Effect of individual or comorbid antenatal depression and anxiety on birth outcomes and moderation by maternal traumatic experiences and resilience

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Abstract

Background: Although antenatal depression and anxiety (e.g., negative antenatal mental health; NAMH) are individually associated with preterm birth (PTB) and infant neurological impairment, few studies account for comorbidity. Understanding how NAMH impacts PTB and infant neurological functioning by either singular (depression or anxiety) or comorbid status, as well as the way in which these effects can be moderated by additional risk or protective factors (traumatic experiences and trait resiliency) can contribute further understanding of NAMH effects on birth outcomes.

Methods: The sample included 3042 mother-infant dyads from U.S. and South Africa cohorts of the Safe Passage Study ($N = 3042$). A four-category NAMH variable was created to categorize depression-only, anxiety-only, comorbid, or no NAMH statuses.

Results: There were no NAMH main effects on PTB, however, anxiety-only and comorbid NAMH increased odds of PTB for mothers with higher rates of traumatic life experiences. Anxiety-only and comorbid NAMH were associated with increased odds of newborn neurological

impairment, and the effect of comorbid NAMH was stronger for mothers with higher rates of traumatic experiences. Resiliency decreased odds of neurological impairment for mothers who reported depression-only or anxiety-only NAMH.

Limitations: Limitations included potential artefacts of two cohorts that differed in rates of almost all variables, a single time point for measuring NAMH, and lack of pregnancy-specific NAMH measures.

Conclusions: Especially when compared to mothers with no NAMH, comorbidity or singular-condition NAMH statuses associate with negative birth outcomes in nuanced ways, especially when considering additional contexts that may foster or protect against NAMH.

Keywords

Antenatal mental health; Birth outcomes; Comorbidity; Trauma; Resilience; Perinatal health

1. Introduction

Approximately 20% of pregnant women will experience negative antenatal mental health (NAMH) issues such as depression and anxiety (Furtado et al., 2018; Yin et al., 2021), both of which are associated with adverse birth outcomes (Staneva et al., 2015), although results are mixed (Smith et al., 2020) given the wide variety of sample populations, models, and analytic strategies. Preterm birth (PTB) is one of the most commonly examined birth outcomes associated with NAMH (Ghimire et al., 2021; Grigoriadis et al., 2018), with a smaller body of literature demonstrating that NAMH is associated with poorer neurological development in neonates and long-term neurological functioning in offspring (e.g., brain growth and connectivity, cognitive and behavioral functioning; Field, 2017; Lautarescu et al., 2020; Wu et al., 2020). Most research on NAMH effects focuses on depression or anxiety individually, despite the prevalence of comorbidity between depression and anxiety (Falah-Hassani et al., 2017; Uguz et al., 2019) and noted subtypes of antenatal depression marked by anxiety (Putnam et al., 2017). The small proportion of studies that examine multiple NAMH conditions vary in statistical methodology, however, a typical strategy is to "control for" one indicator when examining the other (Nasreen et al., 2019 Liou et al., 2016; Ossola et al., 2021), or evaluate conditions separately (Dowse et al., 2020; Szegda et al., 2014), rather than deliberately compare single versus comorbid NAMH (e.g., interactions, categorical differentiation). The few studies comparing depression or anxiety alone to comorbid depression and anxiety indicate mothers comorbid for depression and anxiety are at increased risk of PTB compared to mothers with only depression, only anxiety, or neither depression nor anxiety (Adhikari et al., 2020; Field et al., 2010; Uguz et al., 2019). The impact of comorbidity on neonatal and infant neurological development is less clear, although there is evidence that antenatal depression and anxiety may differentially impact neurological development and functioning (Rifkin-Graboi et al., 2015; Donnici et al., 2021), most of this research did not deliberately evaluate comorbidity versus singular NAMH disorders (Adamson et al., 2018). To our knowledge, the only infant neurological development study (frontal EEG) in which comorbidity was deliberately examined demonstrated that comorbidity may have a stronger negative effect than singular depression or anxiety on some neural functioning outcomes when compared to mothers

without NAMH issues (Field et al., 2010). Taken together, more research is needed for elucidating the specific effects of antenatal depression, anxiety, and comorbidity on infant outcomes (Graignic-Philippe et al., 2014).

Some hypothesized underlying mechanisms can explain associations between both depression and anxiety and negative birth outcomes such as PTB and neonatal neurological development. Higher glucocorticoid and cortisol production (Duthie and Reynolds, 2013; McGowan and Matthews, 2017; Seth et al., 2016), which pass through the placenta and enter the fetal bloodstream, are key biomarkers that have been identified as explanatory mechanisms for the association between NAMH and birth outcomes (Dickens and Pawluski, 2018). Higher corticosteroid levels, particularly in the second trimester, increase the risk of PTB (García-Blanco et al., 2017; Bandoli et al., 2018), through both inflammatory and epigenetic channels (Coussons-Read et al., 2012; Nowak et al., 2020). Excess exposure to glucocorticoid and cortisol in utero also impacts offspring neurological development and subsequent functioning, through both direct influences on brain development and cortisol-related epigenetic change (Isgut et al., 2017; Nazzari et al., 2019), which can result in long-term neurological, cognitive, and behavioral dysfunction (Duthie and Reynolds, 2013). Both antenatal depression and anxiety are associated with elevated glucocorticoid and cortisol levels (Krontira et al., 2020; Serati et al., 2016). Given the complexity and variety of mechanisms that may underlie NAMH –birth/offspring outcome associations, understanding how comorbid versus individual conditions may impact outcomes may guide studies evaluating these channels. For example, cortisol production may be particularly high for individuals with comorbid NAMH anxiety and depression (Evans et al., 2008).

NAMH effects must also be considered within contexts that may serve as risk or protective moderators. The effect of cumulative life traumatic events is less often included in maternal stress studies but appears to have an impact on birth outcomes. Trauma appears to have direct influences on birth outcomes by impacting fetal programming (Conradt et al., 2020) via epigenetic/allostatic load pathways (e.g., through facilitating dysfunction of stress, inflammatory, and immune systems; Moog et al., 2016 Steine et al., 2020; Swales et al., 2018). Furthermore, these pathways also increase sensitivity to stressors and therefore increase the risk of NAMH (Biaggi et al., 2016; Young-Wolff et al., 2019). In addition to this indirect role, prior research has highlighted interactions between trauma and NAMH, such that lifetime trauma increases NAMH severity (Meijer et al., 2014) and the strength of NAMH effects on birth outcomes (Blackmore et al., 2016) in a dose-dependent manner. However, studies evaluating the association between trauma and NAMH rarely account for comorbidity (Choi and Sikkema, 2015; Martini et al., 2015; Verbeek et al., 2019) even though traumatic experiences increase the risk for comorbid anxiety and depression (Hovens et al., 2015, 2010). Thus, more information is needed to discern the intersection between trauma and either comorbid or individual NAMH conditions on birth outcomes.

