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Adolescent depression as a systemic multimorbidity catalyst: integrated genetic and metabolic pathway analysis

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Original Article

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Abstract

Background. Although adolescent depression has been linked to individual chronic conditions, its broader role in shaping multimorbidity risk remains understudied.

Methods. A total of 87,562 UK Biobank participants were included, of whom 18,851 had documented adolescent depression. Cox proportional hazards models were applied to evaluate associations between adolescent depression and 24 chronic diseases, followed by stratified analyses by sex and age. Two-sample Mendelian randomization (MR) was then conducted to infer causality for diseases showing significant associations. Genomic colocalization analyses were performed using relevant GWAS data to identify shared causal variants. Mediation analyses were performed to detect possible mediating factors, including the frailty index, KDM biological age acceleration, allostatic load and 30 circulating biomarkers.

Results. Adolescent depression was associated with elevated risk for 12 chronic diseases, with strongest associations for hypothyroidism (HR = 1.29 [1.18–1.42]), diabetes (HR = 1.25 [1.13–1.38]) and chronic obstructive pulmonary disease (COPD) (HR = 1.74 [1.50–2.01]). Risks were notably higher among females and younger adults. MR confirmed likely causal relationships for hypothyroidism (OR = 1.45 [1.03–2.05]), diabetes (OR = 1.01 [1.01–1.02]) and COPD (OR = 1.04 [1.02–1.06]). Genomic colocalization revealed a shared genetic signal at the *CDSN/PSORS1C1* locus between adolescent depression and hypothyroidism. Mediation analyses revealed disease-specific pathways: creatinine for hypothyroidism, testosterone for diabetes, KDM biological ageing for COPD and frailty index across all three conditions.

Conclusions. Adolescent depression confers systemic vulnerability through genetic and metabolic mechanisms, with amplified risks in females and individuals aged ≤55 years. These findings support early, integrated interventions to mitigate long-term multimorbidity.

Introduction

Depression among adolescents and young adults has become an escalating public health concern, with global data from 1990 to 2019 showing a 21.7% increase in prevalence and a 19.1% rise in incidence rates (Yang *et al.*, 2024). Traditionally conceptualized as a psychiatric condition, depression is increasingly recognized as a potential precursor to broader systemic health deterioration (Copeland *et al.*, 2021; Fleetwood *et al.*, 2025). Emerging evidence suggests that early-onset depression may not only reflect psychological distress but also signal emerging vulnerabilities across multiple physiological systems (Mannan *et al.*, 2016; Goldstein and Korczak, 2020; Frank *et al.*, 2023). For instance, childhood-onset compared to adulthood-onset of major depression is associated with increased rates of serious cardiovascular events, independently of cardiovascular risk factors (Franco *et al.*, 2015).

Despite these insights, most longitudinal studies have concentrated on short-term outcomes, with follow-up typically limited to early adulthood (before age 35) (Franco *et al.*, 2015; Leone *et al.*, 2021). However, emerging data indicate that persistent depressive symptoms in adolescence predict increased healthcare utilization well into midlife, underscoring the need to examine long-term health trajectories (Ssegonja *et al.*, 2019). Critically, prior research has largely examined adolescent depression in relation to individual diseases, such as cardiovascular or autoimmune disorders (Benros *et al.*, 2013; Goldstein and Korczak, 2020), overlooking the

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fact that multimorbidity, where multiple chronic diseases coexist, often serves as a more significant determinant of poor health outcomes (Mannan *et al.*, 2016; Fleetwood *et al.*, 2025). Such epidemiological observations raise critical questions about the biological pathways through which adolescent depression may contribute to later-life multimorbidity.

Recent studies have begun to elucidate shared biological mechanisms linking depression and chronic diseases. For instance, dysregulation of the hypothalamic–pituitary–adrenal axis, alterations in the gut microbiome and metabolic signalling disruptions (e.g., involving adiponectin and leptin) have all been implicated in the depression–diabetes axis (Hood *et al.*, 2012; Mazala-De-Oliveira *et al.*, 2023). In parallel, associations between depression and biological ageing (Lorenzo *et al.*, 2023) and metabolic dysfunction (Goldsmith *et al.*, 2020) have been documented. Nevertheless, few studies have comprehensively investigated how these biological processes might mediate the progression from early-life depression to multimorbidity. To bridge these gaps, we incorporate three synthetic indicators – frailty index, KDM biological age acceleration (KDM-BA) and allostatic load (AL) – as mechanistic mediators, along with a panel of 30 circulating biomarkers representing key metabolic, inflammatory, hepatic, endocrine and renal pathways.

Leveraging the longitudinal phenotypic and genomic data from the UK Biobank (UKB), we test the hypothesis that adolescent depression initiates persistent dysregulation across interconnected physiological systems, thereby increasing susceptibility to multimorbidity in later life. To investigate this, we integrated epidemiological, genetic and multi-omics data to characterize multimorbidity profiles, explore causal pathways and identify potential biological mediators. This comprehensive, multimethod approach enables a systems-level understanding of how early-life mental health can shape long-term physical health outcomes.

