementia. However, we have allowed a 1-year lag time in all analyses to address this issue. Similar results were obtained when additionally applying 5- and 10-year lag times in the sensitivity analysis. Fourth, it is worth noting that the UK Biobank participants are not representative of the U.K. general population, given the low response rate for participation at recruitment [25]. Future studies are therefore warranted to validate our findings in a more representative sample, or to generalize the findings in other populations.

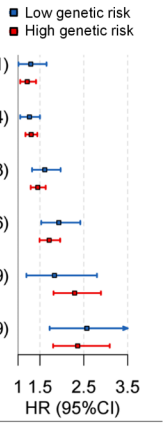
Conclusions

Our study demonstrates that unfavorable psychosocial patterns, including psychological state deterioration and poor social states, are associated with a higher risk of dementia, largely independent of genetic susceptibility of dementia. It is important to take into account how multiple psychosocial factors interact to prevent and monitor dementia.

Psychosocial patterns	APOE ε4 non-carrier: Numbers of cases/ 1,000 person-years (IR)	APOE ε4 non-carrier: HR (95%CI)	APOE ε4 carrier: Numbers of cases/ 1,000 person-years (IR)	APOE ε4 carrier: HR (95%CI)
Good state	561/1057.8 (0.53)	Reference	535/375.98 (1.42)	Reference
Fair state	234/437.77 (0.53)	1.22 (1.04 to 1.42)	231/157.17 (1.47)	1.36 (1.16 to 1.58)
Short education years	790/675.64 (1.17)	1.19 (1.07 to 1.33)	862/236.59 (3.64)	1.37 (1.23 to 1.54)
Living alone	547/370.47 (1.48)	1.56 (1.38 to 1.76)	507/128.73 (3.94)	1.50 (1.32 to 1.70)
Mildly poor psychological state	342/219.19 (1.56)	1.90 (1.65 to 2.19)	293/76.35 (3.84)	1.86 (1.61 to 2.16)
Moderately poor psychological state	57/58.79 (0.97)	1.61 (1.22 to 2.12)	76/21.85 (3.48)	2.59 (2.03 to 3.31)
Extremely poor psychological state	83/48.86 (1.70)	2.92 (2.30 to 3.71)	47/17.88 (2.63)	2.24 (1.65 to 3.03)



Psychosocial patterns	Low genetic risk (PRS < 1st tercile): Numbers of cases/ 1,000 person-years (IR)	Low genetic risk (PRS < 1st tercile): HR (95%CI)	High genetic risk (PRS > 2nd tercile): Numbers of cases/ 1,000 person-years (IR)	High genetic risk (PRS > 2nd tercile): HR (95%CI)
Good state	207/477.68 (0.43)	Reference	627/479.25 (1.31)	Reference
Fair state	95/199.48 (0.48)	1.29 (1.01 to 1.65)	246/198.75 (1.24)	1.21 (1.05 to 1.41)
Short education years	306/303.21 (1.01)	1.26 (1.05 to 1.50)	963/304.18 (3.17)	1.30 (1.17 to 1.44)
Living alone	208/165.03 (1.26)	1.61 (1.32 to 1.97)	585/166.88 (3.51)	1.45 (1.29 to 1.63)
Mildly poor psychological state	132/97.6 (1.35)	1.93 (1.53 to 2.42)	326/98.68 (3.30)	1.71 (1.49 to 1.96)
Moderately poor psychological state	24/26.62 (0.90)	1.83 (1.19 to 2.80)	81/27.37 (2.96)	2.29 (1.81 to 2.89)
Extremely poor psychological state	29/21.53 (1.35)	2.57 (1.72 to 3.84)	61/22.99 (2.65)	2.36 (1.80 to 3.09)



