Brain, Behavior, and Immunity 132 (2026) 106190

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Diagnosis of depression in adolescence signals improved inflammatory health in adulthood: Results from a nationally representative longitudinal study

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ARTICLE INFO

Keywords:
Childhood maltreatment
Inflammation
C-reactive protein
Depression
Diagnosis
Treatment

ABSTRACT

Objective: Childhood maltreatment increases subsequent risk for major depressive disorder (MDD), potentially through inflammatory pathways. The timely diagnosis and treatment of MDD may thus interrupt the association between inflammation and depressive symptoms, but diagnosis is frequently delayed. Additionally, sex-differences may affect timely diagnosis and treatment, contributing to differences in inflammation and depressive symptoms as individuals age.
Method: We used data from the nationally representative National Longitudinal Study of Adolescent to Adult Health to examine how diagnosis of MDD in adolescence vs. adulthood affected associations between childhood maltreatment, C-reactive protein (CRP) levels, and depressive symptoms in adulthood. We used path analysis to examine associations between these variables and then tested for sex differences by moderating pathways by sex.
Results: Childhood maltreatment increased the risk of being diagnosed with MDD at any time, and being diagnosed with MDD was associated with greater depressive symptoms in adulthood. Diagnosis of MDD at any time was associated with greater depressive symptoms, but diagnosis of MDD in adolescence was associated with lower CRP levels relative to diagnosis in adulthood. Sex differences analysis indicated that CRP was greatest for males diagnosed in adulthood despite females being diagnosed in adulthood having a greater body mass index.
Conclusion: These data demonstrate that diagnosing MDD in adolescence was associated with better inflammatory health in adulthood. Diagnosing and treating depression sooner after symptom onset may thus improve overall prognosis, particularly for males, and potentially reduce the risk for other inflammation-related conditions as well.

1. Introduction

Childhood maltreatment is a well-documented risk factor for major depressive disorder (MDD) in adulthood. Evidence suggests that 46 % of people who experience MDD report a history of childhood maltreatment and that a 10–25 % reduction in childhood maltreatment could prevent millions of cases of MDD across the globe (Li et al., 2016; Lippard & Nemeroff, 2020). Experiences of childhood maltreatment often indicate an overall worse course of illness, including a greater number of depressive symptoms, increased risk for death by suicide, and a greater chance for treatment resistance to current front-line treatments (Medeiros et al., 2020; Nanni et al., 2012; Williams et al., 2016).

One potential mechanism linking childhood maltreatment and MDD is an increase in inflammatory signaling that targets areas of the brain associated with depressive symptoms (Miller et al., 2009; Slavich & Cole, 2013; Slavich & Irwin, 2014). Social Safety Theory provides a framework for understanding these effects grounded in three key tenets: (a) humans have evolved to foster socially supportive and friendly bonds (social safety), (b) experiences of social safety are beneficial to health, behavioral outcomes, and longevity; and (c) experiences of social threats are harmful to health, behavioral outcomes, and mortality (Slavich, 2020; Slavich et al., 2023a). Experiences of social safety and social threats influence cognitive schemas that have reciprocal effects with perceptions of social experiences (Slavich et al., 2023a). Through these

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https://doi.org/10.1016/j.bbi.2025.106190
Received 21 July 2025; Received in revised form 27 October 2025; Accepted 18 November 2025
Available online 19 November 2025

mechanisms, early life experiences of social safety and social threats calibrate stress detection and responsivity (Slavich et al., 2023a). Therefore, individuals who have experienced childhood maltreatment may have more frequent activation of the body's stress response than unaffected peers.

Activation of the stress response increases inflammation in both the periphery and the central nervous system through several pathways (Slavich & Irwin, 2014). When a threat is detected, threat detection circuits of the brain activate the hypothalamic–pituitary–adrenal axis, sympathetic nervous system, and efferent vagus nerve (Slavich and Irwin, 2014; Miller and Raison, 2016). Activation of these systems leads to the production of the glucocorticoids, epinephrine, norepinephrine, and acetylcholine that then target immune cells in the periphery. Initially, glucocorticoids and epinephrine suppress the immune system, followed by norepinephrine and acetylcholine causing an increase in the production of pro-inflammatory cytokines (Slavich and Irwin, 2014; Miller and Raison, 2016). These pro-inflammatory cytokines then target the brain through activation of the afferent vagus nerve, traversal of the blood brain barrier (BBB), and/or infiltration of leaky tight-junction spaces in the BBB (Miller and Raison, 2016; Slavich & Irwin, 2014; Slavich et al., 2023b). Proinflammatory cytokines then target cortices of the brain implicated in depressive symptoms as well as threat detection. Repeated activation of these pathways has been found upregulate proinflammatory gene expression, pushing the body towards greater basal inflammation (i.e. the conserved transcriptional response to adversity; Slavich & Irwin, 2014). Inflammation has been most strongly associated with fatigue, sleep disturbance, and anhedonia, while depressive mood states have been associated with negative cognitive biases (Fried et al., 2020; Jokela et al., 2016; Moriarity et al., 2021; Maydych, 2019; Slavich et al., 2023a). These negative cognitive biases then increase the odds of perceiving social interactions as social threats which in turn activates the stress response (Maydych, 2019). Thus, inflammation and depressive symptoms have bidirectional effects that can sustain each other (Beurel et al., 2020).

A diagnosis of MDD soon after the onset of symptoms is likely to yield timelier treatment, and frontline treatments such as SSRI's and CBT have evidence for decreasing inflammation (Shields et al., 2020; Luo et al., 2020; Teicher et al., 2022). Thus, timely MDD treatment may interrupt the dually sustaining effects between inflammation and depressive symptoms, potentially yielding lower basal levels of inflammation and depressive symptoms as individuals age. However, while most individuals who experience MDD are eventually diagnosed, only 37.4 % are diagnosed within the same year that symptoms first occur (de Girolamo et al., 2012; Jones, 2013; Kessler et al., 1998; Wang et al., 2005). Among the remaining individuals who experience MDD but are not diagnosed within the same year, the majority are not diagnosed until 6–8 years after onset (Wang et al., 2005). Notably, MDD is characterized by recurrent major depressive episodes (MDEs), greater numbers of MDEs predict shorter periods of recovery between MDEs, and only around half of MDEs remit within six months after onset when left untreated. In consequence, adolescents who are never treated for MDD are at substantial risk for prolonged periods of increased inflammation and depressive symptoms (Hardeveld et al., 2013; Mueller et al., 1999; Spijker et al., 2002).