Methods

Study design and population

This study utilized data from the UKB, a large-scale prospective cohort comprising over 500,000 participants aged 37–73 years at baseline (2006–2010). Participants provided extensive phenotypic, genomic and health-related data through questionnaires, physical measurements and electronic health records.

This study employed a multi-phase analytical framework to investigate the systemic health impacts of adolescent depression. First, we conducted longitudinal observational analyses using Cox proportional hazards models to examine associations between adolescent depression and 24 chronic diseases. Second, we performed genetic validation through Mendelian randomization (MR) to assess causal relationships between adolescent depression and chronic diseases. Additionally, colocalization analysis was applied to identify shared causal variants within linkage disequilibrium blocks. Third, we explored potential biological pathways using mediation analyses, evaluating the role of 30 circulating serum biomarkers and 3 synthetic indices in linking depression to chronic diseases.

Assessment of adolescent depression

Adolescent depression was operationally defined as depression with first onset between ages 10 and 24 years, capturing depressive episodes emerging during adolescence and the transition to young adulthood. This age range was selected because it is supported by contemporary developmental frameworks and has been widely used in global burden of disease and epidemiological studies of young people and depression (Gore *et al.*, 2011; Sawyer *et al.*, 2018; Yang *et al.*, 2024).

Adolescent depression cases were identified through a multistep validation process using UKB data. Primary case definition required: (1) self-reported age of first depressive episode (UKB Field 20433) between 10 and 24 years; (2) endorsement of either prolonged depressed mood (UKB Field 20446) or anhedonia (UKB Field 20441) lasting ≥2 weeks. Control participants denied lifetime depressive symptoms per the Composite International Diagnostic Interview and maintained PHQ-9 ≤ 5. To further enhance diagnostic precision, individuals with any lifetime diagnosis of depressive disorders (ICD-10 codes F32-F33) documented in electronic health records were excluded. Additionally, participants with a history of adult-onset depression, defined as first onset after age 24, were removed from the control cohort.

Outcome assessment

We assessed 24 physical health conditions based on validated comorbidity frameworks (Charlson and Elixhauser indices [Metcalfe *et al.*, 2019]). These conditions were categorized by physiological systems to reflect a comprehensive spectrum of multimorbidity. The conditions were grouped by physiological system to capture a comprehensive spectrum of multimorbidity: respiratory diseases (asthma; chronic obstructive pulmonary disease [COPD]); cardiovascular diseases (cardiac arrhythmia; congestive heart failure; myocardial infarction; cerebrovascular disease; hypertension; peripheral vascular disease; pulmonary circulation disorders; valvular disease); neurological disorders (epilepsy; multiple sclerosis; Parkinson's disease; seizures, excluding cerebrovascular disease and dementia; paralysis or paresis); endocrine and metabolic disorders (type 1 and type 2 diabetes; hypothyroidism; fluid and electrolyte disorders); gastrointestinal and hepatic diseases (liver disease; peptic ulcer disease); renal disease; oncological conditions (all cancer types); infectious disease (HIV/AIDS); and hematologic disorders (deficiency anaemia; blood loss anaemia; coagulopathy). The ICD-10 codes for all 24 conditions are listed in Supplementary Table S1.

Covariate assessment

The analysis adjusted for a range of demographic, socioeconomic and lifestyle covariates measured at baseline. Demographic factors comprised age (years) and sex. Ethnicity was dichotomized as White or non-White (UKB Field 21000). Socioeconomic status was captured by highest educational attainment (UKB Field 6138) and the Townsend Deprivation Index (TDI; UKB Field 22189), a composite measure of neighbourhood-level deprivation based on postal code. Lifestyle factors included body mass index (BMI), calculated from measured height and weight and categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24 kg/m^2), overweight (24–28 kg/m^2) and obese (≥ 28 kg/m^2); smoking status (never, former, current; UKB Fields 20116); alcohol drinker status (never, former, current; UKB Fields 20117); and physical activity, defined as the number of days performing walking, moderate and vigorous activity (UKB Field 22033). Use of medications for lipid lowering, blood pressure, diabetes or exogenous hormone therapy was recorded (UKB Field 6153). Participants with

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missing data on any covariate were excluded from all multivariable analyses.

Statistical analysis

We performed survival analyses to assess associations between adolescent depression and incident chronic diseases using Cox proportional hazards models. Survival time was calculated from the baseline assessment date (UKB Field 53) until the earliest of: (1) disease diagnosis, (2) death (UKB Field 40000), (3) loss to follow-up (UKB Field 191) or (4) study end (29 October 2022). We constructed two sequential models: Model 1 adjusted for age, sex and race; Model 2 additionally adjusted for BMI, TDI, smoking status, drinking status, educational attainment, physical activity and hormone medication use. To evaluate effect modification, we conducted stratified analyses by sex (male/female) and age (<55/≥55 years). All models satisfied proportional hazards assumptions, verified through Schoenfeld residual testing. Participants with missing covariate data were excluded from analyses. To account for multiple testing, Bonferroni correction was applied across 22 outcomes (excluding two diseases with <100 cases) evaluated in two Cox models, resulting in 44 comparisons. Accordingly, the Bonferroni-adjusted significance threshold was set at $\alpha = 0.05/44 = 0.00114$. All statistical analyses were performed using the 'survival' package (version 3.8.3) in R (version 4.4.1).

