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Psychological resources confer greatest protection against late-life depression in genetically vulnerable adults

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Psychological resources confer greatest protection against late-life depression in genetically vulnerable adults

Abstract

How life-course experiences shape depression in later life remains one of the central questions in human aging. We analyzed approximately 35 years of sociogenomic longitudinal data from 9,005 European-ancestry individuals in the Wisconsin Longitudinal Study. Machine learning models were applied to 426 variables measured at mean ages 35.6, 53.0, and 64.2 to predict depressive symptoms at mean age 70.6. Psychological resources, including environmental mastery, self-acceptance, purpose in life, and optimism, consistently emerged as the strongest predictors, accounting for substantially greater variance (R^2 = 0.20) than socioeconomic, behavioral, or genetic factors. Polygenic risk for neuroticism selectively moderated the negative association between the psychological resource composite and late-life depression, supported by linear regression (β = -0.049; 95% CI, -0.075 to -0.024) and generalized structured component analysis (β = -0.037; 95% CI, -0.060 to -0.017). Our findings suggest psychological resource enhancement in genetically vulnerable adults as a potential precision-prevention strategy for late-life depression.

Introduction

Depression in later life is a major public health challenge in the aging population, with substantial consequences for morbidity, mortality, and quality of life among older adults. Global estimates suggest that 18-30% of older adults experience clinically relevant depressive symptoms,[1–3] and this burden is compounded by associations with cognitive decline and dementia[4–6], functional impairment[7,8], and suicide.[9] Given that depressive symptoms in later life

are often persistent and challenging to treat once established,[10,11] prevention remains a clinical and public health priority, particularly in determining which modifiable factors should be prioritized and which individuals are most likely to benefit from intervention.

Preventive approaches to late-life depression are inherently a problem of prioritization across a high-dimensional landscape of life-course exposures. Depression risk in older adulthood is shaped by a complex interplay among a broad range of social, behavioral, occupational, psychological, and biological factors,[12–15] yet prior studies have typically examined these domains in isolation, focused on a limited set of predictors, or relied on cross-sectional data. As a result, the relative importance of modifiable factors within a multidomain, longitudinal framework remains unclear. Filling this gap is consequential as effective prevention depends not only on identifying risk or protective factors, but also on determining which factors are the most actionable targets for intervention over time.

Beyond identifying what to target, effective prevention must also address whom to target. In this endeavor, polygenic scores (PGSs) may be critical as they now enable the stratification of individuals by genetic susceptibility, revealing meaningful heterogeneity in baseline risk.[16] In particular, given that PGS reflects fixed genetic predisposition established at conception and is therefore invariant to subsequent life experiences, it can serve as a robust moderator in gene-environment interplay research.[19–21] In fact, emerging evidence suggests that genetic liability may index not only risk but also differential responsiveness to environmental and psychological exposures. For example, individuals at high polygenic risk for major depressive disorder exhibited greater sensitivity to both loss and gain of social support,[17] and higher PGSs for psychiatric traits amplified both adverse and protective effects of stress and social support on well-being outcomes.[18] We extend this body of work by examining how genes and environments work

together to affect depressive symptoms in later life. By doing so, our results may help identify subgroups who may differentially benefit from prevention.

Using longitudinal sociogenomic data of 9,005 participants in the Wisconsin Longitudinal Study assessed at mid-adulthood (wave 3; mean age 35.6), late midlife (wave 4; mean age 53.0), and early older adulthood (wave 5; mean age 64.2), we address two questions central to precision prevention—what to target and whom to target. First, we applied an automated machine learning approach to identify life-course factors most strongly associated with late-life depressive symptoms (assessed at wave 6; mean age 70.6) across 426 variables spanning 11 domains in a data-driven manner. Second, we examined whether polygenic risk modified the associations of the top-ranked predictors with late-life depressive symptoms. By integrating multidomain prediction with genetic moderation, this study aims to clarify both the most promising modifiable targets for prevention and the individuals most likely to benefit from them.

Results

Demographics of the study cohort

Table 1 presents demographic characteristics of the study participants. The final sample consisted of 9,005 participants, of whom 52.1% were female. Mean ages were 35.6 years at wave 3, 53.0 years at wave 4, 64.2 years at wave 5, and 70.6 years at wave 6. Socioeconomic indicators included total personal income (TPI), education years (based on highest degree attained), and marital status. These variables were included as covariates in subsequent analyses.

