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**The Mediating Role of Insulin Resistance in Depression
Driving Phenotypic Age Acceleration**

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Abstract

Background: Depression, characterized by significant psychological and physiological alterations, has been proved to tightly associate with insulin resistance (IR) and hallmarks of biological aging. **Phenotypic Age Acceleration (PhenoAgeAccel), which quantifies the discrepancy between biological and chronological age, serves as a robust indicator of accelerated aging.** However, the interplay between depression, IR, and accelerated aging remains unclear. This study aims to explore the relationship between depression and PhenoAgeAccel, and the potential mediating role of IR in this association.

Methods: A total of 4,555 adults participants from the National Health and Nutrition Examination Survey (NHANES) database with complete data on depression, PhenoAgeAccel, and other essential covariates were included in this study. Depression severity was assessed by the nine-item Patient Health Questionnaire (PHQ-9), with a PHQ-9 score ≥ 10 used to define depression. Four indicators, including triglyceride-glucose index (TyG), TyG-body mass index (TyG-BMI), TyG-waist height ratio (TyG-WHTR), and metabolic score for insulin resistance (METS-IR), were used to assess IR. Weighted multivariable linear regression analyses were performed to identify the association of depression/PHQ-9 score with PhenoAgeAccel. Moreover, subgroup analyses, interaction tests, and adjusted restricted cubic spline (RCS) analyses were employed to explore the robustness, stability, and potential nonlinearity of the associations between PHQ-9/depression and PhenoAgeAccel. Additionally, mediation analysis was conducted to investigate the mediating role of IR biomarkers in the association between PHQ-9 score and PhenoAgeAccel.

Results: In the fully-adjusted model, being depressive and one-unit increment in PHQ-9 score were associated with a 1.93-year (95% CI: 0.95-2.92) and 0.14-year (95% CI: 0.07-0.21) increase in PhenoAgeAccel, respectively. A positive linear dose-response relationship between PHQ-9 score and PhenoAgeAccel was identified via RCS analysis (P for overall=0.001, $P_{\text{non-linearity}}=0.867$). Subgroup analyses and interaction tests revealed a more pronounced association between depression/PHQ-9 and PhenoAgeAccel in subgroups with diabetes, **moderate-to-heavy alcohol consumption**, and higher education levels (all

$P_{interaction} < 0.05$). IR biomarkers were observed to mediated 3.6–8.4% of the total effect, with METS-IR showing the highest mediation (8.4%, 95% CI: 0.024–0.222).

Conclusions: Depression was associated with accelerated PhenoAgeAccel, with insulin resistance acting as a partial mediator. In depression management, interventions targeting metabolic issues like insulin resistance should also be considered to mitigate depression-associated aging.

Keywords: PhenoAgeAccel, depression, insulin resistance, PHQ-9, depression-associated aging

Research Insights

-What is currently known about this topic?

- Depression is a metabolic disorder caused by neuropsychiatric factors.
- Depression is associated with increased insulin resistance.
- Insulin resistance is a proven accelerator of biological aging.

-What is the key research question?

- Does depression exhibit a notable and clinically meaningful association with PhenoAgeAccel, and what's the role of insulin resistance in this association?

-What is new?

- Depression was associated with accelerated PhenoAgeAccel.
- Stronger association observed in diabetics, heavy drinkers, and higher-educated subgroups.
- Insulin resistance partially mediated the association between depression and PhenoAgeAccel.

-How might this study influence clinical practice?

- Depression-triggered insulin resistance should be considered to delay accelerated aging.

1. Introduction

Depression, as one of the most common mental disorders, has been reported to affect about 300 million individuals globally. Although its prevalence may vary among different populations, the estimates from recent studies reveal an annual and lifetime prevalence of 10.4% and 20.6%[1], respectively. In addition to its high prevalence, it also remains one of the leading causes of disability worldwide, with typical characteristics of chronic and relapsing course, unfavorable treatment response, and close link to higher incidence of chronic and disabling conditions. For example, evidence from clinical and epidemiological studies has suggested that individuals with depression are more likely to develop multiple pathologies, including cardiovascular and metabolic diseases[2], cognitive impairment[3], Alzheimer's disease[4], vascular dementia[5], etc. Moreover, depression is also reported to associate with higher risk of frailty[6], functional impairments, shortened health span[2], and premature mortality[7]. These features commonly occur during non-pathological aging process, demonstrating that individuals with depression present with, or are more likely to develop a premature aging phenotype.

How to measure aging is an unresolved question currently, with the biggest obstacle underlying it being the heterogeneity of aging pace among different individuals. Since the variations in aging pace is reflected by the differences in susceptibility to death and disease, one possible method to measure aging pace is to compare individuals' observable characteristics to the expected characteristics usually observed in the general population under a specific given chronological age[8]. A series of aging measures have been established based on molecular variables, with the most prominent measures being DNA methylation age and leukocyte telomere length. While these measures perform well in assessing organ-specific aging, their performance in association with aging outcomes is weak after excluding what can be explained by chronological age[8]. Comparatively, aging measures based on clinical variables have been proved to be more accurate and robust indicators for aging outcomes, such as Phenotypic age (PhenoAge) [9,10]. Currently, PhenoAge has been validated as a robust aging predictor across multiple domains, including the assessment of mortality risk and disease onset/progression/prognosis, as well as

the evaluation of accelerated aging rates under diverse conditions such as exposure to environmental factors, dietary interventions, or medical treatments. These advantages of PhenoAge make it more suitable for assessing aging extent on an organismal scale, and identifying individuals as higher risks for disease and mortality. Phenotypic Age acceleration (PhenoAgeAccel, expressed by years) refers to the difference between Phenotypic Age and its predicted value from a linear regression of Phenotypic Age on chronological age[11]. Individuals with positive values in PhenoAgeAccel represents that they are physiologically older than what they should be under their chronological age.

Insulin resistance (IR) is the reduced responsiveness of insulin target tissues, such as adipose tissue, skeletal muscle, and the liver, to insulin signaling, thus leading to hyperglycemia and metabolic dysfunction[12]. Emerging evidence highlights a bidirectional relationship between depression and IR, with IR playing a central pathophysiological role in mediating metabolic perturbations and cellular damage that are associated with the aging process[13]. This suggests that IR may serve as a critical mediator linking depression to biological aging. Mechanistically, depression has been reported to induce IR via multiple pathways, including hypothalamic-pituitary-adrenal (HPA) axis hyperactivation[14], chronic inflammation[15], mitochondrial dysfunction[16,17], oxidative stress[18], and neurotransmitter-induced metabolic dysregulation[19]. Additionally, IR and its downstream consequences are proved to promote accelerated aging via glycolipid toxicity, oxidative stress[17], accumulation of advanced glycation end products (AGEs)[20], epigenetic remodeling of aging-related genes[21], and induction of cellular senescence and telomere attrition[22]. Collectively, these findings outline a plausible "depression-IR-biological aging" mechanistic axis, highlighting that depression is a multisystemic syndrome with aging-accelerating properties, necessitating integrative therapeutic strategies addressing both psychological and metabolic dysfunction. However, previous studies have predominantly focused on segmental validation of the "depression-IR-biological aging" pathway (e.g., isolated links between depression and IR, or IR and aging), while comprehensive mechanistic validation of the entire pathway remains notably absent.

Therefore, leveraging data from the National Health and Nutrition Examination Survey (NHANES) dataset, this study aims to investigate the association between depression and biological aging, and to identify the potential mediating role of insulin resistance indicators in this association.

2. Methods

2.1 Data Source

The National Health and Nutrition Examination Survey (NHANES) is a national survey conducted by the National Center for Health Statistics (NCHS) of American Centers for Disease Control and Prevention (CDC) to assess the health and nutritional status of children and adults across the United States. NHANES has gathered multidimensional data (including demographics, dietary intake, physical examinations, laboratory tests, and questionnaires) by using a stratified multistage sampling design covering approximately 5,000 individuals annually. All the NHANES survey protocols were reviewed and approved by the NCHS Ethics Review Board (ERB), and all the participants have provided written informed consent. Further details can be found at <https://www.cdc.gov/nchs/nhanes/about/index.html>.

2.2 Study Population

The NHANES data of participants aged 20 years and older from 2007 to 2010, and 2015 to 2018 were included in this study ($n=39,911$). The sample design and estimation procedures corresponding to NHANES 2007–2010 and 2015–2018 have been explicitly detailed in previous methodological reports[23,24]. Participants without complete data on PhenoAgeAccel ($n = 19,332$), depression ($n = 1,794$), and essential covariates ($n = 7,228$) were excluded from analyzed population. Additionally, participants lacking information on insulin resistance indicators were also excluded ($n = 7,002$), including triglyceride-glucose index (TyG), TyG-body mass index (TyG-BMI), TyG-waist height ratio (TyG-WHtR), and metabolic score for insulin resistance (METS-IR). Finally, a total of 4,555 participants were included in the current study (**Fig.1**). The flowchart for participant selection can be found in **Fig.1**.

2.3 Assessment of biological aging and PhenoAgeAccel

Biological aging (BA) was assessed using phenotypic age (PhenoAge). PhenoAge was computed using the algorithm established by Levine et al. [9]. Phenotypic Age Acceleration (PhenoAgeAccel) was then calculated as the residual from a linear regression of PhenoAge on chronological age, consistent with the method reported by Liu et al. [10]. Briefly, the variables used to calculate PhenoAge was firstly selected from forty-two multi-system clinical chemistry biomarkers and chronological age using a Cox penalized regression model for mortality. Finally, chronological age and nine biomarkers (including albumin, creatinine, glucose, [log] C-reactive protein [CRP], lymphocyte percent, mean cell volume, red blood cell distribution width, alkaline phosphatase, and white blood cell count) were selected for the calculation of PhenoAge[9,10]. From the perspective of clinical practice, a person's PhenoAge denotes the expected age within a population that reflects a person's estimated risk of mortality. PhenoAgeAccel is calculated as the difference between observed Phenotypic Age and its predicted value from a linear regression of Phenotypic Age on chronological age[11]. A person with a positive value in PhenoAgeAccel represents that he/she is physiologically older than expected, while a person with a negative value in PhenoAgeAccel represents that he/she is physiologically younger than what he/she should be. PhenoAgeAccel was treated as a continuous variable in this study.

2.4 Assessment of depression

The assessment of depression was based on the information from the Mental Health-Depression Screener questionnaire. As previously described[25,26], the Patient Health Questionnaire (PHQ-9), a nine-item depression screening instrument, was utilized to determine the frequency of depression symptoms over the past 2 weeks[27,28]. Subsequently, a follow-up question was included to assess the overall impairment of the symptoms. Four response categories were given to each specific item (including "not at all," "several days," "more than half the days," and "nearly every day"), each assigned a point value ranging from 0 to 3. The detailed item descriptions for PHQ-9 can be accessed at <https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2013/DataFiles/DP>

Q_H.htm#DPQ100. The total score for the PHQ-9 items ranges from 0 to 27, with higher PHQ-9 score signifying more severe depressive symptoms. As previously reported[25,26], an individual with total PHQ-9 score ≥ 10 is defined as having clinically significant depression. In this study, depression and PHQ-9 score were treated as a binary and continuous variables, respectively.