Additional analyses were conducted to provide complementary genetic and mechanistic evidence. MR was used to evaluate potential causal relationships between adolescent depression and related chronic diseases, while colocalization analysis was used to assess shared genetic signals. For mediation analyses, we examined three integrative indices and 30 serum biomarkers selected to capture multisystem physiological dysregulation. Specifically, the frailty index reflected multisystem vulnerability, KDM-BA reflected accelerated biological ageing and AL reflected cumulative metabolic, cardiovascular and inflammatory burden. The 30 serum biomarkers represented metabolic, inflammatory, hepatic, endocrine and renal pathways. Detailed procedures are provided in the Supplementary Methods.

Results

Cohort characteristics

The study included 87,562 participants from the UKB, comprising 68,711 individuals without a history of adolescent depression and 18,851 with documented adolescent depression (Table 1). Participants with adolescent depression were younger (median age 54 vs. 58 years) and more likely to be female (68.3% vs. 46.9%, χ^2 $P < 0.001$). Socioeconomic disparities were evident, with the depression group showing higher Townsend deprivation scores (median: −1.85 vs. −2.62, Mann–Whitney $P < 0.001$) and lower educational attainment (52.9% vs. 44.8% with college-level education, $P < 0.001$). Lifestyle factors differed substantially, with higher smoking prevalence (48.1% vs. 39.7%, $P < 0.001$) and lower physical activity levels (median 26.55 vs. 27.93 MET-hours/week, $P < 0.001$) in the depression group. Medication use patterns revealed greater psychotropic drug utilization among those with adolescent depression (17.8% vs. 11.5%, $P < 0.001$).

Table 1. Baseline characteristics of participants

Characteristics	No. adolescent depression ($n = 68,711$)	Adolescent depression ($n = 18,851$)	*P*
Age, years	58.0 [51.0, 63.0]	54.0 [48.0, 60.0]	<0.001
Sex			<0.001
Female	32,243 (46.9%)	12,875 (68.3%)	
Male	36,468 (53.1%)	5,976 (31.7%)	
Ethnicity			0.028
White race	66,376 (96.9%)	18,235 (97.2%)	
Non-White race	2,117 (3.1%)	521 (2.8%)	
Townsend deprivation index	−2.62 [−3.91, −0.54]	−1.85 [−3.52, 0.80]	<0.001
Education level			<0.001
College degree	30,511 (44.8%)	9,878 (52.9%)	
A levels	8,870 (13.0%)	2,600 (13.9%)	
O levels	13,644 (20.0%)	3,206 (17.2%)	
CSE	2,463 (3.6%)	650 (3.5%)	
NVQ	3,813 (5.6%)	708 (3.8%)	
Professional qualification	3,544 (5.2%)	762 (4.1%)	
Others	5,246 (7.7%)	877 (4.7%)	
Previous/Current smoking	27,229 (39.7%)	9,054 (48.1%)	<0.001
Previous/Current drinking	66624 (97.0%)	18318 (97.3%)	0.086
Physical activity	27.93 [13.50, 53.32]	26.55 [13.20, 51.17]	<0.001
BMI			<0.001
Normal	18,267 (27.0%)	5,759 (31.0%)	
Overweight	27,655 (40.8%)	6,829 (36.8%)	
Obese	21,552 (31.8%)	5,819 (31.3%)	
Hormone medication use	7,890 (11.5%)	3,352 (17.8%)	<0.001

Notes: Data are presented as *n* (%) for categorical variables and median [interquartile range] for continuous variables. *P* values were calculated using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

Association between adolescent depression and chronic disease

Adolescent depression was significantly associated with 12 chronic diseases after Bonferroni correction, spanning cardiovascular, metabolic, respiratory and immune systems (Table 2). Hazard ratios (HRs) ranged from 1.16 to 1.74, with the strongest associations observed for COPD (HR = 1.74, 1.50–2.01) and liver diseases (HR = 1.60, 1.38–1.86). Comparison between minimally adjusted (Model 1) and fully adjusted models (Model 2) revealed limited attenuation of effect sizes.