1.1. Sex differences

Sex differences have long been documented among the associations between childhood maltreatment, inflammation, and MDD. Following the pubertal transition, females have found to have around twice the incidence of MDD as males, with one potential explanatory mechanism being that sex-hormones are able to bind to immune cells that produce inflammatory molecules (Hyde et al., 2008; Nolen-Hoeksema, 1987; Nolen-Hoeksema & Girgus, 1994; Mengelkoch & Slavich, 2024; Slavich & Sacher 2019). Additionally, males and females have been found to differ in their long-term health outcomes, dependent on their childhood maltreatment experiences (Baumeister et al., 2016; O'Shields et al., 2023). For instance, adult males who experience childhood sexual abuse have been found to have higher levels of C-reactive protein (CRP) relative to their female counterparts (Iob et al., 2022; O'Shields et al., 2025). Although, some evidence also suggests that females who experience multiple types of childhood maltreatment have been found to have higher levels of overall inflammation as measured by a composite of several inflammatory molecules, including CRP, relative to their male counterparts (Ehrlich et al., 2021). Furthermore, males and females are both more likely to experience MDD after experiencing emotional abuse, but experiences of physical abuse and physical neglect have been associated with an older age of MDD onset for males only (Dong et al., 2024).

When MDD does occur, several differences have been documented in how males and females interact with treatment services. Some evidence points toward females being more likely to seek help for depressive symptoms, be diagnosed with MDD, and be prescribed an SSRI for treatment (Pratt et al., 2017; Sundbom et al., 2017; Brody & Gu, 2020). Further, because females are more likely to experience childhood maltreatment, they may be at increased risk for MDEs in adolescence and therefore experience greater periods of inflammation (Nelson et al., 2017). However, even when females are more likely to be diagnosed and receive treatment for MDD, childhood maltreatment still places individuals at an increased risk for treatment resistant MDD (Williams et al., 2016; Teicher et al., 2022). With this in mind, females exposed to childhood maltreatment have reduced odds of effective SSRI treatment while leaving them at risk for side-effects such as weight gain which may further increase basal inflammation (Fava, 2000; Rushovich et al., 2023; Williams et al., 2016; Teicher et al., 2022). Conversely, when males do experience MDD they tend to experience milder MDEs, leading to lower recognition of the benefits of seeking help while contributing to the risk for underdiagnosis of MDD (Shi et al., 2021; Sihvola et al., 2007).

1.2. The present study

The timely diagnosis of MDD may play an important role in interrupting the synergistic effects between depressive symptoms and inflammation, potentially reducing inflammation and depressive symptoms as individuals age. At the same time, diagnosing MDD is frequently delayed by several years, meaning that many individuals may not begin treatment until adulthood despite symptom onset in adolescence. Further, there are significant social and biological factors that contribute to differences in the timely diagnosis and effective treatment of MDD between males and females, complicating how a timely diagnosis may lead to sex-differences in inflammation and depressive symptoms in adulthood (Shi et al., 2021). In the present study, we aimed to advance understanding on this topic by investigating how diagnosis timing of MDD affects inflammation and depressive symptoms in adulthood. Based on the literature reviewed above, we hypothesized that: (a) individuals diagnosed with MDD in adulthood would have greater inflammation and depressive symptoms than those diagnosed with MDD in adolescence; and (b) males and females would differ in depressive symptoms and inflammation in adulthood dependent on when they were diagnosed with MDD. Specifically, we hypothesized that females diagnosed in adolescence would have greater inflammation and depressive symptoms than males diagnosed in adolescence.

2. Method

2.1. Data Source

Data were drawn from the National Survey of Adolescent to Adult Health (Add Health; Harris et al., 2019), a panel study that originally sampled 90,118 U.S. adolescents in a school-based survey and followed up with 20,745 of those students for an expanded in-home survey. Since the initial survey, four subsequent waves of data have been collected from the sample. We used data from the Wave 1 in home survey

(1994–1995), Wave 3 (2001–2002), Wave 4 (2008–2009), and Wave 5 (2016–2018). Given the study hypotheses, we only included participants who also participated in the biomarker subproject of Wave 5, leaving a potential data frame of 1,932 participants. From this pool, we analyzed complete cases ($n = 1{,}411$) while using the Wave 5 biomarker weights to provide nationally representative estimates.

2.2. Measures

Childhood Maltreatment: We assessed five types of childhood maltreatment: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Emotional abuse was assessed retrospectively at Wave 4 by asking participants "before your 18th birthday, how often did a parent or other adult caregiver say things that really hurt your feelings or made you feel like you were not wanted or loved?" Physical abuse was assessed retrospectively at Wave 4 by asking participants "how often had your parents or other adult caregivers slapped, hit, or kicked you?" Sexual abuse was assessed retrospectively at Wave 4 by asking participants "How often had one of your parents or other adult caregivers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations?" Emotional neglect was assessed retrospectively at Wave 3 by asking participants "by the time you started 6th grade, how often had your parents or other adult caregivers left you home alone when an adult should have been with you?" Physical neglect was assessed retrospectively by asking participants "How often had your parents or other adult caregivers not taken care of your basic needs, such as keeping you clean or providing food or clothing?" Participant response to each maltreatment variable were recorded via Likert scale: (1) one time, (2) two times, (3) three to five times, (4) six to ten times, (5) more than ten times, (6) this never happened. Maltreatment experiences were indexed, based on any occurrence of each type of maltreatment. This yielded an index ranging from 0 (this never happened) – 5 (more than ten times), with greater values indicating experiencing more types of childhood maltreatment.

Age at Major Depressive Disorder Diagnosis: Age first diagnosed with MDD was assessed via participant self-report at Wave 5. Participants were asked, "has a doctor, nurse, or other health care provider ever told you that you have or had depression?" Participants who affirmed that a health care provider told them they had depression were then asked, "how old were you when you were diagnosed by a doctor, nurse, or other health care provider with depression?" Participant responses were collapsed into three levels: no diagnosis of MDD (reference group), adolescent MDD diagnosis (under the age of 18), adulthood MDD diagnosis (age 18 or older).

Body Mass Index: Body mass index (BMI) was assessed at Wave 5 using the standard formula: weight in kilograms divided by squared height in meters. Both participant height and weight were obtained during the in-home interview portion of the survey by a trained Add Health Interviewer. Height was measured to the nearest 0.05 cm while participants stood upright with their head, shoulders, buttocks, and heels flat against the wall. Weight was measured to the nearest 0.1 kg by a digital scale with the participant standing unassisted.