2.5 Assessment of TyG, TyG-BMI, TyG-WHtR, and METS-IR

The insulin resistance (IR) indicators were calculated using the following formula: (1) $TyG = \ln [\text{triglycerides (mg/dl)} \times \text{glucose (mg/dl)/2}]$ [29]; (2) $TyG\text{-BMI} = TyG \times \text{body mass index (BMI, kg/m}^2)$ [29]; (3) $TyG\text{-WHtR} = TyG \times [\text{waist circumference (cm)}/\text{standing height(cm)}]$ [29]; (4) $METS\text{-IR} = \ln [(2 \times \text{fasting plasma glucose (FPG) (mg/dL)} + \text{fasting triglyceride (TG) (mg/dL)}) \times \text{body mass index (BMI) (kg/m}^2)]/\ln [\text{high-density lipoprotein cholesterol (HDL-C) (mg/dL)}]$ [30].

2.6 Covariates

Several key covariates were included in this study, including demographic details (age, gender, race, education, marital status, poverty income ratio (PIR)), body measurement (BMI, WHtR), behavioral factors (smoking, drinking, physical activity), and health conditions (including diabetes, cardiovascular disease, and hypertension). Individuals were divided into two groups (<65 years, ≥ 65 years) based the cut-off value for age as previously reported[31]. Similarly, poverty income ratio (PIR) was also grouped into three categories, including <1.3, 1.3-3.5, and >3.5 [32]. Race was categorized into five mutually exclusive groups: Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other Race. Education level was classified into three groups as previously described[33]: less than high school, high school or equivalent, and college or above. Marital status was dichotomized into married/living with partner versus living alone, following established criteria[31]. Smoking status was determined using two validated questions: lifetime cigarette consumption (>100 cigarettes) and current smoking status, resulting in three categories: never smokers, former smokers, and current smokers[31]. In terms of alcohol consumption patterns, participants were categorized based on average daily intake over

the past year: mild drinking was defined as ≤ 1 drink/day for women or ≤ 2 drinks/day for men, moderate drinking as 1-3 drinks/day for women or 2-4 drinks/day for men, and heavy drinking as ≥ 4 drinks/day for women or ≥ 5 drinks/day for men[34]. Physical activity (PA) was assessed based on the Global Physical Activity Questionnaire (GPAQ), which captured the information about the frequency and duration of daily activities, leisure-time activities, and sedentary activities. The weekly total PA was quantified by integrating both exercise frequency (sessions per week) and duration (minutes per session) across two intensity categories: vigorous and moderate recreational activities. Following established metabolic equivalence principles (1 minute vigorous PA = 2 minutes moderate PA), leisure-time PA was computed through the formula[35-37]: Total PA = $2 \times$ vigorous PA (minutes) + moderate PA (minutes). Participants were subsequently stratified into low/high PA groups according to national physical activity guidelines[38,39], with <500 MET-minutes/week or ≥ 500 MET-minutes/week thresholds defining low and high PA categories, respectively. Hypertension was defined as meeting one or more of the following criteria[40]: (1) self-reported clinician-diagnosed hypertension, (2) average systolic/diastolic blood pressure (SBP/DBP) $\geq 130/80$ mmHg, or (3) current use of antihypertensive medication. Diabetes diagnosis was established if individuals met any of the following criteria[41]: hemoglobin A1C (HbA1C) $\geq 6.5\%$ or fasting plasma glucose ≥ 126 mg/dL (≥ 7.00 mmol/L); self-reported physician-diagnosed diabetes or current insulin use; two-hour oral glucose tolerance test (OGTT) ≥ 11.10 mmol/L; random blood glucose ≥ 11.10 mmol/L; or receipt of antidiabetic medication/insulin treatment currently. Cardiovascular disease (CVD) was defined using five major clinical events[42]: congestive heart failure (CHF), coronary heart disease (CHD), angina, cardiac arrest, and stroke. Participants were classified as having CVD if they responded "yes" to the question of "Have you ever been told by a physician that you had CHD/CHF/angina/a heart attack or a stroke?". Antidepressant use status was defined based on two variables from the NHANES questionnaire: 1) RXDUSE (i.e., "Taken prescription medicine, past month"), and 2) RXDDRUG (i.e., "Generic drug name"). Participants were classified as antidepressant users if they answered "Yes" to RXDUSE and

reported taking any of the following antidepressant medications in response to RXDDRUG: Citalopram, Escitalopram, Fluoxetine, Sertraline, Bupropion, Naltrexone, Venlafaxine, Desvenlafaxine, Paroxetine, Mirtazapine, Trazodone, Amitriptyline, Nortriptyline, Imipramine, Desipramine, Clomipramine, Fluvoxamine, or Antidepressants - unspecified.

2.7 Statistical Analysis

R software (version 4.3.2) was used to conduct all statistical analyses. Consistent with the explicit instructions in NHANES guidelines[23,43], sample weights, clustering, and stratification were incorporated into all statistical analyses to account for the complexity of NHANES' multistage sampling design. New weights were further computed in accordance with the corresponding NHANES analytic guidelines.

The baseline characteristics are shown based on depressive status. Continuous variables were presented as median and interquartile ranges (IQR) due to skewed distribution characteristics, and Mann-Whitney U test was used to identify the differences between groups. Categorical variables were summarized as numbers (percentages), and Chi-squared test was used to determine intergroup differences.

The weighted multivariable linear regression analyses were used to identify the associations of PHQ-9 score and depression with PhenoAgeAccel. Three regression models were established, including model 1, model 2, and model 3. No potential confounders were adjusted in model 1, and variables of age, gender, race, education, marital status, and PIR were adjusted in model 2, while model 3 was additionally adjusted for variables of BMI, smoking, drinking, PA, CVD, hypertension, and diabetes. In order to explore the potential nonlinear relationship between PHQ-9 score and PhenoAgeAccel, the restricted cubic spline (RCS) model was employed with the adjustment of variables consistent with Model 3. Additionally, subgroup analyses and interaction tests were also conducted to confirm the robustness and stability of the associations between PHQ-9/depression and PhenoAgeAccel based on the variables of age, gender, marital status, education, PIR, smoking, drinking, PA, hypertension, diabetes and CVD. If a significant interaction test was identified, subsequent stratified

RCS analyses based on the effect-modifying variable were performed to detect the variations in the associations of PHQ-9 score and PhenoAgeAccel.

The causal mediation effect analysis was conducted to explore the mediating role of **insulin resistance (IR) biomarkers (including TyG, TyG-BMI, TyG-WHtR, METS-IR)** on the association between PHQ-9 and PhenoAgeAccel. Two sequential steps were included in mediating analysis: (1) a mediator model examining the exposure-mediator relationship (depression → IR biomarkers), and (2) an outcome model estimating the combined effects of exposure and mediator on PhenoAge acceleration (depression + IR biomarkers → PhenoAge acceleration). The mediation proportion, calculated as the ratio of indirect effect to total effect, quantified the magnitude of mediation. Bootstrapping with 1,000 resamples was used to test the statistical significance of the mediation effect.

3. Results

3.1 Baseline Characteristics

A total of 4,555 participants were included in this study, with males accounting for 51.679% and females 48.321%. The median PhenoAge and chronological age of the overall study population were 58.59 (interquartile range, IQR: 44.17–72.36) years and 47 (IQR: 33–61) years, respectively. **Table 1** presents the general characteristics of all participants classified by depression status. In comparison with those without depression, individuals with depression were more prone to being female, having a lower educational level, living alone, being current smokers, being heavy drinkers, engaging in less physical activity, and having a higher prevalence of hypertension and cardiovascular disease (CVD) (all P-values < 0.05).

The depression group also showed significantly higher levels of insulin resistance, as reflected by elevated values of insulin-resistance (IR) indicators such as the TyG, TyG-BMI, TyG-WHtR, and METS-IR (all P-values < 0.05, **Table 1**). Moreover, there was no significant difference in Phenotypic Age between the depressive and non-depressive groups ($P>0.05$) (**Fig. 2A**). However, a significantly higher level of PhenoAgeAccel was observed in the depressive group ($P<0.05$) (**Fig. 2B**).

3.2 Association between depression and PhenoAgeAccel

After adjusting for all potential confounding factors in Model 3, being depressive was associated with a 1.93-year (95%CI: 0.95-2.92) increase in PhenoAgeAccel (**Table 2, Fig.3**). Similarly, PHQ-9 scores showed significant positive associations with PhenoAgeAccel across all regression models: a 1-unit increase in PHQ-9 score was associated with 0.29-year (0.22-0.36), 0.27-year (0.19-0.34), and 0.14-year (0.07-0.21) increases in PhenoAgeAccel for Models 1, 2, and 3, respectively (**Table 2, Fig.3**). Additionally, we further adjusted for the antidepressant use variable given its potential influence on the aging process[44]—and this adjustment yielded consistent findings (see **STable 1**). Specifically, in Model 3, a 1-unit increase in PHQ-9 score was associated with a 0.14-year (95% CI: 0.07-0.21) increase in PhenoAgeAccel, while the presence of depression was linked to a 1.88-year (95% CI: 0.89-2.87) increase in PhenoAgeAccel.

A positive, significant and linear relationship between PHQ-9 score and PhenoAgeAccel was identified by RCS analysis (P for non-linearity=0.867, P for overall<0.001) (**Fig.4A**). Similar trend was observed when PHQ-9 was analyzed as categorical variable, as demonstrated by the graded increase in PhenoAgeAccel rising PHQ-9 tertiles (**Fig.4B**).

3.3 Subgroup Analysis

Subgroup analyses, together with interaction tests, were utilized to investigate the robustness and stability of the associations between PHQ-9/depression and PhenoAgeAccel across subgroups stratified by age, gender, marital status, education, PIR, smoking, drinking, PA, hypertension, diabetes and CVD. As presented in **Table 3**, the associations between depression/PHQ-9 scores and PhenoAgeAccel were more pronounced in subgroups with higher education level, moderate/heavy alcohol consumption, and with diabetes (all P for interaction<0.05). These results were further verified by the results from stratified RCS analysis (**Fig.5**). Additional analyses revealed that the associations between depression, PHQ-9 scores, and PhenoAgeAccel remained consistent across subgroups stratified by antidepressant use (**STable 2**).