Stratified analyses revealed sex- and age-specific variations in depression-related disease risks (Supplementary Tables S2 and S3). Sex-specific patterns revealed both shared and unique vulnerabilities: while asthma emerged as a common risk across

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Table 2. Associations of adolescent depression with incident chronic diseases in full cohort analyses

		Model 1		Model 2	
Disease	CASE/TOTAL	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Asthma	3622/78810	**1.60 (1.48–1.72)**	1.38×10^{-35}	**1.59 (1.47–1.71)**	1.55×10^{-33}
Cancer	6046/78004	0.99 (0.92–1.06)	7.44×10^{-01}	0.97 (0.91–1.04)	3.92×10^{-1}
Cardiac arrhythmia	4596/79394	**1.18 (1.10–1.28)**	1.48×10^{-05}	**1.16 (1.08–1.26)**	1.26×10^{-4}
Cerebrovascular disease	1520/80117	1.21 (1.07–1.39)	3.75×10^{-03}	1.19 (1.04–1.36)	1.21×10^{-2}
Coagulopathy	387/80393	1.22 (0.95–1.56)	1.13×10^{-01}	1.16 (0.91–1.50)	2.36×10^{-1}
Congestive heart failure	951/80332	**1.33 (1.12–1.57)**	9.35×10^{-04}	1.31 (1.11–1.55)	1.82×10^{-3}
COPD	996/80394	**1.74 (1.50–2.01)**	2.93×10^{-13}	**1.60 (1.37–1.86)**	1.61×10^{-9}
Deficiency anaemia	1674/80113	1.19 (1.06–1.34)	3.91×10^{-03}	1.18 (1.04–1.32)	7.33×10^{-3}
Diabetes	2571/79714	**1.25 (1.13–1.38)**	8.04×10^{-06}	**1.20 (1.08–1.32)**	5.06×10^{-4}
Fluid or electrolyte disorders	1498/80357	**1.29 (1.14–1.46)**	8.28×10^{-05}	**1.25 (1.10–1.42)**	8.06×10^{-4}
Hypertension	12140/76720	**1.16 (1.11–1.22)**	3.05×10^{-10}	**1.14 (1.09–1.20)**	3.19×10^{-8}
Hypothyroidism	2392/79793	**1.32 (1.20–1.45)**	2.54×10^{-09}	**1.29 (1.18–1.42)**	5.06×10^{-8}
Liver disease	897/80306	**1.60 (1.38–1.86)**	6.30×10^{-10}	**1.53 (1.31–1.78)**	4.22×10^{-8}
Myocardial infarction	1547/79890	**1.25 (1.09–1.43)**	1.05×10^{-03}	**1.27 (1.11–1.45)**	6.77×10^{-4}
Neurological disorders	972/80100	**1.37 (1.18–1.59)**	4.50×10^{-05}	**1.35 (1.16–1.57)**	1.26×10^{-4}
Paresis or paralysis	210/80445	1.43 (1.02–2.01)	3.57×10^{-02}	1.42 (1.01–1.99)	4.54×10^{-2}
Peptic ulcers	876/80052	**1.37 (1.16–1.61)**	1.52×10^{-04}	**1.36 (1.16–1.61)**	2.12×10^{-4}
Peripheral vascular disease	1012/80326	1.31 (1.11–1.54)	1.34×10^{-03}	1.24 (1.05–1.46)	1.10×10^{-2}
Pulmonary circulation disorders	688/80295	0.97 (0.79–1.19)	7.70×10^{-01}	0.97 (0.79–1.18)	7.35×10^{-1}
Renal disease	1428/80348	1.22 (1.06–1.40)	4.15×10^{-03}	1.24 (1.08–1.42)	2.20×10^{-3}
Rheumatic and collagen disease	1384/80141	**1.34 (1.18–1.52)**	5.38×10^{-06}	**1.33 (1.17–1.51)**	9.02×10^{-6}
Valvular disease	1581/80217	1.22 (1.07–1.39)	2.80×10^{-03}	1.21 (1.06–1.38)	4.78×10^{-3}

Notes: Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. Model 1 was adjusted for age, sex and ethnicity. Model 2 was additionally adjusted for body mass index (BMI), Townsend Deprivation Index (TDI), smoking status, alcohol drink status, educational attainment, physical activity and hormone medication use. Bolded values indicate statistical significance after Bonferroni correction ($P < 0.0011$, i.e., 0.05/44 tests).

both sexes (females HR = 1.67 [1.53–1.84]; males HR = 1.40 [1.23–1.60]), females exhibited exclusive susceptibility to 10 additional conditions including COPD (HR = 1.76 [1.43–2.17]), liver disease (HR = 1.68 [1.39–2.04]) and hypothyroidism (HR = 1.27 [1.15–1.41]). Age-stratified analyses revealed stronger associations among younger individuals (≤55 years). Among ≤55-year-olds, adolescent depression conferred elevated risks for eight distinct conditions, with pronounced effects observed for asthma (HR = 1.69 [1.52–1.89]), COPD (HR = 1.88 [1.34–2.66]) and diabetes (HR = 1.46 [1.24–1.73]). Four conditions demonstrated persistent but diminished associations in older adults, including asthma (≤55 HR = 1.69 vs. >55 HR = 1.50), COPD (≤55 HR = 1.88 vs. >55 HR = 1.53), hypertension (≤55 HR = 1.23 vs. >55 HR = 1.10) and hypothyroidism (≤55 HR = 1.41 vs. >55 HR = 1.22).