In addition to trauma, variables that buffer or protect against the risk of NAMH are also associated with birth outcomes (Davis and Narayan, 2020), including, internal resilience (e.g., ability to adapt to change and handle stressors; Bhatia et al., 2015; McDonald et al., 2014; Montoya-Williams et al., 2021). Although most research on prenatal internal resilience effects evaluates resilience as a mediator between prenatal stressors/vulnerability

to NAMH and NAMH (Ma et al., 2019; Young-Wolff et al., 2019), other studies indicate that resilience may moderate the strength of underlying mechanisms explaining the association between NAMH and birth outcomes (e.g., stress hormones, inflammatory markers; (García-León et al., 2019; Verner et al., 2020). Few studies have also examined how the association between NAMH and resilience may jointly extend to birth outcomes (Rini et al., 1999), although more recent theoretical models of perinatal health have discussed the extent to which both contribute to birth and offspring health (Howland and Cicchetti, 2021; Ramey et al., 2015). Thus, examining the potential joint role of resilience and specific NAMH conditions can further contribute to the understanding of overall NAMH effects on negative birth outcomes.

2. Current study

The purpose of the current study is to better discern the impact of NAMH on PTB and infant cognitive impairment, as both a replication of prior studies that compare singular and comorbid NAMH influence on negative birth outcomes and building upon prior studies by examining contextual factors of singular and comorbid NAMH. Specifically, we compared how PTB and infant cognitive impairment may differ for mothers experiencing only antenatal depression, only antenatal anxiety, or both antenatal anxiety and depression, to better elucidate individual and comorbid NAMH effects. We hypothesized that compared to mothers with no NAMH condition, mothers with any NAMH condition may have higher rates of PTB and infant cognitive impairment outcomes and that this effect would be the strongest for mothers experiencing comorbid anxiety and depression, compared to either mothers with no NAMH conditions, or compared to those experiencing only one NAMH condition. Secondly, we hypothesized that higher rates of lifetime traumatic events would strengthen NAMH effects on PTB and infant cognitive impairment and that resilience would have an attenuating moderating effect, such that higher rates of resilience would weaken NAMH effects on PTB and infant cognitive impairment.

3. Methods

3.1. Sample

Participants were from the Safe Passage Study, a prospective longitudinal study that focused on birth and infant outcomes associated with prenatal exposure of alcohol use, first recruiting mothers during pregnancy, and following up to 12 months after birth. Mothers were recruited from the United States Northern Plains and Cape Town, South Africa; sites were selected due to the high rates of prenatal alcohol use and sudden infant death syndrome. More detail regarding recruitment and methods is found elsewhere (Dukes et al., 2014; Elliott et al., 2020). Only women who were assessed for resilience and trauma (a subsample of the cohort; 38%), those who reported not taking any medication for mood disorders (e.g., antidepressants, as these may moderate or influence NAMH), and those who gave birth to singletons (given higher rates of PTB in multiples) were included in the sample. We only included mothers who were assessed at the same time for NAMH (20–24 weeks, which was 76% of the sample, compared to 2% who were assessed at 28–32 weeks, and 22% who were assessed at 34+ weeks). Given findings that a) NAMH rates vary over

pregnancy (Okagbue et al., 2019), and b) NAMH effects on birth outcomes can vary based on when they are experienced during pregnancy (Doktorchik et al., 2018), we wanted to control for time of "exposure" as much as possible, focusing the second trimester, which appears to be particularly important for underlying mechanisms explaining associations between NAMH and birth outcomes (Bandoli et al., 2018). Finally, due to attrition at one-year follow-up from birth, our sample was smaller for the neurological maturation outcomes (68% of the eligible PTB sample). There were no significant differences in all model variables between participants who were assessed for trauma and resilience and those who were not. Within the preterm birth study sample, only colored race differed between participants who were assessed for neurological maturation impairments and those who were not (F(1, 2943) = 4.85, p = 0.03), which further indicated that a higher proportion of South African participants were lost to attrition at one-year follow-up (34% of the South African PTB sample) compared to the North American sample (30% of the North American PTB sample). The final sample for the PTB outcome included 3032 mother-child dyads (508 American Indian/Alaska Native, 799 White Non-Hispanic, 1696 mixed ancestry [specifically the South African cohort], and 29 other-race dyads). The final sample for the neurological maturation impairment outcome included 2050 mother-child dyads (332 American Indian/Alaska Native, 580 White Non-Hispanic, 1120 mixed ancestry, and 18 other-race dyads).

3.2. Measures

Birth Outcomes.—Two birth outcomes were evaluated. Preterm birth (PTB) was assessed as offspring who were born earlier than / before 37 weeks (no PTB = 90%, PTB = 10%). Infant neurological maturation was assessed using the Amiel-Tison Neurological Assessment (Gosselin et al., 2005) assessed within the first 5 days of life (adjusted for prematurity, such that preterm birth visits were done at approximately 1 month). Newborns were initially classified as no (50%), mild (6%), moderate (44%), and severe (0.5%) degree of impairment. This was then collapsed into a three-category variable that combined moderate and severe degree statuses.

Negative Antenatal Mental Health (NAMH).—NAMH was a multinomial categorical variable representing depression and/or anxiety. The scales used for assessing NAMH have been used in prior research examining comorbidity of antenatal depression and anxiety (Doktorchik et al., 2018; Field et al., 2010; Ibanez et al., 2012). Antenatal depression was assessed by the Edinburgh Postnatal Depression Scale (Cox et al., 1987), a commonly used scale to assess prenatal and postnatal depression (Milgrom and Gemmill, 2014), during 20–24 weeks of pregnancy. We transformed this variable into a binary score, using the recommended cut off of 13, which is less sensitive, but more specific for identifying women with diagnoses of depression (Levis et al., 2020), and following findings that antenatal depression cutoffs are slightly higher than postnatal depression cutoffs (Kozinszky and Dudas, 2015). Antenatal anxiety was assessed using the state anxiety component of the Spielberger State-Trait Anxiety Scale (Spielberger et al., 1983) during 20–24 weeks of pregnancy. We transformed this variable into a binary score, using the recommended cut-off of 40 (Grant et al., 2008). These scores were converted to "depression-only" NAMH, "anxiety-only" NAMH, and "comorbid" (both depression and anxiety) NAMH dummy

codes to reflect a categorical mental health variable, such that a reference score indicated no NAMH condition. 36% of participants reached the threshold for either/or state anxiety or depression; this was split amongst those who had only depression (13% of those with NAMH, 5% of the full sample), only anxiety (61% of those with NAMH, 22% of full sample), or both (26% of those with NAMH, 9% of the full sample).

Lifetime Traumatic Experience.—Traumatic experience was assessed at 28 – 32 weeks antenatally using a modified version of the Life Events Checklist (Gray et al., 2004), which included 15 events (removing "exposure to toxic substance" and "severe human suffering"), in which participants reported if an event had "happened to them", if they had "witnessed it", or if they had "heard about it". For the current study, we included only events that participants reported experiencing directly (e. g., "happened to them), and summed scores reflected the total number of experienced traumatic events. The score was winsorized at 8, as 99.23% of participants reported 8 or fewer events ($M = 2.17$, SD = 1.89).

