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Mixed Features and Symptom Trajectories in Adolescent Major Depressive Disorder: A Naturalistic Cohort Study

ping mo
Mental Health Center, Affiliated Hospital of North Sichuan Medical College
Xingyu He
Mental Health Center, Affiliated Hospital of North Sichuan Medical College
Min Liu
Mental Health Center, Affiliated Hospital of North Sichuan Medical College
Zhaxi Dengzhu
Mental Health Center, Affiliated Hospital of North Sichuan Medical College
Wenxiu Luo
Mental Health Center, Affiliated Hospital of North Sichuan Medical College
Meilin Wu
Mental Health Center, Affiliated Hospital of North Sichuan Medical College
Yujia Zhao
Mental Health Center, Affiliated Hospital of North Sichuan Medical College
Jiaming Luo
jiamingluo@nsmc.edu.cn

Mental Health Center, Affiliated Hospital of North Sichuan Medical College

Research Article

Keywords: mixed features specifier, adolescent depression, symptom trajectories, pharmacological masking, mood disorder questionnaire, naturalistic cohort

Posted Date: July 28th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10346043/v1

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Additional Declarations: No competing interests reported.

Abstract

The clinical significance of the DSM-5 "with mixed features" specifier in adolescent major depressive disorder (MDD)—here termed MDD with mixed features (DMF)—remains uncertain, and its longitudinal course has rarely been examined. In a two-site naturalistic cohort of adolescents with early-course MDD enrolled between May 2024 and April 2025, we tested whether DMF status was associated with differential trajectories of pre-registered outcomes (suicide attempts; depression, SDS) and a post-hoc outcome (anxiety, SAS), and conducted, to our knowledge, the first formal causal mediation test of the pharmacological masking hypothesis—the widely invoked but untested idea that anti-manic prescribing conceals emergent bipolarity. Of 448 baseline participants, 108 (75% female; 34.3% DMF) completed all five scheduled visits (median follow-up 18.1 weeks); the study was retrospectively registered (ChiCTR2400088411). We used linear mixed models with random slopes and Benjamini-Hochberg FDR correction for non-pre-registered outcomes. No suicide attempts occurred, and depression trajectories did not differ by DMF status (β = 0.86, p = 0.311). A post-hoc anxiety signal (DMF × time: β = 2.35, raw p = 0.015) was robust to covariate adjustment but did not survive FDR correction (q = 0.18). Mediation analysis did not support pharmacological masking (ACME = –0.030, p = 0.29). The pre-registered outcomes showed no DMF-related differences; the anxiety signal is reported strictly as hypothesis-generating. Adequately powered, pre-registered replication is required before clinical inference.

Trial registration*: ChiCTR2400088411, retrospectively registered 19 August 2024.*

Introduction

Adolescent major depressive disorder (MDD) is among the leading contributors to global disability in young people, and anxiety comorbidity is one of its most common and disabling clinical features[1, 2]. Persistent anxiety in depressed adolescents predicts poorer treatment response, elevated suicide risk and a more protracted illness course[3]; however, the longitudinal course of anxiety within specific depressive subtypes during real-world treatment remains poorly characterized[3].

The DSM-5 introduced the 'with mixed features' specifier for major depressive episodes, defined by the presence of at least three manic or hypomanic symptoms (excluding the overlapping symptoms of agitation, distractibility, and irritability) during most days of the index episode[4, 5]. Throughout this paper, the term 'MDD with mixed features' (DMF) refers to this DSM-5-defined subgroup. Although originally validated in adults[6, 7, 12], the specifier is increasingly recognised in adolescents, where it has been associated with greater illness severity, functional impairment and suicidal behaviour in cross-sectional studies[8, 9, 10]. Diagnostic recognition of the specifier in youth remains challenging because the “depressive-irritable” mixed presentation may overlap phenomenologically with normative adolescent mood lability or behavioural dysregulation[11]; current evidence in this age group is largely cross-sectional.

Longitudinal evidence on DMF in adolescents is sparse. Most existing studies have focused on bipolar conversion or general depression severity, leaving anxiety trajectory largely unexamined[18, 45]. This gap

is clinically meaningful because mixed features are characterised phenomenologically by a state of heightened arousal—irritability, psychomotor activation, pressured speech—that may plausibly impede the resolution of anxious distress during treatment. In adult studies, mixed depression has been associated with a more chronic course of anxiety, but it remains unclear whether this pattern extends to adolescents[13, 14].

We therefore conducted a registered, naturalistic, longitudinal cohort study of adolescents with early-course MDD. Pre-registered hypotheses (per ChiCTR2400088411) tested whether DMF status was associated with differential trajectories of (i) suicide attempts (registered primary outcome) and (ii) depression severity measured by the SDS (registered secondary outcome). Anxiety trajectory (SAS), although measured at all visits, was not specified in the registry entry and is reported here as a post-hoc outcome with appropriate multiple-testing correction. Exploratory analyses examined a formal causal mediation hypothesis for the DMF–bipolar risk pathway via anti-manic medication, and whether baseline non-suicidal self-injury, hopelessness, or life events modify the DMF–anxiety association.Given the naturalistic design and the pre-registered outcome hierarchy, we regard the rigorous evaluation of these hypotheses in a real-world clinical cohort as valuable in its own right, whether the resulting associations prove positive or null.

Methods

Study design, sites and registration

This was a prospective, naturalistic, longitudinal cohort study conducted at two affiliated clinical sites in southwest China: a tertiary academic hospital (primary site) and a county-level partner hospital (secondary site), approximately 80 km apart. The two sites served different catchment populations: the primary site received broad regional referrals including out-of-prefecture cases, whereas the secondary site predominantly served local residents.