Causal inference via Mendelian randomization

MR analyses using two independent instruments (rs2429657, rs10511068) revealed significant causal effects of genetically COPD (OR = 1.04, 95% CI: 1.02–1.06), diabetes (OR = 1.01, 1.01–1.02) and hypothyroidism (OR = 1.45, 1.03–2.05) (Fig. 1). The limited instrument count precluded leave-one-out analyses, limited instrument count precluded reliable heterogeneity testing; conservative random-effects models were employed.

Colocalization analysis

For the three validated diseases, we further investigated genetic colocalization across these conditions. Our colocalization analysis revealed robust signals for both diabetes and hypothyroidism, implicating specific genetic loci and effector genes (Fig. 2). For hypothyroidism, we observed three independent loci on chromosome 6 with strong colocalization evidence: rs1235162 (250 SNPs, PP.H4 = 0.910), rs3094220 (179 SNPs, PP.H4 = 0.870; implicating *CDSN/PSORS1C1*) and rs9265797 (40 SNPs, PP.H4 = 0.769). Additionally, a moderate colocalization signal was detected on chromosome 17 (rs17320971, 294 SNPs, PP.H4 = 0.504). For diabetes, a 17-SNP locus on chromosome 6 (rs9272426, PP.H4 = 0.508) identified *HLA-DQA1* as the likely effector gene. For COPD, no genomic loci exhibited significant evidence of shared causal variants with adolescent depression (all PP.H4 < 0.5).

Mediation analysis

Mediation analyses suggested outcome-specific indirect-effect patterns for the three prioritized chronic disease outcomes, with

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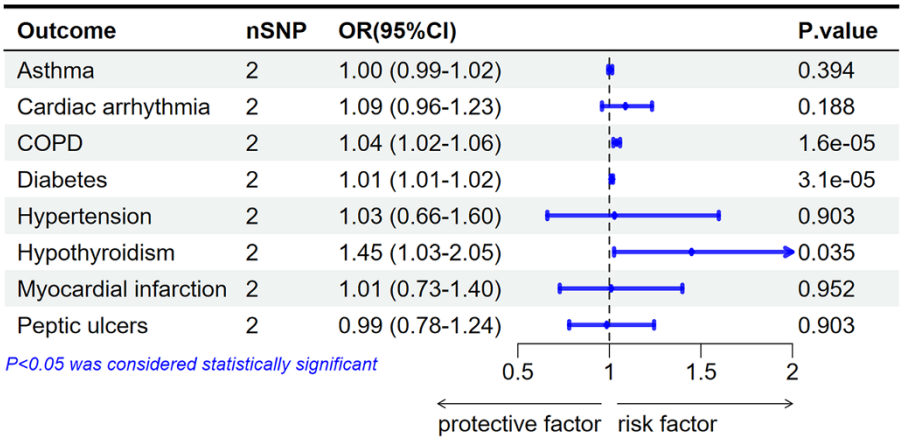


Figure 1. Causal effects of adolescent depression on chronic disease risk.
Notes: Two-sample MR analyses were conducted using independent genome-wide significant SNPs associated with adolescent depression as instrumental variables. The plot displays the ORs and 95% CIs for the effect of genetically predicted adolescent depression on eight physical health outcomes. A vertical dashed line at OR = 1 indicates the null (no effect). Outcomes with OR > 1 suggest a higher risk conferred by adolescent depression, while OR < 1 indicates a protective association. COPD, diabetes and hypothyroidism demonstrated statistically significant associations ($P < 0.05$), consistent with a potential causal relationship. The number of SNPs (nSNP) used as instruments for each outcome is indicated. Horizontal bars represent 95% CIs. The dotted blue text below the figure highlights the threshold for statistical significance.

estimates presented as β and 95% CI (Fig. 3 and Supplementary Table S4). Among the integrative physiological indices, the frailty index showed consistent positive indirect effects for diabetes (β = 0.066, 0.048–0.082), COPD (β = 0.055, 0.028–0.073) and hypothyroidism (β = 0.031, 0.019–0.045). KDM-BA showed the largest indirect effect for COPD (β = 0.174, 0.147–0.214), whereas its indirect effects were not evident for diabetes or hypothyroidism.

Among serum biomarkers, diabetes showed the broadest mediation profile, with notable indirect effects for testosterone (β = 0.085, 0.042–0.109), creatinine (β = 0.059, 0.018–0.088), apolipoprotein A (β = 0.034, 0.017–0.045), HDL cholesterol (β = −0.078, −0.095 to −0.050), direct bilirubin (β = −0.048, −0.074 to −0.031), apolipoprotein B (β = −0.042, −0.053 to −0.026), urea (β = −0.033, −0.046 to −0.022) and alanine aminotransferase (β = −0.027, −0.036 to −0.017). For hypothyroidism, the main biomarker-related indirect effects involved creatinine (β = −0.028, −0.042 to −0.017) and total protein (β = −0.005, −0.007 to −0.002). For COPD, serum biomarker mediation was limited, with the clearest signal observed for total bilirubin (β = 0.016, 0.002–0.029). All mediation effects highlighted in the text were statistically significant at $P < 0.05$, and full indirect-effect estimates, 95% confidence intervals and exact P values are provided in Supplementary Table S4.

