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DIFFERENCES IN EARLY-ADULTHOOD ATYPICAL DEPRESSION, BIOLOGICAL CHARACTERISTICS AND ANXIETY BY ADOLESCENT DEPRESSION TRAJECTORIES

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Abstract

Atypical depression (AD) has historically been characterized by early-onset, distinct biological characteristics, and higher comorbidity with anxiety. However, its developmental course remains understudied in a truly developmental design. The current study used data from the Avon Longitudinal Study of Children and Parents (ALSPAC, n = 4433) to identify depression trajectories (12–18 years) via latent class growth analysis (LCGA). Three classes emerged: early-onset, late-onset, and low-risk. Using the Bolck–Croon–Hagenaars (BCH) method, the relationship between the trajectories and AD, metabolic syndrome, CRP, BMI (age 24), and generalized anxiety (age 21) outcomes were analyzed. The early-onset class showed significantly higher AD than the other classes. While early-onset sample also had higher anxiety, metabolic syndrome, and BMI, these differences were not statistically significant despite small to medium effect sizes, possibly due to the small sample size of this trajectory (n = 140). Interestingly, AD was correlated with anxiety across all classes. These findings underscore the long-term impact of early-onset depression and the need for further research to clarify AD's etiology and correlates.

Keywords: *Atypical depression, developmental depression trajectories, biological characteristics, anxiety, comorbidity.*

1. Introduction

Depression, a heterogeneous disorder, has historically been divided into typical (melancholic) and atypical subtypes (West & Dally, 1959). The DSM-5 defines atypical depression (AD) by mood reactivity, increased appetite or weight gain, hypersomnia, leaden paralysis (often studied as fatigue), and rejection sensitivity (American Psychiatric Association, 2013). However, not all criteria are equally effective in identifying AD (Parker et al., 2002). Compared to typical depression (TD), AD shows higher comorbidity with physical conditions (e.g., obesity, cardiovascular disease; Lamers et al., 2013) and Axis-I disorders, especially anxiety (Zisook et al., 2004), and responds better to MAOIs (Moraczewski & Aedma, 2022). Identifying AD correctly can clarify depression's etiology, improve prognosis prediction, treatment, and resource allocation (Brailean et al., 2020).

Research increasingly suggests that AD and TD differ due to biological factors (Thase, 2009). AD is linked to high BMI, increased inflammation (Lamers et al., 2010), leaden paralysis (Posternak & Zimmerman, 2002), and metabolic syndrome (e.g., high blood pressure, triglycerides; Lamers et al., 2013). However, findings are inconsistent. Some studies report lower inflammation in AD than healthy controls (Dunjic-Kostic et al., 2013), higher inflammation in TD, or no difference between AD and TD (Karlovic et al., 2012). Thus, a bio-psycho-social approach is needed for clarity. In addition, both clinical and epidemiological studies characterize AD with early onset and chronicity (Stewart, McGrath, Quitkin, & Klein, 2009). Some even suggest its biological profile is most pronounced in, or even limited to, early-onset cases (Stewart, Quitkin, McGrath, & Klein, 2005). Finally, anxiety frequently co-occurs with AD, with some proposing AD is primarily an anxiety disorder where anxiety precedes depression (Sargant & Slater, 1972). Empirical studies support this, showing MAOIs are most effective when chronic early-onset anxiety precedes depression (Davidson et al., 1980), and some link MAOI's success in AD treatment to its effectiveness in treating comorbid anxiety (Joyce & Paykel, 1989). More recent studies also confirm that AD is associated with higher levels of anxiety symptoms than TD (Brailean et al., 2020).

Despite this clear relationship between AD and anxiety, the DSM does not include this phenomenon (Thase, 2009).

Thus, clarifying AD's biological characteristics is a crucial step for clarifying AD, and in turn the etiology of depression in general. While AD's unique biological profile is widely recognized, further empirical refinement is needed given inconsistencies between empirical results. AD's relationship with anxiety also remains underexplored, particularly developmentally. No prior study has simultaneously examined depression onset, biological characteristics of AD, and anxiety developmentally, which this study aims to address.

2. Method

2.1. Participants

A subsample from the Avon Longitudinal Study of Children and Parents (ALSPAC; Boyd et al., 2013; Fraser et al., 2013) was used. Participants with data from at least two of six depression assessments were included (Rice et al., 2019). Those without valid data on both key outcomes (i.e., AD at 24 years, generalized anxiety at 21 years) were excluded in Step-1 (n = 4,433), and an additional 51 with extreme CRP values (>10 mg/L) were excluded in Step-2 (n = 4,382).