Psychological resources and Big Five personality traits are the strongest predictors of late-life depression

Across all 426 life-course variables, psychological resources (PR) and neuroticism from the Big Five personality traits emerged as the most influential predictors of late-life depressive symptoms. Among the nine trained models in AutoML, the gradient boosting machine (GBM) achieved the lowest root mean squared error (RMSE) of 0.884 on the training set and was selected as the final model (**Supplementary Table 2, Supplementary Table 3**). On the held-out test set, the model achieved a mean squared error (MSE) of 0.724, RMSE of 0.851, mean absolute error (MAE) of 0.623, and R^2 of 0.243.

SHAP (SHapley Additive exPlanations) analysis showed that higher levels of environmental mastery (wave 4, 5), self-acceptance (wave 4, 5), purpose in life (wave 5), positive relationship (wave 5), and optimism (wave 5) were associated with lower late-life depressive symptoms, whereas neuroticism (wave 4, 5) was positively associated with depressive symptoms. **(Figure 1A, Supplementary Table 4)**. Feature importance yielded similar results, with environmental mastery at wave 5 showing the highest importance **(Figure 1B, Supplementary Table 5)**.

Life-course domain-level comparisons revealed that PR had the highest explanatory power (R^2=0.20) on the test set, followed by Big Five personality (R^2=0.157) and social and community context (R^2=0.106) (**Figure 2A, Supplementary Table 6**), whereas PGS (R^2=0.035) and covariates (R^2=0.032) explained the least variance relative to other domains. These findings were consistent in generalized linear models (GLMs), with PR showing the highest adjusted R^2 of 0.206, followed by Big Five personality (adjusted R^2=0.149) and social and community context (adjusted R^2=0.046) (**Figure 2B, Supplementary Table 7**).

To quantify the explanatory power of individual variables, we fitted ordinary least squares (OLS) models separately for each of the 426 variables, adjusting for sex, age (corresponding to

the wave of each variable), and the first ten genetic principal components. Consistent with the domain-level analyses, variables within the PR domain, including environmental mastery (β = -0.381, ΔR^2 = 0.145), self-acceptance (β = -0.356, ΔR^2 = 0.127), and purpose in life (β = -0.329, ΔR^2 = 0.108) at wave 5 showed the largest incremental contributions to the explained variance in late-life depressive symptoms (**Figure 2C, Supplementary Table 8**).

Across the three metrics (mean SHAP and feature importance from GBM, and ΔR^2 from OLS), nine variables overlapped within the top 20: environmental mastery (wave 4, 5), self-acceptance (wave 4, 5), purpose in life (wave 5), positive relationships (wave 5), optimism (wave 5), and neuroticism (wave 4, 5).

Robust associations of psychological resources across depression-related outcomes

We conducted sensitivity analyses using eight additional depression-related outcomes to assess the generalizability of the findings (**Supplementary Table 9**). GBM models were fitted using all 426 variables and within each life-course domain. Across outcomes, PR consistently emerged as key contributors in SHAP analyses (**Supplementary Figure 1**). In particular, environmental mastery (wave 4, 5) and neuroticism (wave 4, 5) were identified in 7 of 8 outcomes, indicating highly stable associations. Self-acceptance was also frequently identified (5 outcomes at wave 5; 4 at wave 4), along with optimism (5 outcomes) and purpose in life (4 outcomes) at wave 5. In contrast, other personality traits, such as agreeableness, openness, conscientiousness, and extraversion, appeared only in a limited number of outcomes. Domain-level comparison further showed that the PR domain achieved the highest R^2 after the full model in 5 of the 8 outcomes, supporting its dominant role across depression-related phenotypes at later life.

Genetic risk for neuroticism selectively moderates the association between psychological resources and late-life depression

Among the 13 PGSs associated with late-life depression (**Supplementary Table 10**), we examined additive and interaction effects with key predictors identified from machine-learning analyses, namely PR and Big Five personality traits. In additive models, most of the PGSs and the key variables showed independent associations with late-life depressive symptoms across waves 4 and 5, indicating that genetic liability and psychosocial factors contribute additively. Across both waves, neuroticism was the only key predictor positively associated with late-life depressive symptoms, whereas all other personality traits and PR variables were negatively associated. At the genetic level, PGSs for cognitive ability (cognitive performance, IQ, educational attainment), automobile speeding propensity, and general happiness were negatively associated, whereas psychiatric PGSs (e.g., anxiety, depression) showed positive associations (**Supplementary Figure 2-3**, **Supplementary Table 11-12**).