3.4 Mediation effects IR biomarkers on the association

between depression and PhenoAgeAccel

Multivariate weighted linear regression models were used to identify the relationship between depression/PHQ-9 and IR biomarkers, as well as the relationship between IR biomarkers and PhenoAgeAccel. Results showed that PHQ-9 scores were significantly positively associated with all IR biomarkers in the fully-adjusted model: β coefficients (95% CI) were 0.01 (0.00–0.01) for TyG, 0.21 (0.08–0.34) for TyG-BMI, 0.01 (0.00–0.01) for TyG-WHtR, and 0.05 (0.02–0.08) for METS-IR), respectively (**STable 3**). Similarly, depressive status was also associated with higher levels of these biomarkers: β coefficients (95% CI) were 0.07 (0.01–0.14) for TyG, 2.56 (0.64–4.47) for TyG-BMI, 0.06 (0.01–0.11) for TyG-WHtR, and 0.85 (0.38–1.31) for METS-IR, respectively (**STable 3**).

Additionally, multivariate weighted linear regression models were used to examine the associations between IR biomarkers and PhenoAgeAccel. As shown in **STable 4**, all IR biomarkers were significantly positively associated with PhenoAgeAccel across all regression models. β coefficients (95% CIs) in the fully-adjusted models were 0.97 (0.52–1.42) for TyG, 0.03 (0.02–0.05) for TyG-BMI, 1.29 (0.71–1.86) for TyG-WHtR, and 0.20 (0.14–0.26) for METS-IR, respectively.

Mediation analysis was conducted to identify the mediating effects of IR biomarkers on the relationship between depression and PhenoAgeAccel. Results revealed significant partial mediation effects for all tested IR biomarkers (**STable 5–8, Fig.6**), with all mediation P-values<0.05. Specifically, TyG (**STable 5**), TyG-BMI (**STable 6**), TyG-WHtR (**STable 7**), and METS-IR (**STable 8**) accounted for 3.636%, 3.908%, 3.857%, and 8.365% of the indirect effect, respectively. Notably, METS-IR demonstrated the strongest mediating effect among all biomarkers (**Fig.6**). Collectively, these findings indicate that IR biomarkers play a significant role in the depression-PhenoAgeAccel pathway.

4. Discussion

This cross-sectional study of 4,555 adults systematically investigated the association between depression and PhenoAgeAccel, with a focus on the mediating role of insulin resistance. Key findings demonstrated that individuals with depression exhibited a 1.93-year increase in PhenoAgeAccel (95%

CI: 0.95–2.92) compared to non-depressed counterparts. A dose-response relationship was observed, with each 1-point increase in PHQ-9 score corresponding to a 0.14-year acceleration in PhenoAgeAccel (95% CI: 0.07–0.21). Subgroup analyses revealed stronger associations among individuals with higher education, moderate-to-heavy alcohol use, and diabetes (all P for interaction <0.05). Mediation analyses identified significant partial mediation effects through IR biomarkers: TyG, TyG-BMI, TyG-WHtR, and METS-IR accounted for 3.64% to 8.37% of the total effect, with METS-IR showing the strongest mediation proportion (8.37%). These findings suggest that IR partially underlies the depression-accelerated aging pathway, highlighting IR as a potential therapeutic target to mitigate aging-related consequences in depression.

Our results revealed that being depressive was associated with a 1.93-year (95%CI: 0.95–2.92) increase in PhenoAgeAccel, with a significant linear relationship between PHQ-9 score and PhenoAgeAccel being identified by RCS analysis. These findings aligned with evidence from prior studies, which indicated that depression may accelerate biological aging through the following mechanisms: inducing chronic inflammation [45,46], triggering metabolic abnormalities and glycolipid toxicity[46,47], and promoting neuroendocrine disorder[48]. Specifically, a systematic review and meta-analysis conducted by A Gasparini *et al.* revealed that individuals with major depressive disorder (MDD) who failed to respond to antidepressant treatment had significantly higher levels of inflammatory biomarkers, such as C-reactive protein (CRP) and interleukine-8 (IL-8)[45]. Since chronic inflammation is deemed a classical accelerator of biological aging, it's plausible that depression triggers accelerated aging by modulating chronic inflammation. Furthermore, mounting evidence suggests that depression correlates with insulin resistance (IR), indicating that depression-related accelerated aging may be associated with IR-induced metabolic disorders. A cross-sectional study based on NHANES database revealed that individuals with moderate-to-severe depression were significantly linked to increased odds of IR ($OR=1.65$, 95 % CI: 1.04–2.61)[49]. Experimental evidence in humans and animal models has demonstrated that IR and hyperinsulinemia (a consequence of IR) are associated with

increased cellular senescence in metabolic tissues[50], suggesting that IR-induced metabolic abnormalities in depressive individuals may drive accelerated aging. Additionally, elevated IR level are reported to result in higher advanced glycation end products (AGEs)[51], which are responsible for various aging-related diseases like osteoporosis[52] and neurodegeneration[53]. Finally, MDD is reported to associate with hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis and increased cortisol secretion, a validated accelerator of biological aging. Direct support for this comes from evidence that daughters of depressed mothers had significantly shorter telomeres than daughters of never-depressed mothers[54]. Taken together, depression-induced alterations in inflammation, metabolic abnormalities, and neuroendocrine dysfunction may all account for the accelerated aging process.

Mediation analyses in this study revealed that IR biomarkers (including TyG, TyG-BMI, TyG-WHtR, and METS-IR) served as partial mediators for the association between depression and PhenoAgeAccel, accounting for 3.64% to 8.37% of the total effect. Although segmental validation of the "depression-IR-biological aging" pathway (e.g., isolated links between depression and IR, or IR and aging) has been conducted, the comprehensive mechanistic validation of the entire pathway remains underexplored. Our study was the first to validate the pathway of depression-IR-biological aging. Numerous studies have revealed the association between depression and insulin resistance, with unanimous conclusion being reached that depression is associated with increased risk of IR. For example, results from the Dutch cohort study indicated that higher IR levels (reflected by three surrogate measures—triglyceride-high-density lipoprotein ratio, fasting plasma glucose level, and waist circumference)—were positively associated with an increased risk of MDD during a 9-year follow-up period[13]. The hazard ratios (HRs) for MDD associated with these indicators were 1.89 (95% CI: 1.15-3.11), 1.37 (95% CI: 1.05-1.77), and 1.11 (95% CI: 1.01-1.21)[13], respectively. Moreover, results from other study also suggested that IR was correlated with current MDD as opposed to the control individuals ($OR=1.51$, 95%CI: 1.08-2.12)[55]. These findings suggested that a bidirectional association between depression and IR. IR, a status of reduced responsiveness of insulin

target tissues to insulin signaling, is not only a core pathological feature of type 2 diabetes, but also a pivotal driver to accelerated aging. The mechanisms related to IR-induced accelerated aging involve metabolic disorder, inflammatory response, mitochondrial dysfunction, epigenetic regulation, and so on. Just as mentioned above, increased IR level will lead to hyperglycemia, resulting in increased production of AGEs via Maillard reaction and low-grade chronic inflammation[56], and both of which are fundamental accelerators for aging and various aging-related diseases[52,56]. Moreover, it has been verified that mitochondrial dysfunction (e.g., impaired bioenergetics, biogenesis, and mitochondrial dynamics) is an early event in individuals with IR, which exacerbates metabolic disorders via reducing ATP production and enhancing damage inflicted by reactive oxygen species (ROS)[57]. These two aspects (mitochondrial dysfunction-related metabolic disorders and ROS-induced damage) are critical pathogenesis involved in aging[58]. Additionally, significantly different DNA methylation and gene expression patterns are observed in various tissues from individuals with diabetes compared with nondiabetic controls[59], suggesting IR may accelerate the aging process via modulating epigenetic modifications. Actually, a series of epigenetic modifications emerge during cellular senescence, such as alterations in DNA methylation, histone/RNA modification, chromatin remodeling[60]. Collectively, these findings, together with our study results, establish IR as a pivotal mediator in the depression-accelerated aging axis, and highlight its hub role in linking these two processes and underscoring IR as a critical target in formulating strategies to mitigate depression-related aging.

In this study, subgroup analyses and interaction tests revealed that the association between depression/PHQ-9 scores and PhenoAgeAccel was more pronounced in subgroups with higher education level, moderate-to-heavy alcohol consumption, and diabetes. Such differences in the depression-PhenoAgeAccel association can be understood from the following aspects. Firstly, individuals with higher education may be more sensitive to their health status and are more likely to pursue stressful, sedentary careers, which may amplify the effects of depression on accelerating aging. Supporting evidence comes from a study showing that women exposed to perceived chronic stress had

significantly higher oxidative stress, reduced telomerase activity, and shorter telomere length in peripheral blood mononuclear cells compared with low-stress counterparts[61]. Therefore, a higher level of psychological stress associated with higher education levels may strengthen the association between depression and PhenoAgeAccel. Secondly, evidence shows that alcohol consumption correlates with accelerated biological aging (as indicated by PhenoAge acceleration). Dose-response analysis revealed that one additional standard alcoholic drink (\sim 14 grams of ethanol per day) was linked to a 0.71 ± 0.15 -year and 0.60 ± 0.18 -year increase in PhenoAge acceleration in middle-aged and older individuals[62], respectively. This may explain why depressed individuals with moderate-to-heavy alcohol consumption exhibit a faster pace of aging compared to those who are mild drinkers. Thirdly, diabetic individuals exhibit various aging-related features, such as increased insulin resistance, low-grade chronic inflammation, oxidative stress, accumulation of advanced glycation end products, and mitochondrial dysfunction[63]. These characteristics will theoretically enhance depression-associated aging, a phenomenon verified in our study.

Our study has several strengths. Firstly, this study is completed using relatively large-sample data from the Nhanes database. This ensures an abundant number of samples for the application of certain statistical methods and the statistical stability of the observed findings. Secondly, multiple IR markers (such as TyG, TyG-BMI, TyG-WHtR, METS-IR) were used to assess the mediating role of IR in the association between depression and aging. This approach avoids the limitations of a single indicator and ensures the reliability of statistical findings. Thirdly, subgroup analyses revealed that the association between depression and accelerated aging was particularly pronounced in individuals with diabetes, moderate-to-heavy alcohol consumption, and higher education levels. Interaction tests further validated the heterogeneity among high-risk groups, providing a scientific basis for personalized interventions. Finally, mediation analysis established and quantified the role of IR in the depression-aging association, providing direct evidence for IR's central role in aging induced by mental disorders. Additionally, it also revealed potential intervention targets for depression-associated aging, suggesting

that improving IR through lifestyle modifications or pharmacological interventions may help delay the depression-related aging process.

