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Original Article

Depressive symptoms as a risk factor or prodrome of dementia: multi-state cognitive transitions modified by age and polygenic risk☆

Ziyang Ren [a,b,1], Ruyi Zhang [c,d,1], Shuai Guo [c], Yihao Zhao [c], Jufen Liu [a,b,e,*], Xiaoying Zheng [c,f,**]

[a] Institute of Reproductive and Child Health/National Health Commission Key Laboratory of Reproductive Health, School of Public Health, Peking University, No. 38 College Rd, Haidian District, Beijing 100191, China
[b] Department of Epidemiology and Biostatistics, School of Public Health, Peking University, No. 38 College Rd, Haidian District, Beijing 100191, China
[c] School of Population Medicine and Public Health, Chinese Academy of Medical Sciences & Peking Union Medical College, No. 9 Dongdan Santiao, Dongcheng District, Beijing 100730, China
[d] Beijing Ditan Hospital, Capital Medical University, No. 8 Jingshun East Street, Chaoyang District, Beijing 100015, China
[e] State Key Laboratory of Female Fertility Promotion, Peking University, No. 38 College Rd, Haidian District, Beijing 100191, China
[f] Peking University, No.5 Yiheyuan Road, Haidian District, Beijing, China

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ABSTRACT

Background: Whether depressive symptoms signal a risk factor or a prodromal symptom of dementia, and how this depends on age, genetic susceptibility, and cognitive stages, remains controversial.
Objectives: To examine the association between depressive symptoms and incident dementia and cognitive transitions, and to test effect modification by age and AD genetic susceptibility (APOE and AD polygenic risk score [PRS]).
Design: Longitudinal cohort study (1998–2020) using repeated assessments; incident dementia was modeled using Fine-Gray competing-risk models, and cognitive transitions were modeled with multi-state Markov models.
Setting: The U.S. Health and Retirement Study.
Participants: For the main incident dementia analysis, 13,225 dementia-free participants were included at baseline; genetic and repeated-measures analyses were restricted to 12,089 participants with complete PRS/APOE data.
Measurements: Depressive symptoms were assessed with the 8-item CES-D. Cognitive status was classified as normal cognition, subjective memory complaint (SMC), cognitive impairment no dementia (CIND), or dementia. AD genetic susceptibility was indexed by APOE and AD PRS. Outcomes included incident dementia and transitions across cognitive states.
Results: Baseline depressive symptoms (prevalence 11.3%) were associated with a higher incidence of dementia (sHR 1.24, 95% CI 1.10–1.39), with stronger associations in late midlife (50–59y: sHR 1.65) than ≥60y (sHR 1.19; *P* for interaction=0.001). After excluding dementia occurring within 5–10y, the associations for late midlife (but not ≥60y) remained significant (sHR for 5y=1.57; for 10y=1.55, both *P* for interaction≤0.030). AD PRS modified this association: depressive symptoms predicted dementia only among individuals with lower AD PRS, whereas APOE ε4 showed no modification. Multi-state analyses showed depressive symptoms accelerated progression across the cognitive continuum (e.g., normal cognition → SMC, HR=1.49; SMC → CIND, HR=1.33; CIND → dementia, HR=1.17) and reduced reversion to normal cognition. Furthermore, AD genetic susceptibility was positively associated with depressive symptom burden, specifically at the SMC stage.

☆ Depressive Symptoms and Dementia Risk

* Corresponding author at: Institute of Reproductive and Child Health/National Health Commission Key Laboratory of Reproductive Health, School of Public Health, Peking University, No. 38 College Rd, Haidian District, Beijing 100191, China.
** Corresponding author at: School of Population Medicine and Public Health, Chinese Academy of Medical Sciences & Peking Union Medical College, No. 9 Dongdan Santiao, Dongcheng District, Beijing 100730, China.
E-mail addresses: liujufen@bjmu.edu.cn (J. Liu), zhengxiaoying@sph.pumc.edu.cn (X. Zheng).
[1] Ziyang Ren and Ruyi Zhang contributed equally to this work.

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Conclusions: Depressive symptoms in late midlife, especially with lower AD PRS, are more consistent with a potentially modifiable risk marker for dementia, whereas depressive symptoms emerging at SMC in genetically susceptible adults may more often reflect prodromal disease activity.

1. Introduction

Dementia is among the most prevalent and disabling neurological disorders, affecting an estimated 57.4 million people worldwide in 2019, with projections rising to 152.8 million by 2050 [1]. Depressive symptoms are common among dementia patients; a systematic review and meta-analysis reported prevalence estimates of 37–41% [2]. Longitudinal evidence further suggests that depressive symptoms are associated with an elevated risk of subsequent dementia [3].

However, it remains controversial whether depressive symptoms function primarily as a long-term risk factor for dementia or instead reflect a prodromal neuropsychiatric manifestation of neurodegenerative pathology. On the one hand, depressive symptoms can increase neurobiological vulnerability via pathways including neuroinflammation, hypothalamic-pituitary-adrenal axis dysregulation, cerebrovascular injury, and sleep-circadian disruption [4,5]. Consistent with this interpretation, a cohort study reported that depression diagnosed in early or mid-adulthood remains associated with elevated dementia risk decades later [6]. On the other hand, stronger associations for late-life or recent depressive symptoms suggest that, in some individuals, these symptoms may signal dementia processes closer to clinical onset [7–9]. This possibility may be especially relevant in the context of subjective cognitive decline (SCD), where depressive symptoms may co-occur with emerging concerns and reflect early dementia-related change [10]. Collectively, these findings underscore age and cognitive stages as informative for distinguishing risk-factor versus prodromal roles of depressive symptoms.