The study protocol was approved by the Medical Ethics Committee of the participating tertiary hospital (No. 2024ER388-1) on 24 June 2024 and registered with the Chinese Clinical Trial Registry on 19 August 2024 (ChiCTR2400088411). Enrolment commenced on 30 May 2024; during the 25-day interval before formal approval, only consent and baseline assessment were performed, with no protocol-defined intervention. The study is therefore reported as retrospectively registered. All procedures conformed to the Declaration of Helsinki; written electronic informed consent was obtained from legal guardians, with assent from minors aged ≥ 12 years.

Several deviations from the registry record (diagnostic system, follow-up schedule, planned sample size, recruitment dates) are detailed in Supplementary Material.

Participants

Adolescents aged 10–18 years presenting for evaluation between 30 May 2024 and 12 April 2025 were screened consecutively from outpatient psychiatric services at the two sites. Inclusion criteria were: (i) age 10–18 years; (ii) a clinical diagnosis of MDD according to DSM-5 criteria; (iii) either treatment-naïve at presentation or having received antidepressant treatment for ≤ 4 weeks prior to the baseline visit[15]. Exclusion criteria were: (i) inability to complete self-report scales; (ii) comorbid systemic or major neurological disease; (iii) prior diagnosis of bipolar I/II disorder, schizophrenia or other psychotic disorders; (iv) severe neurodevelopmental deficits or conditions precluding reliable clinical interview.

Of 509 adolescents screened, 61 were excluded due to missing baseline SAS or SDS scores, yielding a baseline analytic cohort of 448. Within the analytic sample (n = 108), 93 (86.1%) were experiencing a first episode, and 15 (13.9%) a recurrent episode with ≤ 4 weeks of prior medication, consistent with the early-course nature of this sample. A total of 108 (24.1%) participants completed all five scheduled follow-up visits and constituted the primary analytic sample; the remaining 340 (75.9%) provided baseline data only or incomplete follow-up. This focus on completers was a deliberate design choice to ensure adequate longitudinal observation through the initial treatment stabilisation phase, encompassing the full duration of the five scheduled follow-up assessments. Potential selection bias was addressed by an attrition analysis comparing baseline characteristics of completers and non-completers (Supplementary Table S1).

Follow-up schedule and time variable

As detailed in the participant flow (Fig. 1), 108 completers provided longitudinal data across five scheduled visits. While the study protocol initially intended for follow-up assessments at approximately 1, 3, 7, 11, and 15 weeks post-baseline, actual visit timing varied due to the naturalistic nature of the clinical setting. The observed follow-up duration across all visits ranged from 0 to 41 weeks (median = 6.9 weeks, IQR 1.3–13.2). For the analytic sample, the per-patient maximum follow-up time (time from baseline to last recorded visit) had a median of 18.1 weeks (IQR 16.3–20.2). To account for this irregular spacing, time was modelled as a continuous standardized predictor (weeks_z; mean = 0, SD = 1) in all mixed models.

Outcomes and measures

Pre-registered and Post-hoc Outcomes.

Primary outcome (per ChiCTR)

As specified in the trial registry, the primary focus was the longitudinal trajectory of suicidal attempts. In this analytic sample, this was operationalized and assessed using the total score of the Suicidal Behaviors Questionnaire–Revised (SBQ-R, range 3–18) to capture the continuum of suicidal risk, ideation, and past attempts[19], as actual completed suicide attempts were rare/absent during the short-term follow-up window.

Secondary outcome (per ChiCTR)

Depression severity, measured by the Zung Self-rating Depression Scale (SDS)[20].

Post-hoc outcome

Anxiety severity, measured by the Zung Self-rating Anxiety Scale (SAS)[21].

Standardisation

For SDS and SAS, raw scores (20–80) were converted to standardized index scores (25–100). As SAS was not pre-registered, it is reported as a post-hoc analysis with Benjamini-Hochberg FDR correction applied across all non-pre-registered outcomes.

Exploratory Analyses. Additional outcomes were assessed as follows:

Bipolar screening

Mood Disorder Questionnaire (MDQ)[22, 49], treated as a binary variable (positive screen defined as ≥ 7 endorsed items with concurrent impairment).

Clinical and behavioral outcomes

Non-suicidal self-injury (NSSI), medication adherence (defined strictly as continuous adherence without missed doses or interruptions; coded as 1 = complete adherence, 0 = any non-adherence or interruption, with sub-categories collapsed due to sample size constraints), composite severe exacerbation (defined as psychiatric hospitalisation or recorded refusal), and diagnostic conversion (MDD to bipolar disorder) were all coded as binary variables (0 = absent, 1 = present) at each visit.

Baseline Measures. Assessed variables included the Adolescent Self-Rating Life Events Checklist (ASLEC)[23] and the Beck Hopelessness Scale (BHS)[24, 25]. Demographic, family, and clinical characteristics included age, sex, only-child status, left-behind children's history (i.e., children remaining in rural areas, typically with grandparents, while parents migrate for urban work), family psychiatric history, and concurrent medication use. The Epworth Sleepiness Scale was administered at follow-up visits only[26, 27].

Diagnostic Procedures and DMF Ascertainment

Initial clinical evaluations, including MDD diagnosis and screening for mixed features, were conducted by outpatient psychiatrists at the recruiting sites. Mixed features (DMF) status was determined according to DSM-5 criteria[4, 5], requiring the presence of at least three manic/hypomanic symptoms (excluding overlapping symptoms of agitation and distractibility) during most days of the index episode.

To ensure diagnostic consistency across the cohort, all eligible case records were independently reviewed by a consensus panel comprising two attending psychiatrists and two postgraduate psychiatry trainees. Disagreements were resolved by consensus. Inter-rater reliability on a pilot sample of 20 randomly selected cases was excellent (Fleiss' $\kappa = 0.89$). No structured mixed features instrument (e.g., the Koukopoulos Mixed Depression Rating Scale[KMDRS]) was used[28, 29, 30]; classification relied on consensus clinical judgement guided by the DSM-5 text, which we acknowledge as a methodological limitation.