2.2. Measures

Depression symptoms used as trajectory indicators were assessed with the Short Mood and Feelings Questionnaire (SMFQ; Angold et al., 1995) at ages 11 years 8 months, 12.5, 13.5, 16.5, 17.5, and 18.5. The SMFQ has shown high validity in the ALSPAC sample (Turner et al., 2014). Scores were summed and dichotomized at each time point, with scores above 11 indicating clinically significant symptoms (Rice et al., 2019).

AD symptoms as a distal outcome were measured at age 24 using DSM-5 AD specifier items from the Computerised Interview Schedule–Revised (CIS-R; Patton et al., 1999), a highly valid tool (Lewis, 1994). These four items were dichotomized and used in a confirmatory factor analysis (CFA) to estimate individual factor scores. Factor scores were also estimated via CFA for generalized anxiety at 21, measured via the highly valid and reliable GAD-7 (Spitzer et al., 2006). Metabolic syndrome, measured at 24, was defined by ATP-III criteria (Lamers et al., 2010). The five criteria were dichotomized to represent values above vs. below the sex-specific cut-off points, used as indicators for the CFA to estimate the factor scores. All CFA models showed satisfactory fit. CRP (mg/L) was derived from fasting blood samples, and the BMI was calculated as [weight (kg)] / [height $(m)^2$], both collected at 24 years. Sex, maternal education, and maternal social class were included as covariates.

3. Statistical analysis

In Step-1, depression trajectories were estimated via LCGA using the modified Bolck–Croon–Hagenaars (BCH) method (Bakk, Tekle, & Vermunt, 2013), which was manually applied in Mplus 8.7 (Muthén & Muthén, 2017) and the BCH weights for each individual were saved. The modified BCH method is the most robust and least biased for estimating relationships between class membership and continuous distal outcomes. It preserves the latent class solution, handles non-normality and unequal variances, estimates robust standard errors, and allows covariate inclusion (Bakk & Vermunt, 2016). A 3-class solution, as supported by Rice et al. (2019), was tested using a stepwise model comparison approach based on multiple fit criteria. In Step-2, class membership effects on distal outcomes were examined while controlling for covariates. The Wald Chi-square test (Wald, 1943) was used to compare class-specific means while incorporating individual BCH weights estimated in Step-1 (Asparouhov & Muthén, 2021). FIML (Enders & Bandalos, 2001) was applied to handle missing data in distal outcome variables and covariates.

4. Results and discussion

Three depression trajectories were identified using an approach from Rice et al. (2019): Low-risk (76.6%), late-onset (18.6%), and early-onset (4.8%). The early-onset class exhibited clinically significant depression beginning at age 12.5, with an increase by age 13.5. The late-onset class showed depression onset at age 16.5, rising by age 17.5. Both early-onset (74.6%) and late-onset (74.4%) groups had a high proportion of females than the low-risk class (58%). Maternal education and social class did not differ notably between groups, except that the low-risk class had more participants from a professional social class than the late-onset group. These trajectory classes closely mirrored those identified by Rice and colleagues (2019), and were also consistent with other previous studies (e.g., Mezulis, Salk, Hyde,

Priess-Groben, & Simonson, 2014; Musliner, Munk-Olsen, Eaton, & Zandi, 2016) and epidemiological data showing that depression peaks between 15 and 18 years (late-onset) and is rarer before 13 years (early-onset; Hankin et al., 1998).