Psychosocial patterns	Without family history: Numbers of cases/ 1,000 person-years (IR)	Without family history: HR (95%CI)	With family history: Numbers of cases/ 1,000 person-years (IR)	With family history: HR (95%CI)
Good state	716/1165.12 (0.61)	Reference	274/167.74 (1.63)	Reference
Fair state	322/474.56 (0.68)	1.40 (1.23 to 1.60)	104/67.18 (1.55)	1.13 (0.90 to 1.42)
Short education years	1030/688.49 (1.50)	1.30 (1.18 to 1.43)	364/109.46 (3.33)	1.27 (1.08 to 1.49)
Living alone	670/378.5 (1.77)	1.57 (1.41 to 1.75)	234/64.98 (3.60)	1.43 (1.20 to 1.72)
Mildly poor psychological state	418/218.74 (1.91)	2.08 (1.83 to 2.36)	110/36.6 (3.01)	1.38 (1.09 to 1.74)
Moderately poor psychological state	80/60.09 (1.33)	2.11 (1.67 to 2.66)	38/9.71 (3.91)	2.56 (1.81 to 3.61)
Extremely poor psychological state	85/48.76 (1.74)	3.03 (2.40 to 3.81)	19/7.65 (2.48)	1.66 (1.04 to 2.67)

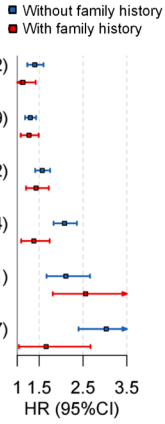


Fig. 4 Association between seven psychosocial patterns and dementia of any type, by *APOE* ε4 genotype, polygenic risk score, and family history of dementia. HRs and 95% CIs were derived from Cox regression models, adjusted for gender, ethnicity, smoking, alcohol drinking, hours of sleep, physical activities, body mass index, Charlson comorbidity index, history of hypertension and hyperlipidemia, grip strength, and hearing loss state. Abbreviations: HR, hazard ratio; CI, confidence interval; PRS, polygenic risk score

Abbreviations

SES	Socioeconomic state
APOE	Apolipoprotein E
AD	Alzheimer's disease
PRS	Polygenic risk score
VD	Vascular dementia
BMI	Body mass index
CCI	Charlson comorbidity index
HRs	Hazard ratios
LCA	Latent class analysis

Supplementary Information

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Supplementary Material 1

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Author contributions
HS, QS were responsible for the study concept and design. HY and YZ did the data and project management. HW, JW, YZ, and WC did the data cleaning and analysis. HW, HS and QS interpreted the data. HW, QS, and HS drafted the paper. All authors approved the final paper as submitted and agree to be accountable for all aspects of the work.

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Data availability
Data from the UK Biobank (http://www.ukbiobank.ac.uk/) are available to all researchers upon making an application. This research has been conducted using the UK Biobank Resource under Application 54803. This work uses data provided by patients and collected by the NHS as part of their care and support. This research used data assets made available by National Safe Haven as part of the Data and Connectivity National Core Study, led by Health Data Research UK in partnership with the Office for National Statistics and funded by UK Research and Innovation (grant ref: MC_PC_20029 and MC_PC_20058).