In interaction analyses, only the neuroticism PGS exclusively showed significant moderation effects, with no other PGS reaching significance after multiple testing correction in both waves 4 and 5 (**Supplementary Figure 4-5, Supplementary Table 13-14**). In wave 5, the neuroticism PGS most strongly moderated the effect of the PR composite (average of the eight variables) on late-life depressive symptoms (β = -0.049; 95% CI, -0.075 to -0.024), followed by self-acceptance (β = -0.037; 95% CI, -0.056 to -0.017), environmental mastery (β = -0.034; 95% CI, -0.053 to -0.015), and positive relationships (β = -0.031; 95% CI, -0.050 to -0.011) (**Figure 3A**). Among the eight individual PR variables, all except autonomy and mattering were significantly moderated by the neuroticism PGS, and only neuroticism (self-reported measure) was significantly moderated among the Big Five personalities. At higher levels of PR composite, the

difference in depressive symptoms between those with high (top 10%) and low (bottom 10%) polygenic risk for neuroticism attenuated and eventually reversed (from 0.58 to −0.07) (**Figure 3B**), such that individuals at high genetic risk no longer exhibited greater symptoms. In wave 4, fewer but directionally consistent interactions were observed, with significant moderation of the neuroticism PGS for personal growth (β = -0.037; 95% CI, -0.057 to -0.017), psychological well-being (β = -0.032; 95% CI, -0.051 to -0.012), and openness (β = -0.026; 95% CI, -0.046 to -0.006) (**Supplementary Figure 6**).

To test robustness to the equal-weight assumption when deriving the PR composite and to examine whether the moderation could be represented as a single parsimonious model, we replicated the analysis using generalized structured component analysis (GSCA), which derives statistically optimal indicator weights. The proportion of variance explained (PVE) of the PR component was 0.561, with self-acceptance (0.842) and environmental mastery (0.833) showing the highest loadings. The weighted PR component was negatively associated with late-life depressive symptoms (β = -0.378; 95% CI, -0.040 to -0.356), while neuroticism PGS was positively associated (β = 0.062; 95% CI, 0.045 to 0.081). Their interaction remained significant (β = -0.037; 95% CI, -0.052 to -0.006) (**Figure 3C**). Model fits, weights and loadings of each variable are presented in **Supplementary Table 15**.

Discussion

By leveraging a multidomain, longitudinal framework, this study reveals not only which factors are associated with late-life depressive symptoms, but also how their relative importance varies across domains and when they exert their most proximal influence over the life course.

Psychological resources (PR) at mid- to late adulthood emerged as the strongest predictors, outperforming socioeconomic, behavioral, and genetic factors (**Figure 1-2**). Polygenic liability to neuroticism moderated these associations: individuals with higher genetic risk initially showed greater predicted symptom levels than the lower genetic risk group, but steeper declines with increasing PR, ultimately falling below the low-risk group (**Figure 3B**; interaction $\beta = -0.049$, 95% CI −0.075 to −0.024). GSCA further showed that PR can be represented as a single component with optimized weights, providing a parsimonious representation of its structure while identifying self-acceptance and environmental mastery as the primary drivers within this system (**Figure 3C**). The persistence of the interaction with neuroticism PGS at this level suggests that enhancing PR as a whole may be a meaningful target for depression prevention among individuals with heightened genetic vulnerability. This pattern is consistent with the principle of vantage sensitivity, whereby biologically indexed individual differences confer heightened responsiveness specifically to positive environmental and internal influences.[22] In this context, modifiable psychological characteristics and stable genetic predisposition appear to jointly shape the distribution of depression risk, and the two together may be more informative for prevention than either alone.

Among the PR examined, environmental mastery (wave 4, 5), self-acceptance (wave 4, 5), purpose in life (wave 5), positive relationships (wave 5), and optimism (wave 5) showed the strongest and most consistent negative associations with late-life depressive symptoms. In addition, neuroticism (self-reported Big Five personality; wave 4, 5), although not part of the PR domain, showed strong and consistent positive associations. Greater environmental mastery, which refers to the capacity to manage one's life and surroundings effectively, may protect against late-life depression by preserving a sense of control, mitigating the psychological impact of age-related functional decline,[23] and enhancing self-efficacy in coping with stressors.[24] Higher self-acceptance,

reflecting a positive attitude toward oneself including one's past, may reduce late-life depression by weakening self-critical responses to aging-related losses, thereby preventing the negative feedback loop in which self-criticism discourages engagement and sustains depressive states.[25] A stronger sense of purpose in life has been prospectively associated with fewer depressive symptoms,[26] potentially through flexible goal reallocation in response to aging-related losses and faster recovery from negative stimuli.[27] Positive relationships may have protective effects through qualitative emotional support and a sense of belonging.[28] Higher dispositional optimism is associated with lower perceived frequency of daily stressors,[29] and promotes approach-oriented coping strategies that limit the escalation of psychological distress.[30] Taken together, these findings support a stress-appraisal account in which late-life depression is proximally shaped by how individuals interpret and emotionally respond to stressors arising from other life-course domains in later life, such as loss, illness, and functional decline. PR may therefore function as internal regulators of this appraisal process, shaping the emotional impact of these stressors.