C-Reactive Protein: CRP was measured at Wave 5. Samples were derived from plasma, collected as venous blood via venipuncture by a phlebotomist as the final stage of the in-home visit. Samples were stored in collection tubes and chilled at 4◦ C for up to 2 h before being processed into serum and plasma via centrifuging. Samples were then shipped overnight to the University of Vermont where they were assayed via CRP-specific particle enhanced immunonephelometric assay via Siemens BNII/BN ProSpec System (Siemens Healthcare Diagnostic Products GmbH, Marburg, Germany). Sensitivity for Wave 5 CRP assay methods was dependent on the lower limit of the reference curve related, determined by the concentration of the protein in the N Rheumatology Standard SL (Whitsel et al., 2024). Reliability testing of CRP found an intra-class correlation coefficient of 0.82, 95 % CI [0.75, 0.89] (Whitsel et al., 2024).

Depressive Symptoms: Depressive symptoms were assessed at Wave 1 and Wave 5 using a 5-item version of the Center for Epidemiological Studies-Depression scale (Radloff, 1977). These items consisted of four affective symptoms "could not shake off the blues," "felt depressed," "you were happy," and "felt sad," as well as one symptom added to the measure by the add health team: "you felt life was not worth living." For each symptom participants were asked to rate their experience as either 0 "rarely or none of the time (less than 1 day)," 1 "some or a little of the time (1–2 days)," 2 "occasionally or a moderate amount of the time (3–4 days)," or 3 "most or all of the time (5–7 days)." Items were summed to create a total score that could have ranged from 0 to 15, with higher scores indicating more depressive symptoms over the past week. Cronbach's alpha for the present study was 0.80 for Wave 1 and 0.84 at Wave 5, indicating good internal consistency.

Sex: Sex was included categorically as female (1) or male (0), based on participant self-report at Wave 1.

Demographic Variables: We also controlled for several relevant sociodemographic variables, including age, race, and ethnicity, all of which were measured at Wave 1. Age was included as a continuous variable with a potential range of 12–21 years. Racial identity was accounted for categorically based on participant self-report as White, (reference group) Black, Native American, Asian, or other/multiple racial identities. Ethnic identity was accounted for categorically as non-Hispanic (reference group) or Hispanic.

Congounding Variables: We controlled for several confounding variables that may affect BMI, CRP, or depressive symptoms: tobacco cigarette smoking status, alcohol consumption, and early life socioeconomic disadvantage. Tobacco cigarette smoking status was accounted for categorically based on participant self-report at Wave 5 as no history of smoking (reference group), prior smoking status, or current smoking status. Alcohol consumption was accounted for continuously based on participant self-report at Wave 5 to the prompt: "Think of all the times you have had a drink during the past 30 days. How many drinks did you usually have each time? A 'drink' is a glass of wine, a can or bottle of beer, a wine cooler, a shot glass of liquor, or a mixed drink." Early socioeconomic disadvantage was approximated via Social Origins score, pre-calculated by the Add Health Team at Wave 1 (Belsky et al., 2018). Social Origins scores were derived via principal components analysis of parental education, parental occupation, household income, and household receipt of public assistance, before then being z-transformed.

2.3. Analytic strategy

To test the effects of childhood maltreatment and diagnosis timing on BMI, CRP, and depressive symptoms in middle adulthood, as well as potential sex differences, we used a series of path models. The first path model we used recalled childhood maltreatment, depression diagnosis timing, and depressive symptoms at Wave 1 as predictors of BMI at Wave 5, CRP at Wave 5, and depressive symptoms at Wave 5. BMI at

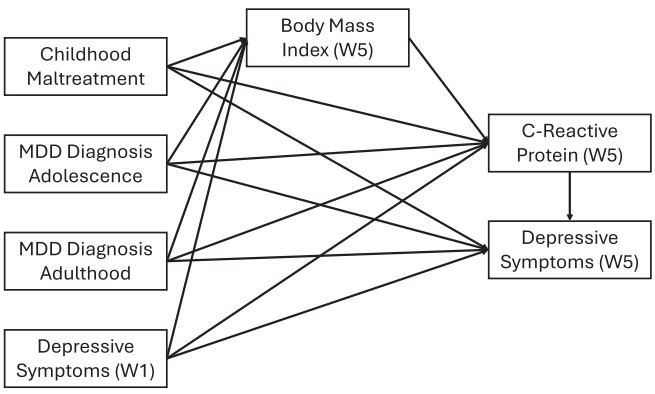

Fig. 1. Theoretical model tested.

Wave 5 was also modeled as a predictor of CRP at Wave 5. CRP at Wave 5 was modeled as a predictor of depressive symptoms at Wave 5. Per findings that the simultaneous inclusion of BMI and CRP as predictors of depressive symptoms may lead to type 2 error, BMI at Wave 5 was not included as a predictor of depressive symptoms at Wave 5 (Moriarity et al., 2023; See Fig. 1 for a graphical depiction of the theoretical model tested.) To assess model fit to the data we report the model fit chi-square test, Comparative Fit Index (CFI), Root Mean Square Error of Approximation (RMSEA), and the Standardized Root Mean Square Residual (SRMR). Analyses accounted for the complex sampling design of the Add Health data set as recommended by the Add Health data team. Analyses used the Survey, Lavaan, and lavaan.survey packages to carry out the analysis using R version 4.4.2 (Lumley, 2004; R Core Team, 2021; Rosseel, 2012; Oberski, 2014).

To explore potential sex differences in the effects of childhood maltreatment and diagnosis timing on BMI, CRP, and depressive symptoms in middle adulthood we used a combination of interaction terms which were integrated into the same statistical procedures explored in the first path model. We first created interaction terms for sex × MDD diagnosis timing, childhood maltreatment, depressive symptoms at Wave 1, BMI at Wave 5, and CRP at Wave 5. We then repeated the same statistical procedure implemented in the first path model while including interaction terms for each path. Sex was also included as a covariate predicting BMI, CRP, and depressive symptoms at Wave 5 per the inclusion of sex interaction terms. Because the inclusion of numerous non-significant interaction terms can result in poor model fit indices and untrustworthy parameter estimates, we first identified significant interaction terms individually in the path model and then tested all significant interactions simultaneously. We then adjusted the model for demographics and confounders as we did in the prior model.

