Archival Report

Biological Psychiatry

Atypical Depression Is Associated With a Distinct Clinical, Neurobiological, Treatment Response, and Polygenic Risk Profile

Mirim Shin, Jacob J. Crouse, Tian Lin, Enda M. Byrne, Brittany L. Mitchell, Penelope A. Lind, Richard Parker, Sarah Mckenna, Emiliana Tonini, Joanne S. Carpenter, Kathleen R. Merikangas, Naomi R. Wray, Sarah E. Medland, Nicholas G. Martin, and Ian B. Hickie

ABSTRACT

BACKGROUND: Atypical depression is considered a distinct clinical subtype of major depression, yet its predictive validity and clinical utility remain contested. We investigated associations between atypical depression and clinical characteristics, genetic profiles, and antidepressant responses.

METHODS: Among 14,897 participants from the Australian Genetics of Depression Study (75% female; mean age 43.7 years), 3098 (21%) were classified phenotypically as having atypical depression based on self-reported weight gain and hypersomnia during their worst depressive episode. Demographic variables and clinical features were compared. Bonferroni-corrected regression models were used to evaluate associations between atypical depression and polygenic scores (PGSs) for mental disorders, metabolic-inflammatory-circadian traits, and self-reported antidepressant response and side effects.

RESULTS: Atypical depression cases had an earlier age of onset, greater illness severity, stronger eveningness, and reduced daylight exposure. Atypical depression cases had higher PGSs for major depression (odds ratio [OR] = 1.10 [95% CI, 1.06–1.15]), attention-deficit/hyperactivity disorder (OR = 1.08 [1.04–1.13]), bipolar disorder (OR = 1.07 [1.02–1.12]), neuroticism (OR = 1.07 [1.02–1.12]), body mass index (OR = 1.35 [1.29–1.42]), type 2 diabetes (OR = 1.22 [1.16–1.28]), C-reactive protein (OR = 1.12 [1.07–1.17]), and insulin resistance (OR = 1.11 [1.06–1.16]) but lower PGSs for high-density lipoprotein cholesterol (OR = 0.91 [0.87–0.95]) and chronotype (indicating eveningness) (OR = 0.94 [0.90–0.98]). Atypical depression was associated with poorer self-reported effectiveness of selective serotonin reuptake inhibitors (OR = 0.88 [0.81–0.96]) and serotonin-norepinephrine reuptake inhibitors (OR = 0.85 [0.77–0.94]), as well as more side effects, particularly weight gain (OR = 2.89 [2.66–3.15]).

CONCLUSIONS: This large, genetically informative study supports the neurobiological and clinical validity of atypical depression, demonstrating distinct clinical and genetic risk profiles alongside differential antidepressant responses. These findings support the use of the atypical subtype to guide treatment selection and physical health management.

https://doi.org/10.1016/j.biopsych.2026.01.003

The concept of atypical depression has evolved over 60 years (1), initially describing patients preferentially responsive to monoamine oxidase inhibitors (MAOIs) while being relatively unresponsive to tricyclic antidepressants (TCAs) or electroconvulsive therapy (1). DSM-5-TR classifies atypical depression by mood reactivity plus at least two of the following features: increased appetite/weight gain, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity (2). Debate persists regarding the relevance and reliable assessment of mood reactivity (3,4) and rejection sensitivity (4–6). Importantly, the core feature of mood reactivity is poorly differentiated from and lacks consistent associations with other atypical features (6–8) and treatment response (4,9). In contrast, the reversed neurovegetative symptoms (i.e., hypersomnia and increased appetite/weight gain) have emerged empirically as more robust markers, showing stronger biological correlates and greater clinical significance (10,11). These features are particularly prominent in severe, recurrent depression (12,13) and are widely used in epidemiologic studies (14–16).

An important measure of the utility of the atypical subtype is whether it can inform treatment selection. Currently, the evidence for the superiority of MAOIs over other antidepressants in atypical depression is mixed. Some studies have shown comparable efficacy between selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, sertraline) and MAOIs (e.g., phenelzine, moclobemide) (17,18), whereas others have

ISSN: 0006-3223

reported poorer response to SSRIs (19,20). Meta-analyses have reported MAOI superiority over TCAs with a medium effect size, but whether there is an MAOI advantage over SSRIs in atypical depression remains unclear (21,22).

Atypical depression is clinically associated with higher female prevalence, earlier onset, greater illness severity, higher recurrence, and more significant impairment (5,15,23–26). Biologically, it is associated with decreased hypothalamic-pituitary-adrenal axis activity (4,27,28), elevated immune mediators (29,30), and metabolic dysregulation, leading to higher risks of diabetes and cardiovascular disease (31–36). In youth, these changes often precede weight gain (37) and include increased inflammatory markers such as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α) (38,39). Some studies suggest a neurobiological link with circadian factors; however, this is underexplored (40,41).

Genetic studies reinforce these distinctions, linking atypical depression to higher polygenic scores (PGSs) for metabolic-inflammatory traits, particularly for CRP, body mass index (BMI), leptin, and triglycerides (10,11,36,42). However, broader immune-inflammatory–related PGSs remain underexplored (42). Despite higher comorbid mental disorder rates (12), the association between PGSs for various mental disorders and atypical depression remains mixed (10,36,42,43). While nonatypical depression shows stronger genetic overlap with schizophrenia (10,44), atypical depression is more strongly associated with bipolar disorders (BDs) (14) and attention-deficit/hyperactivity disorder (ADHD) (36), suggesting distinct genetic risk profiles.

To address the ongoing debate about atypical depression's neurobiological and clinical validity, this study leveraged one of the world's largest genetically informative depressive disorder cohorts (AGDS [Australian Genetics of Depression Study]) (45). Using reversed neurovegetative symptoms (increased weight gain and hypersomnia) as the defining criteria, we hypothesized that compared with adults with other depressive disorders, adults with atypical depression would show 1) different demographic and clinical characteristics (e.g., higher female proportion, more severe illness with comorbidity, earlier onset, delayed sleep-wake schedules, evening chronotype); 2) higher PGSs for some mental health traits or disorders (e.g., major depression [MD], ADHD, BD, and neuroticism), but not all (e.g., schizophrenia); 3) higher PGSs for metabolic markers (e.g., BMI, fasting insulin, type 2 diabetes [T2D], high-density lipoprotein cholesterol [HDL-C], and insulin resistance [IR] derived 2 ways [from the triglyceride:HDL-C ratio and from glucose-insulin indices such as homeostasis model assessment of insulin resistance (HOMA-IR)], as well as coronary artery disease), and immune-related markers (e.g., CRP, IL-6, and TNF-α); 4) significant associations with sleep/circadian markers (e.g., higher sleep midpoint, lower chronotype); 5) lower self-reported effectiveness of common antidepressants (SSRIs, serotonin-norepinephrine reuptake inhibitors [SNRIs], and TCAs); and 6) higher overall rates of side effects, notably weight gain, across antidepressant classes.

These hypotheses were not preregistered.

METHODS AND MATERIALS

Participants and Study Design

Participants were from the AGDS, a cohort study exploring genetic and psychosocial factors influencing depressive disorder etiology and antidepressant response. A cohort profile is described elsewhere (45). Data from the first freeze (September 2016–September 2018) were analyzed. Ethical approval was granted by the Queensland Institute of Medical Research (QIMR) Berghofer Medical Research Institute Human Research Ethics Committee in Brisbane, Australia, and written informed consent was obtained. This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Participants (N = 20,689, 75% female; mean age 43 $\pm$ 15 years [range: 18–90 years]) with a self-reported diagnosis of or treatment for a depressive disorder were recruited; 76% provided a saliva sample. More than 95% were of genetically inferred European ancestry, and PGSs were created for European ancestry participants only. Participants completed online surveys comprising a core module on depressive symptomatology and medication experiences, as well as additional modules, including chronotype and daylight exposure during workdays and free days (see the Supplement).