Genetic moderation was specific to neuroticism polygenic risk, highlighting a targeted interaction between psychological resources and affective vulnerability. Neuroticism reflects a stable tendency toward negative affectivity, heightened emotional reactivity, and a systematic bias toward perceiving situations as threatening.[31,32] At the genetic level, neuroticism shares substantial genetic architecture with major depressive disorder and internalizing psychopathology more broadly, supporting its conceptualization as a transdiagnostic vulnerability factor.[33–38] Prior work in this same cohort[39,40] also showed that both self-reported neuroticism and neuroticism polygenic risk are associated with elevated late-life depressive symptoms, with this relationship partially mediated by psychosocial pathways, including reduced social support and greater exposure to dependent stressful life.[40] In this context, neuroticism indexes affective vulnerability in how

individuals respond to stressors, whereas PR reflect the capacity to adaptively manage those responses. This alignment may explain why the neuroticism PGS was the only polygenic score to show significant moderation, whereas other PGSs likely capture more distal or heterogenous pathways less directly linked to these processes. Moderation effects were more evident for PR in older adulthood (wave 5, mean age 64.2 years) than in midlife (wave 4, mean age 53.0 years), as more PR variables showed significant interactions with neuroticism PGS at wave 5, suggesting that the protective effects of PR is amplified among genetically vulnerable adults when their enhancement occurs closer in time to the onset of late-life depressive symptoms.

These findings may have potential implications for how preventive strategies for late-life depression are conceptualized, although causal interpretations cannot be drawn from the present observational analyses. There is increasing recognition that well-being extends beyond the absence of mental illness and reflects broader dimensions of positive psychological functioning.[41] A growing body of literature suggests that well-being is modifiable and can be enhanced through targeted interventions such as positive psychology interventions (PPIs).[42] These include gratitude exercises, strengths identification, mindfulness, and acts of kindness that enhance hedonic (e.g., positive affect, life satisfaction) and eudaimonic well-being (e.g., purpose and meaning, mastery and competence). Meta-analytic evidence indicates that such interventions are associated with moderate improvements in well-being and reductions in depressive symptoms,[43,44] particularly among older individuals and those with elevated baseline depressive symptoms.[43] This suggests that enhancing PR is a feasible and relevant strategy for the prevention of late-life depression. Our findings add to this literature by suggesting that the associations between PR and depressive symptoms vary according to underlying genetic susceptibility, with potential implications for

heterogeneity in intervention contexts, although such interpretations remain speculative and require further investigation.

There are some limitations to consider. First, the study cohort consists predominantly of non-Hispanic white participants (97%) from a single 1957 Wisconsin high school graduation cohort, limiting the representativeness of the findings to a broader population. Further validation using cohorts with broader racial, ethnic, and socioeconomic characteristics is essential. Second, late-life depression was assessed using the CES-D scale, which captures symptom burden rather than clinically diagnosed depression. Therefore, caution is needed when interpreting the clinical and public health implications of our findings. Third, while our analyses incorporated a broad set of predictors, available measures may not fully capture all relevant PR, such as self-efficacy or self-esteem. Finally, the observational nature of the study precludes causal inference, and future research using experimental or quasi-experimental designs is needed to establish whether strengthening psychological resources can causally attenuate genetic risk for depression.

In summary, PR variables are central correlates of late-life depressive symptoms and appear to selectively buffer genetic liability to neuroticism. These findings support a model in which modifiable psychological capacities and genetic vulnerability jointly shape depression risk in later life, highlighting psychological resource enhancement as a promising target for precision prevention in aging populations.

Methods

Data

The Wisconsin Longitudinal Study (WLS) is a long-term cohort of individuals who graduated from Wisconsin high schools in 1957 and have been followed across multiple waves

from adolescence to older adulthood.[45] Predictors were measured at waves 3 (1975; mean age 35.6), 4 (1993; mean age 53.0), and 5 (2004; mean age 64.2) and the outcome was assessed at wave 6 (2011; mean age 70.6). Genetic data were collected separately in 2006–2007. WLS data collection was approved by the Institutional Review Board (IRB) at the University of Wisconsin–Madison. Informed consent, the content and procedures of which were included in the IRB approval, were obtained from all participants. All methods were performed in accordance with relevant guidelines and regulations.