Alzheimer's disease (AD)-related genetic susceptibility may further shape these associations through shared vulnerability, confounding, and effect modification. Classic longitudinal evidence from the Honolulu-Asia Aging Study showed a marked joint impact of depressive symptoms and apolipoprotein E (APOE) ε4 on dementia risk [11]. Similarly, a population-based study found that depression interacted synergistically with APOE ε4 to further elevate incident dementia risk [12]. However, the Lothian Birth Cohort 1936 reported little evidence that APOE ε4 can moderate associations between depressive symptoms and cognitive aging [13]. In addition, higher AD polygenic risk has been associated with depressive symptoms even after accounting for depression genetic propensity among cognitively normal middle-aged and older adults [14], supporting partially shared vulnerability and early disease processes. A UK Biobank study also found that pre-dementia psychiatric diagnoses predicted subsequent dementia largely independent of polygenic dementia risk, suggesting that observed psychiatric phenotypes cannot be fully explained by genetic factors alone [15]. Such evidence motivates integrating polygenic susceptibility to reduce genetic confounding, to test whether the depressive symptoms-dementia link differs across genetic-risk strata, and to refine inference about when depressive symptoms are more consistent with a long-term risk factor versus a prodromal manifestation across cognitive aging.

To date, limited population-based studies have jointly integrated age, AD polygenic susceptibility, and cognitive stages to distinguish these two interpretations. In addition, the influences of depressive symptoms on dementia risk are typically evaluated using single-endpoint survival models, which may not adequately capture bidirectional transitions across intermediate cognitive states or competing risks such as death. In this study, we leveraged longitudinal data from the Health and Retirement Study (HRS) to address these gaps: we examined how AD polygenic susceptibility relates to depressive symptoms across cognitive states, tested whether depressive symptoms predict incident dementia after excluding prodromal periods and whether associations vary by age and genetic susceptibility, and quantified how depressive symptoms shape transitions among normal cognition, subjective memory complaint (SMC), cognitive impairment no dementia (CIND), dementia, and death using multi-state models.

2. Methods

2.1. Study design and participants

This study utilized longitudinal data from the HRS, a nationally representative cohort of U.S. adults aged ≥ 50 years, with core interviews conducted biennially since 1992 [16]. The HRS was supported by the National Institute on Aging (NIA U01AG009740) and was approved by the University of Michigan (IRB: HUM00061128). Informed consent was obtained from all participants.

For analyses involving genetic associations and repeated measures of depressive symptoms and cognitive status, we included 12,089 participants of European ancestry with complete polygenic risk score (PRS) and APOE data who had available data on depressive symptoms and cognitive status in at least one wave from Wave 4 (1998) to Wave 15 (2020), contributing 99,577 person-wave observations (Fig. 1). For the main incident dementia survival analysis, we used Wave 4 (1998) as the analytic baseline as it was the first post-integration wave of the HRS and Asset and Health Dynamics Among the Oldest Old (AHEAD) cohorts under a harmonized design, improving cross-cohort comparability and enabling the longest follow-up through Wave 15 (2020). We included 13,225 dementia-free participants of European ancestry at Wave 4 and followed them through Wave 15. Participants with missing PRS and/or APOE data were retained in this survival cohort; in adjusted models, missing values for genetic covariates were coded as a separate "Missing" category.

2.2. Data assessment

2.2.1. Depressive symptoms

Depressive symptoms were assessed using the eight-item Center for Epidemiologic Studies Depression (CESD-8), which has been widely validated in older adults [17,18]. Six items were negatively worded (e.g., "felt lonely"), and two were positively worded ("felt happy" and "enjoyed life") and reverse-coded. Item scores were summed (range 0–8), with higher scores indicating more depressive symptoms. Consistent with prior studies, a score ≥4 defined elevated depressive symptoms [19].

2.2.2. Cognitive and vital status

Cognitive status was determined using the validated Langa-Weir (LW) algorithm [20]. For self-respondents, cognition was evaluated through immediate and delayed word recall (0–20), serial 7 subtractions (0–5), and backward counting (0–2), yielding a 27-point total score. Participants scoring 0–6 were classified as having dementia, 7–11 as CIND, and 12–27 as normal cognition. For proxy respondents, cognitive status was based on a proxy cognition score that combines proxy-rated memory (0–4) and functional limitations (0–5), plus an interviewer rating of cognitive impairment (0–2) beginning in 2000 (range 0–11). In 1998, the interviewer rating was not collected; thus, a 9-point proxy score was constructed using proxy-rated memory and functional limitations only. Proxy cut-points were normal (0–2), CIND (3–4 for 1998 and 3–5 for 2000 onward), and dementia (5–9 for 1998 and 6–11 for 2000 onward) [21]. Among individuals without cognitive impairment, subjective memory complaint (SMC) was defined as reporting fair/poor

current memory or worse memory than in the past.

Vital status and date of death were ascertained in each wave using HRS tracking information and reports from core interviews and (when deceased) proxy informant exit/post-exit interviews; deaths were additionally identified and validated through linkage to the U.S. National Death Index (NDI) when available.

2.2.3. Genetic factors

APOE isoforms (ε2/ε3/ε4) were inferred from two single-nucleotide polymorphisms (SNPs) (rs7412 and rs429358), which were genotyped from salivary DNA; when direct genotyping was unavailable, APOE was imputed from previously genotyped genome-wide array data [22]. We derived the six APOE types (i.e., 33, 22, 23, 24, 34, 44) and additionally created a binary indicator for APOE ε4 carrier status (at least one ε4 allele or not).