Declarations

Ethics approval and consent to participate
All UK Biobank participants signed informed consent before information collection and the study has full ethical approval from the NHS National Research Ethics Service (reference number: 16/NW/0274), and this study was also approved by the biomedical research ethics committee of West China Hospital (reference number: 2019 – 1171).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413–46.
2. Ahmadi-Abhari S, Guzman-Castillo M, Bandosz P, Shipley MJ, Muniz-Terrera G, Singh-Manoux A, Kivimaki M, Steptoe A, Capewell S, O'Flaherty M, et al. Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study. BMJ-BRIT MED J. 2017;358:j2856.
3. Ismail Z, Black SE, Camicioli R, Chertkow H, Herrmann N, Laforce R, Montero Odasso M, Rockwood K, Rosa Neto P, Seitz D, et al. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. Alzheimer's Dement. 2020;16(8):1182–95.
4. Zhang Y, Chen S, Deng Y, You J, He X, Wu X, Wu B, Yang L, Zhang Y, Kuo K, et al. Identifying modifiable factors and their joint effect on dementia risk in the UK Biobank. NAT HUM BEHAV. 2023;7(7):1185–95.
5. Klee M, Leist AK, Veldsman M, Ranson JM, Llewellyn DJ. Socioeconomic deprivation, genetic risk, and Incident Dementia. AM J PREV MED. 2023;64(5):621–30.
6. Krasnova A, Tom SE, Valeri L, Crane PK, Bennett DA. Direct effect of Life-Course Socioeconomic Status on Late-Life Cognition and Cognitive decline in the rush memory and Aging Project. AM J EPIDEMIOL. 2023;192(6):882–94.
7. Lai KY, Webster C, Kumari S, Gallacher JEJ, Sarkar C. Association between individual-level socioeconomic position and incident dementia using UK Biobank data: a prospective study. Lancet. 2022;400:S56.
8. Liu C, Ma Y, Hofman A, Waziry R, Koton S, Pike JR, Windham BG, Power MC, Sharrett AR, Gottesman RF. Educational Attainment and Dementia: mediation by Mid-life Vascular Risk factors. ANN NEUROL. 2023;94(1):13–26.
9. McManus E, Haroon H, Duncan NW, Elliott R, Muhlert N. The effects of stress across the lifespan on the brain, cognition and mental health: a UK biobank study. NEUROBIOL STRESS. 2022;18:100447.
10. Nilaweera D, Freak-Poli R, Ritchie K, Chaudieu I, Ancelin ML, Ryan J. The long-term consequences of trauma and posttraumatic stress disorder symptoms on later life cognitive function and dementia risk. PSYCHIAT RES. 2020;294:113506.
11. Amidfar M, Garcez ML, Kim YK. The shared molecular mechanisms underlying aging of the brain, major depressive disorder, and Alzheimer's disease: the role of circadian rhythm disturbances. PROG NEURO-PSYCHOPH. 2023;123:110721.
12. Song H, Sieurin J, Wirdefeldt K, Pedersen NL, Almqvist C, Larsson H, Valdimarsdóttir UA, Fang F. Association of stress-related disorders with subsequent neurodegenerative diseases. JAMA NEUROL. 2020;77(6):700.
13. Yang L, Deng YT, Leng Y, Ou YN, Li YZ, Chen SD, He XY, Wu BS, Huang SY, Zhang YR, et al. Depression, Depression treatments, and risk of Incident Dementia: a prospective cohort study of 354,313 participants. BIOL PSYCHIAT. 2023;93(9):802–9.
14. Elovainio M, Lahti J, Pirinen M, Pulkki-Raback L, Malmberg A, Lipsanen J, Virtanen M, Kivimaki M, Hakulinen C. Association of social isolation, loneliness and genetic risk with incidence of dementia: UK Biobank Cohort Study. BMJ OPEN. 2022;12(2):e53936.
15. Shen C, Rolls ET, Cheng W, Kang J, Dong G, Xie C, Zhao X, Sahakian BJ, Feng J. Associations of Social isolation and loneliness with later dementia. NEUROLOGY. 2022;99(2):e164–75.
16. Bougea A, Anagnostouli M, Angelopoulou E, Spanou I, Chrousos G. Psychosocial and trauma-related stress and risk of dementia: a Meta-Analytic systematic review of Longitudinal studies. J GERIATR PSYCH NEUR. 2022;35(1):24–37.