Major depressive disorder (MDD) was operationalized using DSM-5 criteria. The AGDS cohort predominantly comprises severe, recurrent depression cases, with only 4% reporting one depressive episode (45). Consistent with other studies that rely on self-report rather than clinically administered instruments (12,13), those reporting both weight gain and hypersomnia during their worst depressive episode were classified as having atypical depression given the stronger and more consistent associations of these features with biological markers compared with other atypical features. The core DSM-5 mood reactivity criterion (criterion A) was not assessed, as this clinical concept requires direct reporting or observation during depressive episodes, which was not feasible given the retrospective, self-report nature of the AGDS design. Increased appetite was not recorded. All other cases were categorized as "other depressive disorders."

Polygenic Scores

DNA samples were collected using saliva kits and genotyped using the Illumina Global Screening Array version 2.0. Pre-imputation quality control used PLINK version 1.9 (46,47). Quality control removed single nucleotide polymorphisms (SNPs) with a minor allele frequency <0.005, SNP call rate $<97.5\%$, and Hardy-Weinberg equilibrium ($p < 1 \times 10^{-6}$) before imputation using the TopMed r2 reference panel (48). Ancestry was inferred using the first 3 principal components (PCs) by projecting PCs on 1000 Genomes data using Genome-wide Complex Trait Analysis (49). Samples within 6 standard deviations (SDs) of each ancestry's PC cluster in 1000 Genomes were assigned as the same ancestry. The latest publicly available genome-wide association study (GWAS) results for mental disorders, metabolic, inflammatory, and circadian traits (see the Supplement) were used as weights in the calculation of PGSs. Where applicable, leave-one-out summary statistics were used for GWASs that

included participants from the AGDS to avoid overestimation. SBayesRC was used to generate allele weights for each PGS (50). Posterior SNP effects for each disorder/trait were used to generate PGSs for each participant using the *PLINK* score function (46). Each PGS was standardized using the scale() function. Effect sizes are interpretable as SD units of the AGDS PGSs. In our previous analysis of this cohort (51), SDs were similar between AGDS cases and the control cohort, but mean PGS values (particularly for MD) were significantly higher in AGDS cases, consistent with the case-control study design.

Antidepressants: Self-Reported Effectiveness and Side Effects

The survey assessed participants' experiences with 10 common antidepressants. Self-reported effectiveness (i.e., how well each antidepressant worked) was rated on an ordinal scale (0 = "not at all well," 1 = "moderately well," 2 = "very well"), excluding "I don't know" responses. Self-reported effectiveness was compared across 3 major classes: SSRIs (sertraline, escitalopram, citalopram, fluoxetine, paroxetine), SNRIs (venlafaxine, desvenlafaxine, duloxetine), and TCAs (amitriptyline, mirtazapine). When effectiveness ratings differed within the same class, the highest effectiveness rating was used. Side effects were assessed as a binary variable (0 = "no," 1 = "yes") across 25 possible symptoms. Participants reported side effects only for antidepressants that they had taken.

Statistical Analysis

Analyses were conducted in RStudio (R version 4.5.0) (52). Demographic and clinical characteristics of participants with atypical versus other depressive disorders were compared using Welch's *t* test for age, analysis of covariance (adjusting for age and sex) for other continuous variables, and Pearson's χ^2 test for categorical variables. For these exploratory comparisons, multiple testing was controlled using the false discovery rate, with adjusted *p* values ($q < .05$) considered significant. Complete case analysis was used without imputation, which may introduce bias. For PGS analyses, logistic regression was used to estimate associations with atypical depression, adjusting for age, sex, and the first 10 genetic PCs (to account for population stratification). Treatment response analyses used logistic regression for side effects (across 10 antidepressants) and ordinal regression for self-reported antidepressant effectiveness, while adjusting for age and sex. Bonferroni correction was applied to hypothesis-driven analyses, requiring stricter control of type I error:

1. Genetic: Logistic regression tested associations between atypical depression and 3 PGS sets: i) mental disorders (Bonferroni-corrected *p*-value threshold: .0071 for 7 PGS), ii) 16 metabolic/inflammatory traits (Bonferroni-corrected *p*-value threshold = .0031), and iii) 5 sleep/circadian traits (Bonferroni-corrected *p*-value threshold = .01).
2. Self-reported antidepressant effectiveness: Ordinal regression was used to assess atypical depression's effect on reported effectiveness of 3 classes of medications (SSRIs, SNRIs, TCAs; Bonferroni *p*-value threshold = .0167 [.05/3]).
3. Side effects: Logistic regression was used to examine associations with 25 side effects (Bonferroni *p*-value threshold: .002 [.05/25]).

In addition, we conducted 5 sensitivity analyses: 1) restricting to participants meeting DSM-5 MDD criteria, 2) sex-stratified analyses, 3) adding BMI as a covariate, 4) adding the number of lifetime stressful life events as a covariate, and 5) 3-group comparisons (atypical depression meeting both hypersomnia and weight gain vs. participants with one feature vs. neither feature).

RESULTS

Demographic and Clinical Characteristics

Of 14,897 participants (75% female; mean ± SD = 43.7 ± 15.3 years) with available genetic data passing quality control who answered questions about weight and sleep changes during their worst depressive episode, 21% ($n = 3098$) met our case definition for atypical depression.

Compared with cases with "other depressive disorders," atypical depression cases were younger (42.9 ± 14.4 years vs. 43.9 ± 15.6 years, $q = .002$), had higher BMI (31.8 ± 6.7 vs. 27.2 ± 6.2, $q < .001$; noting 31% missingness), and were more often female (79% vs. 73%, $q < .001$) (Table 1). Among all participants, 88% met DSM-5 criteria for a lifetime major depressive episode (MDE). Clinically, atypical depression cases had an earlier onset (age 21.7 ± 10.7 years vs. 22.3 ± 11.5 years, $q = .003$) and higher MDE (99.6% vs. 84.8%) and generalized anxiety disorder (53% vs. 48%) rates and reported more lifetime depressive episodes, and greater severity across questionnaires for hypo/mania, psychosis, suicidality, psychological distress, eveningness preference, seasonality, and less time spent outdoors on workdays and free days (all qs < .001). Atypical cases had significantly higher rates of severe substance use disorder (particularly nicotine and drug use) and increased prevalence of diabetes (8% vs. 5%) and high blood pressure (18% vs. 14%) (all qs < .001).

Polygenic Risk and Atypical Depression

Atypical depression was significantly associated with higher MD-PGSs (odds ratio [OR], 1.10; 95% CI, 1.06–1.15; $p = 1.37 \times 10^{-5}$), ADHD-PGSs (OR, 1.08; 95% CI, 1.04–1.13; $p = .0005$), BD-PGSs (OR, 1.07; 95% CI, 1.02–1.12; $p = .0031$), and neuroticism-PGSs (OR, 1.07; 95% CI, 1.02–1.12; $p = .0045$) (Figure 1A and Table S1). As hypothesized, the schizophrenia-PGS was not significantly associated with atypical depression (OR = 0.98; 95% CI, 0.93–1.03; $p = .37$), supporting a distinct genetic architecture from nonatypical depression. Atypical depression was also associated with higher PGSs for BMI (OR, 1.35; 95% CI, 1.29–1.42; $p = 2.49 \times 10^{-37}$), T2D (OR, 1.22; 95% CI, 1.16–1.28; $p = 8.38 \times 10^{-15}$), CRP (OR, 1.12; 95% CI, 1.07–1.17; $p = 5.51 \times 10^{-7}$), and IR (OR, 1.11; 95% CI, 1.06–1.16; $p = 3.29 \times 10^{-6}$), and lower PGSs for HDL-C (OR, 0.91; 95% CI, 0.87–0.95; $p = 3.60 \times 10^{-5}$) (Figure 1B and Table S5). Atypical depression was significantly associated with lower chronotype-PGSs (indicating a genetic predisposition toward eveningness) (OR, 0.94; 95% CI, 0.90–0.98; $p = .0055$) (Figure 1C and Table S9). Although the insomnia-PGS

Table 1. Demographic and Clinical Characteristics of the Included Sample (*N* = 14,897)