PRSs for depressive symptoms and for AD (without the APOE region) [23] were calculated based on effect estimates from large genome-wide association study (GWAS) meta-analyses in European-ancestry samples [24,25]. All PRSs were standardized within the analytic sample so that effect estimates corresponded to a 1-standard deviation (SD) increase, and were additionally categorized into quartiles and low/high groups. Ten ancestry-specific principal components (PCs; PC1-PC10) supplied by HRS were included to control for population stratification.

2.2.4. Covariates

Covariate information was collected through structured questionnaires, including age, sex (men, women), educational attainment (high school or lower, college or higher), household assets per capita (low, high), marital status (partnered or not), smoking and drinking history (never, ever), regular vigorous physical activity (three times per week or not), body weight status (abnormal: body mass index [BMI] <18.5 kg/m^2 or ≥25 kg/m^2; normal otherwise), and chronic diseases (including hypertension, diabetes, cancer, lung disease, heart disease, stroke, and arthritis).

2.3. Statistical analysis

We estimated the partial Pearson correlation between the depressive-symptoms PRS and the AD PRS (without APOE), adjusting for age, sex, and the top ten ancestry principal components. We then fitted generalized linear mixed models (GLMMs) with a cumulative logit link and a participant-specific random intercept to examine associations between genetic factors and corresponding ordinal outcomes repeatedly measured across HRS waves. Fixed effects included age, sex, wave indicators, and the top ten ancestry principal components. Furthermore, we fitted GLMMs stratified by cognitive status to assess the associations between genetic factors related to AD and depressive symptoms, additionally adjusting for the depressive symptoms PRS.

The Fine-Gray subdistribution hazard regression was used to explore the association (subdistribution hazard ratio [sHR] and 95% confidence interval [CI]) between baseline depressive symptoms (Wave 4, 1998) and incident dementia through Wave 15 (2020), with death as a competing event. All models were adjusted for age, sex, educational attainment, household assets, marital status, smoking history, drinking history, leisure time physical activity, body weight status, number of chronic diseases, PRS for depressive symptoms, APOE alleles, and PRS for AD (without APOE). We repeated the models after excluding dementia diagnoses occurring within 5 and 10 years post-baseline. Subgroup analyses were performed across age, sex, and genetic groups, and multiplicative interactions were assessed.

To examine how depressive symptoms are associated with cognitive transitions, we fitted a multistate Markov model with 5 stages (cognitive

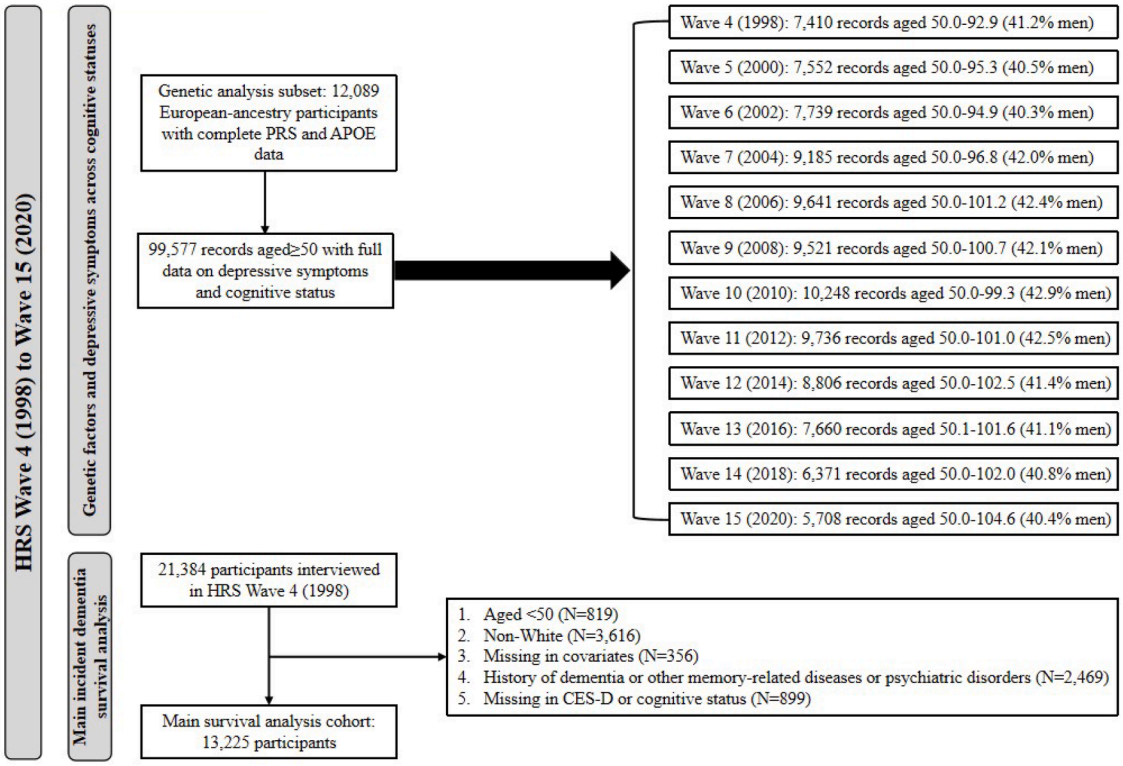


Fig. 1. Study design and participant enrolment flow chart.
Abbreviation: APOE, Apolipoprotein E. CES-D, Centre for Epidemiological Studies Depression Scale. HRS, Health and Retirement Study. PRS, polygenic risk score. The full baseline cohort for the main incident dementia survival analysis comprised 13,225 dementia-free participants of European ancestry at Wave 4 (1998). Genetic analyses were further restricted to the subset with complete PRS and APOE data (n = 12,089), who had available depressive-symptom and cognitive-status data in at least one wave from 1998 to 2020 and contributed 99,577 person-wave observations.