Statistical analysis

All statistical analyses were conducted using R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria). Linear mixed-effects models (LMMs) were fitted using the lme4 package[31], with p-values calculated via Satterthwaite's degrees of freedom method using the lmerTest package[32]. Missing data were handled via multiple imputation using the mice package[33]. Marginal means and standardized effect sizes were extracted using the emmeans and effectsize packages[47, 48], respectively. Mediation analyses were performed using the mediation package[34]. Statistical significance was defined as a two-tailed $p < 0.05$, with Benjamini-Hochberg false discovery rate (FDR) corrections applied for multiple comparisons where appropriate[35]. For the SDS model, the random intercept variance estimated at the boundary (zero); we retained the structure for consistency across primary outcomes but note this as a model diagnostic finding.

Sample size considerations. No a priori sample size calculation was performed specifically for the present analyses. The analytic sample of 108 completers reflects the number of participants who had completed the early-stabilisation phase (first five visits) of an ongoing 12-month cohort at the time of data lock. We therefore did not pre-specify a target sample size for the interim analyses reported here. Consistent with current guidance on the limited utility of post-hoc statistical power for studies whose data are already collected[36], we report 95% confidence intervals as the primary measure of precision for all effect estimates, and explicitly flag findings most likely to be precision-limited (notably the three-way interaction analyses) in the Discussion.

Random-effects structure. A likelihood ratio test compared random-intercept-only versus random-intercept-plus-random-slope structures using the SAS model under maximum likelihood estimation ($\chi^2 = 26.27$, $df = 2$, $p < 0.001$), supporting the inclusion of a random slope for time. All LMMs therefore used the structure (1 + weeks_z | ID) (see causal directed acyclic graph in Supplementary Fig. S5). For generalized linear mixed models (GLMMs) with binary outcomes, random intercepts only were retained, since random slopes for binary outcomes with n = 108 are prone to non-convergence.

Pre-registered analyses. The DMF × time interaction for the registered primary outcome (suicide attempts; GLMM with logit link) and the registered secondary outcome (SDS; LMM) were tested at a two-tailed $\alpha = 0.05$, without multiple-testing correction, as these were pre-specified.

Post-hoc and non-pre-registered analyses. All other outcomes (SAS, SBQ-R, MDQ, NSSI, medication adherence, severe exacerbation, diagnostic conversion) were analysed with the same LMM/GLMM structure, with Benjamini-Hochberg FDR correction applied across this family of outcomes to control the false discovery rate at $q < 0.05$. The SAS DMF × time interaction is reported with both raw and FDR-adjusted p-values for transparency.

Mediation analysis. To examine whether anti-manic medication use mediates the DMF–MDQ association, formal causal mediation analysis was conducted using the mediation package with 1,000 bootstrap resamples. Treatment: DMF status. Mediator: anti-manic medication use (atypical antipsychotic or mood stabiliser) at first follow-up. Outcome: MDQ positivity at first follow-up. Covariates: baseline SDS, age, sex. The analysis used a first follow-up cross-section because of the short interval between treatment initiation and the first MDQ assessment.

Exploratory analyses. Three-way interactions (DMF × time × baseline NSSI/ASLEC/BHS) were tested with random-intercept LMMs; random-slope variants failed to converge given the sample size. These are reported as exploratory only.

Sensitivity analyses. (i) Complete-case analysis of the SAS model. (ii) Multiple imputation by chained equations (MICE) with 50 imputations, using predictive mean matching; a linear regression approximation was used at the imputation stage as MICE does not natively support random-slope LMMs. Because the lm-based imputation ignores within-person clustering, it tends to inflate residual variance and underestimate the precision of fixed effects, biasing toward null findings. The persistence of the DMF × time interaction under this conservative test ($p = 0.014$) supports the robustness of the primary signal[37]. (iii) Attrition analysis comparing baseline characteristics between completers and non-completers (Wilcoxon rank-sum for continuous variables, Fisher's exact test for categorical variables).

Covariate sensitivity analyses. To examine robustness of the primary SAS DMF × time interaction to potential confounding by baseline characteristics that differed between completers and non-completers, we re-fit the primary LMM with family psychiatric history and left-behind duration (continuous, z-scored; non-left-behind participants coded as zero exposure) added as covariates, separately and jointly. We also tested exploratory three-way interactions (DMF × time × family psychiatric history; DMF × time × left-behind duration) with random-intercept models, on the same parsimony grounds applied to the other three-way analyses.

Model diagnostics, effect size, and precision. Variance inflation factors (VIF), residual normality (Q-Q plot), homoscedasticity, posterior predictive checks, normality of random effects, and influential observations were assessed for the primary SAS model. Standardised regression coefficients and marginal/conditional R^2 are reported. Following Hoenig and Heisey[36], post-hoc statistical power calculations are not reported; rather, the 95% confidence intervals provide the appropriate measure of precision.

Results

Sample characteristics and attrition profile

Of 509 adolescents presenting within the analytic window, 448 (88%) had complete baseline SAS and SDS data and constituted the baseline cohort. Of these, 108 (24%) completed all five scheduled follow-up visits and form the primary analytic sample. Baseline characteristics of the analytic sample, stratified by DMF status, are presented in Table 1.