Additionally, we calculated univariate and bivariate statistics to describe our sample. Univariate statistics were quantified in terms of means and ranges or frequencies and percentages. To understand how differences between MDD diagnosis timing groups we calculated means for relevant continuous variables across each level of the diagnosis timing variable and then used simple linear regression to provide a significance test, rotating the reference groups between the three levels of diagnosis timing. This method is akin to comparing means between groups using an ANOVA while incorporating sampling weights. Given the relevance of sex-differences to the paper, we also used a χ^2 differences test understand how sex may be differently distributed across MDD diagnosis timing. We report the means for these tests as relevant in the text and provide the simple linear regression models used for significance testing in the supplementary materials. Last, we conducted two sensitivity analyses to understand how different types of childhood maltreatment may affect our results. The first sensitivity analysis replaced our index of childhood maltreatment with the categorical experience of each type of childhood maltreatment. The second sensitivity analysis explored the effects of the frequency of each type of childhood maltreatment.

3. Results

3.1. Sample description

At the time of initial data collection, participants had a mean age of 15.86 ($SE = 0.13$), were majority White (74.88 %) or Black (12.02 %) in racial identity, and were majority female (68.80 %). Depressive symptoms were consistently low at both Wave 1 ($M = 2.52$, $SE = 0.09$) and Wave 5 ($M = 2.58$, $SE = 0.10$); however, a sizeable minority of participants had been diagnosed with MDD at some point in their life (39.42 %), the majority of which were diagnosed in adulthood (29.66 % of total sample). Most participants had experienced at least one form of childhood maltreatment ($M = 1.22$, $SE = 0.04$), with the most common form being emotional abuse (50.83 %), followed by emotional neglect (39.25 %), and physical abuse (19.79 %). See Table 1 for a complete review of the sample description.

Table 1
Sample Description.

	M (*SE*) or *N*	Range or %
Depressive symptoms (W5)	2.58 (0.10)	0 – 15
CRP mg/L (W5)	4.41 (0.21)	0.16–44.20
Logged CRP (W5)	0.81 (0.05)	−1.85 – 3.79
BMI (W5)	31.09 (0.35)	16.40–79.60
MDD diagnosed in adulthood	1,957250	29.66 %
MDD diagnosed in adolescence	644,508	9.76 %
No MDD diagnosis	3,995,529	
Childhood Maltreatment	1.22 (0.04)	0 – 5
Depressive Symptoms (W1)	2.52 (0.09)	0 – 15
Demographics:		
Age (W1)	15.86 (0.13)	12 – 21
Sex: Male	2,062,018	31.20 %
Race: Black	794,206	12.02 %
Race: Native American	48,632	0.73 %
Race: Asian	153,388	2.32 %
Race: Other	664,610	10.05 %
Ethnicity: Hispanic	628,101	9.54 %
Potential Confounders:		
Tobacco smoking: current	1,441,135	22.08 %
Tobacco smoking: prior	1,541,923	23.63 %
Alcoholic drinks per day	2.00 (0.07)	0 – 30
Family socioeconomic index	0.26 (0.07)	−4.66 – 3.35

Note that all statistics, including *n*, are calculated using survey weights.
CRP: C-reactive protein; BMI: body mass index; MDD: major depressive disorder.

Exploring differences between MDD diagnosis timing groups yielded several important insights. Females were more likely to be diagnosed with MDD than males, with 8.80 % of females being diagnosed with MDD in adolescence vs 2.11 % of males, and 23.08 % of females being diagnosed in adulthood vs 8.93 % of males ($\chi^2(127) = 4.62$, $p < 0.05$). Participants never diagnosed with MDD had lower depressive symptoms at Wave 1 ($M = 2.20$ $SE = 0.10$) compared to those diagnosed in adulthood ($M = 2.71$, $SE = 0.14$), whereas those diagnosed in adulthood had lower depressive symptoms at Wave 1 ($M = 2.17$, $SE = 0.14$) than those diagnosed in adolescence ($M = 3.82$, $SE = 0.33$). Differences in depressive symptoms were consistent at Wave 5, with those never diagnosed with MDD showing lower depressive symptoms at Wave 5 ($M = 1.65$, $SE = 0.09$) relative to Wave 1 as well as relative to other MDD timing groups. Participants diagnosed with MDD in adolescence had the greatest depressive symptoms at Wave 5 ($M = 4.71$, $SE = 0.38$). Participants who were never diagnosed with MDD also reported experiencing significantly fewer types of childhood maltreatment ($M = 1.05$, $SE = 0.05$) relative to those diagnosed with MDD in adolescence ($M = 1.62$, $SE = 0.13$) and in adulthood ($M = 1.41$, $SE = 0.07$), but no differences were observed between those diagnosed in adolescence and those diagnosed in adulthood. We observed no differences in BMI across MDD diagnosis timing groups. However, participants who were diagnosed with MDD in adulthood did have greater CRP at Wave 5 ($M = 1.01$, $SE = 0.08$) relative to those never diagnosed ($M = 0.69$, $SE = 0.05$) and those diagnosed in adulthood ($M = 0.80$, $SE = 0.16$), while there was no difference in CRP between participants diagnosed in adolescence and participants never diagnosed. See Supplementary Tables 1 – 6 for a complete reporting of means and corresponding significance testing.

3.2. Effects of childhood maltreatment and MDD diagnosis timing on BMI, CRP, and depressive symptoms

Model fit indices identified that the path model exploring the effects of maltreatment and depression diagnosis timing was a good fit to the data (See Table 2). For each type of childhood maltreatment experienced, there was an increase in participant BMI ($b = 0.90$, $SE = 0.35$, $p < 0.01$); greater BMI was in turn related to higher CRP ($b = 0.07$, $SE = 0.005$, $p < 0.001$). Additionally, individuals who were first diagnosed

Table 2
Multivariate Model Testing Effects of Childhood Maltreatment and MDD diagnosis timing on BMI, CRP, and Depressive Symptoms.

	BMI (W5)	CRP (W5)	Depressive symptoms (W5)
CRP (W5)	–	–	0.04 (0.07)
BMI (W5)	–	0.07 (0.00)***	–
MDD diagnosed in adulthood	0.46 (0.76)	0.21 (0.07)**	1.85 (0.24)***
MDD diagnosed in adolescence	−0.02 (1.20)	0.04 (0.16)	2.40 (0.56)***
Maltreatment	0.90 (0.35)**	0.03 (0.04)	0.20 (0.09)*
Depressive symptoms (W1)	0.21 (0.12)	−0.02 (0.01)	0.18 (0.05)***

Model $\chi^2 = 0.49$, $p = 0.48$; CFI = 1.00; TLI = 1.02; RMSEA = 0.00, 95 % CI: [0.00–0.02]; SRMR = 0.005.
All parameters are reported as *b* (*SE*).
CRP: C-reactive protein; BMI: body mass index; MDD: major depressive disorder.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 3
Multivariate Model Controlling for Demographics.