health, SMC, CIND, dementia, and death), where depressive symptoms were modeled as a time-varying exposure, and covariate adjustments and subgroup analyses mirrored those in the Fine-Gray models. A predefined transition structure was specified to allow clinically plausible transitions. Direct transitions from cognitive health or SMC to dementia were not modeled because, under biennial assessment, such apparent jumps were rare and were considered likely to reflect unobserved intermediate states between visits rather than true single-step transitions. We retained the cognitive health → CIND transition because subjective memory complaint is not necessarily observed before objective impairment in all individuals. In this multistate model, hazard ratios (HRs) represent transition-specific relative intensities conditional on occupying the origin state at that time, and should therefore be interpreted within each origin state, as transitions from different origin states reflect different baseline transition intensities and clinical contexts.

Analyses adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and were conducted using SAS statistical software version 9.4 (SAS Institute) and R version 4.4.3. All analyses were two-sided, and *P* values <0.05 were considered statistically significant.

3. Results

The depressive-symptoms PRS was weakly but statistically significantly correlated with the AD PRS without the APOE region (partial r = 0.022, $P = 0.016$). Higher AD PRS were associated with worse cognitive status: strongest in Q4 (β=0.212, $P < 0.001$), and per-SD increases (β=0.098, $P < 0.001$). APOE4 carriers had elevated risk (any APOE4 β=0.317; ε44 β=0.635, both $P < 0.001$). Depressive-symptom PRS increased CESD-8 dose-dependently (Q4 β=0.598; $P < 0.001$). (**Table S1**).

As shown in Fig. 2, quartiles 2–4 (vs. quartile 1) of the AD PRS (without APOE) were positively associated with depressive symptoms in the SMC group (β=0.154 [0.011 to 0.296], 0.245 [0.103 to 0.388], and 0.173 [0.025 to 0.320], respectively), which differed significantly across cognitive status (*P* for interaction=0.049). Also, the APOE ε4/ε4 (44) genotype (vs. ε3/ε3 [26]) was associated with more depressive symptoms in SMC (β=0.409, 95% CI 0.055 to 0.763). No corresponding associations were observed among cognitively healthy participants or those with CIND/dementia.

Among the 13,225 participants included in survival analyses, 1499 (11.3%) had depressive symptoms at baseline, and 2664 (20.1%) developed incident dementia over 22 years of follow-up **(Table S2)**. Baseline depressive symptoms were more common among those who subsequently developed dementia than among those who did not (15.0% vs. 10.4%). In Fine-Gray competing-risk models accounting for death, baseline depressive symptoms (vs. no) were associated with higher dementia risks (sHR=1.24, 95% CI 1.10–1.39; Table 1). This association was stronger among participants aged <60 years (sHR =1.65, 95% CI 1.24–2.18) than among those aged ≥60 years (sHR=1.19, 95% CI 1.05–1.34; *P* for interaction=0.001). After excluding dementia occurring within 10 years, the association persisted in <60 years (sHR=1.55, 95% CI 1.09–2.19) but further attenuated in ≥60 years (sHR=1.10, 95% CI 0.91–1.34; *P* for interaction=0.030). Sex did not significantly modify associations (*P* for interaction=0.154), although the point estimate was numerically higher in women (sHR=1.29, 95% CI 1.12–1.48) than in men (sHR=1.11, 95% CI 0.88–1.38). Similar patterns were observed in lag analyses excluding dementia occurring within 5 and 10 years after baseline.

AD polygenic susceptibility also modified dementia risk. The association between baseline depressive symptoms (vs. no) and incident dementia was more pronounced among individuals with low AD PRS (without APOE) (sHR=1.88, 95% CI 1.45–2.43), but was not observed among those with high AD PRS (sHR=1.03, 95% CI 0.78–1.37; *P* for interaction=0.004; Table 2). Similar patterns were observed after excluding dementia occurring within 5 and 10 years after baseline (*P* for interaction=0.003 and 0.006, respectively). The contrast was most pronounced in late midlife: among participants aged <60 years with low AD PRS without APOE, depressive symptoms were associated with approximately 2.7-fold higher dementia incidence (sHR=2.75, 95% CI 1.65–4.59), whereas estimates were near-null among those with high AD PRS. In sex-stratified analyses, the pattern for AD PRS without APOE was generally similar in men and women, although the interaction was evident only in women (Table 2). Among women, baseline depressive symptoms were associated with a higher risk of incident dementia in the low AD PRS group (sHR=1.97, 95% CI 1.45–2.68), whereas no association was observed in the high AD PRS group (sHR=1.06, 95% CI 0.76–1.48; *P* for interaction=0.010). Among men, baseline depressive symptoms were also associated with a higher risk of incident dementia in the low AD PRS group (sHR=1.77, 95% CI 1.08–2.90), but not in the high AD PRS group, although the interaction was not statistically significant (*P* for interaction=0.196). Similar patterns were observed in analyses excluding dementia onset within 5 and 10 years after baseline. In contrast, APOE ε4 carrier status did not modify the association in the overall sample, age-stratified analyses, or sex-stratified analyses (all *P* for interaction >0.05).