Resilience.—Resilience was assessed using the Connor Davidson Resilience Scale (Connor and Davidson, 2003), a highly reliable and valid scale for assessing trait resilience (Windle et al., 2011). Mothers were assessed at approximately 28 – 32 weeks pregnant ($M = 72.08$, SD = 14.79).

Control Variables.—Given potential differences in spontaneous versus medically induced birth outcomes, we controlled for spontaneous labor (71% of the sample, 66% of PTB). Other maternal control variables included race/ethnicity, age during pregnancy ($M = 25.69$, SD= 5.56), marital/partner status at the start of pregnancy (91% married/partnered), mother's highest level of education (primary school 4%, some high school 44%, completed high school 20%, some college 15%, completed college 11%, post-graduate 5%), gravidity ($M = 2.41$, SD = 1.46), and gestational diabetes or gestational hypertension during pregnancy (7% reporting either gestational diabetes or hypertension). Three-level variables representing drinking alcohol or smoking cigarettes during the pregnancy (representing no drinking or smoking during pregnancy (47% / 56%), quitting drinking or smoking during pregnancy (31% / 24%), and continuous drinking or smoking throughout pregnancy (22% / 20%) were also included. Infant control variables included infant gender (49% male).

3.3. Analytic plan

All analyses were conducted using SAS Version 9.4, using proc SURVEYLOGISTIC to account for site-clustering-related interdependence. Categorical/nominal predictors were parameterized using reference coding rather than effect coding, to directly compare categorical levels to each other (for example, direct comparison of no NAMH to depression-only NAMH, no NAMH to anxiety-only NAMH, and no NAMH to comorbid NAMH in a model). For both outcomes, we examined three models, a main-effects model, a model which included the NAMH x lifetime traumatic experience interaction, and a model which included the NAMH x resilience interaction. To evaluate comparisons between NAMH conditions, we examined models in which the reference was no NAMH condition, depression-only NAMH, and anxiety-only NAMH.

3.4. Results

3.4.1. Descriptive results—Table 1 presents all variable correlations. There were no significant correlations between individual NAMH conditions (using no NAMH as a reference) and preterm birth (depression-only NAMH $r = 0.01$, $p = 0.82$; anxiety-only NAMH $r = 0.03$, $p = 0.08$; comorbid NAMH $r = 0.02$, $p = 0.31$). NAMH conditions did not significantly correlate with mild neurological maturation impairments (depression-only NAMH $r = -0.02$, $p = 0.37$; anxiety-only NAMH $r = 0.01$, $p = 0.78$; comorbid NAMH $r = 0.01$, $p = 0.058$), but did significantly correlate with moderate-severe neurological maturation impairments (depression-only NAMH $r = -0.02$, $p = 0.57$; anxiety-only NAMH $r = 0.13$, $p < 0.0001$; comorbid NAMH $r = 0.09$, $p = 0.0001$). Lifetime traumatic experience did not significantly correlate with PTB ($r = 0.03$, $p = 0.16$) nor neurological maturation impairments (mild $r = -0.0001$, $p = 0.99$; moderate-severe $r = 0.02$, $p = 0.28$). Although resilience did not significantly correlate with PTB ($r = -0.02$, $p = 0.31$) or mild neurological maturation impairments ($r = 0.02$, $p = 0.31$), there was a significant negative association with moderate-severe neurological correlation ($r = -0.13$, $p < 0.0001$). Finally, NAMH conditions positively correlated with lifetime traumatic events (depression-only NAMH $r = 0.06$, $p = 0.002$; anxiety-only NAMH $r = 0.08$, $p < 0.0001$; comorbid NAMH $= 0.13$, $p < 0.0001$) and negatively correlated with resilience (depression-only NAMH $r = -0.11$, $p < 0.0001$; anxiety-only NAMH $r = -0.19$, $p < 0.0001$; comorbid NAMH $= -0.23$, $p < 0.0001$).

Depression and anxiety NAMH conditions (not accounting for comorbidity) were correlated as both continuous ($r = 0.52$, $p < 0.0001$) and categorical cut-off ($r = 0.32$, $p < 0.0001$) variables.

3.4.2. Premature birth (PTB)—Table 2 displays the main effect and interaction odds ratios for PTB using no NAMH as the reference group. There was no effect of any NAMH compared to no NAMH on PTB, or when comparing NAMH conditions with each other (Supplemental Table 1). There were also no main effects of lifetime traumatic experience or resiliency. However, there was an interaction between lifetime traumatic experience and NAMH, such that the effect of trauma on PTB differed for mothers with anxiety-only NAMH or comorbid NAMH compared to mothers with no NAMH. Fig. 1 displays the interaction between NAMH for all individual conditions and trauma. As seen in Fig. 1, although there were overall low odds of mothers reporting PTB, higher trauma was associated with higher odds of PTB for mothers with either anxiety-only or comorbid NAMH. However, for mothers with no NAMH, higher trauma was associated with lower odds of PTB There were no differences in the effect of trauma between any of the NAMH statuses (Supplemental Table 1). There was no interaction between NAMH status and resilience.

3.4.3. Neurological maturation—Table 3 displays the main effect and interaction odds ratios for neurological maturation impairment using no neurological impairment as the reference group. There were main effects of NAMH odds of mild neurological impairment, such that mothers who reported either anxiety-only or comorbid NAMH had higher odds of offspring with mild neurological impairments when compared to mothers with no NAMH. There were no differences in effects between NAMH conditions (Supplemental

Figure 2). There was also a slight main effect of resilience, such that resilience increased odds of mild neurological impairment. Lifetime traumatic experience differed by NAMH condition (Fig. 2a–b) but only for moderate/severe outcomes (Fig. 2b), such that higher traumatic experience was associated with higher odds of moderate/severe outcomes for mothers who reported comorbid NAMH compared to no NAMH and anxiety-only NAMH. There were interactions between NAMH and resilience for both mild and moderate/severe neurological impairment outcomes (Fig. 3a–b). Higher rates of resilience decreased odds of mild neurological impairment for mothers who reported depression-only NAMH compared to mothers who reported no NAMH (Fig. 3a) and decreased odds of moderate/severe neurological impairment for mothers who reported anxiety-only NAMH compared to mothers with no NAMH.

3.5. Discussion

The purpose of this study was to build on prior work examining effects of NAMH on birth outcomes (PTB and neurological maturation) by a) discerning between comorbid and singular conditions of antenatal depression and anxiety, and b) examining how different NAMH conditions may be moderated by lifetime trauma and resilience as risk or protective factors. Although NAMH was only studied once, the prospective design of this study allows for inferring the directionality of predictor influences on outcomes. Overall, our results lent support for the role of NAMH on negative birth outcomes, and even potential differences between NAMH statuses; however, much of this required understanding within the contexts of trauma or resilience, as there were few main effects of NAMH on outcomes. Unique to this study is are the findings that for neurological maturation, moderation effects of resilience and trauma differed by some NAMH conditions. It should also be noted, however, as seen in that overall odds of either PTB or neurological impairments were fairly low; and risk should be considered based on the strengthening or weakening of this low likelihood of birth outcomes.