	BMI (W5)	CRP (W5)	Depressive symptoms (W5)
CRP (W5)	–	–	0.06 (0.07)
BMI (W5)	–	0.07 (0.005)***	–
MDD diagnosed in adulthood	0.69 (0.76)	0.19 (0.07)*	1.89 (0.23)***
MDD diagnosed in adolescence	−0.04 (0.15)	−0.04 (0.15)	2.40 (0.52)***
Maltreatment	0.80 (0.36)*	0.03 (0.04)	0.15 (0.10)
Depressive symptoms (W1)	0.17 (0.12)	−0.02 (0.01)	0.14 (0.05)**
Race: Black	3.60 (1.29)**	0.05 (0.11)	0.23 (0.27)
Race: Native American	2.92 (2.88)	−0.04 (0.38)	−0.002 (0.61)
Race: Asian	−2.09 (1.25)	−0.37 (0.31)	0.19 (0.46)
Race: Other	2.26 (1.22)	0.06 (0.19)	1.30 (0.67)
Ethnicity: Hispanic	0.34 (1.31)	0.01 (0.17)	0.18 (0.53)
Age	−0.09 (0.17)	−0.01 (0.02)	0.08 (0.06)
Sex: male	0.62 (0.81)	−0.45 (0.09)***	0.46 (0.26)

Model $\chi^2 = 1.58$, $p = 0.20$; CFI = 0.98; TLI = 0.94; RMSEA = 0.02, 95 % CI: [0.00–0.05]; SRMR = 0.004.
All parameters are reported as *b* (*SE*).
CRP: C-reactive protein; BMI: body mass index; MDD: major depressive disorder.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 4
Multivariate Model Controlling for Demographics and Potential Confounders.

	BMI (W5)	CRP (W5)	Depressive symptoms (W5)
CRP (W5)	–	–	0.022 (0.06)
BMI (W5)	–	0.07 (0.005)***	–
MDD diagnosed in adulthood	1.18 (0.84)	0.16 (0.07)*	1.746 (0.23)***
MDD diagnosed in adolescence	0.71 (1.25)	−0.09 (0.15)	2.148 (0.53)***
Maltreatment	0.53 (0.38)	0.01 (0.04)	0.150 (0.11)
Depressive symptoms (W1)	0.15 (0.13)	−0.02 (0.01)	0.122 (0.06)*
Race: Black	2.72 (1.43)	−0.01 (0.12)	0.023 (0.31)
Race: Native American	2.07 (3.19)	−0.12 (0.42)	0.378 (0.67)
Race: Asian	−2.21 (1.38)	−0.45 (0.36)	0.546 (0.50)
Race: Other	1.99 (1.36)	0.04 (0.20)	1.170 (0.72)
Ethnicity: Hispanic	0.01 (1.37)	0.06 (0.17)	0.172 (0.56)
Age (W1)	−0.23 (0.18)	−0.009 (0.02)	0.045 (0.06)
Sex: Male	1.00 (0.87)	−0.50 (0.10)***	0.307 (0.29)
Alcoholic drinks per day	0.03 (0.11)	0.01 (0.02)	0.081 (0.08)
Smoking: Current	−1.66 (0.88)	0.25 (0.12)*	0.881 (0.30)**
Smoking: Prior	0.75 (0.74)	0.05 (0.09)	−0.355 (0.20)
Family SES (W1)	−1.57 (0.32)***	−0.01 (0.03)	−0.141 (0.11)

Model $\chi^2 = 2.20$, $p = 0.13$; CFI = 0.99; TLI = 0.85; RMSEA = 0.02, 95 % CI: [0.00–0.05]; SRMR = 0.004.
All parameters are reported as *b* (*SE*).
CRP: C-reactive protein; BMI: body mass index; MDD: major depressive disorder.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 5
Multivariate Model Testing for Sex-Differences while Controlling for Demographics and Potential Confounders.

	BMI (W5)	CRP (W5)	Depressive symptoms (W5)
CRP (W5)	–	–	0.02 (0.06)
BMI (W5)	–	0.07 (0.005)***	–
MDD diagnosed in adulthood	2.56 (0.86)**	0.03 (0.08)	1.74 (0.23)***
MDD diagnosed in adolescence	1.21 (1.43)	−0.15 (0.17)	2.14 (0.53)***
Maltreatment	0.52 (0.38)	0.01 (0.04)	0.15 (0.11)
Depressive Symptoms	0.14 (0.13)	−0.02 (0.01)	0.12 (0.06)*
Race: Black	2.81 (1.43)*	−0.02 (0.12)	0.02 (0.31)
Race: Native American	−1.53 (3.23)	−0.07 (0.42)	0.37 (0.67)
Race: Asian	−2.41 (1.39)	−0.43 (0.36)	0.54 (0.50)
Race: Other	1.92 (1.36)	0.05 (0.20)	1.17 (0.72)
Ethnicity: Hispanic	−0.06 (1.36)	0.07 (0.17)	0.17 (0.56)
Age (W1)	−0.19 (0.18)	−0.01 (0.02)	0.04 (0.06)
Sex: Male	2.48 (1.09)*	−0.64 (0.12)***	0.30 (0.29)
Alcoholic drinks per day	0.008 (0.12)	0.02 (0.02)	0.08 (0.08)
Smoking: Current	−1.44 (0.86)	0.24 (0.11)*	0.88 (0.30)**
Smoking: Prior	0.86 (0.74)	0.04 (0.09)	−0.35 (0.20)
Family SES (W1)	−1.54 (0.32)***	−0.01 (0.03)	−0.14 (0.11)
Adulthood diagnosis * male	−4.80 (1.55)**	0.436 (0.20)*	–
Adolescent diagnosis * male	−1.67 (2.56)	0.249 (0.36)	–

Model $\chi^2 = 2.08$, $p = 0.55$; CFI = 1.00; TLI = 1.04; RMSEA = 0.00, 95 % CI: [0.00–0.02]; SRMR = 0.003.
All parameters are reported as *b* (*SE*).
CRP: C-reactive protein; BMI: body mass index; MDD: major depressive disorder.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

with MDD in adulthood had greater CRP ($b = 0.21$, $SE = 0.07$, $p < 0.01$) as well as depressive symptoms ($b = 1.85$, $SE = 0.22$, $p < 0.001$) relative to those who were never diagnosed. Participants first diagnosed with MDD in adolescence also had greater depressive symptoms relative to those who were never diagnosed ($b = 2.40$, $SE = 0.56$, $p < 0.001$), but not CRP ($p = 0.77$). Surprisingly, depressive symptoms at Wave 1 did not relate to CRP at Wave 5 ($p = 0.09$), nor did CRP at Wave 5 relate to depressive symptoms at Wave 5 ($p = 0.51$) in this sample.