In multistate models with time-varying depressive symptoms, depressive symptoms were associated with higher intensities of several forward cognitive transitions and with reduced reversion to normal cognition. These HRs were transition-specific and should be interpreted within each origin state rather than compared directly across different transitions. Depressive symptoms (vs. no) were associated with higher

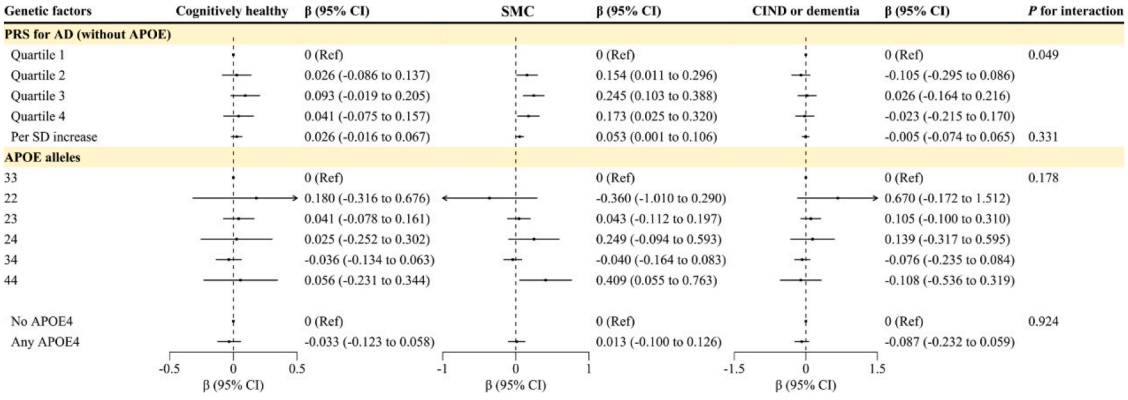


Fig. 2. Genetic factors of Alzheimer's disease in relation to depressive symptoms across cognitive statuses in the Health and Retirement Study, 1998–2020.
Abbreviation: AD, Alzheimer's disease. APOE, Apolipoprotein E. CIND, cognitive impairment no dementia. PRS, polygenic risk score. SMC, subjective memory complaint. SD, standard deviation. Analyses were performed using generalized linear mixed models with full adjustment for PRS for depressive symptoms, age, sex, interview waves, and ten genetic principal components.

Table 1
Depressive symptoms at baseline and risk of incident dementia after baseline, 5-year post baseline, and 10-year post baseline, 1998–2020.

Population groups	Events/ participants (%)	No depressive symptoms sHR (95% CI)	Depressive symptoms	P for interaction
		All incident dementia during follow-ups		
Total samples	2664/13,225 (20.1%)	1.00 (Ref)	1.24 (1.10–1.39)	
Age-stratified				0.001
Aged<60	311/3953 (7.9%)	1.00 (Ref)	1.65 (1.24–2.18)	
Aged≥60	2353/9272 (25.4%)	1.00 (Ref)	1.19 (1.05–1.34)	
Sex-stratified				0.154
Men	998/5785 (17.3%)	1.00 (Ref)	1.11 (0.88–1.38)	
Women	1666/7440 (22.4%)	1.00 (Ref)	1.29 (1.12–1.48)	
		Excluding dementia onset within 5 years post baseline		
Total samples	2041/10,749 (19.0%)	1.00 (Ref)	1.23 (1.07–1.41)	
Age-stratified				0.008
Aged<60	276/3564 (7.7%)	1.00 (Ref)	1.57 (1.16–2.12)	
Aged≥60	1765/7185 (24.6%)	1.00 (Ref)	1.17 (1.00–1.36)	
Sex-stratified				0.101
Men	754/4597 (16.4%)	1.00 (Ref)	1.03 (0.78–1.37)	
Women	1287/6152 (20.9%)	1.00 (Ref)	1.31 (1.11–1.53)	
		Excluding dementia onset within 10 years post baseline		
Total samples	1453/8562 (17.0%)	1.00 (Ref)	1.18 (1.00–1.41)	
Age-stratified				0.030
Aged<60	225/3234 (7.0%)	1.00 (Ref)	1.55 (1.09–2.19)	
Aged≥60	1228/5328 (23.1%)	1.00 (Ref)	1.10 (0.91–1.34)	
Sex-stratified				0.503
Men	537/3579 (15.0%)	1.00 (Ref)	1.09 (0.77–1.52)	
Women	916/4983 (18.4%)	1.00 (Ref)	1.24 (1.01–1.51)	

Abbreviation: CI, confidence interval. sHR, subdistribution hazard ratio.
Analyses were performed using Fine-Gray subdistribution hazard models with full adjustment for age, sex, educational attainment, household assets, marital status, smoking history, drinking history, leisure time physical activity, body weight status, number of chronic diseases, polygenic risk score for depressive symptoms, polygenic risk score for Alzheimer's disease, and APOE alleles. All-cause death was treated as the competing event.

risks of forward transitions (e.g., normal cognition → SMC HR=1.49, 95% CI 1.35–1.65; SMC → CIND HR=1.33, 95% CI 1.18–1.49; CIND → dementia HR=1.17, 95% CI 1.00–1.36), reduced reversion to normal cognition (SMC → normal cognition HR=0.88, 95% CI 0.79–0.97; CIND → normal HR=0.58, 95% CI 0.48–0.70), and was strongly associated with mortality from earlier states (normal cognition → death HR=2.13, 95% CI 1.69–2.67; SMC → death HR=2.06, 95% CI 1.67–2.54) (Table 3). These transition-specific associations were broadly similar in men and women, with no consistent pattern of sex modification across the cognitive continuum; the only nominal interaction was observed for reversion from SMC to normal cognition, where depressive symptoms were associated with lower reversion in women than in men.