Table 1
Baseline Characteristics

Characteristics	Overall N = 108[1]	Non-DMF N = 71[1]	DMF N = 37[1]	p-value[2]
Age (years)				**0.017**
11	1 (0.9%)	1 (1.4%)	0 (0%)	
12	6 (5.6%)	1 (1.4%)	5 (14%)	
13	20 (19%)	11 (15%)	9 (24%)	
14	17 (16%)	15 (21%)	2 (5.4%)	
15	16 (15%)	8 (11%)	8 (22%)	
16	28 (26%)	22 (31%)	6 (16%)	
17	15 (14%)	9 (13%)	6 (16%)	
18	5 (4.6%)	4 (5.6%)	1 (2.7%)	
Sex				0.558
Male	27 (25%)	19 (27%)	8 (22%)	
Female	81 (75%)	52 (73%)	29 (78%)	
Only Child				0.128
0	81 (75%)	50 (70%)	31 (84%)	
1	27 (25%)	21 (30%)	6 (16%)	
Family Psychiatric History				0.506
0	97 (90%)	65 (92%)	32 (86%)	
1	11 (10%)	6 (8.5%)	5 (14%)	
Left-Behind Status				0.821
0	48 (44%)	31 (44%)	17 (46%)	
1	60 (56%)	40 (56%)	20 (54%)	
Age at Left-Behind Onset (years)	3.53 (3.18)	3.47 (3.38)	3.67 (2.77)	0.592
Left-Behind Duration (years)	8.3 (5.7)	8.4 (6.1)	8.2 (4.8)	0.984
Life Events Stress (ASLEC)	50 (21)	52 (19)	47 (25)	0.277

[2]Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test

Characteristics	Overall N = 108[1]	Non-DMF N = 71[1]	DMF N = 37[1]	p-value[2]
Age (years)				**0.017**
Hopelessness (BHS)	9.92 (2.28)	9.87 (2.43)	10.00 (1.99)	0.909
Anxiety (SAS)	65 (11)	65 (10)	65 (11)	0.961
Depression (SDS)	74 (9)	75 (8)	74 (10)	0.798
Suicidality (SBQ-R)	13.50 (3.00)	13.49 (3.08)	13.51 (2.87)	0.987
Baseline NSSI	72 (67%)	47 (66%)	25 (68%)	0.886
Antidepressant Use	81 (75%)	54 (76%)	27 (73%)	0.725
Atypical Antipsychotic Use	31 (29%)	21 (30%)	10 (27%)	0.781
Mood Stabilizer Use	14 (13%)	1 (1.4%)	13 (35%)	**< 0.001**

[1]n (%); Mean (SD)

[2]Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test

The two DMF groups were generally comparable, with the exception of mood stabiliser use (35.1% in DMF vs 1.4% in non-DMF, $p < 0.001$), reflecting clinicians' recognition of mixed-feature presentations, and a slightly different age distribution ($p = 0.017$). There were no significant baseline differences in anxiety, depression, suicidality, NSSI or life events between DMF and non-DMF groups.

Attrition analysis compared the 108 completers with the 340 non-completers across 13 baseline characteristics (Supplementary Table S1). Critically, the two groups did not differ significantly on key analytic variables: baseline anxiety (SAS: 65 vs. 67, $p = 0.087$), DMF status (34.3% vs. 29.4%, $p = 0.340$), NSSI (66.7% vs. 62.9%, $p = 0.566$), hopelessness (BHS: 9.92 vs. 10.15, $p = 0.440$), life events (ASLEC: 50 vs. 51, $p = 0.945$), and left-behind history (60 (56%) vs. 203 (60%), $p = 0.501$)[16, 17].

Four variables showed statistically significant or borderline differences. Completers had slightly lower baseline depression (SDS: 74 vs. 77, $p = 0.003$) and a lower rate of family psychiatric history (10.2% vs. 22.4%, $p = 0.005$). Conversely, completers showed higher baseline suicidality (SBQ-R: 13.5 vs. 11.4, $p < 0.001$) and had a borderline higher proportion of only-children (25.0% vs. 17.0%, $p = 0.066$).

Rather than representing a distinct clinical sub-population, these differences likely reflect real-world compliance patterns in naturalistic outpatient settings. For instance, adolescents with greater familial psychiatric burden may face systemic barriers to sustained follow-up, whereas those with marked suicidal ideation may receive more intensive retention efforts and closer monitoring from clinicians[46].

Overall, the comparability on the principal analytic variables supports the internal validity of the longitudinal models.

Pre-registered primary outcome: suicide attempts

Contrary to the pre-registered hypothesis, no actual suicide attempts were recorded during the short-term follow-up window in either group, precluding the use of generalized linear mixed models. Consequently, longitudinal trajectories for this primary outcome could not be compared.

Pre-registered secondary outcome: depression (SDS)

Also contrary to expectation, the DMF × time interaction for depression severity was non-significant (LMM β = 0.86, 95% CI − 0.82 to 2.54, p = 0.311; Table 2). Both DMF and non-DMF groups showed comparable reductions in depression severity over the follow-up period. Marginal R^2 for the SDS model was 0.05; conditional R^2 was 0.21.

Post-hoc analysis: anxiety (SAS)

The DMF × time interaction for anxiety severity reached the conventional significance threshold (β = 2.35, 95% CI 0.47–4.22, raw p = 0.015; Table 2).

Table 2
Linear Mixed Models for Clinical Outcomes(The Table 2 continuous on next page)

Characteristic	Anxiety (SAS)			Depression (SDS)		
	Beta	**95% CI**	**p-value**	**Beta**	**95% CI**	**p-value**
DMF (vs Non-DMF)	1.2	-2.3, 4.7	0.5	0.22	-1.4, 1.8	0.8
Follow-up Time (Z-score)	-2.9	-4.0, -1.8	< 0.001	-4.3	-5.3, -3.3	< 0.001
Age (Z-score)	-0.44	-2.1, 1.2	0.6	-0.51	-1.3, 0.29	0.2
Female (vs Male)	3.7	-0.11, 7.5	0.057	-0.25	-2.1, 1.6	0.8
Interaction: DMF × Time						
DMF * Follow-up Time (Z-score)	2.4	0.47, 4.2	0.015	0.86	-0.81, 2.5	0.3
Abbreviation: CI = Confidence Interval						

Table 2
Linear Mixed Models for Clinical Outcomes(Continued)