Variables with more than 30% missingness among the participants were excluded from analysis, and remaining missing values were imputed using k-nearest neighbors (kNN) imputation.[46] After excluding individuals without genetic data and removing duplicate records, the final analytic sample included 9,005 participants. All continuous variables were standardized to z-scores. A complete list of variables is presented in **Supplementary Table 1**.

Polygenic score

Polygenic scores (PGSs) aggregate the cumulative effect of multiple genetic variants to quantify an individual's genetic predisposition for target traits.[47,48] For this study, PGSs were constructed using summary statistics from genome-wide association studies for 26 cognitive, psychiatric, behavioral, and health-related traits: cognitive performance[49], educational attainment[49], IQ[50], major depressive disorder (MDD)[51], post-traumatic stress disorder (PTSD)[52], obsessive-compulsive disorder (OCD)[53], anxiety[54], depression[33], neuroticism[33], bipolar disorder[55], autism spectrum disorder (ASD)[56], schizophrenia[57], cross disorder[58], risk tolerance[59], drinking[59], smoking[59], automobile speeding propensity (ASP)[59], the first principal component of four risky

behaviors[59], eating disorder[60], cannabis use[61], general happiness[62], belief that own life is meaningful[62], snoring[63], insomnia[63], alcohol dependence (AD)[64], and Alzheimer's disease[65].

PGSs were generated using the PRS-CSx framework[66], a high-dimensional Bayesian regression approach employing a continuous shrinkage prior on SNP effect sizes to improve cross-population polygenic prediction.

Late-life depression score

The main outcome, depressive symptoms in later life (wave 6, mean age 70.60) was assessed using a subset of items from the Center for Epidemiologic Studies-Depression (CES-D) scale, a self-report tool designed to assess the current level of depressive symptomatology.[67] In the WLS, items were coded by number of days (0–7) rather than standard categorical responses (less than 1 day, 1-2 days, 3-4 days, or 5-7 days), yielding a total score range of 0–140. Internal consistency was high (Cronbach's $\alpha = 0.88–0.92$).[45]

Machine learning

Machine learning analyses were conducted to identify the most predictive variables of late-life depressive symptoms, using H2O AutoML to reduce model selection bias.[68] H2O AutoML is an automated supervised learning framework that trains, tunes, and cross-validates a multitude of machine learning models to identify the best-performing model. Data were split randomly into training (80%) and test (20%) sets.

AutoML was configured to train up to 1,000 models per run with a maximum runtime of 600 seconds, incorporating models such as generalized linear models, gradient boosting machines, extreme gradient boosting, deep neural networks, distributed random forests, extremely

randomized trees, and stacked ensembles. Model selection was based on 5-fold cross-validation performance with automated hyperparameter tuning. For regression tasks, both early stopping and model ranking were based on root mean squared error (RMSE) (i.e., stopping_metric = "RMSE", sort_metric = "RMSE"). For classification tasks, the area under the receiver operating characteristic curve (AUC) was used for both early stopping and model ranking (stopping_metric = "AUC", sort_metric = "AUC"). The final model was selected from the training set based on the leaderboard, choosing the model with the lowest RMSE. The selected model was then evaluated on the test set by performance metrics including mean squared error (MSE), RMSE, mean absolute error (MAE), and R-squared (R^2).

Domain classification across the life course

Study variables were grouped a priori into 11 life-course domains to compare their relative associations with late-life depressive symptoms: (1) economic stability (100 variables), (2) educational access and quality (8 variables), (3) social and community context (116 variables), (4) health care access and quality (15 variables), (5) work characteristics (80 variables), (6) health behaviors (e.g., smoking, alcohol use, and physical activity; 32 variables), (7) Big Five personality (10 variables), (8) psychological resources (PR) (25 variables), (9) environmental stressors, including childhood and adulthood exposure to smoking or drinking and traumatic experiences (7 variables), (10) genetic vulnerability, quantified by PGS (26 variables), and (11) covariates including age, sex, body mass index, and the first ten genetic principal components (17 variables). The first four domains correspond to social determinants of health as defined by the US Department of Health and Human Services (2023).[69]

Psychological resources (PR) were conceptualized as a distinct domain to capture internal adaptive capacities separate from external factors. Within the Conservation of Resources (COR) theory, PR encompass psychological traits that facilitate adaptation and goal attainment, including mastery, self-esteem, self-efficacy, and optimism.[70,71] Guided by this framework, PR were operationalized using eight variables, comprising optimism, mattering[73], and the six dimensions of Ryff's psychological well-being (PWB) model[72] (autonomy, environmental mastery, personal growth, purpose in life, self-acceptance, and positive relationship). Optimism and mattering were not measured at wave 4, whereas a summary score for PWB (PsychWellbeing_R4) was available at wave 4 but not at wave 5.