17. Macleod J, Davey Smith G. Psychosocial factors and public health: a suitable case for treatment? J EPIDEMIOL COMMUN H. 2003;57(8):565–70.
18. Fuentes S, Brondeel R, Franco M, Sureda X, Traissac P, Cleary LK, Chaix B. Psycho-social factors related to obesity and their associations with socioeconomic characteristics: the RECORD study. EAT WEIGHT DISORD-ST. 2020;25(3):533–43.
19. Khachatryan K, Otten DL, Beutel ME, Speerforck S, Riedel-Heller SG, Ulke C, Brähler E. Mental resources, mental health and sociodemography: a cluster analysis based on a representative population survey in a large German city. BMC Public Health. 2023;23(1):1–1827.
20. Raffagnato A, Iannattone S, Fasolato R, Rossaro MP, Spoto A, Gatta M. Psycho-behavioral profiles of Pediatric inpatients with Past and recent onset of Non-suicidal Self-Injury: a cluster analysis Approach. J CLIN MED. 2022;11(15):4602.
21. 2022 Alzheimer's disease facts and figures. *Alzheimer's & Dementia* 2022, 18(4):700–789.
22. Reitz C, Pericak-Vance MA, Foroud T, Mayeux R. A global view of the genetic basis of Alzheimer disease. NAT REV NEUROL. 2023;19(5):261–77.
23. Serrano-Pozo A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. Lancet Neurol. 2021;20(1):68–80.
24. Thompson DJ, Wells D, Selzam S, Peneva I, Moore R, Sharp K, Tarran WA, Beard EJ, Riveros-Mckay F, Duncan et al. UK Biobank release and systematic evaluation of optimised polygenic risk scores for 53 diseases and quantitative traits. Preprint at https://www.medrxiv.org/content/https://doi.org/10.1101/2022.06.16.22276246v1 (2022).
25. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, 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.
26. Jorde LB, Wooding SP. Genetic variation, classification and 'race'. NAT GENET. 2004;36(11 Suppl):S28–33.
27. Okbay A, Beauchamp JP, Fontana MA, Lee JJ, Pers TH, Rietveld CA, Turley P, Chen G, Emilsson V, Meddens SFW, et al. Genome-wide association study identifies 74 loci associated with educational attainment. Nature. 2016;533(7604):539–42.
28. Irwin MR, Vitiello MV. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. LANCET NEUROL. 2019;18(3):296–306.
29. Chern A, Golub JS. Age-related hearing loss and dementia. ALZ DIS ASSOC DIS. 2019;33(3):285–90.
30. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of patients. BMC MED RES METHODOL. 2011;11:83.
31. Petermann-Rocha F, Lyall DM, Gray SR, Esteban-Cornejo I, Quinn TJ, Ho FK, Pell JP, Celis-Morales C. Associations between physical frailty and dementia incidence: a prospective study from UK Biobank. Lancet Healthy Longev. 2020;1(2):e58–68.
32. Seripa D, D'Onofrio G, Panza F, Cascavilla L, Masullo C, Pilotto A. The genetics of the human APOE polymorphism. REJUV RES. 2011;14(5):491–500.
33. Zhang H, Greenwood DC, Risch HA, Bunce D, Hardie LJ, Cade JE. Meat consumption and risk of incident dementia: cohort study of 493,888 UK Biobank participants. AM J CLIN NUTR. 2021;114(1):175–84.
34. Zhu J, Ge F, Zeng Y, Qu Y, Chen W, Yang H, Yang L, Fang F, Song H. Physical and Mental Activity, Disease susceptibility, and risk of Dementia. NEUROLOGY. 2022;99(8):e799–813.
35. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562(7726):203–9.
36. Sun M, He Q, Sun N, Han Q, Wang Y, Zhao H, Li G, Ma Z, Feng Z, Li T, et al. Intrinsic capacity, polygenic risk score, APOE genotype, and risk of dementia: a prospective cohort study based on the UK Biobank. NEUROLOGY. 2024;102(12):e209452.
37. Benjamini Y, Hochberg Y. Controlling the false Discovery rate: a practical and powerful Approach to multiple testing. J Royal Stat Soc Ser B (Methodological). 1995;57(1):289–300.