Characteristic	Suicidality (SBQ-R)			Sleepiness (Epworth)		
	Beta	95% CI	p-value	Beta	95% CI	p-value
DMF (vs Non-DMF)	0.04	-1.1, 1.1	> 0.9	0.45	-1.5, 2.4	0.6
Follow-up Time (Z-score)	-0.56	-0.92, -0.19	0.003	-0.86	-1.4, -0.31	0.003
Age (Z-score)	-0.61	-1.2, -0.08	0.026	-0.60	-1.5, 0.34	0.2
Female (vs Male)	-0.14	-1.4, 1.1	0.8	0.52	-1.6, 2.7	0.6
Interaction: DMF × Time						
DMF * Follow-up Time (Z-score)	-0.30	-0.92, 0.33	0.4	0.26	-0.68, 1.2	0.6
Abbreviation: CI = Confidence Interval						

Standardised effect size for the interaction was 0.12 (95% CI 0.02–0.22) (see Supplementary Table S2 for full effect size and R^2 metrics). Simple slopes analysis indicated that non-DMF participants experienced a significant decline in anxiety across follow-up (slope per SD of standardised time = − 2.88, 95% CI − 3.98 to − 1.77, $p < 0.001$), while the DMF group showed a flat trajectory (slope = − 0.52, 95% CI − 2.06 to 1.01, $p = 0.50$). Across the observed follow-up window (median 18.1 weeks per patient), the predicted between-group SAS difference grew from negligible at baseline to approximately 5–6 points by the median end-of-follow-up time, corresponding to a moderate clinical effect.

Across the full FDR family (12 tests; Supplementary Table S5), no other outcome's DMF × time interaction remained significant after correction.

Other non-pre-registered outcomes

Medication adherence declined substantially across follow-up in both groups (OR for each SD of standardized time = 0.23, 95% CI 0.14–0.38, $p < 0.001$), with no significant DMF × time interaction (OR for interaction = 0.74, 95% CI 0.27–2.07, $p = 0.567$) (Supplementary Table S3A; Supplementary Fig. S3). Models for severe exacerbation (n = 1 event among 75 observations, 52 unique participants) and diagnostic conversion (n = 2 events) did not converge to interpretable estimates due to quasi-complete separation arising from extremely low event rates. We therefore report only descriptive event counts and do not provide model-based effect estimates for these outcomes. The data are presented in Supplementary Table S3B for completeness, with explicit annotation that estimates should not be interpreted.

Sensitivity to additional covariates

The DMF × time interaction for SAS was robust to adjustment for family psychiatric history (β = 2.35, 95% CI 0.49–4.22, $p = 0.015$), left-behind duration (β = 2.34, 95% CI 0.34–4.34, $p = 0.024$), and both

covariates simultaneously (β = 2.34, 95% CI 0.34–4.34, p = 0.024). Point estimates varied by less than 0.5% across models, indicating that the primary signal was not driven by these baseline differences between completers and non-completers (Supplementary Table S7). Exploratory three-way interactions DMF × time × family psychiatric history (β = − 1.27, p = 0.612) and DMF × time × left-behind duration (β = 0.41, p = 0.620) were both non-significant, suggesting that the DMF × time effect was not differentially expressed across these subgroups.

Exploratory mediation analysis

Formal causal mediation analysis (1,000 bootstrap resamples; first-follow-up cross-section) did not support the hypothesis that anti-manic medication mediates the DMF–MDQ association(Fig. 2). Of the 108 completers, three participants were excluded due to incomplete data on the mediator or outcome at the first follow-up assessment, yielding a final mediation sample of n = 105. The average causal mediation effect (ACME) was small and non-significant (estimate = − 0.030, 95% CI − 0.103 to 0.018, p = 0.29). The direct effect was also non-significant (ADE = − 0.193, 95% CI − 0.399 to 0.013, p = 0.072). The negative total effect (DMF associated with lower MDQ positivity) is consistent with effective anti-manic treatment in DMF patients, but the non-significant indirect effect does not support a specific pharmacological mediation pathway. The estimated proportion mediated had a wide confidence interval spanning zero (13.4%, 95% CI − 18% to 85%). These findings do not support the hypothesis that anti-manic prescribing systematically masks emergent bipolarity in DMF adolescents within the present sample and follow-up window (Table 3).

Table 3
MDQ Null Findings

Characteristic	**Model 1: Unadjusted**			**Model 2: Adjusted**		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
DMF (vs Non-DMF)	1.07	0.72, 1.60	0.7	1.02	0.67, 1.56	> 0.9
Follow-up Time (Z-score)	0.71	0.55, 0.92	0.009	0.76	0.62, 0.92	0.007
Age (Z-score)	0.86	0.71, 1.05	0.14	0.84	0.70, 1.02	0.076
Female (vs Male)	1.05	0.67, 1.64	0.8	1.03	0.66, 1.60	0.9
Interaction: DMF × Time						
DMF * Follow-up Time (Z-score)	1.27	0.85, 1.90	0.2			
Antidepressant Use				0.77	0.49, 1.20	0.2
Atypical Antipsychotic Use				0.90	0.51, 1.61	0.7
Mood Stabilizer Use				1.40	0.68, 2.90	0.4
Abbreviations: CI = Confidence Interval, OR = Odds Ratio						

Exploratory three-way interactions

None of the exploratory three-way interactions for anxiety were significant: DMF × time × baseline NSSI (β = 1.28, p = 0.391); DMF × time × ASLEC (p = 0.582); DMF × time × BHS (p = 0.407). Stratified simple-slope estimates suggested numerically different patterns by NSSI status, but with widely overlapping confidence intervals; these descriptive observations should be regarded as hypothesis-generating only (Supplementary Table S6; Supplementary Fig. S4).