Characteristic	Total Sample, *N* = 14,897	Nonatypical, *n* = 11,799	Atypical, *n* = 3098	*p* Value	*q* Value
Age, Years	43.70 ± 15.32; 43.0 [30.0–56.0]	43.90 ± 15.55; 43.0 [30.0–57.0]	42.93 ± 14.41; 42.0 [31.0–55.0]	.001	.002
Sex					
Female	11,088 (74.4%)	8655 (73.4%)	2433 (78.5%)	<.001	<.001
Male	3809 (25.5%)	3144 (26.6%)	665 (21.5%)		
Information not provided	14 (0.1%)	10 (0.1%)	4 (0.1%)		
BMI	28.15 ± 6.53; 26.9 [23.3–31.7]	27.19 ± 6.15; 26.0 [22.7–30.4]	31.75 ± 6.67; 30.8 [26.8–35.8]	<.001	<.001
Information not provided	4684 (31.4%)	3739 (31.7%)	945 (30.5%)		
Marital Status					
Married or de facto relationship	7976 (53.5%)	6457 (54.7%)	1519 (49.0%)	<.001	<.001
Never married	4389 (29.5%)	3414 (28.9%)	975 (31.5%)		
Separated or divorced	2245 (15.1%)	1698 (14.4%)	547 (17.7%)		
Widowed	255 (1.7%)	208 (1.8%)	47 (1.5%)		
Information not provided	32 (0.2%)	22 (0.2%)	10 (0.3%)		
Education					
Postgraduate	4123 (27.7%)	3306 (28.0%)	817 (26.4%)	.013	.017
Degree	5198 (34.9%)	4144 (35.1%)	1054 (34.0%)		
Certificate or diploma	3509 (23.6%)	2713 (23.0%)	796 (25.7%)		
Senior high school	1181 (7.9%)	917 (7.8%)	264 (8.5%)		
Junior high school or less	854 (5.7%)	692 (5.9%)	162 (5.2%)		
No formal education	7 (0.0%)	6 (0.1%)	1 (0.0%)		
Information not provided	25 (0.2%)	21 (0.2%)	4 (0.1%)		
Meeting MDD Criteria					
No	1804 (12.1%)	1791 (15.2%)	13 (0.4%)	<.001	<.001
Yes	13,093 (87.9%)	10,008 (84.8%)	3085 (99.6%)		
Depressive Episodes					
1–2 episodes	1602 (10.8%)	1345 (11.4%)	257 (8.3%)	<.001	<.001
3–4 episodes	5951 (39.9%)	4384 (37.2%)	1567 (50.6%)		
5–6 episodes	3013 (20.2%)	2426 (20.6%)	587 (18.9%)		
7–9 episodes	2155 (14.5%)	1664 (14.1%)	491 (15.8%)		
10+ episodes	762 (5.1%)	577 (4.9%)	185 (6.0%)		
Information not provided	1414 (9.5%)	1403 (11.9%)	11 (0.4%)		
Age of Onset, Years	22.12 ± 11.30; 18.0 [15.0–27.0]	22.26 ± 11.46; 18.0 [15.0–27.0]	21.66 ± 10.74; 18.0 [15.0–26.0]	.002	.003
Mania, ASRM	2.49 ± 2.00; 3.0 [0.0–5.0]	2.43 ± 1.99; 2.0 [0.0–4.0]	2.73 ± 2.00; 3.0 [0.0–5.0]	<.001	<.001
Psychosis, CAPE	0.90 ± 1.36; 0.0 [0.0–1.0]	0.87 ± 1.33; 0.0 [0.0–1.0]	1.03 ± 1.45; 0.0 [0.0–2.0]	<.001	<.001
Suicidality, SIDAS	8.34 ± 9.81; 6.0 [0.0–13.0]	8.06 ± 9.70; 3.0 [0.0–13.0]	9.38 ± 10.16; 10.0 [0.0–15.0]	<.001	<.001
GAD					
No	7543 (50.6%)	6082 (51.5%)	1461 (47.2%)	<.001	<.001
Yes	7321 (49.1%)	5687 (48.2%)	1634 (52.7%)		
Information not provided	33 (0.2%)	30 (0.3%)	3 (0.1%)		
K10	22.97 ± 9.06; 22.0 [15.0–29.0]	22.50 ± 9.03; 21.0 [15.0–29.0]	24.79 ± 8.97; 24.0 [17.0–31.0]	<.001	<.001
Information not provided	2096 (14.1%)	1630 (13.8%)	466 (15.0%)		
Family History[a]	10,381 (69.7%)	8180 (69.3%)	2201 (71.0%)	.067	.079
Lifetime Stressful Life Events	2.10 ± 2.34; 1.0 [0.0–3.0]	2.07 ± 2.32; 1.0 [0.0–3.0]	2.24 ± 2.42; 2.0 [0.0–4.0]	<.001	<.001
Alcohol Use Disorder					
Mild	2328 (15.6%)	1869 (15.8%)	459 (14.8%)	.062	.077
Moderate	1724 (11.6%)	1355 (11.5%)	369 (11.9%)		
Severe	3601 (24.2%)	2802 (23.7%)	799 (25.8%)		
Nicotine Use Disorder					
Mild	1453 (9.8%)	1165 (9.9%)	288 (9.3%)	<.001	<.001
Moderate	1482 (9.9%)	1190 (10.1%)	292 (9.4%)		
Severe	1741 (11.7%)	1300 (11.0%)	441 (14.2%)		

Table 1. Continued

Characteristic	Total Sample, N = 14,897	Nonatypical, n = 11,799	Atypical, n = 3098	p Value	q Value
Cannabis Use Disorder					
Mild	1033 (6.9%)	809 (6.9%)	224 (7.2%)	.346	.390
Moderate	538 (3.6%)	420 (3.6%)	118 (3.8%)		
Severe	1128 (7.6%)	875 (7.4%)	253 (8.2%)		
Drug Use Disorder					
Mild	1149 (7.7%)	897 (7.6%)	252 (8.1%)	.001	.002
Moderate	642 (4.3%)	525 (4.4%)	117 (3.8%)		
Severe	1268 (8.5%)	955 (8.1%)	313 (10.1%)		
Medical Conditions					
Diabetes or high blood sugar	842 (5.7%)	594 (5.0%)	248 (8.0%)	<.001	<.001
Heart attack	136 (0.9%)	105 (0.9%)	31 (1.0%)	.638	.663
Heart disease	275 (1.8%)	220 (1.9%)	55 (1.8%)	.800	.800
High blood pressure	2261 (15.2%)	1697 (14.4%)	564 (18.2%)	<.001	<.001
Stroke	107 (0.7%)	82 (0.7%)	25 (0.8%)	.591	.635
Chronic fatigue syndrome	888 (6.0%)	681 (5.8%)	207 (6.7%)	.063	.074
Chronotype, rMEQ	14.60 ± 4.16; 15.0 [12.0–18.0]	14.80 ± 4.16; 15.0 [12.0–18.0]	13.83 ± 4.08; 14.0 [11.0–17.0]	<.001	<.001
Morning	2729 (18.3%)	2313 (19.6%)	416 (13.4%)	<.001	<.001
Neither	5065 (34.0%)	4023 (34.1%)	1042 (33.6%)		
Evening	2540 (17.1%)	1901 (16.1%)	639 (20.6%)		
Information not provided	4563 (30.6%)	3562 (30.2%)	1001 (32.3%)		
Global Seasonality Score	6.59 ± 4.69; 6.0 [3.0–9.0]	6.39 ± 4.57; 6.0 [3.0–9.0]	7.37 ± 5.06; 7.0 [4.0–10.0]	<.001	<.001
≥ Moderate seasonality	2190 (14.7%)	1613 (13.7%)	577 (18.6%)	<.001	<.001
Information not provided	3692 (24.8%)	2912 (24.7%)	780 (25.2%)		
Daylight Exposure Workdays, h	1.79 ± 1.85; 1.0 [0.5–2.0]	1.84 ± 1.89; 1.0 [0.7–2.0]	1.61 ± 1.69; 1.0 [0.5–2.0]	<.001	<.001
Information not provided	4471 (30.0%)	3520 (29.8%)	951 (30.7%)		
Daylight Exposure Free Days, h	3.04 ± 2.15; 3.0 [1.0–4.0]	3.16 ± 2.18; 3.0 [2.0–4.0]	2.57 ± 1.97; 2.0 [1.0–4.0]	<.001	<.001
Information not provided	3761 (25.2%)	2972 (25.2%)	789 (25.5%)		

Data are presented as mean ± SD and median [interquartile range] or n (%). Analysis of covariance adjusting for age and sex was used for continuous variables; Pearson's χ^2 test was for categorical variables. p Values are unadjusted, and q values represent false discovery rate correction for multiple testing.