Based on studies that specifically evaluated for comorbidity (Adhikari et al., 2020; Field et al., 2010; Uguz et al., 2019), we had hypothesized that mothers with comorbid anxiety and depression would be more likely to experience PTB or to have children with neurological maturation impairments compared to mothers with anxiety or depression alone. Mothers who reached the clinical thresholds for NAMH conditions did not differ in PTB outcomes. Although mothers with comorbid NAMH had higher odds of having an infant with mild neurological impairment, mothers who reported comorbid NAMH did not significantly differ from other NAMH statuses. Mothers with an anxiety-only NAMH condition also had higher odds of having an infant with mild neurological impairment compared to mothers with no NAMH.

Overall, our hypotheses for main effects were not supported, although results suggest comorbid and anxiety NAMH can impact neural development. It is possible that examining NAMH at different time points (e.g., each trimester), may have provided different results. The second trimester (when NAMH was evaluated for this study), appears to be particularly important in regards to the impact of distress-related biomarker levels on negative birth outcomes (e.g., underlying mechanism explaining NAMH effects on birth outcomes such as

corticosteroids; Bandoli et al., 2018). However, longitudinal patterns may be more important compared to NAMH status at a single time point, as studies indicate subgroups of NAMH trajectories (e.g., increasing, decreasing, persistent; Baron et al., 2017), and depression and anxiety as individual NAMH conditions may have different trajectory subgroups (Lee et al., 2021). Evaluating parallel depression and anxiety trajectories, while accounting for comorbidity, may provide additional insight beyond single time point findings.

We also hypothesized that trauma and resilience would interact with NAMH. Based on other studies examining contexts of trauma or resilience as risk or protective factors on negative birth outcomes (Moog et al., 2016; Rini et al., 1999), as well as research demonstrating the role of trauma in increasing vulnerability to NAMH (Young-Wolff et al., 2019), we hypothesized that trauma would increase effects of NAMH on negative birth outcomes, while resilience would serve as a buffer against NAMH effects. All significant interactions between NAMH and trauma followed the hypothesized directions. Although Most interactions only strengthened or weakened NAMH effects when compared to the no-NAMH condition, there were some differences in the effects of trauma or resilience on birth outcomes when comparing NAMH conditions to each other. Traumatic lifetime experience was more strongly associated with increased odds of moderate/severe neurological impairment for mothers reporting comorbid NAMH compared to mothers who reported either no NAMH or anxiety-only NAMH. There are a few possibilities that can explain these results, although more research is required to understand potential underlying mechanisms and to replicate study findings. Prior research suggests that antenatal depression and anxiety affect fetal neurological development in unique ways (Donnici et al., 2021; Rifkin-Graboi et al., 2015), and these differences may be further facilitated by prior traumatic experiences. Another potential explanation is that trauma and NAMH may have a nonlinear multiplicative effect (such that trauma increases the effect of any NAMH, but a stronger interaction is only evident when comparing more severe outcomes). However, it is also possible that results would have differed if using more refined measures of trauma, given that there appear to be differences in the way that childhood versus adult traumatic experiences (Blackmore et al., 2016) and pregnancy-related versus non-pregnancy related traumatic experiences are associated with antenatal depression and anxiety (Meijer et al., 2014). Taken together, these results contribute to the prevailing narrative that NAMH and trauma jointly contribute to negative birth outcomes, but that this relationship requires nuanced measurement and analysis given potential differences in ways that antenatal depression and anxiety impact neurological development.

Interactions between resilience and NAMH were also in the hypothesized direction (resilience effects reduced negative effects of NAMH). Although these interactions did not appear to differ between NAMH groups, moderation of depression-only and anxiety-only NAMH was associated with different levels of neurological impairment severity. Compared to mothers reporting no NAMH, higher resilience was associated with lower odds of mild neurological impairment for mothers who experienced depression-only NAMH, and lower odds of moderate/severe impairment for mothers who experienced anxiety-only NAMH. Taking main effects and interaction effects on neurological impairments into account, the proposed differential effects of antenatal depression and anxiety (Rifkin-Graboi et al., 2015) on neural development may also include differences in how risk and protective factors

can moderate these effects. However, the current study did not examine mediation of resilience or trauma on birth outcomes (Ma et al., 2019; Young-Wolff et al., 2019) in addition to moderation. Resilience may play more of an indirect protective role (e.g., a mediation pathway) compared to a moderating pathway. This would also explain the lack of interactions between NAMH and resilience when examining PTB outcomes.

3.6. Limitations

Results of the current study must be considered within the context of its limitations. Anxiety and depression were examined only one time during pregnancy. Women experience fluctuations in NAMH throughout pregnancy (Okagbue et al., 2019; Viswasam et al., 2019), although the extent to which fluctuations and timing of symptoms over trimesters influence birth outcomes is mixed (Doktorchik et al., 2018). Although both the Edinburgh Postnatal Depression Scale and the Spielberger State-Trait Anxiety Scale have been repeatedly validated in literature with pregnant women (Kozinszky and Dudas, 2015; Meades and Ayers, 2011), other studies indicate that there are unique qualities of NAMH within pregnancy (e.g., pregnancy-related anxiety, e.g., anxiety and/or depression specifically related to the pregnancy itself; Sinesi et al., 2019) that may have unique effects on birth outcomes, but may not be captured by the measures used for the current study (Adhikari et al., 2021; Molgora et al., 2020). Similarly, our measure of trauma was limited, and we were unable to discern the timing of trauma experiences (e.g., childhood trauma versus adult trauma), or assess pregnancy-specific traumatic experiences, both of which have nuanced associations with birth outcomes (Tu et al., 2021{Bowers, 2018 #100). Our resilience measure was specifically for trait resilience, which is considered a protective factor against mood disorders (Hu et al., 2015), however, "individual-level" resilience is a multifaceted construct with both internal and external factors dependent upon cultural, demographic, and geographic contexts (Southwick et al., 2014; Yates et al., 2015). Other aspects of resilience, especially social support, may be more relevant for moderating NAMH effects (Biaggi et al., 2016; Nie et al., 2017; Racine et al., 2018), such that lower social support is a context for higher NAMH (Dadi et al., 2020). Paternal partner support in particular is a strong source of external resiliency (Razurel et al., 2017), but paternal distress can also exacerbate maternal distress (Vismara et al., 2016). although we controlled for partner status, we did not examine the extent to which mothers received support from partners or were impacted by their partners' distress. Finally, it should be noted that although we controlled for interdependence between all sites, the South African and United States cohorts differed on most variables, such that the South African cohort had higher rates of all negative birth outcomes, anxiety-only, and comorbid NAMH, and had significantly lower and significantly higher resilience and lifetime traumatic experiences respectively (results upon request). Differences may have also been exacerbated by broader contextual factors, such as average lower socioeconomic status in South African compared to the Northern Plains cohort (Campbell et al., 2018), which can explain higher rates of NAMH (Verbeek et al., 2019). Given the complexity of analyses (e.g., categorical predictors and outcomes), we included both cohorts to ensure adequate sample size both overall and for individual cells, however, results may have been influenced by differences between cohorts (either difference in data or unobserved third-variable explanations).