Model diagnostics

Diagnostic plots for the SAS primary model showed acceptable fit: posterior predictive checks demonstrated close agreement between observed and model-predicted SAS distributions; residual Q-Q plots and the fitted-versus-residuals plot were consistent with normality and homoscedasticity; random-effect Q-Q plots for both intercept and slope showed normal distributions, supporting the random-slope structure; variance inflation factors were all below 1.6, indicating no multicollinearity (Supplementary Table S4; Supplementary Fig. S1A and S1B).

Discussion

Summary of findings

In this naturalistic cohort of 108 adolescents with early-course MDD followed for a median of 18.1 weeks, neither pre-registered outcome differed by DMF status: suicide attempts and depression trajectories were comparable between DMF and non-DMF groups. In a post-hoc analysis, DMF was associated with a slower anxiety improvement (raw p = 0.015), an effect that did not survive FDR correction across multiple non-pre-registered outcomes (q = 0.18). The formal mediation analysis did not support the hypothesis that anti-manic medication mediates a DMF–bipolar risk link. Exploratory three-way interactions were uniformly non-significant.

Interpretation of the anxiety signal

Before interpreting the post-hoc anxiety observation, three caveats must be foregrounded: the analysis was not pre-registered, the finding did not survive FDR correction (q = 0.18), and the sample size (n = 108) provides limited precision for detecting interactions of this magnitude. With these limitations explicit, the pattern—slower anxiety improvement in DMF adolescents in the absence of comparable differences for depression or suicidality—is preliminarily consistent with the phenomenological description of mixed depression as a state of heightened arousal and inner tension[5, 13, 29, 40], and parallels observations from adult mixed-depression samples[12, 14]. One speculative interpretation is that the mixed features specifier identifies adolescents whose anxious arousal is less responsive to standard naturalistic treatment, even when core depressive symptoms improve; this would, if reproduced, have implications for personalised treatment planning[12]. We emphasise, however, that the present data do not support this interpretation as established. The observation should be regarded as a

candidate hypothesis for pre-registered replication, not as a clinical signal warranting changes in adolescent depression management.

Null mediation analysis: implications for the masking hypothesis

Anti-manic medications such as atypical antipsychotics and mood stabilisers[44] are often invoked as a potential mechanism by which subthreshold bipolarity in DMF patients might be “masked” in routine clinical care[42, 43]. Our formal mediation analysis did not support this hypothesis: the indirect effect was small and non-significant (ACME p = 0.29), and the total effect was in the opposite direction to that predicted by a masking framework. Several explanations are plausible: a true effect may exist but be too small to detect at the present sample size; the follow-up window may be too short for bipolar conversion to emerge[18, 38, 39, 45]; or the heterogeneity of real-world prescribing may dilute any mediating signal. Nonetheless, the present data do not provide empirical support for the strong form of the pharmacological masking hypothesis in adolescent samples of this size and duration.

Attrition and the risk-enriched analytic sample

Regarding the generalizability of our findings, the attrition analysis warrants careful consideration. The analytic sample represents a clinically high-risk subgroup retained through active care. Our findings should therefore generalise to clinically engaged, monitored adolescents rather than the broader MDD population. We acknowledge that completers may differ from non-completers on unmeasured variables (e.g., motivation, family support).

Strengths and limitations

Strengths. The study used a registered protocol with a publicly accessible trial registration, applied an a priori likelihood ratio test to justify the random-slope structure, and used Benjamini-Hochberg FDR correction across all non-pre-registered outcomes[35]. A formal causal mediation analysis was used to interrogate the pharmacological masking hypothesis directly. Pre-specified covariate sensitivity analyses further demonstrated that the primary anxiety signal was not attributable to baseline differences in family psychiatric history or left-behind duration between completers and non-completers (Supplementary Table S7). All analyses, including null and exploratory results, are reported transparently with both raw and adjusted statistics.

Limitations. Several limitations must be acknowledged.

First, the trial was registered approximately 12 weeks after enrolment began, and the present study is therefore retrospectively registered. Although the registered primary and secondary outcomes were specified before data lock, the registration cannot be considered fully prospective.

Second, anxiety (SAS) was not specified as an outcome in the registry entry. Its analysis here is post-hoc, and the corresponding finding (raw p = 0.015) did not survive FDR correction (q = 0.18). The signal should

be considered hypothesis-generating only and requires independent pre-registered replication before clinical application. Nevertheless, the fact that the raw p-value reached 0.015 despite wide confidence intervals suggests a non-negligible effect that warrants testing in a larger, pre-registered study.

Third, with n = 108 the analytic sample provides limited precision for interaction effects, as reflected in the relatively wide confidence interval for the DMF × time interaction (0.47 to 4.22). Three-way interaction analyses are particularly underpowered and should be regarded as hypothesis-generating only.

Fourth, DMF status was ascertained by consensus clinical judgement based on DSM-5 criteria rather than a structured instrument such as the KMDRS[30]. Although inter-rater reliability was excellent (κ = 0.89; estimated on a pilot sample of 20 cases), this estimate is itself imprecise and should be regarded as a preliminary reliability indicator.

Fifth, the initial clinical diagnosis at each site was made using ICD-10, the standard system in routine Chinese psychiatric practice and as recorded in the trial registry; DMF status was determined by independent DSM-5 re-classification. While this reflects a structural feature of the present diagnostic landscape rather than an analytic deficiency, it introduces a non-trivial risk of misclassification at the boundary between DSM-5-defined DMF and ICD-10-defined "agitated depression."

Sixth, follow-up duration (median 18.1 weeks per patient) characterises the early-to-mid stabilisation phase only. Longer-term outcomes, particularly diagnostic conversion to bipolar disorder[29], would require extended follow-up; the very small number of conversion events in the present window (n = 2) precluded meaningful modelling.

Seventh, medication use was not randomised; the mediation analysis is therefore subject to confounding by indication, and causal interpretation should be conservative.