ASRM, Altman Self-Rating Mania Scale; BMI, body mass index; CAPE, Community Assessment of Psychic Experience; GAD, generalized anxiety disorder; MDD, major depressive disorder; rMEQ, reduced Morningness-Eveningness Questionnaire; SIDAS, Suicidal Ideation Attributes Scale.

[a]Family history indicates those with their first-degree relative(s) with any mental health disorder.

had a nominally significant association with atypical depression (OR = 1.05; 95% CI, 1.00–1.09; p = .048), it did not survive Bonferroni correction. The sleep midpoint PGS and other sleep-/circadian-related PGSs were not significantly associated with atypical depression (Figure 1C and Table S9).

Treatment Outcomes and Atypical Depression

Atypical depression was associated with poorer self-rated effectiveness of SSRIs (OR, 0.88; 95% CI, 0.81–0.96; p = .003) and SNRIs (OR, 0.85; 95% CI, 0.77–0.94; p = .002) (Figure 2 and Table S13). No significant associations were found for TCA effectiveness (OR, 0.93; 95% CI, 0.80–1.08). Individual antidepressant medication associations are detailed in the Supplement (Table S17).

Of the 25 queried side effects, 12 were significantly associated with atypical depression (Figure 3 and Table S21). The strongest were an increased likelihood of weight gain (OR, 2.89; 95% CI, 2.66–3.15; $p = 1.07 \times 10^{-133}$) and a decreased likelihood of weight loss (OR, 0.37; 95% CI, 0.28–0.48; $p = 5.09 \times 10^{-13}$); both were expected given the definition of atypical depression. Other significant side effects included drowsiness (OR = 1.47), muscle pain (OR = 1.41), fatigue (OR = 1.39), reduced sexual desire/function (OR = 1.38), dry mouth (OR = 1.36), suicidal attempts (OR = 1.31) and thoughts (OR = 1.30), blurred vision (OR = 1.28), headache (OR = 1.27), and sweating (OR = 1.27). No significant association was found for reporting "no side effects."

Sensitivity Analyses

To assess the robustness of these findings, we conducted 5 sensitivity analyses focusing on 1) participants meeting DSM-5 MDD criteria (88%), 2) sex-stratified analysis, 3) adding BMI as an additional covariate, 4) adding number of stressful life events as a covariate, and 5) 3-group comparisons. In MDD-confirmed cases only, similar patterns were observed, with slightly attenuated effect sizes compared with the main analysis. In sex-stratified analyses, females showed more significant associations than males (e.g., higher PGSs for MD, ADHD, and BD in females vs. only MD in males), likely due to the higher proportion of females in this sample (74%). The chronotype association was no longer Bonferroni significant in the sex-stratified analysis. When stressful life events were added as a covariate, all genetic and treatment response associations remained significant, demonstrating independence

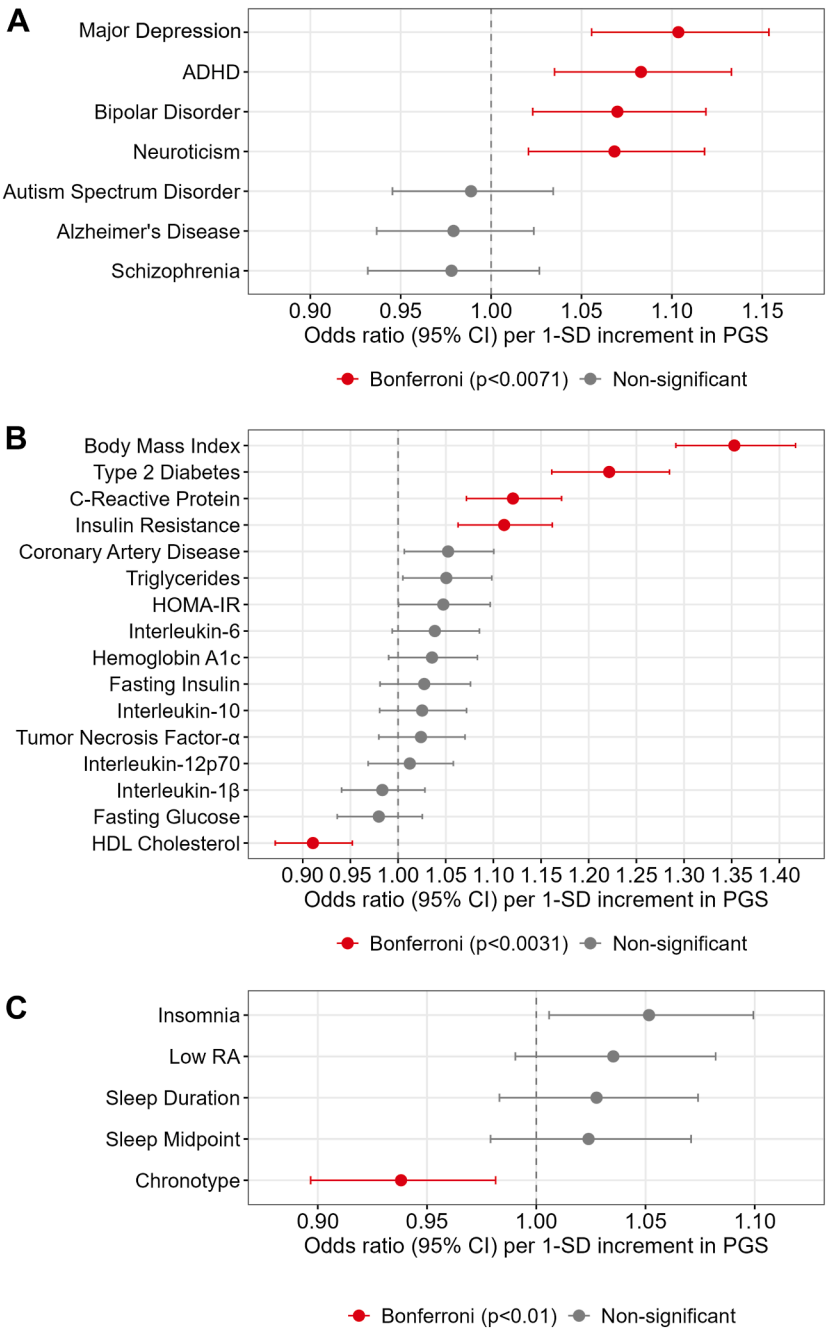

Figure 1. Associations between atypical depression caseness and polygenic scores (PGSs) for **(A)** mental disorders, **(B)** physical health (metabolic and inflammatory-related markers), and **(C)** sleep and circadian-related traits (n = 2495 with atypical depression; n = 9506 with other depressive disorders). Results shown are the association of each PGS with atypical depressive subtypes from separate regression models with covariates of age, sex, and the first 10 genetically inferred ancestry principal components (PCs) in logistic regression. Bars indicate 95% CI. Color coding represents significance levels: red indicates Bonferroni-corrected, and gray indicates nonsignificant. ADHD, attention-deficit/hyperactivity disorder; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance (derived from glucose and insulin); RA, relative amplitude.

from stress exposure. The 3-group comparison revealed a dose-response relationship: compared with the no-criteria reference group, the atypical group (both criteria) showed the strongest associations, and the partial group (one criterion) demonstrated intermediate effect sizes across most outcomes, supporting the validity of the atypical specifier criteria. The details are discussed in the Supplement.