Discussion

This study provides evidence that adolescent depression is associated with increased vulnerability to 12 chronic conditions across metabolic, cardiovascular, immune and respiratory systems. Genetic analyses further supported potential links with diabetes, COPD and hypothyroidism, while mediation analyses highlighted potential endocrine, metabolic, ageing-related and frailty-related pathways involved in these associations.

Adolescent depression was also significantly associated with a higher risk of hypothyroidism in adulthood, a relationship that has gained growing research attention (Hirtz *et al.*, 2021, 2022; Leone *et al.*, 2021). Emerging evidence has highlighted that chronic psychological stress may alter hypothalamic–pituitary–thyroid axis function (Xu *et al.*, 2017), contributing to thyroid hormone dysregulation. Our results support this link and further identify creatinine as a potential biomarker involved in this pathway. Although the mechanistic role of creatinine remains unclear, it may reflect disrupted cellular energy metabolism and oxidative stress – processes implicated in both depression and hypothyroidism (Glombik *et al.*, 2020, 2021; Liu *et al.*, 2025). Animal studies demonstrate hypothyroidism and depression synergistically disrupt brain glycolysis and mitochondrial activity, key pathways where creatinine metabolism might reflect underlying deficits (Glombik *et al.*, 2020, 2021).

Adolescent depression was strongly associated with an elevated risk of diabetes in adulthood. This finding is consistent with previous longitudinal studies demonstrating that depressive symptoms during adolescence predict insulin resistance and elevated fasting insulin, independent of adiposity (Shomaker and Goodman, 2015; Suglia *et al.*, 2016; Olive *et al.*, 2017; Shomaker *et al.*, 2020). Mediation and colocalization analyses suggested two complementary pathways potentially involved in this relationship. First, several metabolic biomarkers mediated the depression–diabetes link, including testosterone, creatinine and apolipoprotein A. Notably, testosterone emerged as a key mediator, likely through its regulatory roles in neuroinflammation, insulin sensitivity and vascular function (Seidman *et al.*, 2001; Tully *et al.*, 2016; Atallah *et al.*, 2017; Peng *et al.*, 2022). Low testosterone levels are associated with both depression and diabetes risk (Kapoor *et al.*, 2005; Tully *et al.*, 2016), and testosterone replacement has shown efficacy in improving mood and glycemic control in clinical (Seidman *et al.*, 2001; Corona *et al.*, 2011) and animal studies (Atallah *et al.*, 2017; Peng *et al.*, 2022). Second, colocalization analysis identified *HLA-DQA1* as a shared genetic locus linking adolescent depression and diabetes. Prior studies have reported associations between HLA variants and depression (Cheng *et al.*, 2024), while *HLA-DQA1* specifically has been strongly implicated in diabetes susceptibility through both genetic predisposition and immune activation (Farina *et al.*, 2019). Together, these findings suggest that endocrine, metabolic and immune dysregulation may contribute to the depression–diabetes association.

The association between adolescent depression and COPD was modest but significant, with mediation analysis identifying frailty as a key intermediate factor. Longitudinal and cross-sectional studies have consistently shown that depression elevates frailty risk over time, which in turn heightens susceptibility to health deterioration, including pulmonary dysfunction (Borges *et al.*, 2021; Campo-Arias *et al.*, 2024; Sun *et al.*, 2024). This pathway may be reinforced by behavioural contributors, as depressed adolescents are more likely to initiate smoking (Groenman *et al.*, 2017), a well-established risk factor for COPD. Notably, frailty is highly prevalent among COPD patients and is associated with increased exacerbations and reduced lung