However, several limitations of this study should also be considered. First, some variables came from the self-reported questionnaire (e.g., smoking, drinking, CVD, physical activity), which may introduce some unexpected bias to the results of our study. Second, the cross-sectional design cannot confirm the temporal relationship between depression and aging, thus precluding causal inference. Further validation using longitudinal cohorts is needed to confirm the observed findings. Third, the NHANES database lacks organ-specific aging markers, thus precluding the assessment of which organ system is most affected by depression-related aging. Future studies integrating multi-omics analysis, serial histological sections and single-cell sequencing are expected to elucidate the impact of depression on organ-specific aging.

5. Conclusion

Depression is associated with accelerated PhenoAgeAccel (1.93-year increase), with each 1-point increment in PHQ-9 score corresponding to a 0.14-year increase in PhenoAgeAccel (95% CI: 0.07-0.21). Insulin resistance biomarkers, particularly METS-IR, mediate up to 8.4% of this association, highlighting IR as a pivotal mechanistic pathway. These findings suggest that targeting IR may mitigate depression-associated accelerated aging, especially in high-risk subgroups (e.g., individuals with diabetes, heavy alcohol use). Future longitudinal studies are needed to validate causality and explore complementary pathways to inform multidomain interventions against depression-related aging.

Clinical trial number

Not applicable

Acknowledgments

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Funding

None.

Data availability

These survey data are freely accessible to the public and may be directly downloaded by researchers and users globally from the NHANES website: <https://www.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Demographics>.

Ethics approval and consent to participant

The program was approved by the National Center for Health Statistics Ethics Review Board. All of the participants provided written informed consent. No additional ethical review board approval was required to analyze the anonymized NHANES data.

Consent for publication

Not applicable.

Competing Interests

The authors declared that no potential conflicts of interests existed in this study.

Authors' contributions

All authors have made significant contributions to this study. ***Yue Hu*** and ***Jie Yu*** supervised the entire research process, from formulating the research design to performing data analysis and guiding the writing of the article. ***Li Zhang*** undertook the statistical analysis, interpretation of results, revision of the initial manuscript, and completion of the revised manuscript. ***QianKun Yang*** assisted in conducting data extraction, cleaning and analysis. All authors have approved the final version for publication and have agreed to be accountable for all aspects of the work.

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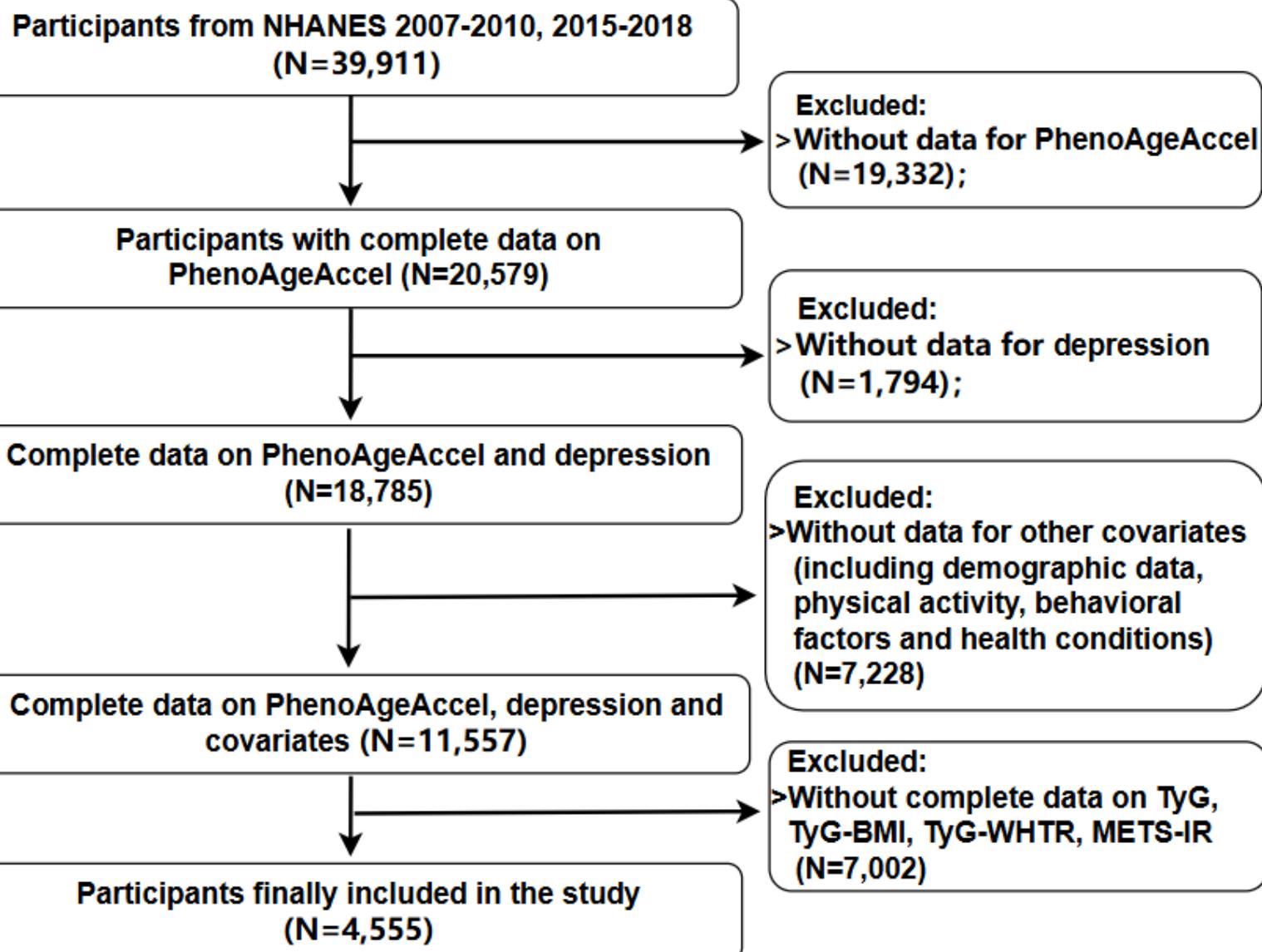
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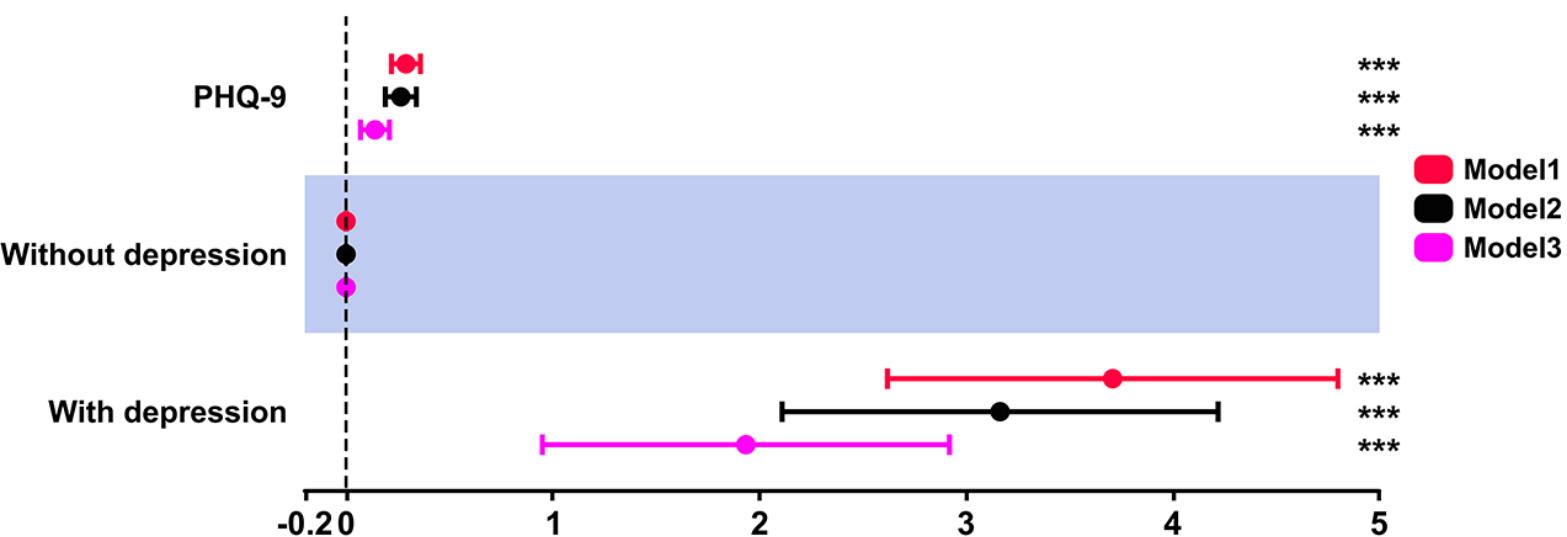
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Graphical abstract

The Mediating Role of Insulin Resistance in Depression-Driving PhenoAge Acceleration



Study design:

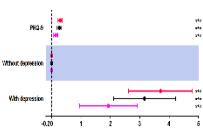
- Cross-sectional study based on NHANES database
- Exposure: Depression/PHQ-9 score
- Outcome: PhenoAge Acceleration (PhenoAgeAccel)
- Covariates: age, gender, race, education, etc.
- Mediator: insulin resistance indicators



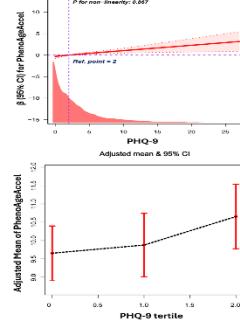
Results:

1. Multivariable linear regression analyses

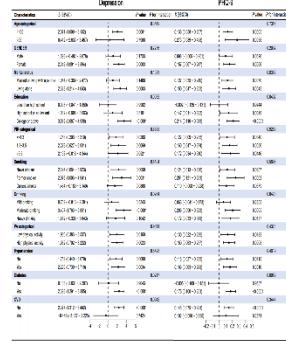
Exposure	Model 3 β (95% CI) P-value
PHQ-9	0.14 (0.07, 0.21) <0.0001
Depression	No 0 Yes 1.93 (0.95, 2.92) 0.0001



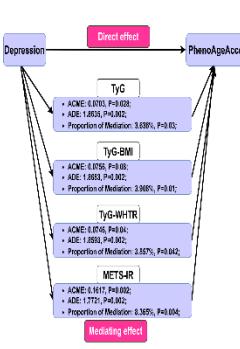
2. Adjusted restricted cubic spline (RCS) analyses



3. Subgroup analyses



4. Mediating effect analyses



Conclusion:

Depression was associated with accelerated PhenoAgeAccel, with insulin resistance acting as a partial mediator. In depression management, interventions targeting metabolic issues like insulin resistance should also be considered to mitigate depression-associated aging.