38. Mori M, Krumholz HM, Allore HG. Using Latent Class Analysis to identify hidden clinical phenotypes. JAMA-J AM MED ASSOC. 2020;324(7):700–1.
39. Weller BE, Bowen NK, Faubert SJ. Latent class analysis: a guide to best practice. J BLACK PSYCHOL. 2020;46(4):287–311.
40. Calvin CM, Wilkinson T, Starr JM, Sudlow C, Hagenaars SP, Harris SE, Schnier C, Davies G, Fawns-Ritchie C, Gale CR, et al. Predicting incident dementia 3–8 years after brief cognitive tests in the UK Biobank prospective study of 500,000 people. ALZHEIMERS DEMENT. 2019;15(12):1546–57.
41. Fawns-Ritchie C, Deary IJ. Reliability and validity of the UK Biobank cognitive tests. PLoS ONE. 2020;15(4):e231627.
42. Johansson L, Guo X, Waern M, Ostling S, Gustafson D, Bengtsson C, Skoog I. Midlife psychological stress and risk of dementia: a 35-year longitudinal population study. Brain. 2010;133(Pt 8):2217–24.
43. Mirza SS, Wolters FJ, Swanson SA, Koudstaal PJ, Hofman A, Tiemeier H, Ikram MA. 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. LANCET PSYCHIAT. 2016;3(7):628–35.
44. Gerritsen LPD, Wang HPD, Reynolds CAPD, Fratiglioni LMDP, Gatz MPD, Pedersen NLPD. Influence of negative life events and Widowhood on Risk for Dementia. Am J Geriatric Psychiatry. 2017;25(7):766–78.
45. Tschanz JT, Pfister R, Wanzek J, Corcoran C, Smith K, Tschanz BT, Steffens DC, Ostbye T, Welsh-Bohmer KA, Norton MC. Stressful life events and cognitive decline in late life: moderation by education and age. The Cache County study. INT J GERIATR PSYCH. 2013;28(8):821–30.
46. Burrage E, Marshall K, Santanam N, Chantler P. Cerebrovascular dysfunction with stress and depression. BRAIN CIRC. 2018;4(2):43–53.
47. Han B, Wang JH, Geng Y, Shen L, Wang HL, Wang YY, Wang MW. Chronic stress contributes to cognitive dysfunction and hippocampal metabolic abnormalities in APP/PS1 mice. Cell Physiol Biochem. 2017;41(5):1766–76.
48. Dhana K, Evans DA, Rajan KB, Bennett DA, Morris MC. Healthy lifestyle and the risk of Alzheimer dementia: findings from 2 longitudinal studies. NEUROLOGY. 2020;95(4):e374–83.
49. Rohr S, Pabst A, Baber R, Engel C, Glaesmer H, Hinz A, Schroeter ML, Witte AV, Zeynalova S, Villringer A, 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(4):1523–34.
50. Clare L, Wu YT, Teale JC, MacLeod C, Matthews F, Brayne C, Woods B. Potentially modifiable lifestyle factors, cognitive reserve, and cognitive function in later life: a cross-sectional study. PLOS MED. 2017;14(3):e1002259.
51. Clark TA, Lee HP, Rolston RK, Zhu X, Marlatt MW, Castellani RJ, Nunomura A, Casadesus G, Smith MA, Lee HG, et al. Oxidative stress and its implications for future treatments and management of Alzheimer Disease. Int J Biomed Sci. 2010;6(3):225–7.
52. Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, Stijnen T, Hofman A, Witteman JC, Breteler MM. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. Arch Neurol. 2004;61(5):668–72.
53. Pandit M, Frishman WH. The Association between Cardiovascular Disease and Dementia: a review of trends in Epidemiology, Risk factors, pathophysiologic mechanisms, and clinical implications. CARDIOL REV 2023.
54. De Looze C, Demnitz N, Knight S, Carey D, Meaney J, Kenny RA, McCrory C, Anderson RM. Examining the Impact of Socioeconomic Position across the Life Course on cognitive function and brain structure in healthy aging. J Gerontol A. 2023;78(6):890–901.
55. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. LANCET NEUROL. 2012;11(11):1006–12.

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