Genetic risk modified certain transitions. Among individuals with high AD PRS without APOE, depressive symptoms were associated with less frequent reversion from SMC to normal cognition (HR=0.76, 95% CI 0.64–0.90; *P* for interaction=0.006). In APOE-stratified analyses, depressive symptoms were also associated with higher risks of CIND → dementia (HR=1.47, 95% CI 1.13–1.91) and dementia → death (HR=1.61, 95% CI 1.15–2.26) among APOE ε4 non-carriers **(Table S3).**

4. Discussion

Our findings suggest that depressive symptoms may function both as a long-term risk factor and as a prodromal marker of dementia, with their clinical meaning varying by age, Alzheimer's genetic susceptibility, and cognitive stage. Evidence for a long-term risk-marker role comes primarily from the baseline and lagged survival analyses: baseline depressive symptoms predicted incident dementia over 22 years, with stronger associations among adults < 60 years and among those with low AD PRS, and these associations remained evident after excluding dementia occurring within 5 and 10 years. By contrast, evidence for a prodromal or co-emergent disease-related role comes primarily from late-life and the stage-specific findings: in older adults, the association weakened after excluding near-term dementia, while time-varying depressive symptoms were associated with forward transitions along the cognitive continuum and reduced reversion to normal cognition, and higher AD genetic susceptibility was associated with greater depressive symptom burden specifically at the SMC stage.

Our results are consistent with and extend evidence that depressive symptoms act as a long-term risk factor for dementia. Meta-analyses and large registries indicate that a meaningful proportion of dementia cases may be attributable to depression at the population level [6,27,28], and cohort studies show that clinically diagnosed depression is associated with more than two-fold increased risk of dementia even decades before onset [6,28]. Several biological mechanisms further support this interpretation, including chronic hypothalamic-pituitary-adrenal axis activation, inflammation, cerebrovascular dysfunction, and reduced neurotrophic support, all of which may increase brain vulnerability and represent potentially modifiable pathways [4,6,29]. Neuropathological findings that long-standing depression is associated with loss of monoaminergic neurons in the locus coeruleus and raphe nuclei suggest that chronic depression may reduce the brain's resilience to dementia-related pathological changes [30]. The weaker relative association observed at higher AD PRS should not be interpreted as evidence that depressive symptoms are unimportant in genetically susceptible individuals. Rather, we interpret this pattern as reflecting etiologic heterogeneity and reduced incremental predictive value on a higher baseline-risk background. In individuals with higher inherited AD susceptibility, AD-related biological pathways may already contribute substantially to baseline dementia risk, such that depressive symptoms add less additional relative risk. By contrast, among individuals with lower AD PRS, depressive symptoms may capture a broader set of potentially modifiable non-genetic pathways, including vascular, inflammatory, behavioral, and stress-related processes, and therefore show greater predictive value for subsequent dementia. This interpretation is consistent with prior studies showing that the relative contribution of modifiable risk profiles may be more apparent at lower or intermediate levels of genetic susceptibility than at the highest levels [31]. Our own multistate analyses further indicate that depressive symptoms remained clinically relevant in some higher-risk subgroups; for example, among those with high AD PRS without APOE, depressive symptoms were associated with a lower likelihood of reversion from SMC to normal cognition. Together with our repeated-measures findings that higher AD genetic susceptibility was associated with greater depressive symptom burden specifically at the SMC stage, these results suggest that depressive symptoms in lower-PRS individuals may function more as a long-term, potentially modifiable risk marker, whereas in higher-PRS individuals they may more often reflect shared or disease-related processes.

This interpretation is also compatible with the possibility that, in

Table 2
Genetic susceptibility-stratified association between depressive symptoms at baseline and incident dementia after baseline, 5-year post baseline, and 10-year post baseline, 1998–2020.