Genetic moderation analyses

Polygenic scores (PGSs) were specified as moderators to assess genetic modification of associations between key predictors and late-life depressive symptoms. Among 26 PGSs, 13 showed significant Pearson correlations with late-life depressive symptoms after false discovery rate correction (Benjamini–Hochberg) for multiple testing ($p < 0.05$) and were included in analyses (**Supplementary Table 10**).

Additive and interaction effects between key variables identified from machine learning analyses (i.e., independent variables) and PGS on late-life depressive symptoms were examined using linear regression. We also constructed a PR composite by averaging the eight variables described above to represent an overall score. All models were adjusted for sex, age, the first ten genetic principal components, personal income, educational attainment, and marital status. The wave of personal income, educational attainment, and age was aligned with that of the independent variable. When the highest degree information was unavailable (e.g., wave 4), years of college

completed was used as a proxy for educational attainment. Marital status was dichotomized as married (1) versus all other categories (0). False discovery rate correction was applied to interaction terms, treating tests across independent variables within each PGS as a single hypothesis family.

To address potential limitations of equal weighting in the PR composite, generalized structured component analysis (GSCA Pro 1.2.1.0 software[74]) was used as a robustness analysis.[75] GSCA is a component-based structural equation modeling approach that constructs weighted components from observed variables and enables estimation of interactions at the component level. This approach allows heterogeneous psychological resource indicators to be combined into a single PR component while preserving their differential contributions. The same set of covariates used in linear regression was applied in GSCA. Model fit was evaluated using FIT, AFIT, goodness-of-fit index (GFI), standardized root mean square residual index (SRMR), and out-of-sample prediction error (OPE).[76] Statistical significance of weights, loadings, and path coefficients was assessed using 1000 bootstrap samples to derive 95% confidence intervals. Detailed information on GSCA is provided in **Supplementary Methods**.

Table 1. Demographics of the study cohort

Variables			**Wave 3**	**Wave 4**	**Wave 5**	**Wave 6**
Age, mean (SD)			35.6 (2.43)	53.0 (3.94)	64.2 (4.09)	70.60 (4.09)
Sex, n (%)	Male	4317 (47.9)				
	Female	4688 (52.1)				
Total Personal Income (TPI, $), mean (SD)			91.9 (94.94) *	36195.4 (137548.47)	52397.4 (156810.35)	33259.4 (136793.9 8)
Education years (Years of education based on highest degree), mean (SD)			1.5 (2.12)	2.0 (2.68)	13.8 (2.34)	13.8 (2.34)
Marital status, n (%)	Married		8256 (91.7)	7330 (81.4)	6913 (76.8)	6184 (68.7)
	Separated		121 (1.3)	186 (2.1)	250 (2.8)	335 (3.7)

	Divorced		257 (2.9)	932 (10.3)	886 (9.8)	1042 (11.6)
	Widowed		25 (0.3)	251 (2.8)	661 (7.3)	1161 (12.9)
	Never married (Single in wave 3)		346 (3.8)	306 (3.4)	295 (3.3)	283 (3.1)

*For wave 3, total personal income is measured as participant's total earnings last year in $100's.

Figure 1. Key variables associated with late-life depression

A, SHAP summary plot showing each feature's contribution to model predictions. Features are ordered by mean absolute SHAP values. **B**, Top 10 feature importances. For regression tasks in gradient boosting machines, importance is measured as the total reduction in mean squared error (MSE) attributed to each feature across all splits in the ensemble. The values were scaled to fall between 0 and 1. R5 and R4 denote wave 5 and wave 4.