Eighth, the analytic sample was restricted to five-visit completers; high attrition (76%), partly reflecting the large left-behind population, may limit generalisability, though sensitivity analyses adjusting for family psychiatric history did not alter the primary finding (Supplementary Table S7).

Ninth, the study was conducted at two geographically proximate sites within a single province in southwest China, and the cohort included a high proportion of left-behind children (56% of the sample). Although this provides rare longitudinal data on a vulnerable and understudied population, generalisability to adolescents without such backgrounds, to other Chinese regions, and to non-Chinese adolescent populations remains to be established.

Implications for clinical practice and research

Clinical implications. The present evidence does not support the use of the DMF specifier in adolescents to predict a worse short-term trajectory of depression or suicide attempts in routine outpatient care. The post-hoc anxiety signal is too fragile to alter clinical practice in isolation. Clinicians should continue to monitor anxiety symptoms in adolescents with DMF presentations, but should not assume that standard

treatment will be ineffective in this group based on present evidence alone. The substantial and DMF-independent decline in medication adherence over follow-up represents a more pressing real-world clinical challenge in this population.

Research implications. Future studies should: (i) be pre-registered with outcome hierarchy specified prior to enrolment; (ii) use samples of sufficient size to detect small-to-moderate interaction effects (n ≥ 300 for two-way; substantially larger for three-way); (iii) employ structured DMF instruments such as the KMDRS; (iv) implement fixed follow-up intervals to reduce timing bias; (v) include longer follow-up to assess diagnostic conversion[45]; (vi) prospectively test anxiety trajectory as a primary outcome, ideally leveraging data-driven approaches such as group-based trajectory modeling (GBTM) to identify distinct, latent sub-trajectories of anxiety within adolescent mixed depression; and (vii) incorporate multimodal neuroimaging (e.g., functional MRI and diffusion tensor imaging) alongside objective behavioral metrics (e.g., eye-tracking) to elucidate the neurobiological and physiological mechanisms driving persistent anxious arousal in this vulnerable population.

Conclusions

In this naturalistic cohort of adolescents with early-course MDD, neither suicide attempts (registered primary outcome) nor depression severity (registered secondary outcome) differed by DSM-5 mixed features status over a median follow-up of 18.1 weeks. A post-hoc analysis suggested that anxiety improvement may be slower in DMF adolescents, but this finding did not survive correction for multiple testing. Formal mediation analysis did not support the pharmacological masking hypothesis. These findings are best regarded as hypothesis-generating and should be tested in adequately powered, pre-registered replication studies before any clinical application.

Declarations

Funding

This work was supported by the Scientific Research Development Plan of the Clinical Medical College and Affiliated Hospital of North Sichuan Medical College (Grant No. 2025LC018).

Competing interests

The authors declare no competing interests.

Ethics approval

The study was approved by the Medical Ethics Committee of the participating tertiary hospital (No. 2024ER388-1) and conducted in accordance with the Declaration of Helsinki.

Consent to participate

Written electronic informed consent was obtained from legal guardians, with assent from minors aged ≥12 years.

Consent for publication

Not applicable (no identifiable individual data).

Data availability

The de-identified dataset and full R analysis pipeline are deposited in Harvard Dataverse (private review URL in cover letter); the repository will be made public upon acceptance, subject to ethics committee approval.

Author contributions

Ping Mo:Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Visualization, Investigation, Data curation.

Xingyu He:Investigation, Data curation, Project administration, Writing - review & editing.

Min Liu:Investigation, Data curation, Writing - review & editing.

Zhaxi Dengzhu:Investigation, Data curation, Writing - review & editing.

Wenxiu Luo: Investigation, Data curation, Writing - review & editing.

Meilin Wu:Investigation, Data curation, Writing - review & editing.

Yujia Zhao:Investigation, Data curation, Writing - review & editing.

Jiaming Luo: Conceptualization, Supervision, Project administration, Resources, Funding acquisition, Writing – review & editing.