When BMI was added as a covariate, no mental health or metabolic/inflammatory PGS remained significant after Bonferroni correction, although significant associations from the main analysis retained their direction (Figure 4; Tables S4 and S8). Notably, the BMI-PGS was no longer significant (OR, 1.02; 95% CI, 0.96–1.09) when controlling for BMI itself. However, the chronotype-PGS remained significant (OR, 0.92; 95% CI, 0.87–0.97; p = .004). For treatment response, associations for both SSRI (OR, 0.82; 95% CI, 0.74–0.91; p = .0001) and SNRI (OR, 0.79; 95% CI, 0.70–0.89; p = .0002) were stronger compared with the main analysis, whereas TCA

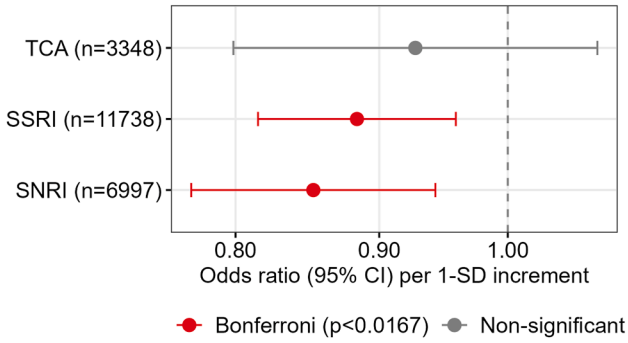

Figure 2. Associations of atypical depression and self-reported effectiveness of antidepressants. Results shown are the association of each antidepressant's self-reported effectiveness with atypical depressive subtypes from separate regression models with covariates of age and sex in ordinal logistic regression. Bars indicate 95% CI. Color coding represents significance levels: red indicates Bonferroni corrected, and gray indicated nonsignificant. SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

did not survive Bonferroni correction (p = .037). The number of significant side effects was reduced from 12 to 8: weight gain, drowsiness, reduced sexual function, dry mouth, fatigue, suicidal thoughts, and decreased weight loss remained significant, while constipation became newly significant (Table S24 and Figure S5).

DISCUSSION

Using a large, genetically informative cohort of individuals with predominantly severe or recurrent depression (36,42), we identified 3 distinct factors supporting atypical depression's neurobiological or clinical validity: 1) clinical characteristics, including earlier onset, greater severity, higher BMI, increased comorbidity, and pronounced evening preference with less daylight exposure; 2) elevated PGSs for some, but not all, independent mental disorders (higher PGSs for MD, ADHD, BD, and neuroticism, but not increased for autism, Alzheimer's disease, and schizophrenia), metabolic-inflammatory traits (higher PGSs for BMI, T2D, CRP, and IR, but lower PGS for HDL-C), and circadian traits (lower PGSs for chronotype); and 3) lower self-reported effectiveness and more side effects from common SSRIs and SNRIs. Given the centrality of weight gain to the case definition of atypical depression, sensitivity analysis controlling for BMI revealed that mental health and metabolic-inflammatory PGS associations disappeared, whereas chronotype-PGS and treatment response differences persisted, suggesting both BMI-mediated and BMI-independent pathways.

Our case definition prioritized reversed neurovegetative symptoms (hypersomnia and weight gain) due to their stronger and more consistent biological associations than other atypical features (10,11). In severe, recurrent depression (characteristic of this sample), neurovegetative symptoms

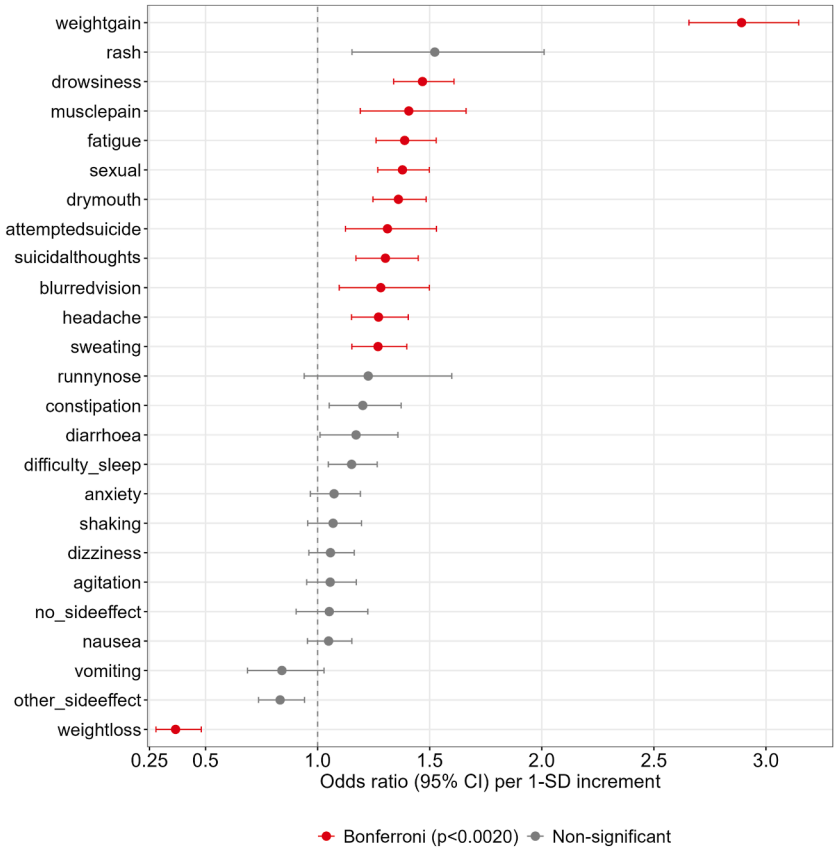

Figure 3. Association between atypical depression and side effects of 10 antidepressant medications (n = 2901 with atypical depression; n = 10,584 with other depressive disorders). Results shown are the association of each antidepressant's self-reported effectiveness with atypical depressive subtypes from separate regression models with covariates of age and sex in logistic regression. Bars indicate 95% CI. Color coding represents significance levels: Red indicates Bonferroni corrected, gray indicates nonsignificant.

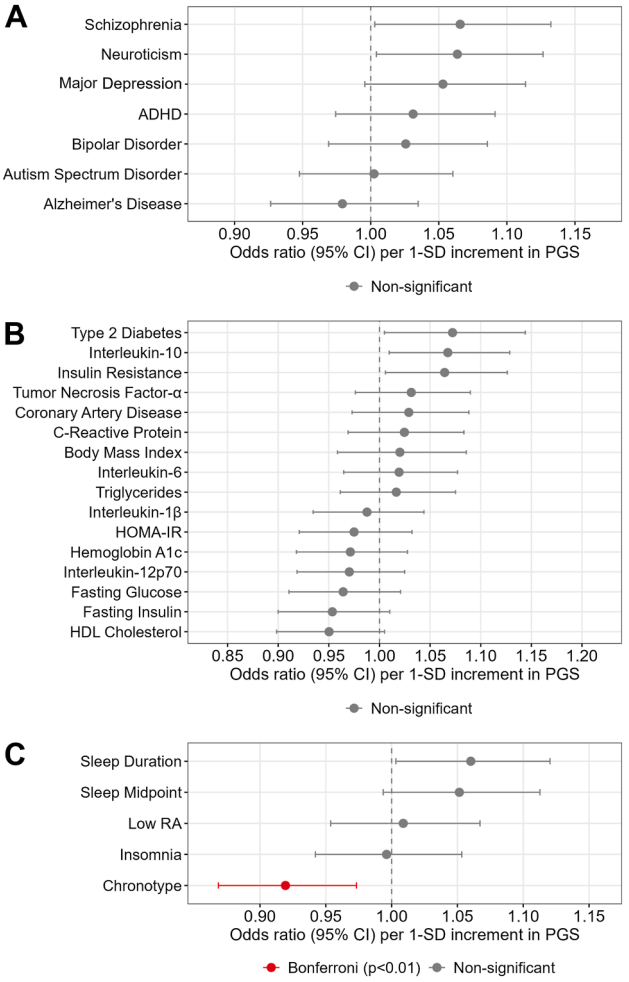

Figure 4. Sensitivity analysis with body mass index (BMI) controlled: associations between atypical depression caseness and polygenic scores (PGSs) for **(A)** mental disorders, **(B)** physical health (metabolic and inflammatory-related markers), and **(C)** sleep and circadian-related traits (n = 1740 with atypical depression; n = 6511 with other depressive disorders). Results shown are the association of each PGS with atypical depressive subtypes from separate regression models with covariates of age, sex, the first 10 genetically inferred ancestry principal components (PCs), and BMI in logistic regression. Bars indicate 95% CI. Color coding represents significance levels: Red indicates Bonferroni corrected, and gray indicates nonsignificant. ADHD, attention-deficit/hyperactivity disorder; HOMA-IR, homeostasis model assessment of insulin resistance (derived from glucose and insulin); RA, relative amplitude.

tend to be more stable across episodes (12,13). Consistent with previous research, atypical depression cases were more likely to be female, with earlier onset, more depressive episodes, higher suicidality, and greater comorbidity with anxiety, psychotic, and manic features (12,15,25,53,54). We also found more severe nicotine and drug use disorders in atypical depression, extending prior findings of high smoking rates across mental disorders to show subtype-specific substance use vulnerabilities (55). Notably, we identified stronger evening preference, greater seasonality, and significantly less time in daylight, suggesting circadian disruption as a potential biological marker.