The early-onset class had the highest AD score, followed by the late-onset class and the low-risk class, with significant differences between all three. Thus, the results empirically show for the first time that chronic early-onset depression throughout adolescence is associated with AD and that these are considerably long-term effects (i.e., elevated depression from 12 to 18 years is associated with higher AD at 24 years). For anxiety, both the early-onset and late-onset classes had a significantly higher score than the low-risk class. However, the difference between the early-onset and late-onset classes was not significant, even though the early-onset class had a higher score and the difference had a medium effect size (d = 0.4). Early-onset class (4.8%, n = 210) also had the highest metabolic syndrome and BMI scores, however, the differences were not significant, possibly due to the small sample size, which hinders statistical power needed to detect differences between factor scores (Angst, Aeschlimann, & Stucki, 2001) and might have masked some effects. For example, metabolic syndrome scores showed no significant difference between the early-onset class (M = 0.369) and the low-risk class (M = 0.279, d = 0.2), while the difference between late-onset class (M = 0.364) and low-risk class was significant despite having a smaller effect size (d = 0.19). Given the limited research on statistical power in latent class modeling, particularly for distal outcomes using the BCH method (Gudicha, Tekle, & Vermunt, 2016), the required sample size per trajectory class to achieve enough statistical power cannot be directly calculated. However, the results provide strong evidence that future studies with larger early-onset samples are needed to clarify potential relationships between early- and late-onset depression and AD-related variables. Similarly, regarding BMI, both the early-onset and late-onset classes had a significantly higher score than the low-risk class (respectively, d = 0.52 and d = 0.18). No significant difference was found between the early-onset and late-onset classes despite the early-onset class having a higher score with a medium effect size (d = 0.34). On the other hand, results regarding CRP were completely contrary to expectations. Not only there were no significant differences in CRP scores between classes, the early-onset class had the lowest CRP score. This contradicts prior findings linking higher CRP to AD (e.g., Lamers et al., 2013). Still other studies that found no difference in CRP between AD and TD also exist (Karlovic et al., 2012; Osimo et al., 2020), suggesting CRP may not be a reliable marker. Alternatively, only a recent increase in CRP may be associated with depression (Osimo et al., 2019), which would not be detected in this study. Finally, the CRP score of the early-onset class had a very large standard error, again possibly due to the small sample size, which indicates the early-onset class CRP score may not represent its "true" value. This further emphasizes the need for future studies with a larger early-onset sample.

Additionally, AD was significantly correlated with anxiety in all classes, suggesting this association exists regardless of the age of depression onset and even in individuals with chronically low levels of depressive symptoms (i.e., subthreshold symptoms) throughout adolescence. Similarly, BMI was significantly correlated with both metabolic syndrome and CRP in all trajectory classes. Metabolic syndrome and CRP were significantly correlated in the early-onset and low-risk classes, but not in the late-onset class.

Despite limitations, the current study is the first to comprehensively examine the link between developmental depression trajectories, AD, its biological characteristics, and anxiety. Overall, the study has two main clinical implications: It provides the first empirical evidence that chronic early-onset depression throughout adolescence is associated with higher AD in early adulthood and that a consistent correlation between AD and anxiety is observed across all classes, suggesting this association exists even in those with chronically low (i.e., subthreshold) depressive symptoms. Additionally, given there is strong evidence that insufficient statistical power may have obscured potential relationships, ongoing monitoring of the physical health of individuals with early-onset depression, especially concerning BMI and metabolic syndrome, is essential.

Table 1. Descriptive statistics for study variables.

	Early-onset class					Late-onset class					Low-risk class				
	AD	**GAD**	**MS**	**BMI**	**CRP**	**AD**	**GAD**	**MS**	**BMI**	**CRP**	**AD**	**GAD**	**MS**	**BMI**	**CRP**
AD	1					1					1				
GAD	0.186*	1				0.214*	1				0.313*	1			
MS	0.029	0.007	1			0.027	0.010	1			0.028	0.014	1		
BMI	0.015	-0.011	0.620*	1		0.015	-0.014	0.651*	1		0.015	-0.020	0.684*	1	
CRP	-0.027	0.013	0.161*	0.240*	1	-0.013	0.090	0.091	0.132*	1	-0.015	0.014	0.102*	0.154*	1
M	0.043[ab]	0.459[b]	0.369	29.889[b]	0.379	0.021[ac]	0.265[c]	0.364[c]	28.311	0.511	-0.023[bc]	-0.270[bc]	0.279[c]	27.468[b]	0.496
SD	0.055	0.865	0.462	5.001	0.822	0.063	0.680	0.445	4.945	1.509	0.063	0.484	0.440	4.746	1.354

*Abbreviations: AD, atypical depression; GAD, generalized anxiety disorder; MS, metabolic syndrome; BMI, body mass index; CRP, c-reactive protein; M, mean score; SD, standard deviation. * Correlation coefficient is significant at $p < 0.05$ level. a Mean score difference is significant between the early-onset and late-onset classes. b Mean score difference is significant between the early-onset and low-risk classes. c Mean score difference is significant between the late-onset and low-risk classes.*

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