Adjusting the model for participant racial identity, ethnic identity, age, and sex resulted in model fit indicates that were weaker than the initial model but still provided excellent fit to the data. Finding from the prior model were fully robust to statistical adjustment (see Table 3), with the sole exception being that childhood maltreatment experiences no longer related to greater depressive symptoms at Wave 5 ($p = 0.14$). Beyond substantive variables, participants who identified as Black had greater BMI at Wave 5 relative to participants who identified as White ($b = 3.60$, $SE = 1.29$, $p < 0.01$), and male participants had lower CRP at Wave 5 relative to female participants ($b = -0.45$, $SE = 0.09$, $p < 0.001$).

Adjusting the model for alcohol consumption, tobacco smoking status, and family socioeconomic disadvantage in addition to demographics continued to yield good model fit indices; however, TLI (0.85) did drop below the conventional 0.90 cut off (See Table 4). After adjustment, neither childhood maltreatment nor Black racial identity related to greater BMI, although participants who experienced greater family level socioeconomic disadvantage at Wave 1 had greater BMI at Wave 5 ($b = -1.57$, $SE = 0.32$, $p < 0.001$). Additionally, participants who currently smoked tobacco cigarettes had both greater CRP ($b = 0.25$, $SE = 0.12$, $p < 0.05$) and depressive symptoms ($b = 0.88$, $SE = 0.30$, $p < 0.01$) at Wave 5.

3.3. Testing for potential sex differences

Systematically testing for sex differences across paths between substantive models while still controlling for demographic and confounding variables identified two significant differences. First, we identified a significant sex × MDD diagnosis timing interaction when predicting BMI at Wave 5 for MDD diagnosed in adulthood ($b = -4.80$, $SE = 1.55$, $p < 0.01$), but not for MDD diagnosed in adolescence ($p = 0.51$). Second a significant sex × diagnosis timing predicting CRP was also identified for those who were diagnosed with MDD in adulthood ($b = 0.43$, $SE = 0.20$, $p < 0.05$), but not for MDD diagnosed in adolescence ($p = 0.49$).

When including both these interactions in the same multivariate model, simultaneously, both significant effects persisted. Simultaneous inclusion of these interactions continued to result in strong model fit indices, again with the sole exception being TLI (0.87) (See Table 5). Plotting of interaction terms predicting BMI showed that males diagnosed with MDD in adulthood had lower BMI at Wave 5 than those who had never been diagnosed with MDD or were diagnosed in adolescence, while females who were diagnosed with MDD in adulthood had greater BMI at Wave 5 than females who were never diagnosed with MDD or

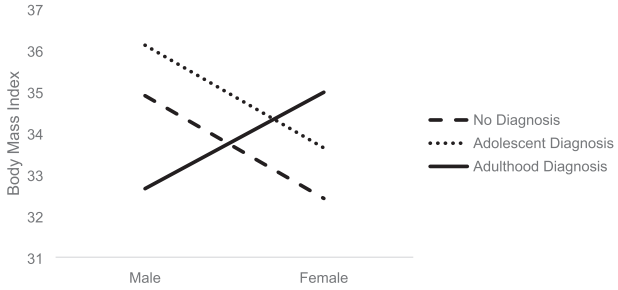

Fig. 2. Plotted differences in body mass index for males vs females depending on the timing of MDD Diagnosis.

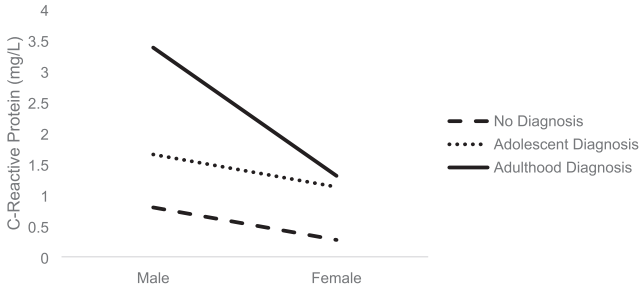

Fig. 3. Plotted differences in C-reactive protein for males vs females depending on the timing of MDD diagnosis.

were diagnosed in adolescence (See Fig. 2). Plotting interaction terms predicting CRP while exponentiating parameters to yield more interpretable values, showed that both males and females diagnosed with MDD in adulthood had greater CRP compared to their same sexed participants. Overall, Males diagnosed with MDD had the greatest CRP, followed by males diagnosed in adolescence, and then by females diagnosed with MDD in adulthood, holding all other predictors constant (See Fig. 3).

3.4. Sensitivity analyses

We conducted two additional analyses to further contextualize our results. First, we explored the effects of including individual types of childhood maltreatment as predictors in the model, categorically. The central results of our models were unaltered, identifying participants first diagnosed with MDD in adulthood had greater CRP ($b = 0.16$, $SE = 0.07$, $p < 0.05$) vs those never diagnosed, but those diagnosed with MDD in adolescence did not differ from participants never diagnosed ($p = 0.55$). Notably, participants who reported experiences of emotional abuse had greater depressive symptoms at Wave 5 ($b = 0.59$, $SE = 0.23$, $p < 0.05$), but no other significant associations were identified between experiences of childhood maltreatment and depressive symptoms, BMI, or CRP. Despite these insights, model fit indexes indicated that the model had a poorer fit to the data, and the so results should be interpreted with caution. See Supplementary Table 7 for a complete report of multivariate statistics exploring the effects of each type of childhood maltreatment.

Second, we explored the effects of accounting for the frequency of individual childhood maltreatment types. These results continued to support our main findings. Additionally, these results indicated that participants who reported more instances of emotional abuse had more severe depressive symptoms at Wave 5 ($b = 0.15$, $SE = 0.05$, $p < 0.05$). Further, these results indicated that participants who reported more instances of physical abuse had a greater BMI by Wave 5 ($b = 0.66$, $SE = 0.30$, $p < 0.05$), whereas those that reported more instances of sexual abuse had a lower BMI by Wave 5 ($b = -0.70$, $SE = 0.32$, $p < 0.05$). As with the prior model, model fit indexes indicated that the model had a poorer fit to the data, and so results should be interpreted with caution. See Supplementary Table 8 for a complete report of multivariate statistics exploring the effects of childhood maltreatment type frequency.