Previous AGDS reports demonstrated differential genetic associations across depressive subtypes (43). We build on this using a larger sample, analyzing metabolic, inflammatory, and circadian PGSs, assessing treatment response differences, using updated PGS scoring methods with better-powered GWASs, and examining sex-stratified and BMI-adjusted associations. Four mental health PGSs (ADHD, MD, BD, and neuroticism) showed significant associations with atypical depression. These findings are consistent with clinical evidence showing higher atypical feature rates in BD type II or bipolar spectrum disorder (56,57). The MD-PGS association may reflect atypical depression's greater severity and functional impairment (12,13), while the ADHD- and neurotism-PGSs imply neurodevelopmental and emotional regulation pathways, consistent with heightened emotional reactivity and impulsivity (1,56,58–60). A previous AGDS study also reported an MD-PGS association with dimensional somatic symptoms related to atypical features (51). Genetic associations with metabolic-inflammatory traits further validate the biologic basis of atypical depression (10,11,29,38,42,61,62). Notably, the association was observed with the IR-PGS (derived from triglyceride:HDL-C ratio), but not for the HOMA-IR-PGS (derived from glucose and insulin), possibly reflecting different insulin resistance aspects or weaker genetic instruments for the HOMA-IR-PGS (63). However, genetic associations with metabolic traits should be interpreted cautiously, given that our atypical depression definition includes weight gain as one of two central features.

In BMI-covariate sensitivity analyses, all metabolic-inflammatory PGS associations became nonsignificant, and most mental health PGS associations were substantially attenuated (BD-PGS, MD-PGS, ADHD-PGS), potentially reflecting either BMI's mediating role or reduced statistical power due to substantial BMI missingness (31%). While our cross-sectional design limits causal inference, previous research provides relevant context. Mendelian randomization evidence suggests that higher BMI causally influences increased appetite (an atypical feature) but not atypical depression as a whole (62). Conversely, prospective data show that atypical depression predicts subsequent weight gain and metabolic dysfunction (64). These suggest complex bidirectional relationships between BMI and atypical depression. Notably, the neuroticism-PGS and the schizophrenia-PGS were nominally associated with atypical depression (both p = .04) in BMI-controlled analyses, although neither survived multiple testing correction. While speculative, this pattern may capture genetic liability to mood reactivity, interpersonal rejection sensitivity, and emotional lability (core non-neurovegetative features of atypical depression that we could not assess in our study).

Notably, the chronotype-PGS remained robust after BMI adjustment, suggesting that circadian-related genetic factors contribute to atypical depression through pathways not fully captured by BMI alone. This finding, combined with observed evening preference and reduced daylight exposure, provides evidence for circadian disruption as a core feature of atypical depression (40,65).

Consistent with our hypothesis, atypical depression was associated with lower self-reported SSRI and SNRI effectiveness and more side effects. Critically, treatment differences were stronger after BMI adjustment, demonstrating that poor response extends beyond weight-related factors. This is consistent with another AGDS study showing that phenotypic eveningness was associated with lower self-reported antidepressant effectiveness and more side effects (66). The side-effect profile in atypical depression remained largely unchanged after BMI adjustment. Research suggests that antidepressant side effects may share common underlying factors (e.g., genetic liability to higher BMI or insomnia) rather than being drug specific (67). The persistence of both chronotype-PGS associations and treatment resistance after BMI adjustment suggests that circadian disruption may be a key mechanism underlying treatment resistance in atypical depression (40). This is further supported by research showing that later sleep midpoint and reduced physical activity partially mediated the relationship between atypical depression and elevated BMI and metabolic syndrome (68). These findings suggest that people with atypical depression may benefit from 1) earlier consideration of alternatives to SSRIs/SNRIs and 2) circadian-targeted interventions as adjunctive treatments. The BMI-independent chronotype associations and treatment resistance patterns indicate that circadian-based interventions (i.e., therapies that aim to improve the timing, strength, and stability of circadian rhythms, such as bright light therapy, sleep-wake schedule regularization, chronotherapy, or time-restricted feeding) may be particularly relevant for this population, potentially improving both sleep-wake regulation and antidepressant response (69–71).

To evaluate environmental exposures, we examined whether cases with atypical depression had a higher load of self-reported stressful life events. Although atypical depression cases did report more lifetime stressful life events than nonatypical cases, sensitivity analyses adjusting for stressful life events showed that all PGS associations and treatment response associations remained unchanged (Figures S1–S5). This suggests that the observed genetic associations—specifically involving metabolic-inflammatory-circadian processes—and treatment associations are not clearly confounded by exposure to adversity and do not simply reflect a greater overall genetic burden.

Our study has several limitations. First, our atypical depression definition did not include mood reactivity (DSM's criterion A for atypical depression) and relied on retrospective self-report during worst depressive episodes. While prior research indicates that mood reactivity shows poor differentiation from and weak associations with other atypical features, the definition used in this study may capture a partially overlapping but distinct subgroup, which limits comparability to studies using DSM-defined atypical depression. Second, defining atypical depression using weight gain and hypersomnia may introduce circularity when interpreting genetic associations with BMI, although BMI-adjusted sensitivity analyses help address this concern. The substantial BMI missingness (31%) limits interpretation of covariate analyses. Third, the cross-sectional design limits causal inference about whether the observed genetic associations reflect mediation, confounding, or reverse causation. The retrospective design also prevents evaluation of temporal relationships between antidepressant use and weight gain, although BMI-adjusted analyses attempt to address weight gain regardless of its etiology. Fourth, the AGDS survey about experiences with antidepressants was restricted to the 10 most commonly prescribed antidepressants at the time in Australia and did not query about experiences with other medications with diverse mechanisms (e.g., bupropion, MAOIs). Fifth, binary classification of depression subtypes may oversimplify heterogeneity. Finally, our sample is limited to individuals with genetically inferred European ancestry, which may reduce generalizability.

Conclusions

Altogether, this study provides evidence that atypical depression represents a clinically meaningful subtype predicting differential treatment response patterns and polygenic risk profiles, some of which are independent of BMI status. The robust chronotype-PGS association and persistent treatment resistance after BMI adjustment support the concept that circadian disruption is a key pathway warranting targeted interventions. While genetic associations with mental disorder and metabolic traits largely reflected BMI-related variance, the BMI-independent findings support investigation of circadian-based treatments and alternative pharmacological approaches for this depressive subtype.

ACKNOWLEDGMENTS AND DISCLOSURES

The AGDS was primarily funded by a grant (Grant No. 1086683) from the National Medical Health and Research Council (NHMRC) of Australia. This work was further supported by philanthropic donations from families who are affected by mental illness (who wish to remain anonymous) (to MS); NHMRC EL1 Investigator Grants (Grant Nos. GNT2008196 [to JJC] and GNT2017176 [to BLM]); an NHMRC L1 Investigator Grant (Grant No. APP117291 [to SEM]); and an NHMRC L3 Investigator Grant (Grant No. GNT2016346 [to IBH]). This work was supported by the Wellcome Trust (Grant No. 227089/Z/23/Z [principal investigator, IBH]).