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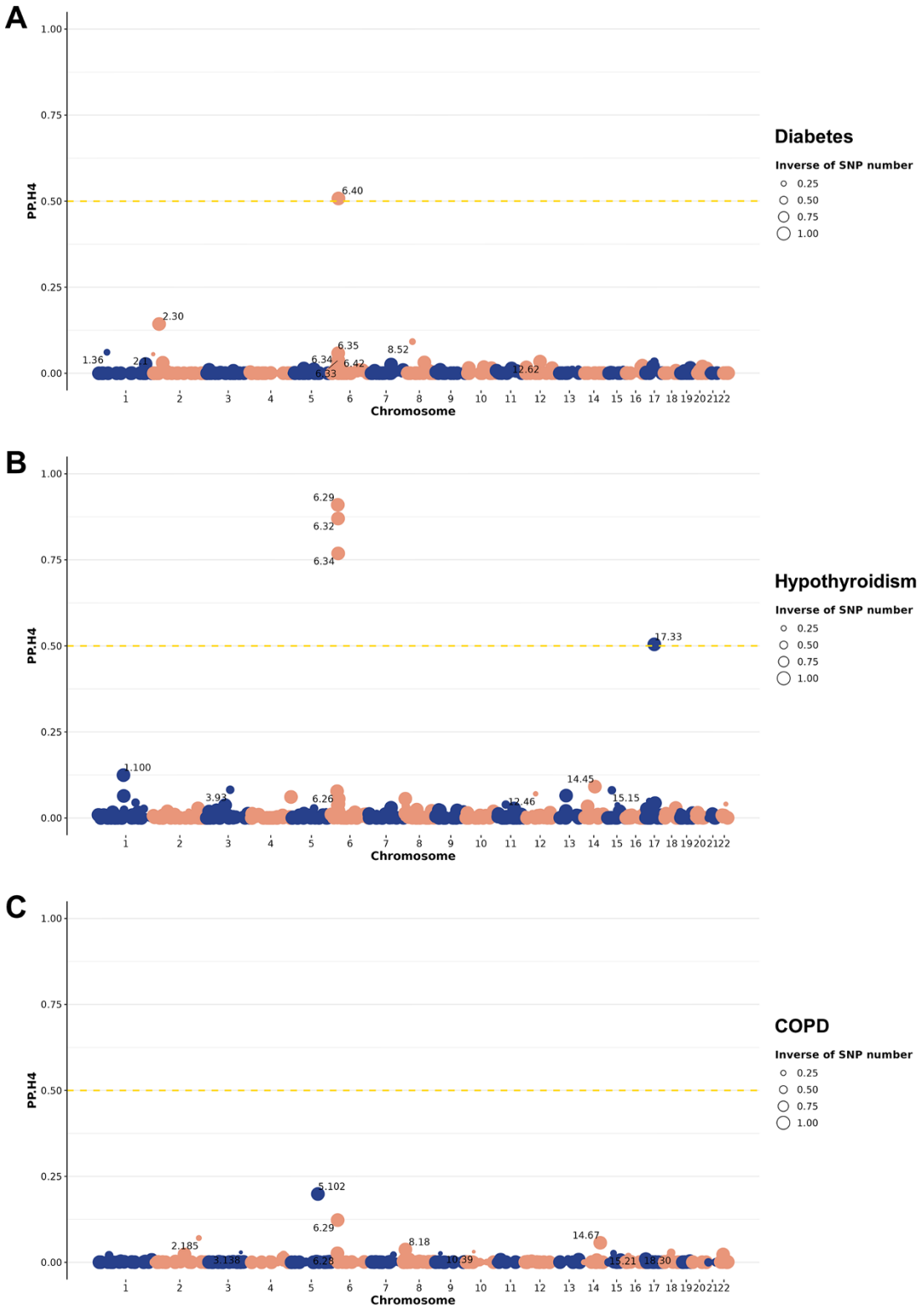


Figure 2. Colocalization analysis of genetic loci associated with adolescent depression and three chronic diseases.
Notes: Posterior probability (PPH4) plots for colocalization between genetic variants associated with adolescent depression and those associated with (A) diabetes, (B) hypothyroidism and (C) chronic obstructive pulmonary disease (COPD). Each point represents a genomic region, mapped by chromosome on the x-axis and posterior probability of a shared causal variant (PPH4) on the y-axis. Circle size reflects the inverse number of SNPs in the region. The horizontal dashed yellow line indicates the PPH4 = 0.5 threshold.

function (Campo-Arias *et al.*, 2024; Dutta *et al.*, 2024). Thus, adolescent depression may initiate a trajectory of early physiological vulnerability that amplifies long-term pulmonary risk.

The sex- and age-specific correlations observed in our study, particularly the heightened risks in females and individuals

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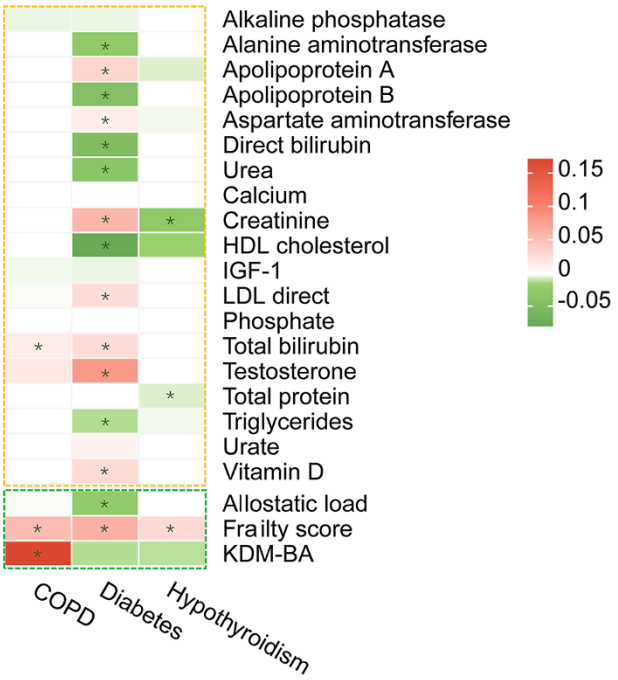