4. Discussion

The present study is the first that we know of to investigate how childhood maltreatment and MDD diagnosis timing may affect BMI, inflammation, and depressive symptoms into adulthood. Participants diagnosed with MDD in adolescence had greater depressive symptoms at Wave 1 (ages 12–21) and Wave 5 (ages 33–43) compared to participants diagnosed with MDD in adulthood. Supporting our hypotheses, we found that individuals diagnosed with MDD in adolescence had lower CRP, but not depressive symptoms, than those diagnosed in adulthood. Additionally, we found that males and females differed in their basal inflammation at Wave 5, dependent on when they were diagnosed with MDD, with males first diagnosed in adulthood having the greatest levels of inflammation. Interestingly, males vs females may have different pathways toward greater inflammation in adulthood given that a diagnosis of MDD in adulthood was associated with greater BMI in females relative to other females but lower BMI for males relative to other males (Moriarity et al., 2023; Zagaria et al., 2024).

The finding that the diagnosis timing of MDD is associated with CRP, but not depressive symptoms, is an important novelty of our study and is supported by several lines of evidence. First, some studies have yielded inconsistent results when testing associations between CRP and depressive symptoms, particularly in younger samples and longitudinal studies (Copeland et al., 2012; Iob et al., 2022; O'Shields et al., 2025). However, some longitudinal evidence from the Great Smoky Mountains study identified that the number of MDEs an individual experiences predicts greater CRP even when there is no significant association between CRP and depressive symptoms (Copeland et al., 2012). Second, epidemiological studies have identified a significant lag time between the onset of mental disorders and their diagnosis, with the majority of those experiencing MDD not being diagnosed until years after onset (de Girolamo et al., 2012; Jones, 2013; Kessler et al., 1998; Wang et al., 2005). Third, common frontline treatments for MDD are known to have an anti-inflammatory effect even though the treatment may not be as effective at reducing depressive symptoms in individuals who have experienced childhood maltreatment (Hannestad et al., 2011; Hiles et al., 2012; Shields et al., 2020; Więdłocha et al., 2018; Williams et al., 2016). Thus, our findings may indicate that individuals who have not been diagnosed with MDD until adulthood have been experiencing longer periods of chronic inflammation relative to those who were never diagnosed or those diagnosed in adolescence, delaying treatment that would otherwise reduce chronic inflammation. This is further supported by our finding that those diagnosed with MDD in adolescence and in adulthood also reported experiencing more types of childhood maltreatment. Optimistically, this does indicate that those who experience the most severe depressive symptoms and childhood maltreatment are most likely being identified as having MDD closer to the actual onset timing. At the same time, results also indicate that those with less severe depressive symptoms are being missed.

Although individuals who are diagnosed with MDD in adolescence may be more likely to receive treatments with anti-inflammatory effects, other social factors may be accounting for the lower CRP among those diagnosed in adolescence. A central tenant of SST is that experiences of social safety are also have lasting downstream effects on inflammation (Slavich 2020, Slavich et al., 2023a). The opportunity to discuss depressive symptoms which then leads to a health care provider diagnosing an individual with MDD, may itself be an opportunity to experience psychological safety. Indeed, a 'common factor' across psychotherapy modalities is a strong therapeutic alliance in which an individual is able to experience safety (Rosenzweig, 1936; Wampold, 2015; Cuijpers et al., 2019). Contact with a treatment provider who is able to facilitate psychological safety with patients while discussing depressive symptoms may be one pathway towards decreasing the inflammatory response. Furthermore, many adolescents who reach out for help may do so through a trusted family member or guardian per legal requirements to consent for treatment. The process of asking a trusted person for help and then being referred to a healthcare provider, may itself be a process through which adolescents can experience psychological safety. However, a crucial caveat in our study is that we were unable to account for the effects of therapeutic alliance or treatment type, be it pharmacotherapy, psychotherapy, or general support. Future studies accounting for the effects of these factors on inflammation while also accounting for the potential delay time between symptom onset and initiation of treatment would yield important insights.

The results of our analyses exploring sex differences further supports this explanation, while also highlighting differences in pathways towards greater inflammation for people who experience MDD. After plotting predicted CRP levels for males vs females across different MDD diagnosis timing (see Fig. 3), our results showed that males who were diagnosed with MDD in adulthood had the greatest levels of CRP. This may indicate that males are less likely to be diagnosed in adolescence, resulting in a greater duration of untreated depressive symptoms that then relates to greater chronic inflammation. Indeed, our bivariate results support this conclusion with our sample showing that females were around 4 times as likely to be diagnosed in adolescence, but females were only 2.5 times more likely to be diagnosed in adulthood. As noted by others, males are less likely to seek help for MDD when experiencing milder depressive symptoms relative to females (Shi et al., 2021). Indeed, our results indicate that those diagnosed in adulthood had lower depressive symptoms at Wave 1. Thus, results still support the decades of epidemiological evidence that females are more likely to experience

MDD than their male counterparts (Slavich & Sacher, 2019). However, our results also point towards a need to improve MDD screening in adolescents to reduce disparities in diagnosis as one path towards reducing chronic inflammation in males who experience MDD.

Surprisingly, experiences of childhood maltreatment did not predict BMI or CRP after adjusting for both demographic and confounding variables. Sensitivity analyses were mostly confirmatory of this finding, identifying no significant association between the categorical experience of individual maltreatment types and BMI or CRP. Although, sensitivity analyses also identifying that a greater frequency of physical abuse related to greater BMI at Wave 5 while a greater frequency of sexual abuse related to lower BMI at Wave 5. Although, models exploring the effects of individual maltreatment types had a significant model χ^2, indicating that the model was a poor fit to the data and that results should be interpreted with caution. Despite this, a consistent finding across each of these models is that greater early life socioeconomic disadvantage related to greater BMI at Wave 5, and a greater BMI related to greater CRP at Wave 5. Although it is unlikely that childhood maltreatment does not impact inflammation either directly or through increases in adipose tissue (see Zagaria et al., 2024), results may indicate that the conditions in which childhood maltreatment commonly occur are also important for understanding inflammatory health. Early life socioeconomic disadvantage is associated with both increased risk for experiencing childhood maltreatment as well as food insecurity, both of which have pointed towards greater BMI that then drive increases in basal inflammation (Kim & Drake, 2018; Senese et al., 2009).