Population groups	All incident dementia during follow-ups		Excluding dementia onset within 5 years post baseline		Excluding dementia onset within 10 years post baseline	
	sHR (95% CI)	P for interaction	sHR (95% CI)	P for interaction	sHR (95% CI)	P for interaction
PRS for AD (without APOE)-stratified		0.004		0.003		0.006
Low PRS for AD (without APOE)	1.88 (1.45–2.43)		1.73 (1.32–2.26)		1.74 (1.30–2.33)	
High PRS for AD (without APOE)	1.03 (0.78–1.37)		0.92 (0.68–1.25)		0.89 (0.63–1.24)	
APOE4-stratified		0.760		0.925		0.929
No APOE4	1.33 (1.05–1.69)		1.23 (0.96–1.58)		1.23 (0.93–1.62)	
Any APOE4	1.46 (1.05–2.03)		1.28 (0.90–1.81)		1.25 (0.86–1.83)	
PRS for AD (without APOE)-stratified in aged<60		0.007		<0.001		0.002
Aged<60; Low PRS for AD (without APOE)	2.75 (1.65–4.59)		2.97 (1.77–4.98)		2.87 (1.61–5.09)	
Aged<60; High PRS for AD (without APOE)	0.75 (0.35–1.61)		0.41 (0.15–1.15)		0.34 (0.10–1.14)	
PRS for AD (without APOE)-stratified in aged≥60		0.076		0.176		0.181
Aged≥60; Low PRS for AD (without APOE)	1.64 (1.22–2.22)		1.42 (1.03–1.95)		1.46 (1.04–2.06)	
Aged≥60; High PRS for AD (without APOE)	1.08 (0.79–1.46)		1.01 (0.74–1.39)		0.99 (0.70–1.41)	
APOE4-stratified in aged<60		0.875		0.567		0.656
Aged<60; No APOE4	1.60 (0.96–2.68)		1.61 (0.94–2.78)		1.48 (0.79–2.76)	
Aged<60; Any APOE4	1.55 (0.78–3.11)		1.28 (0.61–2.69)		1.21 (0.55–2.67)	
APOE4-stratified in aged≥60		0.667		0.724		0.771
Aged≥60; No APOE4	1.26 (0.96–1.64)		1.14 (0.86–1.51)		1.16 (0.86–1.58)	
Aged≥60; Any APOE4	1.41 (0.98–2.05)		1.25 (0.85–1.84)		1.23 (0.81–1.89)	
PRS for AD (without APOE)-stratified in men		0.196		0.146		0.107
Men; Low PRS for AD (without APOE)	1.77 (1.08–2.90)		1.56 (0.92–2.64)		1.75 (1.01–3.03)	
Men; High PRS for AD (without APOE)	0.94 (0.51–1.70)		0.73 (0.37–1.46)		0.64 (0.29–1.38)	
PRS for AD (without APOE)-stratified in women		0.010		0.010		0.025
Women; Low PRS for AD (without APOE)	1.97 (1.45–2.68)		1.84 (1.34–2.52)		1.81 (1.28–2.55)	
Women; High PRS for AD (without APOE)	1.06 (0.76–1.48)		0.97 (0.68–1.38)		0.98 (0.66–1.44)	
APOE4-stratified in men		0.243		0.299		0.541
Men; No APOE4	1.49 (0.96–2.32)		1.25 (0.77–2.02)		1.22 (0.72–2.07)	
Men; Any APOE4	1.06 (0.50–2.26)		0.90 (0.40–2.03)		0.98 (0.42–2.28)	
APOE4-stratified in women		0.334		0.522		0.687
Women; No APOE4	1.29 (0.96–1.72)		1.23 (0.91–1.66)		1.26 (0.91–1.74)	
Women; Any APOE4	1.66 (1.14–2.43)		1.48 (1.00–2.18)		1.42 (0.92–2.20)	

Abbreviation: AD, Alzheimer's disease. APOE, Apolipoprotein E. CI, confidence interval. PRS, polygenic risk score. sHR, subdistribution hazard ratio.
Models were adjusted for age, sex, educational attainment, household assets, marital status, smoking history, drinking history, leisure time physical activity, body weight status, number of chronic diseases, and PRS for depressive symptoms. PRS-stratified models were additionally adjusted for APOE ε4 carrier status; APOE ε4-stratified models were additionally adjusted for AD PRS without the APOE region.
P for interaction refers to the interaction between baseline depressive symptoms and the corresponding stratification variable. In this table, the stratification variable is the genetic susceptibility measure (AD PRS without APOE or APOE4 carrier status).

Table 3
Time-dependent depressive symptoms and cognitive transitions from 1998 to 2020.

Cognitive transitions		Total population	Men	Women	P for interaction
Start stage	End stage	HR (95% CI)			
Number of records		99,815	42,269	57,546	
Cognitive health	SMC	1.49 (1.35–1.65)	1.55 (1.28–1.87)	1.47 (1.30–1.65)	0.448
Cognitive health	CIND	1.35 (1.15–1.59)	1.59 (1.19–2.12)	1.33 (1.11–1.61)	0.692
Cognitive health	Death	2.13 (1.69–2.67)	2.51 (1.76–3.56)	2.09 (1.55–2.81)	0.682
SMC	Cognitive health	0.88 (0.79–0.97)	1.07 (0.90–1.27)	0.83 (0.73–0.93)	0.043
SMC	CIND	1.33 (1.18–1.49)	1.30 (1.07–1.58)	1.33 (1.15–1.53)	0.716
SMC	Death	2.06 (1.67–2.54)	2.35 (1.72–3.21)	1.73 (1.28–2.34)	0.291
CIND	Cognitive health	0.58 (0.48–0.70)	0.48 (0.31–0.74)	0.60 (0.48–0.75)	0.576
CIND	SMC	1.19 (1.03–1.38)	1.40 (1.12–1.76)	1.09 (0.90–1.32)	0.180
CIND	Dementia	1.17 (1.00–1.36)	1.26 (0.95–1.66)	1.13 (0.94–1.36)	0.620
CIND	Death	1.52 (1.23–1.87)	1.57 (1.16–2.11)	1.51 (1.11–2.04)	0.691
Dementia	CIND	0.94 (0.75–1.17)	1.05 (0.72–1.54)	0.91 (0.69–1.19)	0.675
Dementia	Death	1.17 (0.94–1.44)	1.14 (0.79–1.67)	1.15 (0.88–1.51)	0.926

Abbreviation: CI, confidence interval. CIND, cognitive impairment no dementia. HR, hazard ratio. SMC, subjective memory complaint.
Analyses were performed using multistate models with full adjustment for age, sex, educational attainment, household assets, marital status, smoking history, drinking history, leisure time physical activity, body weight status, number of chronic diseases, polygenic risk score for depressive symptoms, polygenic risk score for Alzheimer's disease, and APOE alleles.