4. Conclusions and future directions

Given the increased interest in interventions to promote positive maternal mental health and reduce stress during pregnancy, understanding the extent to which individuals may be at risk and levels of risk for specific NAMH conditions will enhance current interventions. For example, prior research indicates that individuals who have experienced trauma are more resistant to perinatal depression treatment or interventions (Grote et al., 2012; Talbot et al., 2011). Specific treatment may be required to address needs for those who are either experiencing comorbid NAMH conditions, or those who have previous traumatic experiences or low psychological resilience. Additionally, as specific biological underlying mechanisms explaining individual NAMH conditions and birth outcomes are still unclear, examining both comorbidities of NAMH conditions and contexts of trauma and resilience can provide new insight in biologically informed studies (e.g., collecting information on cortisol or neurological imaging outcomes).

It is clear that antenatal mental health plays a role in wellbeing for both mother and offspring, both individually and dyadically (Davis and Narayan, 2020; Ramey et al., 2015). Pregnancy provides unique biological and environmental changes and experiences, which are reflected in the nuanced ways that mental health, stress, and distress can manifest throughout pregnancy, are exacerbated or attenuated by broader contexts, and the specific outcomes they contribute to (Biaggi et al., 2016). As antenatal mental health becomes an increasingly important area of concern and intervention for both practitioners and researchers, this should be paired with increasing nuance for how it is evaluated and assessed (Force, 2019; Kimmel et al., 2020).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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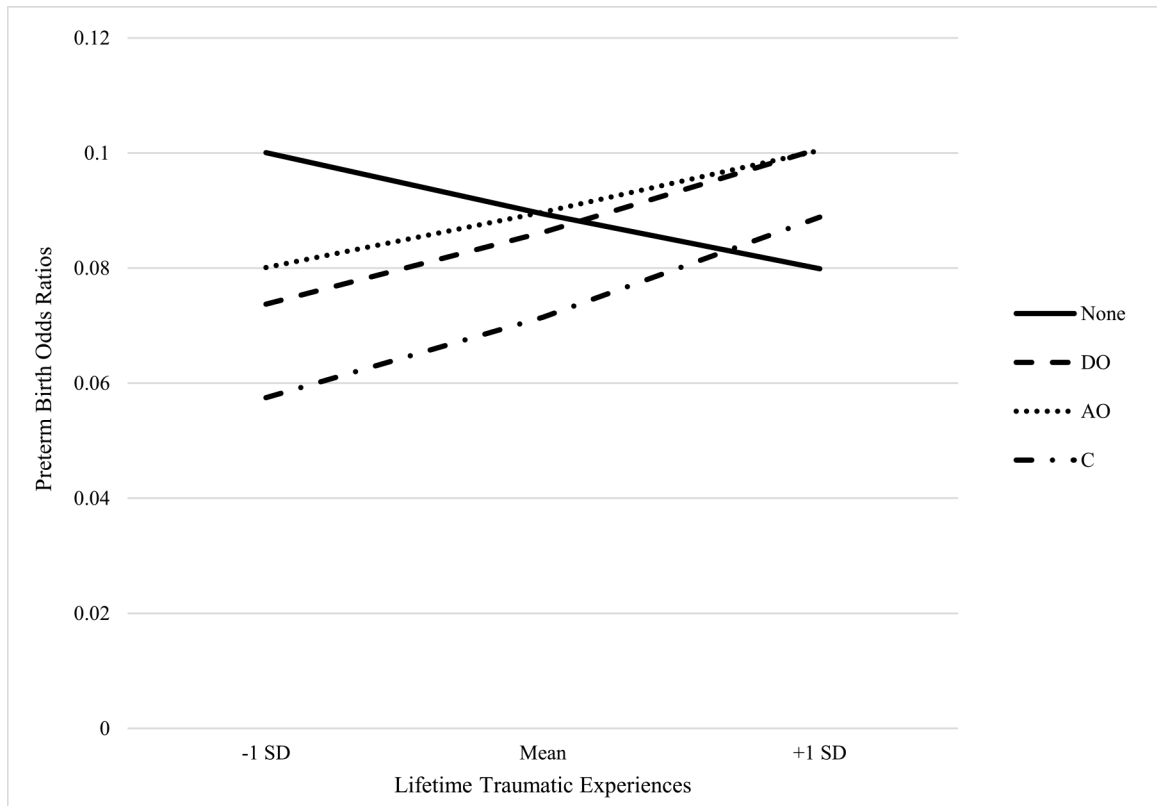
Fig. 1.
Interaction between NAMH condition and lifetime traumatic experiences for odds of preterm birth
Note: DO = depression-only NAMH status, AO = anxiety-only NAMH status, C = comorbid NAMH status.
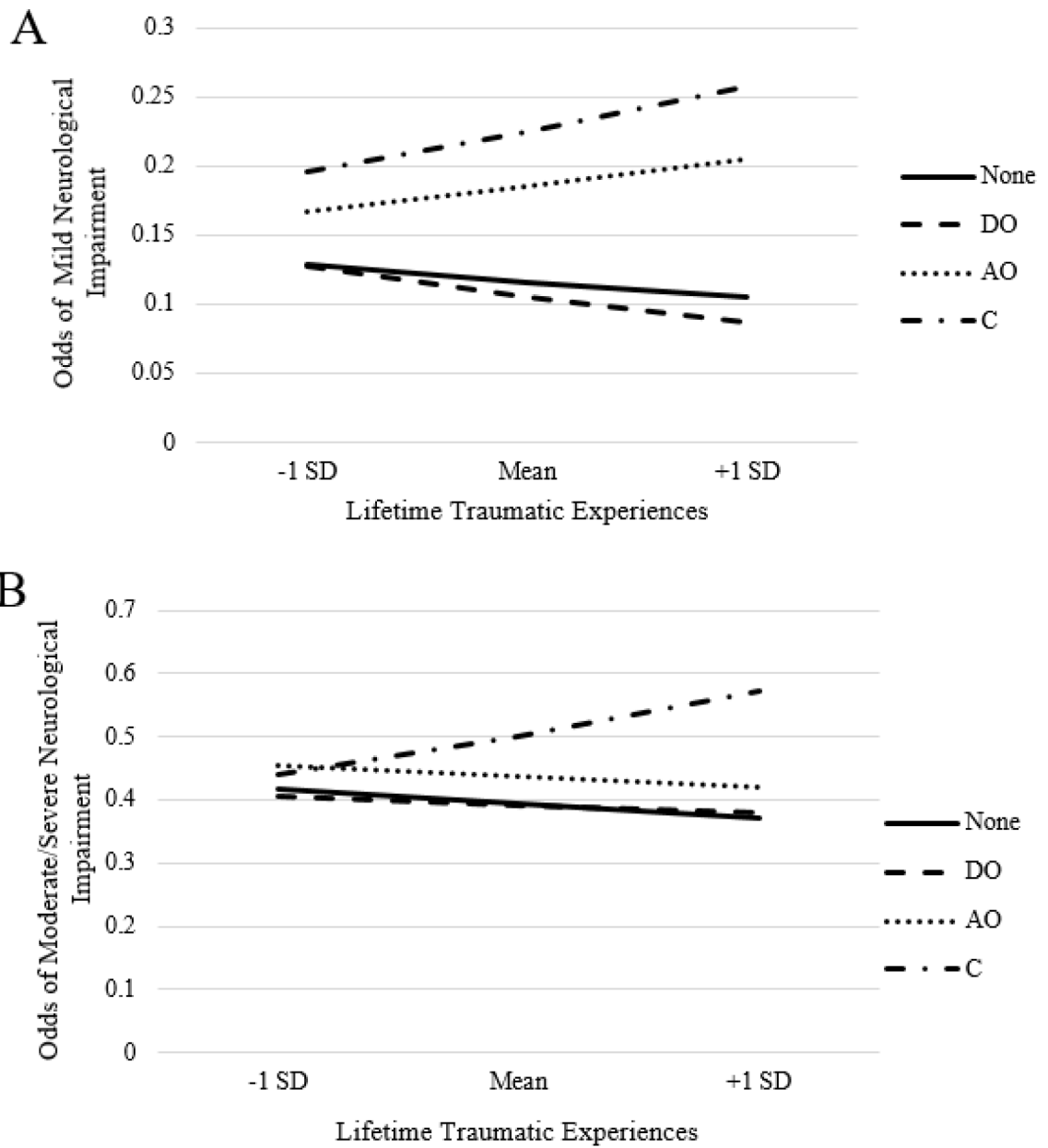
Fig. 2.
A-B. Interaction between NAMH condition and lifetime traumatic experiences for odds of mild (A) and moderate/severe (B) neurological impairment