This cross-sectional study explored the association between depression and PhenoAge acceleration (PhenoAgeAccel) using data from 4,555 NHANES participants. Through multivariable linear regression, subgroup analyses, mediation analysis, and restricted cubic spline (RCS) regression, a significant positive association between depression/PHQ-9 score and PhenoAgeAccel was identified. Stronger associations were observed in subgroups with diabetes, moderate-to-heavy alcohol consumption, and higher education levels. The results highlighted the need to consider depression-triggered metabolic disorders (e.g., insulin resistance) in depression management to mitigate depression-associated accelerated aging.

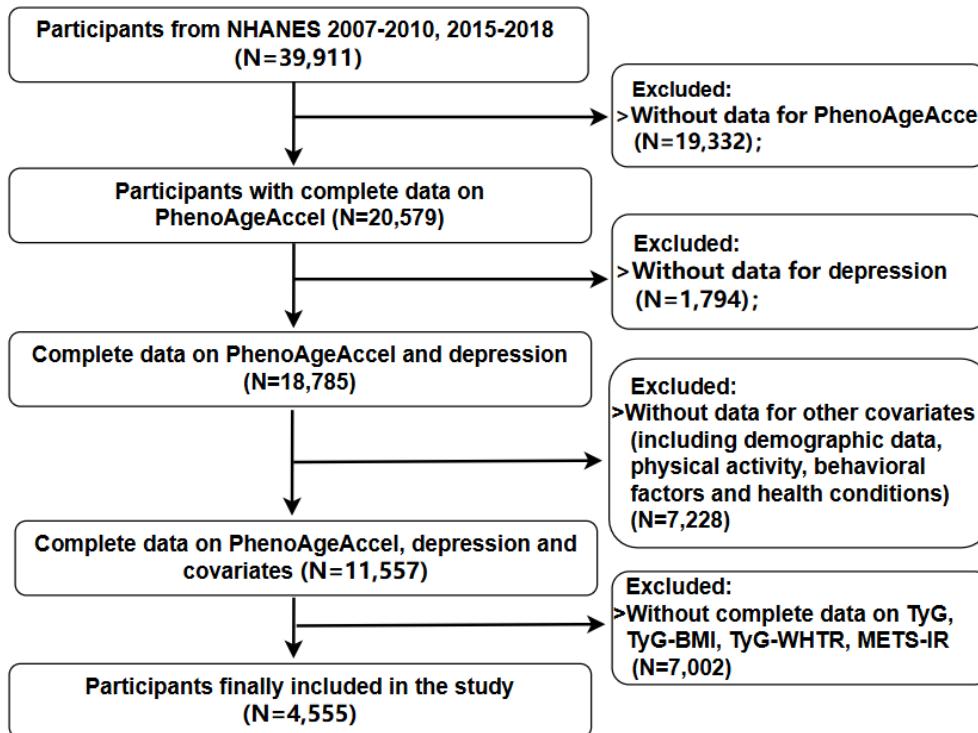


Figure 1. Flow chart of participants selection.

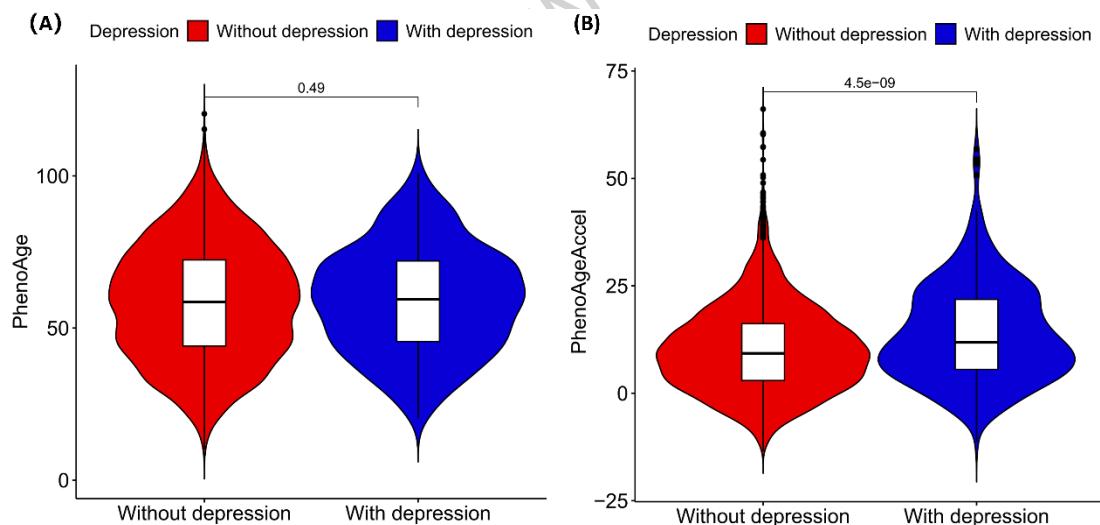


Figure 2. The violin plot reveals the difference of PhenoAge and PhenoAgeAccel between individuals with and without depression.

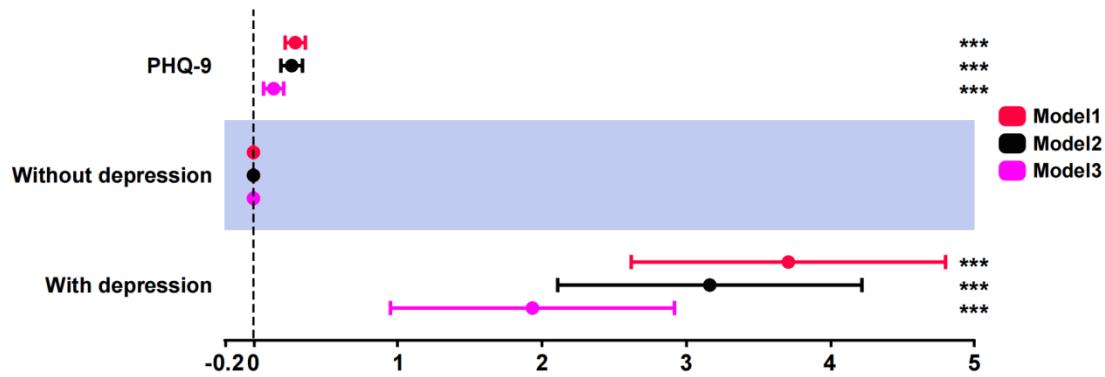


Figure 3. The association of PHQ-9 and depression with PhenoAgeAccel (related to Table 2).

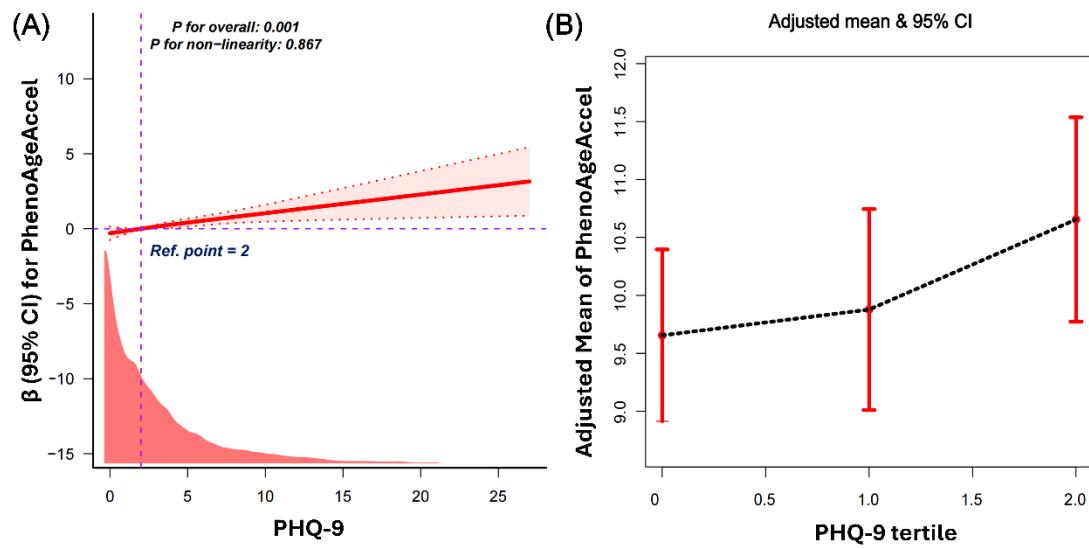


Figure 4. Smooth curve fitting analyses identify the relationship between PHQ-9 and PhenoAgeAccel. (A) RCS curve revealing the association between PHQ-9 (as continuous variable) and PhenoAgeAccel; (B) RCS curve revealing the association between PHQ-9 (as categorical variable) and PhenoAgeAccel.

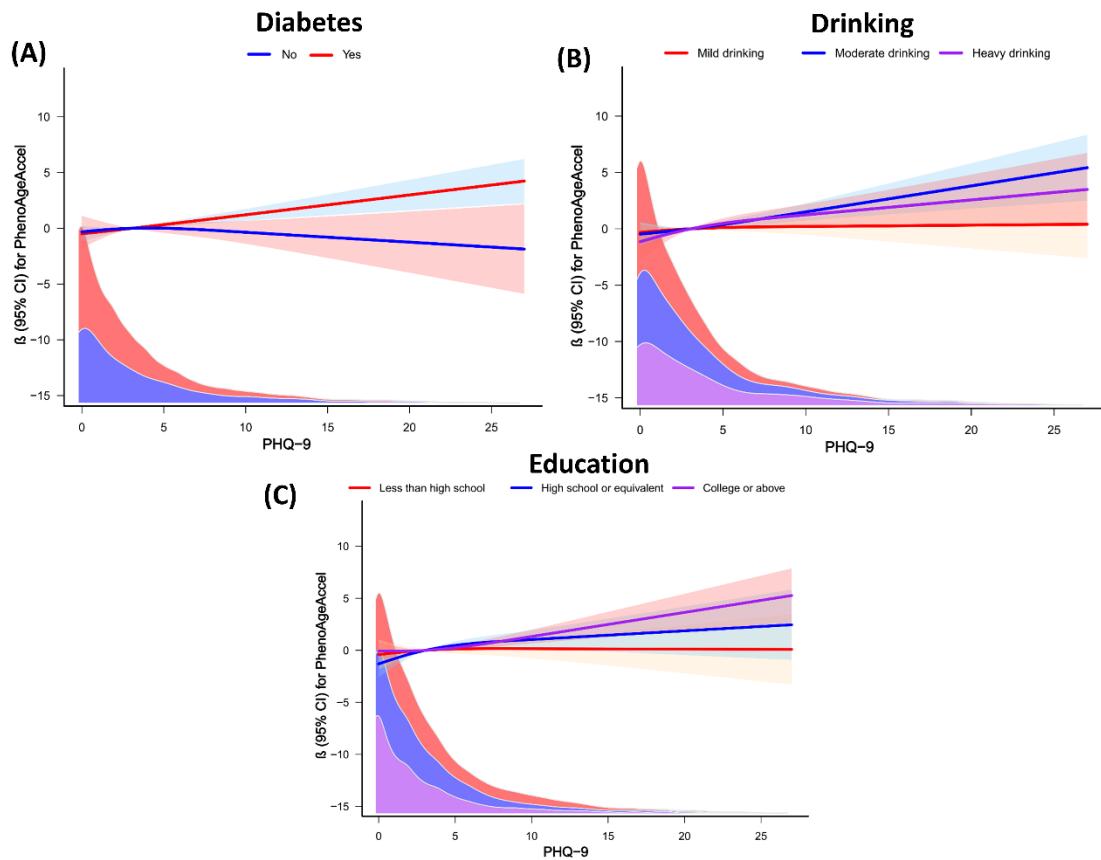


Figure 5. Stratified RCS analyses revealed the association between PHQ-9 and PhenoAgeAccel in different subgroups. (A) diabetes; (B) drinking; (C) education.