genetically susceptible individuals, depressive symptoms are more likely to overlap with AD-related processes emerging around the SMC stage, rather than serving primarily as an independent long-term risk marker. In this study, the prodromal signal appears to be stage-dependent, being most evident when depressive symptoms co-occur with SMC and AD genetic susceptibility [32]. Prior trajectory studies have shown that the association between depressive symptoms and dementia is strongest in short- and intermediate-term follow-up, with little association when follow-up exceeds 10 years [7,33], and that depressive symptoms arising later in life may be more closely linked to processes proximal to clinical onset [26]. This temporal pattern may also explain why late-life depressive symptoms were not associated with a stronger long-term

overall hazard in our older participants, as a baseline prodromal signal would be expected to attenuate over extended follow-up. Also, our multistate analyses are consistent with this interpretation, as time-varying depressive symptoms were associated with forward transitions along the cognitive continuum and reduced reversion to normal cognition. These multistate findings cannot by themselves prove a prodromal mechanism; rather, they indicate that depressive symptoms are particularly informative when they occur contemporaneously with active cognitive-state changes, especially around the SMC stage. This interpretation is further strengthened by the Subjective Cognitive Decline Initiative (SCD-I) framework, which conceptualizes subjective cognitive decline as a potential symptomatic indicator of late-stage preclinical AD [34]. Although SMC is closely related to depressive symptoms, they are not fully explained by mood and may provide additional information on future cognitive decline and dementia risk [35]. Moreover, subjective complaints have been linked to preclinical AD biomarkers, including amyloid-β deposition, in cognitively unimpaired adults [36]. In parallel, higher cortical amyloid-β burden has been prospectively associated with worsening anxious-depressive symptoms over time, suggesting that AD-related pathology may contribute to affective symptoms during the preclinical stage [37]. Against this background, our observation that higher AD PRS (without APOE) was associated with greater depressive symptom burden only among individuals with SMC, together with multi-state evidence, supports that depression symptoms emerging alongside SMC in genetically susceptible adults may reflect prodromal or concurrent disease processes.

This study included integration of APOE, AD PRS without APOE, and a depressive-symptoms PRS in a large, nationally representative cohort, together with multi-state modeling that captures progression, reversion, and competing mortality. In younger and genetically lower-risk individuals, depressive symptoms represent a modifiable target for early intervention, and integrated management of vascular risk, sleep disturbance, and physical inactivity may improve long-term cognitive trajectories [38,39]. In contrast, among older adults with SMC and high AD PRS, depressive symptoms should be treated as a clinical warning signal warranting closer surveillance for underlying neurodegenerative or vascular pathology [40]. Although the point estimates in the main survival models were numerically higher in women than in men, we found no consistent statistical evidence that sex broadly modified the association between depressive symptoms and dementia risk. The additional sex-stratified analyses suggested that the lower-PRS pattern appeared more pronounced in women, but the broader literature on sex differences in the depressive symptoms-dementia association remains mixed [41]. These findings therefore support reporting possible sex-related heterogeneity while avoiding strong conclusions about a women-specific effect.

However, we have several limitations. Cognitive status was measured using the validated Langa-Weir algorithm based on cognitive tests and proxy information, rather than biomarker-confirmed or neuropathologically confirmed AD diagnosis. Accordingly, the incident dementia outcome represents all-cause dementia and may include non-AD dementia, which limits the etiologic specificity of the AD-related interpretation. The SMC was self-reported and may be mood-sensitive, which does not fully align with the more comprehensive SCD-I and further SCD-plus [42]. Furthermore, our analyses were restricted to participants of European genetic ancestry, limiting generalizability to other populations. Finally, the observational design precludes definitive conclusions about causality.

In conclusion, our study demonstrated that depressive symptoms were related to dementia in ways that depended on age, AD genetic susceptibility, and cognitive stage. Early- and midlife depressive symptoms, particularly in individuals with lower AD PRS, behaved as a risk factor. Accordingly, depression screening and evidence-based treatment should be strengthened as a core component of life-course dementia prevention. For older adults with SMC, especially those with higher AD genetic susceptibility, depressive symptoms may reflect prodromal or co-emergent disease-related processes and should prompt closer cognitive follow-up.

Ethics approval and consent to participate

The HRS was supported by the National Institute on Aging (NIA U01AG009740) and was approved and conducted by the University of Michigan (IRB: HUM00061128). All participants provided written informed consent.

Consent for publication

All participants provided written informed consent.

Availability of data and materials

Data for the study came from the HRS project and are available to all researchers for purely scientific purposes upon request on the website: https://hrsdata.isr.umich.edu/data-products.

Competing interests

The authors declare no conflict of interest regarding this manuscript.

Declaration of the use of generative AI and AI-assisted technologies

The authors used generative AI and AI-assisted technologies only for language polishing and readability improvement during the preparation of this manuscript. All scientific content, data interpretation, and conclusions are the sole work of the authors, who reviewed and approved the final version and take full responsibility for its content. No AI-generated figures, images, or artwork were used.

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CRediT authorship contribution statement

Ziyang Ren: Methodology, Formal analysis, Conceptualization. **Ruyi Zhang:** Writing – original draft, Methodology, Formal analysis. **Shuai Guo:** Writing – review & editing, Data curation. **Yihao Zhao:** Writing – review & editing, Data curation. **Jufen Liu:** Writing – review & editing, Methodology. **Xiaoying Zheng:** Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100577.

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