Figure 3. Mediation effects of biomarkers and synthetic indices in the associations between adolescent depression and chronic diseases.
Notes: This heatmap illustrates the mediation effects of 30 circulating biomarkers and 3 synthetic indices (frailty index, KDM biological age acceleration [KDM-BA] and allostatic load) on the associations between adolescent depression and three chronic diseases: COPD, diabetes and hypothyroidism. The colour scale indicates the magnitude and direction of mediation effects, with darker green representing negative mediation and darker red representing positive mediation. Asterisks denote statistically significant mediation effects ($P < 0.05$). Key blood biomarkers are outlined in the yellow dashed box, while composite ageing indicators are grouped in the green dashed box.

under 55 years. Several studies found sex-specific effects in the relationship between adolescent depression and disease risk, particularly for type 2 diabetes (Suglia *et al.*, 2016; Olive *et al.*, 2017). The primary mechanisms underlying these disparities include hormonal regulation (Stumper and Alloy, 2023), metabolic responses (Suglia *et al.*, 2016), behavioural differences and social risk factors (Collishaw, 2015). Additionally, age differences in these associations, along with mediation analyses identifying KDM-BA as a mediator, suggest that adolescent depression may accelerate biological ageing, thereby contributing to the earlier onset of chronic diseases.

The consistent mediation by the frailty index across the three focal disease outcomes highlights its potential value as a pragmatic marker of multisystem vulnerability. Frailty, operationalized as depleted physiological reserves across multiple systems (Fried *et al.*, 2001), may provide a quantifiable metric to assess long-term multisystem risk in individuals with adolescent depression. From a clinical perspective, incorporating brief frailty-informed assessment into routine follow-up for adolescents and young adults with depression, using validated tools such as the FRAIL (Romero-Ortuno *et al.*, 2010) scale or Fried (Fried *et al.*, 2001) phenotype where appropriate, could enhance early identification of high-risk individuals. In parallel, biomarker panels reflecting multisystem physiological dysregulation may further support risk stratification by identifying biological profiles associated with long-term chronic disease vulnerability. Although these approaches require prospective validation before clinical implementation, they provide a practical framework for integrating mental healthcare with long-term chronic disease prevention.

Our study's integration of observational, genetic and mediation analyses provides a robust triangulation of evidence rarely achieved in multimorbidity research. The application of validated tools, such as the Charlson/Elixhauser indices, enhances comparability with global burden studies. From a public health perspective, these findings advocate for integrating depression screening into chronic disease prevention programmes, particularly for women and younger populations. Nevertheless, several limitations warrant consideration. First, although UKB provides a large and deeply phenotyped cohort, its volunteer-based design and predominance of participants of White European ancestry should be considered when interpreting the generalizability of our findings to broader and more diverse populations. Second, adolescent depression was identified using retrospective self-reported age at first depressive episode and depressive symptoms. Although this approach enabled the assessment of early-life depression in a large adult cohort and was strengthened by our multi-step case definition, recall error remains possible. Third, the lack of MR support for four other diseases may stem from residual confounding or insufficient sample sizes, underscoring the need for larger, more diverse cohorts to confirm the broader applicability of these results. Finally, many mediating variables were measured at a single baseline time point, which limits the ability to fully characterize longitudinal biological trajectories. Future studies with repeated biomarker assessments and prospective ascertainment of early-life mental health are warranted.

Conclusion

Adolescent depression was associated with increased long-term vulnerability to multiple chronic diseases, with particularly consistent evidence for hypothyroidism, diabetes and COPD. Genetic and mediation analyses suggested potential involvement of endocrine, metabolic, immune, ageing-related and frailty-related pathways, while stronger associations in females and younger adults point to the need for targeted prevention. These findings support integrating early mental health assessment with long-term physical health monitoring. Frailty-informed assessment and biomarker-based risk profiling may offer a future framework for identifying high-risk individuals, pending validation in prospective and diverse populations.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2045796026100821

Availability of data and materials. The datasets generated during and/or analysed during the current study are available from the corresponding authors upon reasonable request.

Acknowledgements. As the lead author and guarantor of this manuscript, I hereby affirm that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted.

Author contributions. W.W. and B.C.: material preparation, data collection and analysis; W.W.: first draft of the manuscript; X.Q., D.H., S.C., X.Y. and J.F.: figures and tables; C.P., J.H., Y.G., B.Z., Y.W., H.L., L.L. and Y.J.: literature searches; F.Z.: study design. W. Wei and B. Cheng contributed equally to this article.

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Ethical standards. The UK Biobank has received ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference: 21/NW/0157). The initial approval was granted in 2011 and subsequently renewed in 2016 and 2021, with the next renewal due in 2026. All participants provided written informed consent. Access to the UK Biobank data was obtained under approved application number 46478.

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