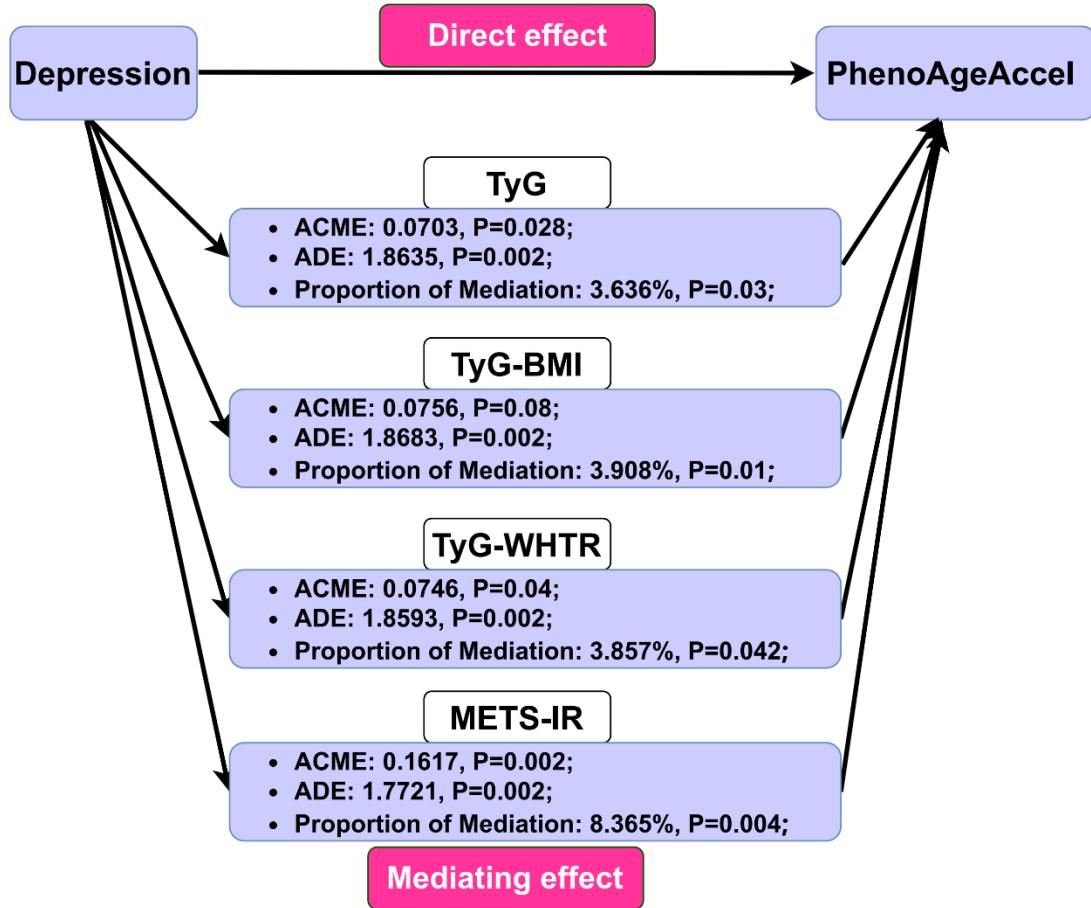
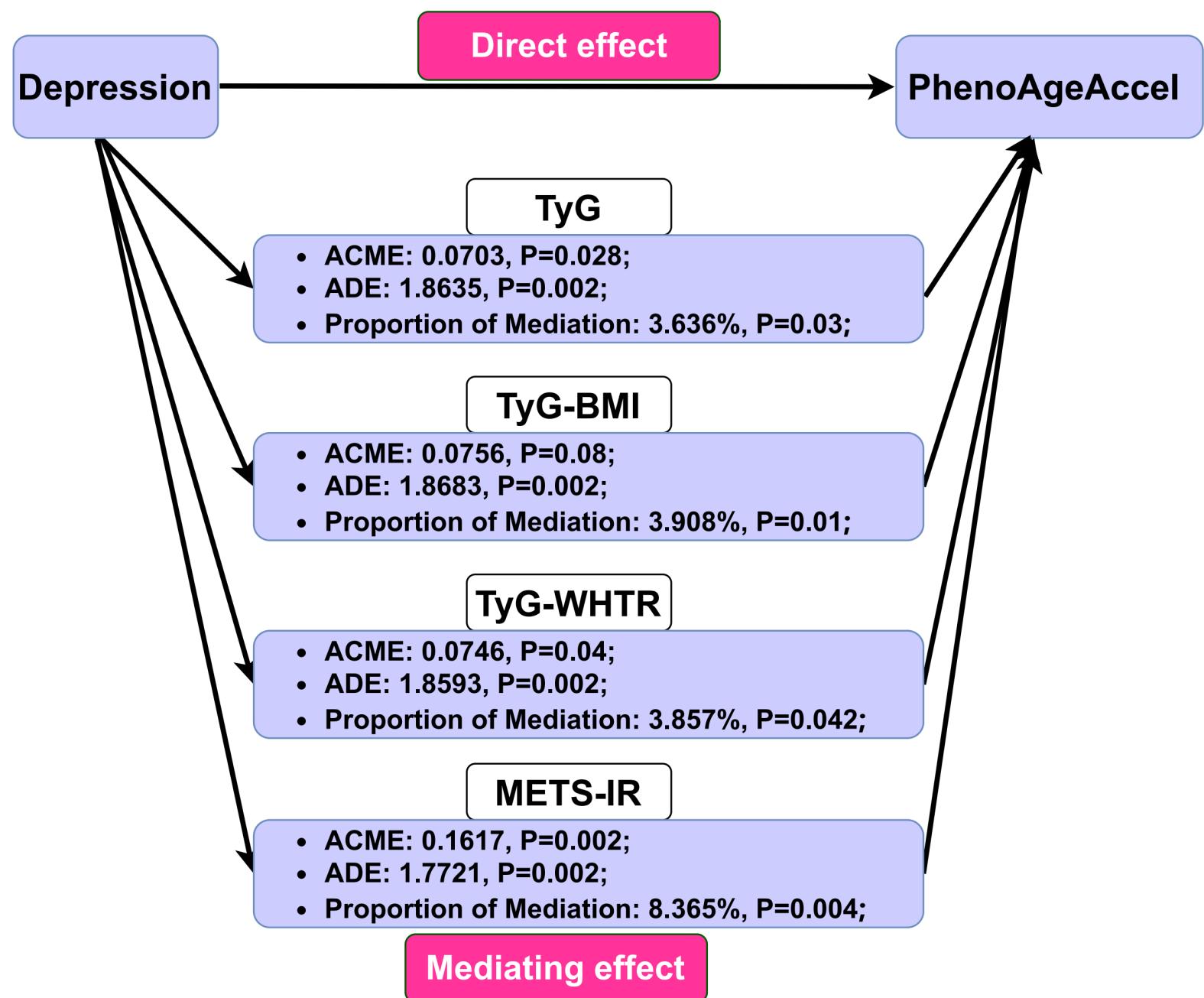
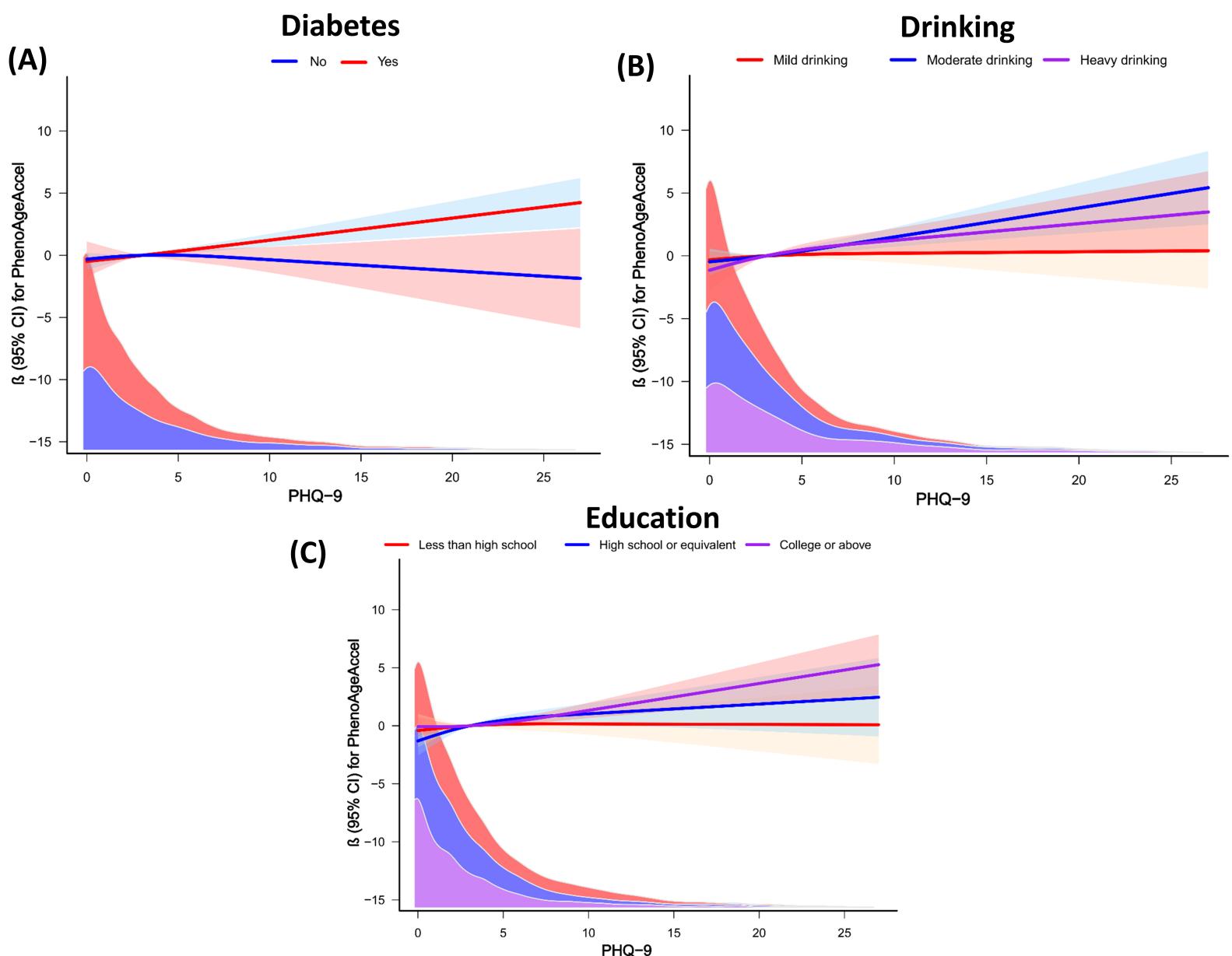
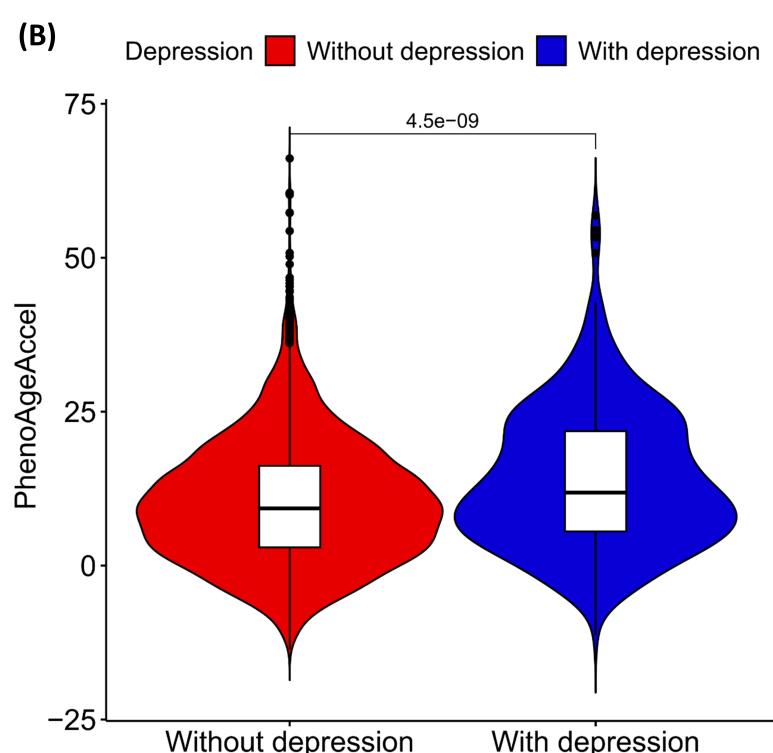
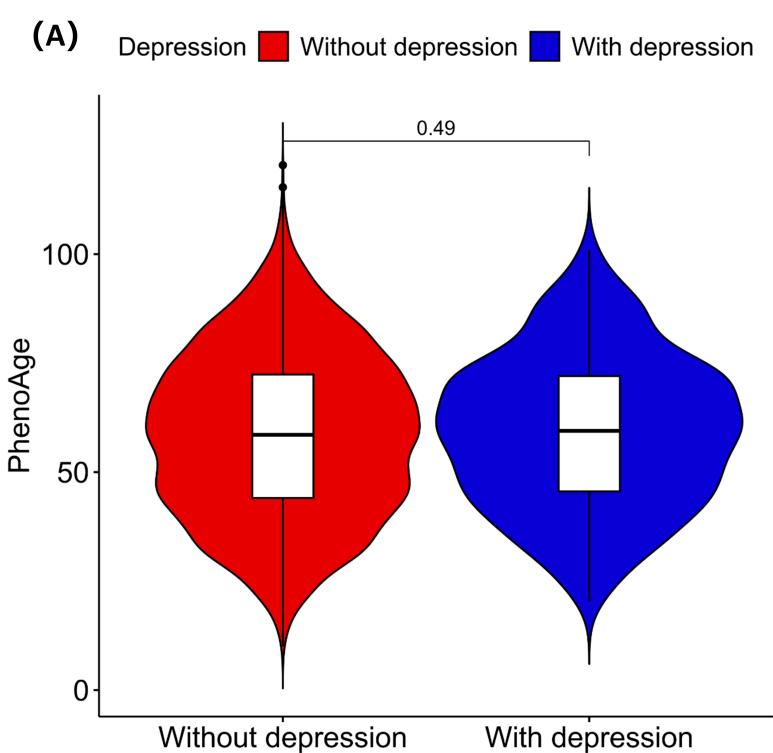
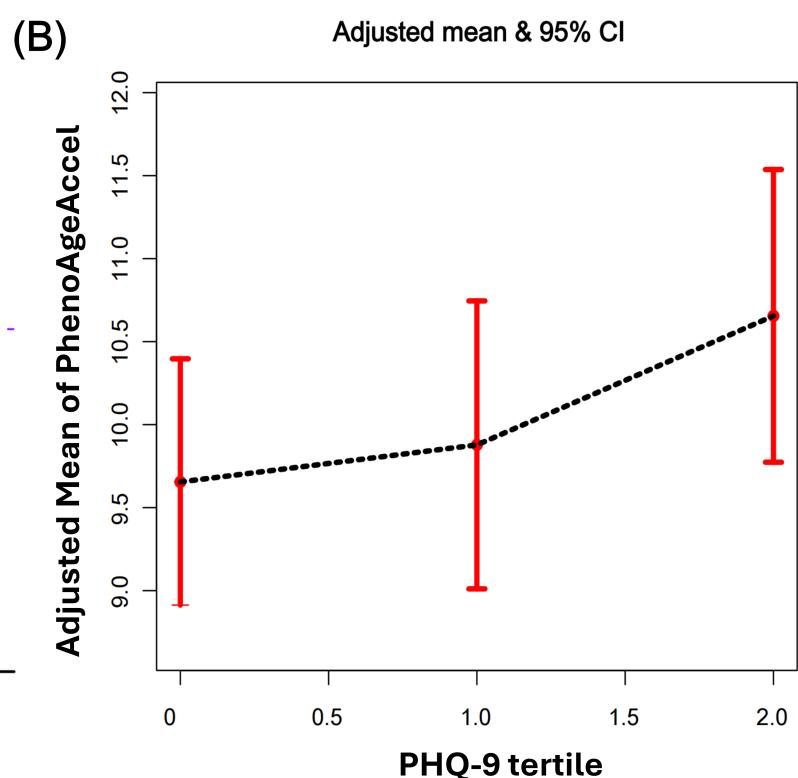
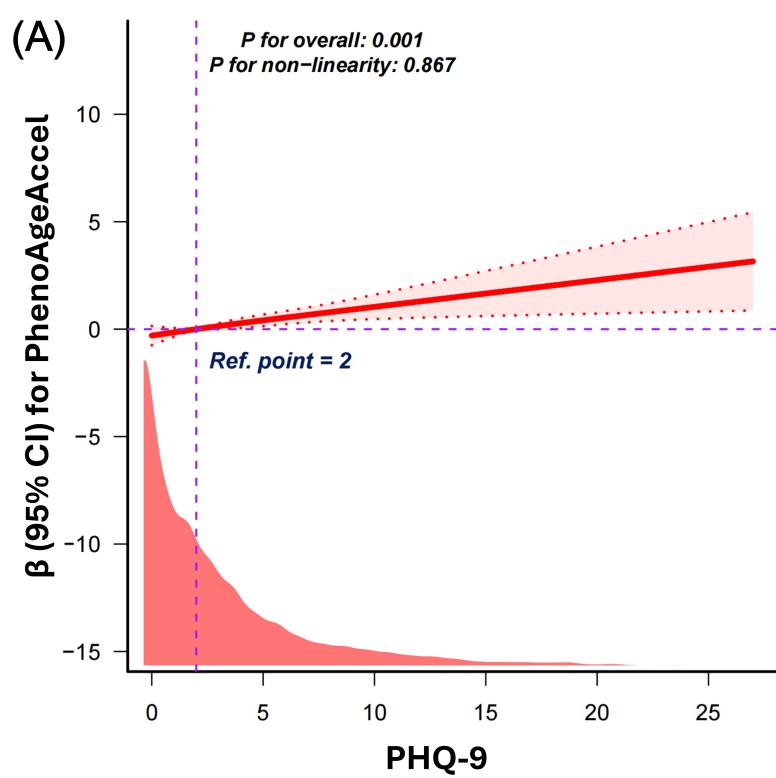