4.1. Implications

Our results have important implications for how we understand who is at risk for worsening MDD over time and how we may be able to improve the overall prognosis of those affected. At the bivariate level, we identified that participants differed in the severity of their depressive symptoms in adolescence and that these differences grew as participants aged. Participants who were never diagnosed with MDD had the lowest level of depressive symptoms at Wave 1 and symptom severity decreased by Wave 5. However, for those who were diagnosed at some point, depressive symptom severity worsened over time, with those diagnosed with MDD in adolescence showing the most severe symptoms. Interestingly, participants who were diagnosed with MDD at some point also reported experiencing more types of childhood maltreatment than those who were never diagnosed with MDD. Thus, results indicate that childhood maltreatment experiences may help explain why a diagnosis of MDD, regardless of timing, relates to greater depressive symptom severity at Wave 5. Epidemiological evidence indicates that MDD is a growing issue among adolescents (Mojtabai et al., 2016; Miller and Campo, 2021). Identifying adolescents who have experienced childhood maltreatment, particularly multiple forms of childhood maltreatment, may be one method for identifying who is at the greatest risk for worsening MDD over time. Furthermore, several studies have highlighted that subsyndromal depressive symptoms, or 'minor depression', is a risk factor for the development of a future MDE (Cuijpers and Smit, 2004). Childhood maltreatment experiences, even in the context of subsyndromal depression, could help identify who is at increased risk for future MDD and would benefit from early treatment vs those that would remit without intervention (Hermens et al., 2004).

Critically, individuals who experience MDD at some point in their life die significantly younger than those who are unaffected, even after controlling for the effects of suicide (Jia et al., 2015; Laursen, et al., 2016; Reynolds et al., 2008). One driver of this shorter lifespan is the increased risk for cardiometabolic diseases such as heart diseases and diabetes after the onset of MDD (Gold et al., 2020; Park et al., 2013). Chronic inflammation, in addition to other factors such as tobacco and alcohol use, are known to contribute to the development of many of these diseases (Furman et al., 2019; Slavich, 2015). Our results indicate that even though those who are diagnosed with MDD may continue to experience depressive symptoms at Wave 5, a diagnosis of MDD in adolescence relates to CRP levels that are similar to those who were never diagnosed with MDD. Although progress still needs to be made in identifying effective treatments for those affected by MDD, timely identification after symptom onset may be one method for harm-reduction, reducing the risk for cardiometabolic disease. At present, both CBT and SSRI medications have been found to decrease inflammation (Hannestad et al., 2011; Hiles et al., 2012; Shields et al., 2020; Więdłocha et al., 2018; Williams et al., 2016). Screening adolescents for depressive symptoms and childhood maltreatment, particularly in socioeconomically disadvantaged communities at risk for greater inflammation through greater BMI, may reduce the incidence of cardiometabolic diseases in those at risk for poor outcomes.

4.2. Strengths and limitations

The present study has several strengths. First, we used longitudinal data from a nationally representative sample United States while accounting for the complex survey design of the Add Health study, showing how early MDD diagnosis has impacted the health of American adults. Second, although evidence has shown that there is a delay between the onset and diagnosis of MDD, little work has explored sex-differences in diagnosis timing, and none has evaluated how diagnosis timing affects inflammation. Given that greater inflammation is associated with an increased risk for several leading causes of disease across the globe, these results are an important step for identifying how gaps in health occur between males and females. Third, we use peripheral CRP levels as an index of basal inflammation. Although numerous inflammatory molecules are implicated in MDD, CRP has been shown to correlate with other inflammatory markers in both the peripheral and in cerebrospinal fluid, including interleukin-6 and tumor necrosis factor-α (Felger et al., 2020).

Despite these strengths, several limitations should also be noted. First, our analyses explored the effects of MDD diagnosis timing, not MDD onset timing. Although we did control for depressive symptoms at this time (Wave 1), future studies could advance this work further by measuring the effects of delay time between onset and diagnosis on CRP and depressive symptoms. Second, our analysis only accounted for CRP measured at a single time point. Future studies that are able to account for CRP during adolescence could improve causal inference through the use of a cross-lagged panel model design (see Huang et al., 2019, for an example). This would allow for a clearer understanding of how factors like diagnosis timing affect CRP over time. Third, collection of childhood maltreatment data in the Add Health study does not have the same degree of precision as more recent methods and could be under accounting for the effects on health in adulthood. Future studies could use more recent developments in this area such as the STRAIN (Slavich & Shields, 2018). Fourth, the effects of various health problems and their treatment on basal inflammation and depressive symptoms was not accounted for in our analyses. Additionally, the effects of comorbid health problems such as generalized anxiety and the overlapping treatments commonly implemented (i.e. SSRIs) were not accounted for. Future studies, particularly those of older adults could yield valuable insights by understanding associations between comorbidities, comorbidity treatments, inflammation, and MDD diagnosis timing. Last, although we do use a longitudinal design to strengthen causal inference, true causation needs to be established through experimental design. Future studies could build on our findings by using a factorial design to compare inflammatory reactivity elicited using a laboratory-based stressor paradigm in a cross-section childhood maltreatment vs non-childhood maltreatment and delayed vs non-delayed MDD diagnosis individuals (Shields & Slavich, 2017).

4.3. Conclusion

In conclusion, the present data are among the first we know of to

show that the timing at which MDD is diagnosed has important consequences for inflammatory health in adulthood. Our results indicate that individuals who experience milder depressive symptoms may go undiagnosed with MDD until adulthood, potentially delaying care that would otherwise be associated with better inflammatory health as individuals age. Additionally, we identified that individuals who experience childhood maltreatment as well as those who are male may be at increased risk to go undiagnosed with MDD until adulthood, leading to disparities in inflammatory health. A more timely diagnosis of MDD, particularly for those with symptom onset in adolescence, may be one method for reducing the risk of inflammatory related depressive symptoms and health conditions.

CRediT authorship contribution statement

Jay O'Shields: Conceptualization, Formal analysis, Visualization, Writing – original draft preparation, Writing – review & editing. **George M. Slavich:** Writing – review & editing, Supervision. **Orion Mowbray:** Writing – review & editing, Supervision, Resources.

Funding

J.O. was supported by grant #F31MH134508 from the National Institute of Mental Health. G.M.S. was supported by grant #OPR21101 from the California Governor's Office of Planning and Research/California Initiative to Advance Precision Medicine. The findings and conclusions in this article are those of the authors and do not necessarily represent the views or opinions of these organizations, which had no role in designing or planning this study; in collecting, analyzing, or interpreting the data; in writing the article; or in deciding to submit this article for publication.

Appendix A. Supplementary data

Supplementary data for this article can be found online at https://doi.org/10.1016/j.bbi.2025.106190.

Data availability

Data for the Add Health study are available through the University of North Carolina - Carolina Population Center.

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