Note: DO = depression-only NAMH status, AO = anxiety-only NAMH status, C = comorbid NAMH status.
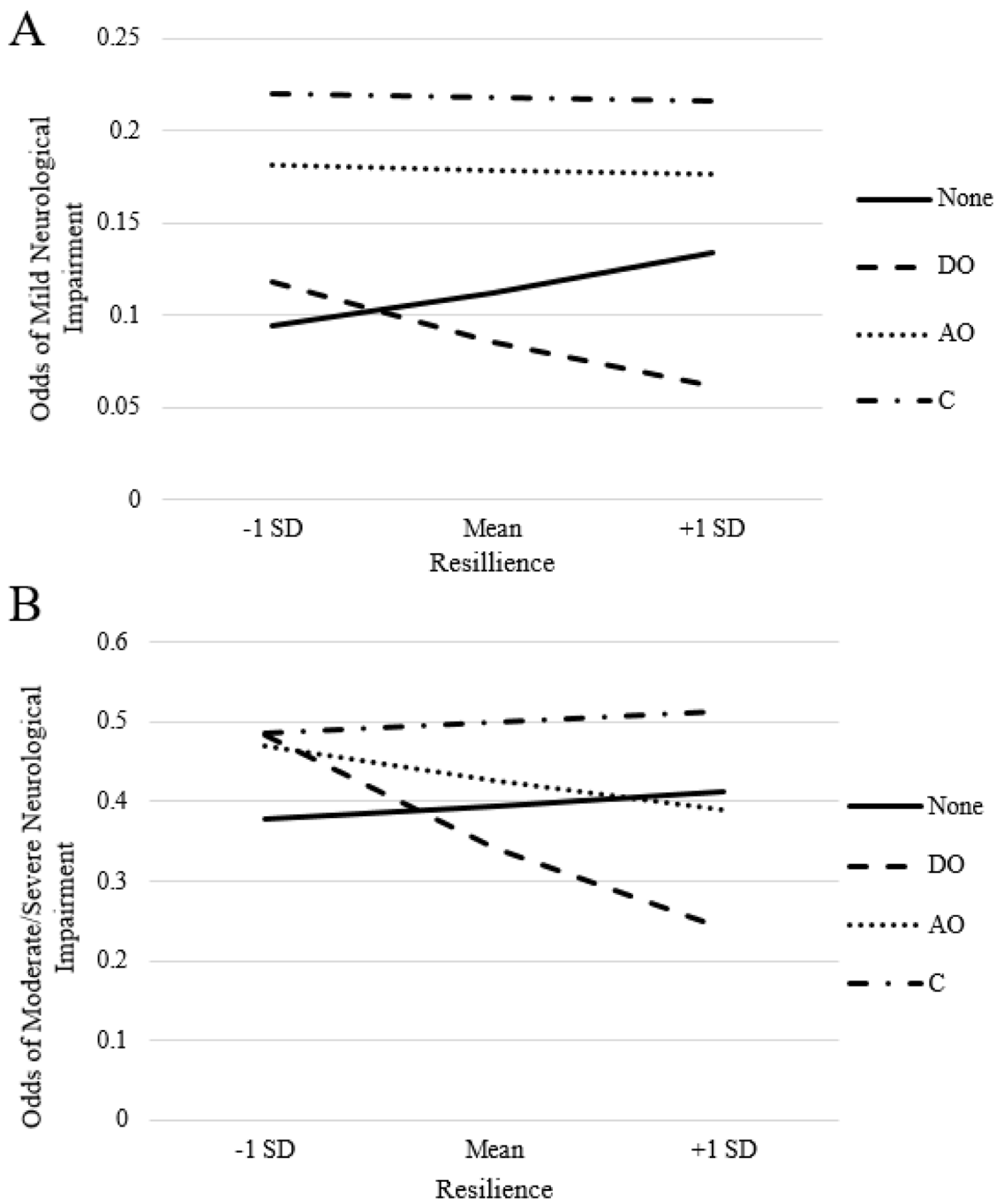
Fig. 3.
A-B. Interaction between NAMH condition and resilience for odds of mild (A) and moderate/severe (B) neurological impairment
Note: DO = depression-only NAMH status, AO = anxiety-only NAMH status, C = comorbid NAMH status.