Figure 6. Assessment of the mediating role of insulin resistance surrogates in the relationship PHQ-9 and PhenoAgeAccel (related to STable 3-6).









The Mediating Role of Insulin Resistance in Depression-Driving PhenoAge Acceleration



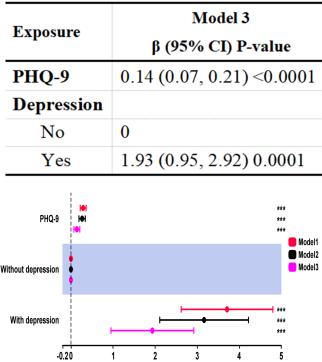
Study design:

- Cross-sectional study based on NHANES database
- Exposure: Depression/PHQ-9 score
- Outcome: PhenoAge Acceleration (PhenoAgeAccel)
- Covariates: age, gender, race, education, etc.
- Mediator: insulin resistance indicators

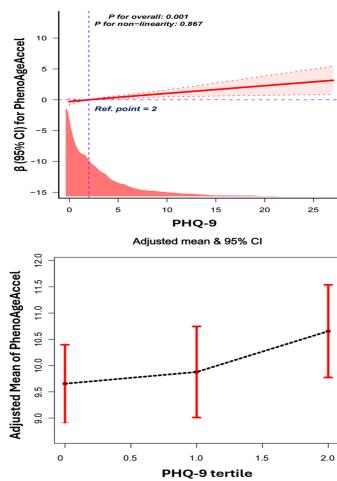


Results:

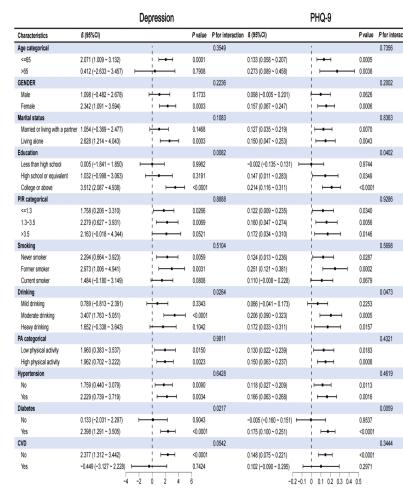
1. Multivariable linear regression analyses



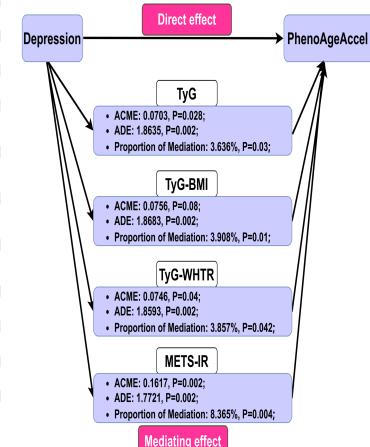
2. Adjusted restricted cubic spline (RCS) analyses



3. Subgroup analyses



4. Mediating effect analyses



Conclusion:

Depression was associated with accelerated PhenoAgeAccel, with insulin resistance acting as a partial mediator. In depression management, interventions targeting metabolic issues like insulin resistance should also be considered to mitigate depression-associated aging.