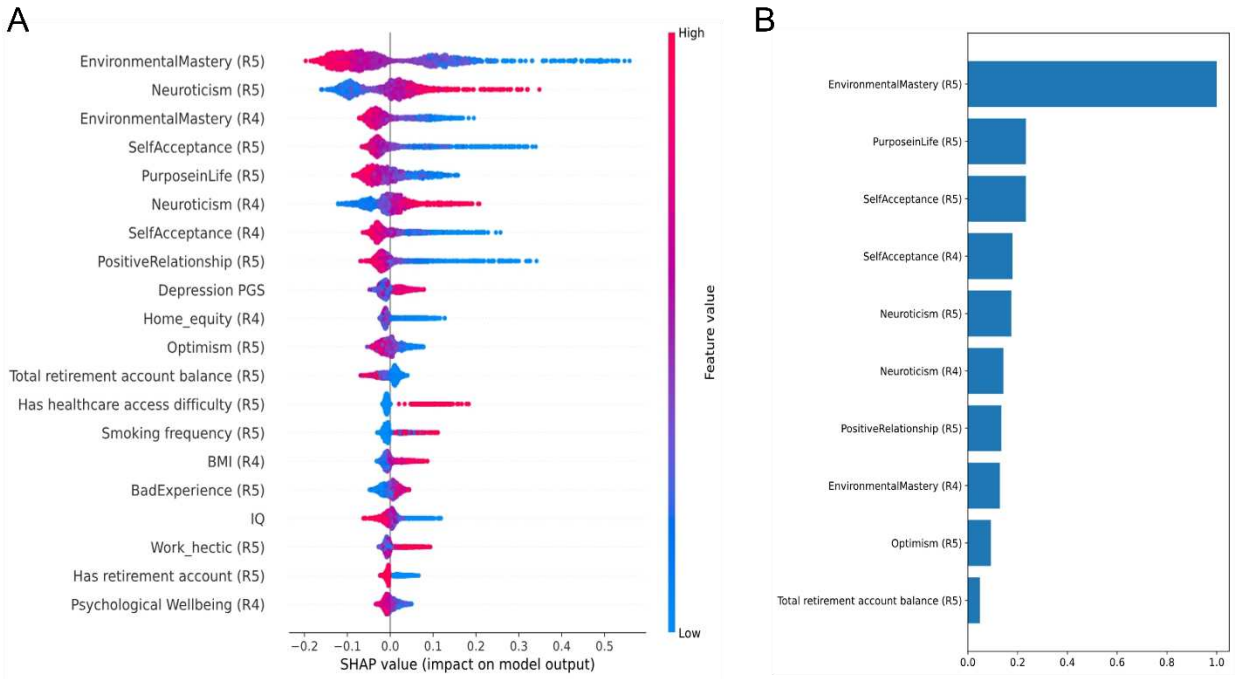


Figure 2. Explained variance across domains and individual variables.

A, R^2 from gradient boosting machine (GBM) models trained separately for each domain and evaluated on the test set. The full model indicates a model with all 426 variables. **B**, Adjusted R^2 from generalized linear models (GLMs) fitted separately for each domain on the test set. **C**, Incremental explained variance (ΔR^2) for individual variables estimated from ordinary least squares models. ΔR^2 was calculated as the difference in R^2 between models including the variable of interest and a base model including covariates only (sex, age corresponding to the wave of the variable, and the first 10 genetic principal components). Age was not included as a covariate when polygenic risk score (PGS) was the variable of interest.