We are indebted to all the AGDS participants for giving their time to contribute to this study. We thank all the people who helped with the conception, implementation, beta testing, media campaign, and data cleaning. The study protocol used by 23andMe, Inc. was approved by an external Association for the Accreditation of Human Research Protection Programs (AAHRPP)-accredited institutional review board. We would like to thank the research participants and employees of 23andMe Research Institute for making this work possible.

IBH is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney, Australia. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. IBH has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca, Janssen-Cilag) projects focused on the identification and better management of anxiety and depression. He is the Chief Scientific Advisor to, and a 3.2% equity shareholder in, InnoWell Pty Ltd., which aims to transform mental health services through the use of innovative technologies. All other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Brain and Mind Centre, The University of Sydney, Sydney, Australia (MS, JJC, SM, ET, JSC, IBH); Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, Australia (TL, NRW); Child Health Research Centre, The University of Queensland, Brisbane, Queensland, Australia (EMB); Brain and Mental Health Program, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia

(BLM, PAL, RP, SEM, NGM); School of Biomedical Sciences, Queensland University of Technology, Brisbane, Queensland, Australia (PAL); Faculty of Medicine, School of Biomedical Sciences, University of Queensland, Brisbane, Queensland, Australia (PAL); Genetic Epidemiology Research Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, Maryland (KRM); Department of Psychiatry, University of Oxford, Oxford, United Kingdom (NRW); and Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, United Kingdom (NRW).

JJC and IBH contributed equally to this work.

Address correspondence to Mirim Shin, Ph.D., at mirim.shin@sydney.edu.au.

Received Aug 8, 2025; revised Dec 6, 2025; accepted Jan 5, 2026.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2026.01.003.

REFERENCES

1. West ED, Dally PJ (1959): Effects of iproniazid in depressive syndromes. Br Med J 1:1491–1494.
2. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington, DC: American psychiatric association.
3. Thase ME (2007): Recognition and diagnosis of atypical depression. J Clin Psychiatry 68(suppl 8):11–16.
4. Thase ME (2009): Atypical Depression: Useful Concept, but it's Time to Revise the DSM-IV Criteria. Neuropsychopharmacology 34:2633–2641.
5. Stewart JW, McGrath PJ, Rabkin JG, Quitkin FM (1993): Atypical Depression: A Valid Clinical Entity? Psychiatr Clin North Am 16:479–495.
6. Parker G, Roy K, Mitchell P, Wilhelm K, Malhi G, Hadzi-Pavlovic D (2002): Atypical depression: A reappraisal. Am J Psychiatry 159:1470–1479.
7. Posternak MA, Zimmerman M (2002): Partial validation of the atypical features subtype of major depressive disorder. Arch Gen Psychiatry 59:70–76.
8. Parker G, Parker K, Mitchell P, Wilhelm K (2005): Atypical depression: Australian and US studies in accord—Special commentary. Curr Opin Psychiatry 18:1–5.
9. Quitkin F, McGrath P, Stewart J, Harrison W, Wager S, Nunes E, *et al.* (1990): Phenelzine and imipramine in mood reactive depressives. Further delineation of the syndrome of atypical depression. J Clin Psychopharmacol 10:138.
10. Milaneschi Y, Lamers F, Peyrot WJ, Abdellaoui A, Willemsen G, Hottenga JJ, *et al.* (2016): Polygenic dissection of major depression clinical heterogeneity. Mol Psychiatry 21:516–522.
11. Milaneschi Y, Lamers F, Peyrot WJ, Baune BT, Breen G, Dehghan A, *et al.* (2017): Genetic association of major depression with atypical features and obesity-related immunometabolic dysregulations. JAMA Psychiatry 74:1214–1225.
12. Brailean A, Curtis J, Davis K, Dregan A, Hotopf M (2020): Characteristics, comorbidities, and correlates of atypical depression: Evidence from the UK Biobank Mental Health Survey. Psychol Med 50:1129–1138.
13. Vreijling SR, van Haeringen M, Milaneschi Y, Huider F, Bot M, Amin N, *et al.* (2023): Sociodemographic, lifestyle and clinical characteristics of energy-related depression symptoms: A pooled analysis of 13,965 depressed cases in 8 Dutch cohorts. J Affect Disord 323:1–9.
14. Benazzi F (2002): Can only reversed vegetative symptoms define atypical depression? Eur Arch Psychiatry Clin Neurosci 252:288–293.
15. Matza LS, Revicki DA, Davidson JR, Stewart JW (2003): Depression with atypical features in the National comorbidity survey: Classification, description, and consequences. Arch Gen Psychiatry 60:817–826.
16. Lee S, Ng KL, Tsang A (2009): Prevalence and correlates of depression with atypical symptoms in Hong Kong. Aust N Z J Psychiatry 43:1147–1154.
17. Pande AC, Birkett M, Fechner-Bates S, Haskett RF, Greden JF (1996): Fluoxetine versus phenelzine in atypical depression. Biol Psychiatry 40:1017–1020.
18. SÖgaard J, Lane R, Latimer P, Behnke K, Christiansen PE, Nielsen B, *et al.* (1999): A 12-week study comparing moclobemide and sertraline in the treatment of outpatients with atypical depression. J Psychopharmacol 13:406–414.
19. Lonnqvist J, Sihvo S, Syvälahti E, Kiviruusu O (1994): Moclobemide and fluoxetine in atypical depression: A double-blind trial. J Affect Disord 32:169–177.
20. McGrath PJ, Stewart JW, Janal MN, Petkova E, Quitkin FM, Klein DF (2000): A placebo-controlled study of fluoxetine versus imipramine in the acute treatment of atypical depression. Am J Psychiatry 157:344–350.
21. Henkel V, Mergl R, Allgaier A-K, Kohnen R, Möller H-J, Hegerl U (2006): Treatment of depression with atypical features: A meta-analytic approach. Psychiatry Res 141:89–101.
22. Suchting R, Tirumalajaru V, Gareeb R, Bockmann T, de Dios C, Aickareth J, *et al.* (2021): Revisiting monoamine oxidase inhibitors for the treatment of depressive disorders: A systematic review and network meta-analysis. J Affect Disord 282:1153–1160.
23. Nierenberg AA, Alpert JE, Pava J, Rosenbaum JF, Fava M (1998): Course and treatment of atypical depression. J Clin Psychiatry 59(suppl 18):5–9.
24. Agosti V, Stewart JW (2001): Atypical and non-atypical subtypes of depression: Comparison of social functioning, symptoms, course of illness, co-morbidity and demographic features. J Affect Disorders 65:75–79.
25. Blanco C, Vesga-López O, Stewart JW, Liu S-M, Grant BF, Hasin DS (2012): Epidemiology of major depression with atypical features: Results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). J Clin Psychiatry 73:224–232.
26. Withers AC, Tarasoff JM, Stewart JW (2013): Is depression with atypical features associated with trauma history? J Clin Psychiatry 74:500–506.
27. Fries E, Hesse J, Hellhammer J, Hellhammer DH (2005): A new view on hypocortisolism. Psychoneuroendocrinology 30:1010–1016.
28. Newport DJ, Heim C, Bonsall R, Miller AH, Nemeroff CB (2004): Pituitary-adrenal responses to standard and low-dose dexamethasone suppression tests in adult survivors of child abuse. Biol Psychiatry 55:10–20.
29. Lamers F, Vogelzangs N, Merikangas KR, De Jonge P, Beekman AT, Penninx BW (2013): Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Mol Psychiatry 18:692–699.
30. Lamers F, Milaneschi Y, Vinkers CH, Schoevers RA, Giltay EJ, Penninx BWJH (2020): Depression profilers and immuno-metabolic dysregulation: Longitudinal results from the NESDA study. Brain Behav Immun 88:174–183.
31. Pan A, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, Hu FB (2012): Bidirectional association between depression and metabolic syndrome: A systematic review and meta-analysis of epidemiological studies. Diabetes Care 35:1171–1180.
32. Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, *et al.* (2015): Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: A systematic review and meta-analysis. World Psychiatry 14:339–347.
33. Silva DA, Coutinho EDSF, Ferriani LO, Viana MC (2020): Depression subtypes and obesity in adults: A systematic review and meta-analysis. Obes Rev 21:e12966.
34. Shell AL, Crawford CA, Cyders MA, Hirsh AT, Stewart JC (2024): Depressive disorder subtypes, depressive symptom clusters, and risk of obesity and diabetes: A systematic review. J Affect Disord 353:70–89.
35. Bunker SJ, Colquhoun DM, Esler MD, Hickie IB, Hunt D, Jelinek VM, *et al.* (2003): "Stress" and coronary heart disease: Psychosocial risk factors. Med J Aust 178:272–276.
36. Nguyen TD, Harder A, Xiong Y, Kowalec K, Hägg S, Cai N, *et al.* (2022): Genetic heterogeneity and subtypes of major depression. Mol Psychiatry 27:1667–1675.
37. Scott EM, Carpenter JS, Iorfino F, Cross SPM, Hermens DF, Gehue J, *et al.* (2019): What is the prevalence, and what are the clinical correlates, of insulin resistance in young people presenting for mental health care? A cross-sectional study. BMJ Open 9:e025674.