Table 1. Baseline characteristics of the study participants.

Characteristics	Overall (n=4555)	Depression		P- valu e
		Without depression (n=4191)	With depression (n=364)	
Age	47 (33-61)	48 (33-62)	44 (35-56)	0.001
PhenoAge	58.59 (44.17- 72.36)	58.56 (44.08- 72.39)	59.47 (45.59- 72.04)	0.51
PhenoAgeAccel	9.52 (3.11- 16.55)	9.29 (2.960- 16.205)	11.86 (5.55-21.83)	<0.0 01
TyG	8.56 (8.14-8.99)	8.55 (8.135-8.98)	8.68 (8.23-9.14)	0.001
TyG-BMI	241.37 (204.33- 287.86)	240.63 (203.96- 286.31)	252.14 (209.17- 314.80)	<0.0 01
TyG-WHTR	5.02 (4.33-5.74)	5.01 (4.33-5.71)	5.29 (4.49-6.12)	<0.0 01
METS-IR	41.14 (34.13- 50.20)	40.95 (34.01- 49.80)	43.63 (35.49- 53.91)	<0.0 01
PHQ9	2 (0-4)	1 (0-3)	13 (11-16)	<0.0 01
BMI	27.98 (24.370- 32.60)	27.90 (24.32- 32.36)	28.67 (24.88- 34.74)	<0.0 01
PIR	2.46 (1.29-4.56)	2.61 (1.36-4.67)	1.36 (0.76-2.71)	<0.0 01
Gender				<0.0 01
Male	2354 (51.679%)	2218 (52.923%)	136 (37.363%)	
Female	2201 (48.321%)	1973 (47.077%)	228 (62.637%)	
Race				0.146
Mexican American	694 (15.236%)	640 (15.271%)	54 (14.835%)	
Other Hispanic	454 (9.967%)	413 (9.854%)	41 (11.264%)	
Non-Hispanic White	2170 (47.640%)	2014 (48.055%)	156 (42.857%)	
Non-Hispanic Black	851 (18.683%)	767 (18.301%)	84 (23.077%)	
Other Race	386 (8.474%)	357 (8.518%)	29 (7.967%)	
Education				<0.0 01
Less than high school	822 (18.046%)	717 (17.108%)	105 (28.846%)	
High school or equivalent	1050 (23.052%)	963 (22.978%)	87 (23.901%)	
College or above	2683 (58.902%)	2511 (59.914%)	172 (47.253%)	
Marital status				<0.0 01
Married or living with a partner	2786 (61.164%)	2635 (62.873%)	151 (41.484%)	
Living alone	1769 (38.836%)	1556 (37.127%)	213 (58.516%)	
Smoking				<0.0 01
Never smoker	2332 (51.196%)	2206 (52.637%)	126 (34.615%)	
Former smoker	1222 (26.828%)	1142 (27.249%)	80 (21.978%)	
Current smoker	1001 (21.976%)	843 (20.115%)	158 (43.407%)	
Drinking				<0.0 01
Mild drinking	2311 (50.735%)	2179 (51.992%)	132 (36.264%)	
Moderate drinking	1488 (32.667%)	1355 (32.331%)	133 (36.538%)	
Heavy drinking	756 (16.597%)	657 (15.676%)	99 (27.198%)	
PA categorical				0.011
Low PA	1502 (32.975%)	1360 (32.450%)	142 (39.011%)	

High PA	3053 (67.025%)	2831 (67.550%)	222 (60.989%)	
Hypertension				0.007
No	2793 (61.317%)	2594 (61.895%)	199 (54.670%)	
Yes	1762 (38.683%)	1597 (38.105%)	165 (45.330%)	
Diabetes				0.171
No	3713 (81.515%)	3426 (81.747%)	287 (78.846%)	
Yes	842 (18.485%)	765 (18.253%)	77 (21.154%)	
CVD				<0.001
No	4125 (90.560%)	3821 (91.172%)	304 (83.516%)	
Yes	430 (9.440%)	370 (8.828%)	60 (16.484%)	
Taking Antidepressants				<0.001
No	4400 (96.60%)	4070 (97.11%)	330 (90.66%)	
Yes	155 (3.40%)	121 (2.89%)	34 (9.34%)	

Note: Variables of age, PIR, PHQ-9, BMI, PhenoAge, PhenoAgeAccel, TyG, TyG-BMI, TyG-WHTR, METS-IR, and HOMA-IR were presented as Median (Q1-Q3) due to their non-normal distribution characteristics. **Abbreviations:** PhenoAge, phenotypic age; PIR, ratio of family income to poverty; BMI, body mass index; CVD, cardiovascular disease; PA, physical activity; TyG, triglyceride-glucose index; TyG-BMI, TyG body mass index; TyG-WHtR, TyG-waist height ratio; METS-IR, metabolic score for insulin resistance; **PhenoAgeAccel**, **Phenotypic Age Acceleration**.

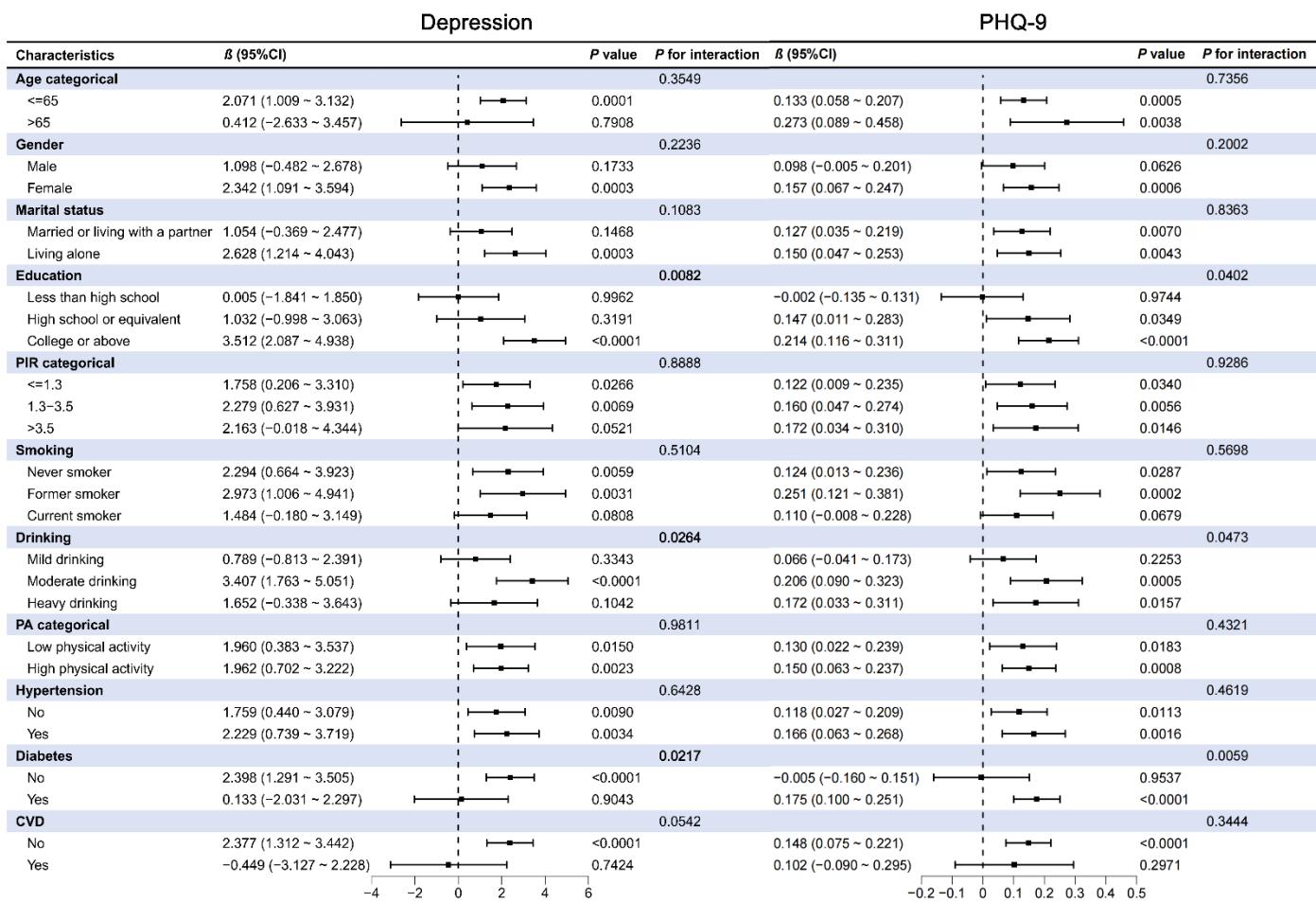
Table 2. Association between depression and PhenoAgeAccel.

Exposure	Model 1		Model 2		Model 3	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
PHQ-9	0.29 (0.22, 0.36)	<0.0001	0.27 (0.19, 0.34)	<0.0001	0.14 (0.07, 0.21)	<0.0001
Depression						
No	0		0		0	
Yes	3.71 (2.62, 4.80)	<0.0001	3.16 (2.11, 4.22)	<0.0001	1.93 (0.95, 2.92)	0.0001

Model 1: adjusted for no covariates. Model 2: adjusted for variables of age, gender, race, education, marital status, and PIR.

Model 3: adjusted for variables of age, gender, race, education, marital status, PIR, BMI, smoking, drinking, PA, CVD, hypertension, and diabetes. **Abbreviations:** CVD, cardiovascular disease; PIR, ratio of family income to poverty; BMI, body mass index; **PA, physical activity;** PHQ, patient health questionnaire.

Table 3. Association of depression and PHQ-9 with PhenoAgeAccel in different subgroups



Abbreviations: CVD, cardiovascular disease; PIR, ratio of family income to poverty; BMI, body mass index; PA, physical activity; PHQ, patient health questionnaire. Except for the stratifying variable, the variables adjusted in subgroup analyses were consistent with Model 3 in Table 2.