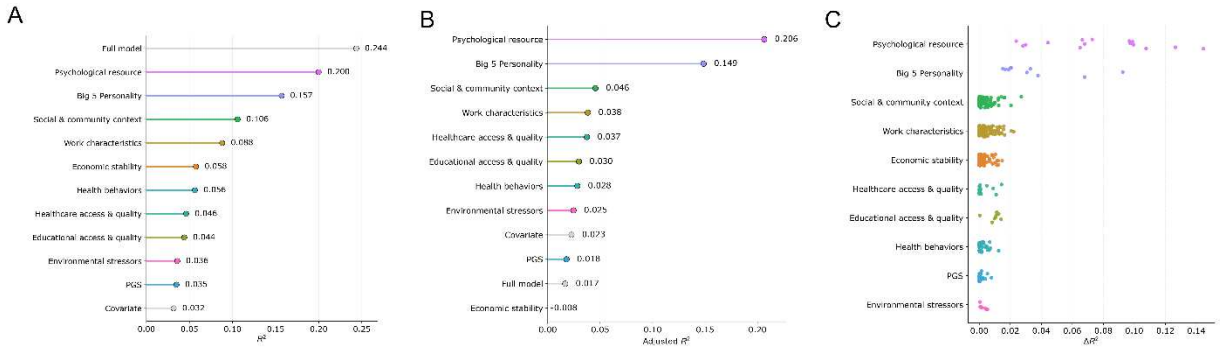
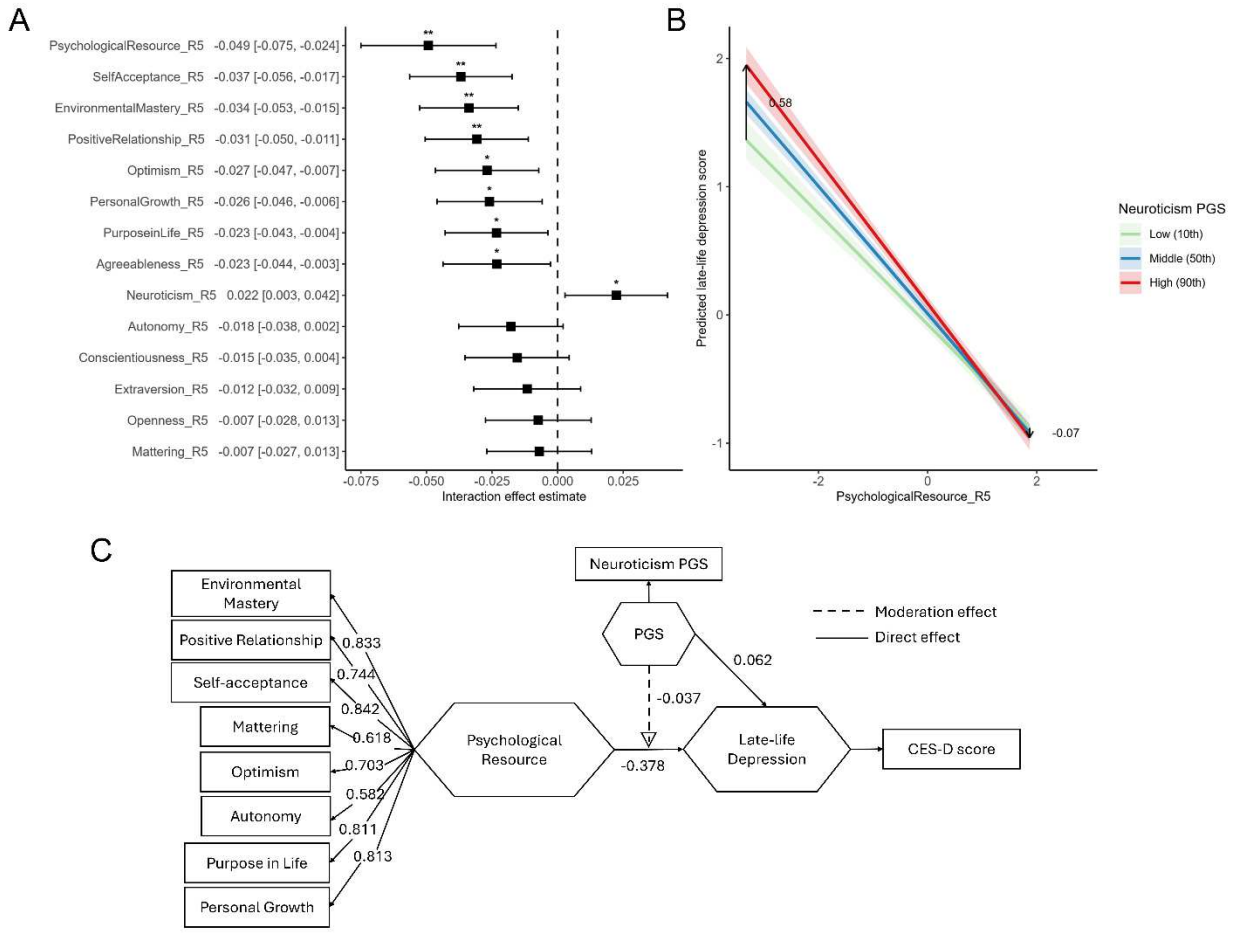


Figure 3. Neuroticism PGS moderates the association between psychological resources and late-life depression.

A, Forest plot of interaction effects between neuroticism PGS and key variables (wave 5). Points represent standardized regression coefficients (β) for the interaction terms, and horizontal bars denote 95% confidence intervals. P values were corrected for multiple testing using the Benjamini–Hochberg false discovery rate (FDR) procedure and significance levels are denoted as

*** p-FDR<0.001, ** p-FDR<0.01, * p-FDR<0.05. **B**, Predicted late-life depression score across levels of the psychological resource (PR) composite. Participants were stratified by low (10th percentile), middle (10–90th percentile), and high (90th percentile) neuroticism PGS. Black arrows mark the difference in predicted scores between the high- and low-PGS groups at the minimum (–4) and maximum (+2) PR composite values. Shaded areas represent 95% confidence intervals. **C**, Generalized structured component analysis. Path diagram illustrating the moderating effect of neuroticism PGS on the association between the PR component and late-life depression. Path coefficients and component loadings are displayed on the arrows. All estimated paths and loadings were statistically significant, with 95% confidence intervals not including zero.



Data availability

The data are available from the Wisconsin Longitudinal Study (WLS) (https://researchers.wls.wisc.edu/data/) upon application and approval.

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