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Figures

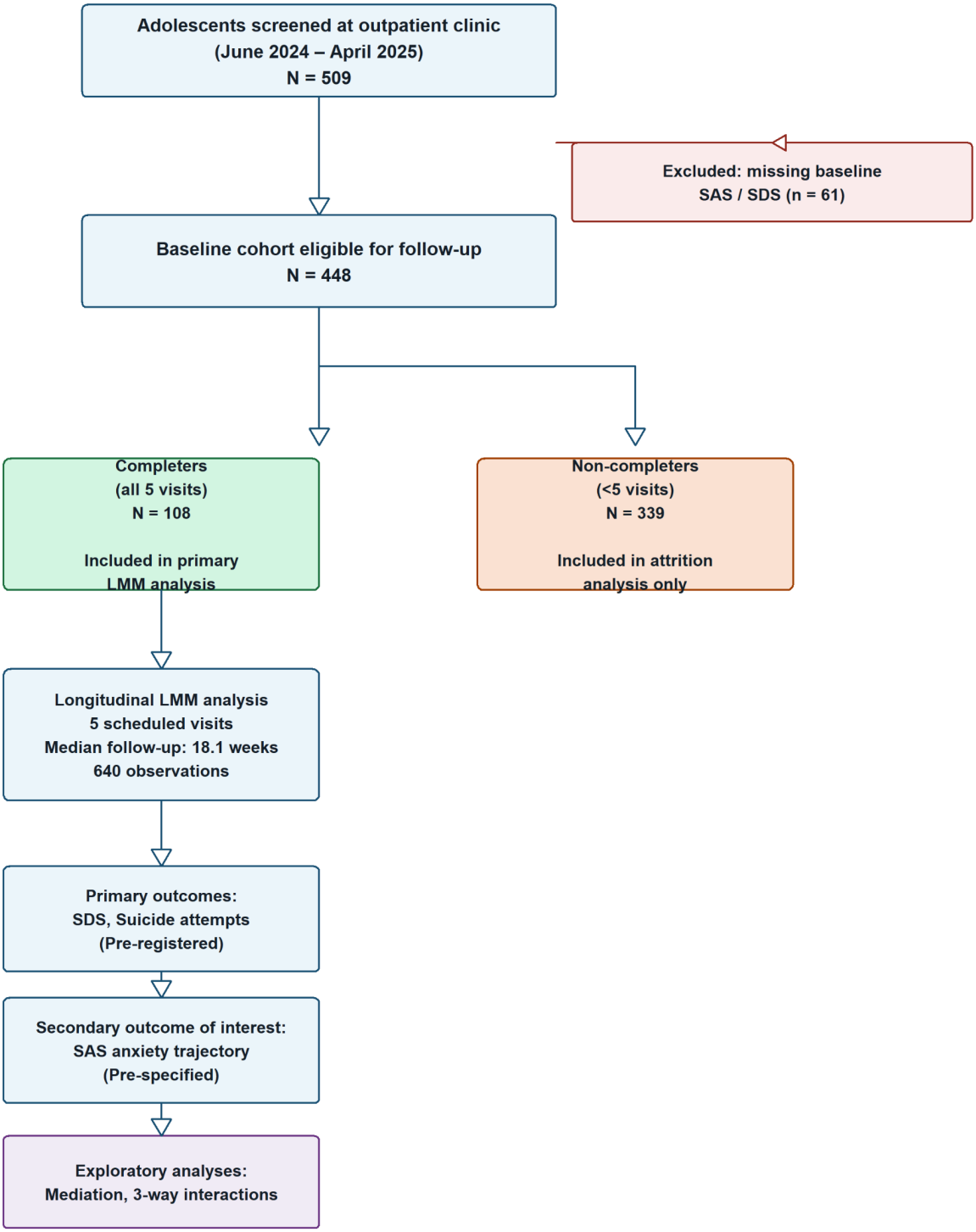


Figure 1

Participant flow diagram

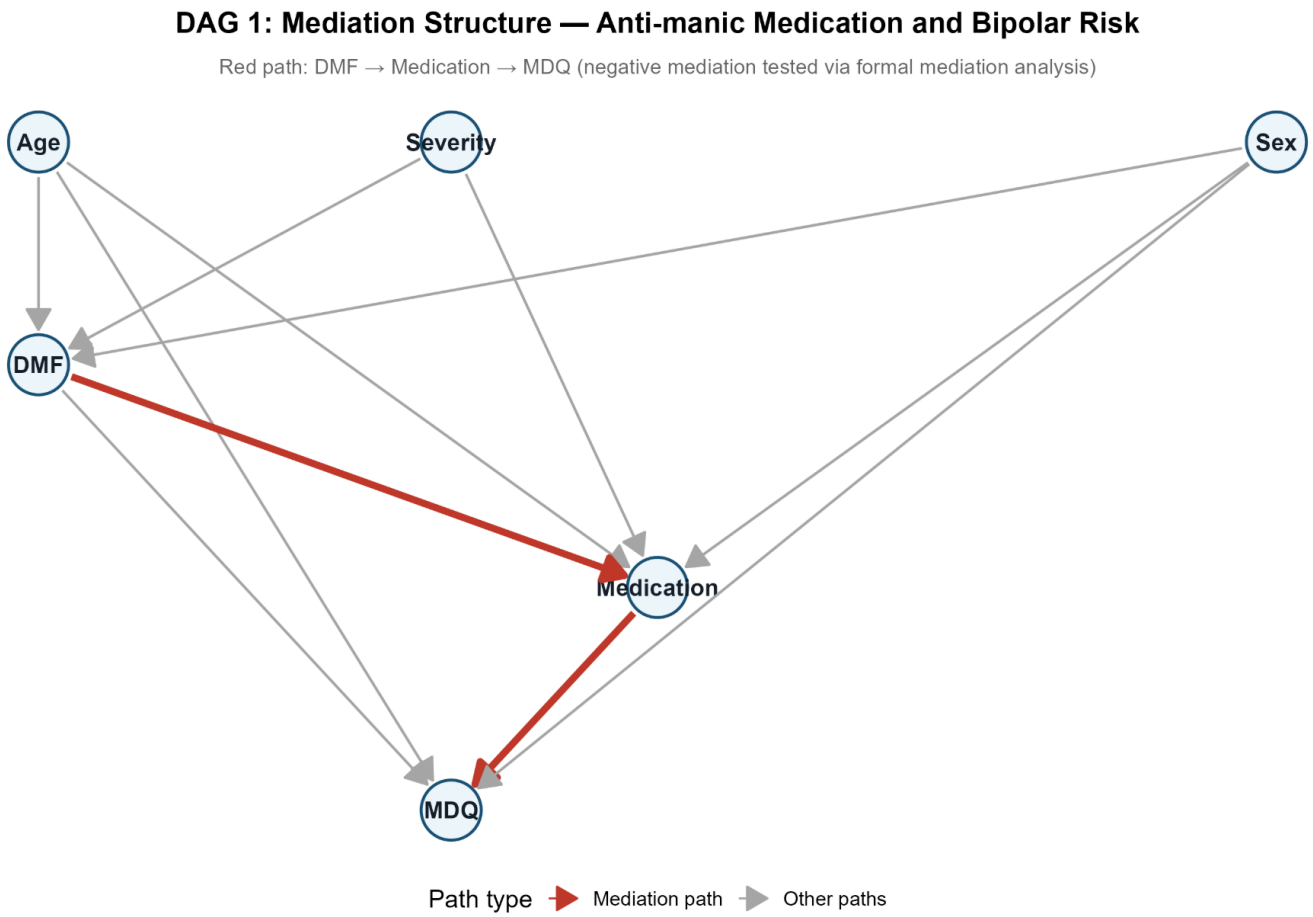


Figure 2

Mediation analysis of the DMF–medication–MDQ pathway

Supplementary Files

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