Table 1

Correlations for all model variables, with categorical variable separation for neurological development and NAMH status multinomial categorical variables.

| Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1 PTB	–																		
1 Mild Neuro Imp. (ref = none)	–0.08**	–																	
1 Mod/Sev Neuro Imp. (ref = none)	0.01	X	–																
1 Dep Only NAMH (ref = no NAMH)	0.01	–0.02	–0.01	–															
1 Anx Only NAMH (Ref = no NAMH)	0.03	0.01	0.13**	X	–														
1 Com. NAMH (Ref = no NAMH)	0.02	0.01	0.08**	X	X	–													
1 Tram. Exp.	0.03	0.00	0.02	0.06**	0.08**	0.13**	–												
1 Resiliance	–0.02	0.02	–0.13**	–0.11**	–0.18**	–0.23**	–0.03	–											
1 Alc Use in Preg.	0.01	0.02	0.05*	0.01	0.12**	0.12**	0.11**	–0.11**	–										
1 Smok. in Preg.	0.08**	–0.01	0.12**	0.03	0.15**	0.14**	0.20**	–0.19**	0.25**	–									
1 Spont. Labor (ref = yes)	–0.04	–0.02	0.11**	0.01	0.08**	0.07**	0.06**	–0.08**	0.08**	0.12**	–								

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1 Gest. Diab/Hyp. (ref = no)	0.01	0.01	0.01	-0.01	-0.03	-0.05*	0.04*	0.05*	-0.05*	-0.03	-0.14**	-							
1 Infant Gender (ref = male)	-0.03	-0.03	0.01	0.04	0.04*	0.01	0.01	0.01	0.02	0.01	0.02	0.03	-						
1 Mat. Educ	-0.08**	0.06**	-0.24**	-0.06**	-0.30**	-0.19**	-0.14**	0.38**	-0.12**	-0.39**	-0.23**	0.08**	-0.03	-					
1 Mari / Part (ref =single)	0.01	0.01	0.05*	-0.04*	0.04*	-0.03	-0.07**	0.02	-0.02	-0.05*	0.01	-0.02	0.01	0.07**	-				
1 Ma. Age	0.01	0.01	-0.08**	-0.02	-0.14**	0.01	0.04*	0.24**	-0.04*	-0.10**	-0.13**	0.05**	0.01	0.32**	0.08**	-			
1 Gravidity	0.02	0.01	-0.07**	0.02	-0.09**	0.06**	0.15**	0.07**	-0.06**	0.04*	-0.05*	0.01	0.01	-0.02	-0.03	0.52**	-		
1 AIAN (Ref = White)	0.02	-0.01	-0.14**	0.10**	-0.17**	-0.04*	0.09**	0.03	-0.12**	0.01	-0.04*	0.07**	-0.01	-0.03	-0.27**	-0.09**	0.21**	-	
1 Colored (Ref = White)	0.06**	-0.05*	0.33**	-0.03	0.40**	0.17**	0.07**	-0.30**	0.19**	0.31**	0.27**	-0.08**	0.01	-0.64**	0.15**	-0.17**	-0.16**	X	-
1 Other Race (Ref = White)	0.01	-0.01	-0.04*	-0.01	-0.04*	0.02	0.01	0.01	-0.05*	-0.04**	0.01	0.01	0.01	0.08**	-0.02	0.01	-0.03	X	X

X indicates a correlation between two non-reference categories in the same variable – for example, between depression-only and anxiety-only NAMH.

*
$p<0.05$

**
$p < 0.01$.

Table 2

Odds ratio for preterm birth outcome models comparing full-term (reference) to preterm birth. (N = 3032).

Variable	Main Effects	Trauma × NAMH Interaction	Resilience × NAMH Interaction
Depression-Only MH (Ref = No NAMH)	1.00 (0.65 – 1.54)	0.96 (0.54 – 1.71)	0.93 (0.52 – 1.66)
Anxiety-Only MH (ref = no NAMH)	1.00 (0.82 – 1.22)	1.00 (0.81 – 1.25)	1.02 (0.85 – 1.22)
Comorbidity MH (Ref = no NAMH)	0.86 (0.60 – 1.24)	0.80 (0.54 – 1.19)	0.92 (0.68 – 1.25)
Traumatic Life Experiences	1.01 (0.95 – 1.06)	0.95 (0.87 – 1.03)	1.01 (0.95 – 1.06)
Resilience	1.00 (1.00 – 1.01)	1.00 (1.00 – 1.01)	1.00 (0.99 – 1.01)
Alcohol Use – Quit during pregnancy (Ref = no use)	1.06 (0.92 – 1.22)	1.07 (0.96 – 1.19)	1.06 (0.92 – 1.23)
Alcohol Use continual during pregnancy (Ref = no use)	0.99 (0.78 – 1.25)	0.98 (0.80 – 1.21)	0.99 (0.78 – 1.26)
Smoking – Quit during pregnancy (Ref = no use)	1.25 [**] (1.02 – 1.54)	1.26 [*] (1.00 – 1.57)	1.26 [*] (1.02 – 1.55)
Smoking continually during pregnancy (Ref = no use)	1.64 [**] (1.26 – 2.14)	1.64 [**] (1.25 – 2.14)	1.65 [**] (1.25 – 2.15)
Spontaneous Labor Status (ref = not spontaneous labor)	0.59 (0.27 – 1.28)	0.59 (0.27 – 1.29)	0.60 (0.28 – 1.28)
Gestational Diabetes/Hypertension (ref = no diabetes or hypertension)	1.01 (0.59 – 1.73)	1.03 (0.59 – 1.79)	1.01 (0.60 – 1.72)
Infant Gender (Ref = Male)	0.86 (0.65 – 1.14)	0.86 (0.65 – 1.14)	0.86 (0.65 – 1.14)
Maternal Education	0.84 [**] (0.77 – 0.93)	0.84 [**] (0.76 – 0.93)	0.86 [**] (0.78 – 0.93)
Marital/Partner Status (Ref = Single)	1.33 (1.00 – 1.77)	1.34 (0.98 – 1.82)	1.34 [*] (1.00 – 1.78)
Maternal age at pregnancy	1.02 [**] (1.00 – 1.03)	1.02 [*] (1.00 – 1.03)	1.02 [**] (1.01 – 1.03)
American Indian/Alaska Native (ref = Nonhispanic White)	1.76 [**] (1.09 – 2.86)	1.82 [*] (1.13 – 2.94)	1.75 [*] (1.07 – 2.88)
Mixed Ancestry (ref = Nonhispanic White)	1.70 [**] (1.48 – 1.95)	1.73 [**] (1.52 – 1.98)	1.68 [**] (1.46 – 1.94)
Other Race / Ethnicity (ref Nonhispanic White)	2.17 (0.88 – 5.37)	2.19 (0.86 – 5.61)	2.18 (0.87 – 5.47)
Gravidity	0.98 (0.89 – 1.08)	0.98 (0.89 – 1.07)	0.98 (0.89 – 1.08)
Depression-Only NAMH X Trauma		1.14 (0.83 – 1.58)	
Anxiety-Only NAMH X Trauma		1.12 [*] (1.01 – 1.24)	
Comorbidity X Trauma		1.18 [*] (1.03 – 1.35)	
Depression-Only NAMH × Resilience			0.99 (0.96 – 1.02)
Anxiety-Only NAMH × Resilience			1.01 (0.99 – 1.02)
Comorbidity × Resilience			1.01 (1.00 – 1.02)

[*]
p <0.05

[**]
p<0.01.