38. Penninx BWJH, Milaneschi Y, Lamers F, Vogelzangs N (2013): Understanding the somatic consequences of depression: Biological mechanisms and the role of depression symptom profile. BMC Med 11:129.
39. Tickell AM, Rohleder C, Ho N, McHugh C, Jones G, Song YJC, *et al.* (2022): Identifying pathways to early-onset metabolic dysfunction, insulin resistance and inflammation in young adult inpatients with emerging affective and major mood disorders. Early Interv Psychiatry 16:1121–1129.
40. Carpenter JS, Crouse JJ, Scott EM, Naismith SL, Wilson C, Scott J, *et al.* (2021): Circadian depression: A mood disorder phenotype. Neurosci Biobehav Rev 126:79–101.
41. Hickie IB, Naismith SL, Robillard R, Scott EM, Hermens DF (2013): Manipulating the sleep-wake cycle and circadian rhythms to improve clinical management of major depression. BMC Med 11:79.
42. Badini I, Coleman JRI, Hagenaars SP, Hotopf M, Breen G, Lewis CM, Fabbri C (2022): Depression with atypical neurovegetative symptoms shares genetic predisposition with immuno-metabolic traits and alcohol consumption. Psychol Med 52:726–736.
43. Mitchell BL, Campos AI, Whiteman DC, Olsen CM, Gordon SD, Walker AJ, *et al.* (2022): The Australian genetics of depression study: New risk loci and dissecting heterogeneity between subtypes. Biol Psychiatry 92:227–235.
44. Oliva V, Fanelli G, Kasper S, Zohar J, Souery D, Montgomery S, *et al.* (2023): Melancholic features and typical neurovegetative symptoms of major depressive disorder show specific polygenic patterns. J Affect Disord 320:534–543.
45. Byrne EM, Kirk KM, Medland SE, McGrath JJ, Colodro-Conde L, Parker R, *et al.* (2020): Cohort profile: The Australian genetics of depression study. BMJ Open 10:e032580.
46. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, *et al.* (2007): PLINK: A tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 81:559–575.
47. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ (2015): Second-generation PLINK: Rising to the challenge of larger and richer datasets. GigaScience 4:7.
48. Taliun D, Harris DN, Kessler MD, Carlson J, Szpiech ZA, Torres R, *et al.* (2021): Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. Nature 590:290–299.
49. Jiang L, Zheng Z, Qi T, Kemper KE, Wray NR, Visscher PM, Yang J (2019): A resource-efficient tool for mixed model association analysis of large-scale data. Nat Genet 51:1749–1755.
50. Zheng Z, Liu S, Sidorenko J, Wang Y, Lin T, Yengo L, *et al.* (2024): Leveraging functional genomic annotations and genome coverage to improve polygenic prediction of complex traits within and between ancestries. Nat Genet 56:767–777.
51. Mitchell BL, Thorp JG, Wu Y, Campos AI, Nyholt DR, Gordon SD, *et al.* (2021): Polygenic risk scores derived from varying definitions of depression and risk of depression. JAMA Psychiatry 78:1152–1160.
52. R Core Team (2022): R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. Available at: https://cran.r-project.org/doc/manuals/r-release/fullrefman.pdf. Accessed April 30, 2025.
53. Novick JS, Stewart JW, Wisniewski SR, Cook IA, Manev R, Nierenberg AA, *et al.* (2005): Clinical and demographic features of atypical depression in outpatients with major depressive disorder: Preliminary findings from STAR*D. J Clin Psychiatry 66:1002–1011.
54. Xin L-M, Chen L, Su Y-A, Yang F-D, Wang G, Fang Y-R, *et al.* (2019): Prevalence and clinical features of atypical depression among patients with major depressive disorder in China. J Affect Disord 246:285–289.
55. Glaus J, Vandeleur C, Gholam-Rezaee M, Castelao E, Perrin M, Rothen S, *et al.* (2013): Atypical depression and alcohol misuse are related to the cardiovascular risk in the general population. Acta Psychiatr Scand 128:282–293.
56. Perugi G, Fornaro M, Akiskal HS (2011): Are atypical depression, borderline personality disorder and bipolar II disorder overlapping manifestations of a common cyclothymic diathesis? World Psychiatry 10:45–51.
57. Łojko D, Rybakowski JK (2017): Atypical depression: Current perspectives. Neuropsychiatr Dis Treat 13:2447–2456.
58. Davidson JR, Miller RD, Turnbull CD, Sullivan JL (1982): Atypical depression. Arch Gen Psychiatry 39:527–534.
59. Angst J, Gamma A, Sellaro R, Zhang H, Merikangas K (2002): Toward validation of atypical depression in the community: Results of the Zurich cohort study. J Affect Disord 72:125–138.
60. Chopra KK, Bagby RM, Dickens S, Kennedy SH, Ravindran A, Levitan RD (2005): A dimensional approach to personality in atypical depression. Psychiatry Res 134:161–167.
61. Penninx BWJH (2017): Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. Neurosci Biobehav Rev 74:277–286.
62. Pistis G, Milaneschi Y, Vandeleur CL, Lasserre AM, Penninx BWJH, Lamers F, *et al.* (2021): Obesity and atypical depression symptoms: Findings from Mendelian randomization in two European cohorts. Transl Psychiatry 11:96.
63. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, *et al.* (2010): New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nat Genet 42:105–116.
64. Lasserre AM, Glaus J, Vandeleur CL, Marques-Vidal P, Vaucher J, Bastardot F, *et al.* (2014): Depression with atypical features and increase in obesity, body mass index, waist circumference, and fat mass: A prospective, population-based study. JAMA Psychiatry 71:880–888.
65. Crouse JJ, Carpenter JS, Song YJC, Hockey SJ, Naismith SL, Grunstein RR, *et al.* (2021): Circadian rhythm sleep-wake disturbances and depression in young people: Implications for prevention and early intervention. Lancet Psychiatry 8:813–823.
66. Crouse JJ, Park SH, Byrne EM, Mitchell BL, Chan K, Scott J, *et al.* (2024): Evening chronotypes with depression report poorer outcomes of selective serotonin reuptake inhibitors: A survey-based study of self-ratings. Biol Psychiatry 96:4–14.
67. Campos AI, Mulcahy A, Thorp JG, Wray NR, Byrne EM, Lind PA, *et al.* (2021): Understanding genetic risk factors for common side effects of antidepressant medications. Commun Med (Lond) 1:45.
68. Glaus J, Kang SJ, Guo W, Lamers F, Strippoli MF, Leroux A, *et al.* (2023): Objectively assessed sleep and physical activity in depression subtypes and its mediating role in their association with cardiovascular risk factors. J Psychiatr Res 163:325–336.
69. Hickie IB, Crouse JJ (2024): Sleep and circadian rhythm disturbances: Plausible pathways to major mental disorders? World Psychiatry 23:150–151.
70. Panda S (2019): The arrival of circadian medicine. Nat Rev Endocrinol 15:67–69.
71. Hickie IB, Rogers NL (2011): Novel melatonin-based therapies: Potential advances in the treatment of major depression. Lancet 378:621–631.