Table 3

Odds ratios for neurological maturation models comparing no neurological impairment (reference) to mild or moderate/severe impairment. ($N = 2050$).

	None vs Mild			None vs Moderate/Severe		
	Main Effects	Trauma × NAMH Interaction	Resilience × NAMH Interaction	Main Effects	Trauma × NAMH Interaction	Resilience × NAMH Interaction
Depression-Only NAMH (Ref = No NAMH)	0.86 (0.16 – 4.59)	0.91 (0.17 – 4.83)	0.76 (0.15 – 3.74)	0.99 (0.72 – 1.36)	0.99 (0.73 – 1.36)	0.86 (0.53 – 1.41)
Anxiety-Only NAMH (ref = no NAMH)	1.63** (1.12 – 2.37)	1.59** (1.21 – 2.10)	1.59* (1.01 – 2.50)	1.11 (0.91 – 1.34)	1.11 (0.91 – 1.35)	1.08 (0.91 – 1.29)
Comorbidity NAMH (Ref = no NAMH)	2.05** (1.36 – 3.10)	1.94** (1.23 – 3.04)	1.94* (1.17 – 3.23)	1.35 (0.98 – 1.87)	1.27 (0.88 – 1.83)	1.26 (0.86 – 1.86)
Traumatic Life Experiences	0.99 (0.88 – 1.12)	0.95 (0.80 – 1.13)	0.99 (0.88 – 1.11)	0.98 (0.92 – 1.06)	0.97 (0.89 – 1.06)	0.99 (0.92 – 1.05)
Resilience	1.01* (1.00 – 1.01)	1.01* (1.00 – 1.01)	1.01 (0.99 – 1.03)	1.00 (0.99 – 1.00)	1.00 (0.99 – 1.00)	1.00 (1.00 – 1.01)
Alcohol use – quit during pregnancy (Ref = no use)	1.09 (0.87 – 1.36)	1.10 (0.87 – 1.38)	1.09 (0.87 – 1.37)	0.98 (0.71 – 1.10)	0.89 (0.72 – 1.10)	0.89 (0.72 – 1.10)
Alcohol use continual during pregnancy (Ref = no use)	1.18 (0.91 – 1.53)	1.17 (0.91 – 1.51)	1.18 (0.91 – 1.55)	0.88* (0.84 – 0.93)	0.89** (0.84 – 0.93)	0.89** (0.84 – 0.94)
Smoking – Quit during pregnancy (Ref = no use)	1.41 (0.78 – 2.57)	1.24 (0.77 – 2.64)	1.42 (0.78 – 2.61)	1.11 (0.92 – 1.35)	1.12 (0.92 – 1.35)	1.05 (0.78 – 1.42)
Smoking continual during pregnancy (Ref = no use)	1.18* (1.03 – 1.34)	1.18* (1.03 – 1.36)	1.18* (1.04 – 1.33)	1.05 (0.77 – 1.42)	1.05 (0.78 – 1.41)	1.05 (0.78 – 1.42)
Spontaneous Labor Status (ref = not spont. labor)	1.14 (0.71 – 1.84)	1.14 (0.70 – 1.85)	1.14 (0.73 – 1.79)	1.06 (0.74 – 1.50)	1.06 (0.74 – 1.50)	1.06 (0.74 – 1.51)
Gest. Diabetes/Hype. (ref = no diabetes/hype.)	1.19 (0.89 – 1.59)	1.22 (0.91 – 1.64)	1.19 (0.90 – 1.59)	1.36 (0.91 – 2.02)	1.36 (0.93 – 2.00)	1.36 (0.91 – 2.04)
Infant Gender (Ref = Male)	0.78 (0.47 – 1.30)	0.78 (0.47 – 1.29)	0.78 (0.47 – 1.31)	0.93 (0.82 – 1.06)	0.93 (0.82 – 1.06)	0.94 (0.83 – 1.06)
Maternal Education	1.15 (0.97 – 1.36)	1.14 (0.96 – 1.35)	1.13 (0.96 – 1.34)	0.99 (0.89 – 1.11)	0.99 (0.89 – 1.11)	0.98 (0.88 – 1.10)
Marital/Partner Status (Ref = Single	1.00 (0.34 – 2.99)	0.99 (0.34 – 2.86)	0.99 (0.33 – 2.97)	1.13 (0.80 – 1.60)	1.14 (0.81 – 1.60)	1.12 (0.79 – 1.57)
Maternal age at pregnancy	0.98 (0.95 – 1.02)	0.98 (0.95 – 1.02)	0.98 (0.95 – 1.02)	1.00 (0.97 – 1.04)	1.00 (0.97 – 1.04)	1.00 (0.97 – 1.04)
Amer. Indian/Alaska Native (ref = Nonhispanic White)	0.69 (0.36 – 1.33)	0.70 (0.36 – 1.34)	0.69 (0.36 – 1.34)	1.27 (0.67 – 2.40)	1.28 (0.68 – 2.41)	1.27 (0.68 – 2.40)
Mixed Ancestry (ref = Nonhispanic White)	0.99 (0.65 – 1.51)	1.02 (0.65 – 1.58)	1.00 (0.62 – 1.63)	4.01** (3.03 – 5.31)	4.03** (3.07 – 5.30)	4.07 (3.01 – 5.51)
Other Race / Ethnicity (ref = Nonhispanic White)	0.65 (0.25 – 1.69)	0.67 (0.25 – 1.77)	0.65 (0.24 – 1.74)	0.75 (0.44 – 1.30)	0.77 (0.44 – 1.34)	0.75 (0.42 – 1.33)

	None vs Mild			None vs Moderate/Severe		
	Main Effects	Trauma × NAMH Interaction	Resilience × NAMH Interaction	Main Effects	Trauma × NAMH Interaction	Resilience × NAMH Interaction
Gravidity	1.00 (0.76 – 1.31)	1.00 (0.76 – 1.31)	1.00 (0.76 – 1.31)	0.95 (0.85 – 1.06)	0.95 (0.85 – 1.06)	0.94 (0.84 – 1.06)
Dep.-Only NAMH X Trauma		0.96 (0.84 – 1.09)			1.01 (0.85 – 1.21)	
Anxiety-Only NAMH X Trauma		1.11 (0.83 – 1.48)			1.01 (0.92 – 1.11)	
Comorbidity X Trauma		1.13 (0.87 – 1.45)			1.00[*] (1.00 – 1.00)	
Dep.-Only NAMH × Resilience			0.97[**] (0.94 – 0.99)			0.97 (0.93 – 1.02)
Anxiety-Only NAMH × Resilience			0.99 (0.95 – 1.03)			0.99[*] (0.98 – 1.00)
Comorbidity × Resilience			0.99 (0.97 – 1.01)			0.99 (0.98 – 1.00)

[*] $p < 0.05$

[**] $p < 0.01$.