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Maternal prenatal psychological distress and vitamin intake with children's neurocognitive development

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BACKGROUND: Maternal prenatal psychological distress (PPD) is increasingly linked to sub-optimal child neurodevelopment. Daily intake of prenatal vitamin during pre-conception and early pregnancy may ameliorate the effects of PPD on cognition in the offspring.
METHODS: PPD was assessed in early (12–16 weeks) and late (28–32 weeks) gestation in the Ontario Birth Study. Prenatal vitamin supplement intake information was collected in early gestation. Child cognition at 4 years was assessed using the NIH Toolbox. Poisson regression was used to investigate associations between PPD and/or prenatal vitamin intake and child cognition.
RESULTS: Four hundred and eighteen mother–child dyads were assessed. Moderate–severe PPD experienced during early gestation was associated with reduced cognition (adjusted incidence rate ratio (IRR_{adj}) = 3.71, 95% confidence interval (CI): 1.57–8.77, $P = 0.003$). Daily intake of prenatal vitamins was not associated with cognition ($IRR_{adj} = 1.34$, 95% CI: 0.73–2.46, $P = 0.34$). Upon stratification, the experience of mild–severe PPD with daily intake of prenatal vitamins was associated with higher incident rates of suboptimal cognition compared to children of women with daily prenatal vitamin intake without any episode of PPD ($IRR_{adj} = 2.88$, 95% CI: 1.1–7.4).
CONCLUSIONS: Moderate–severe PPD in early pregnancy is associated with poor cognition in children and daily intake of prenatal vitamin did not ameliorate this association.

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IMPACT:

- Our findings expand on existing literature by highlighting that exposure to prenatal psychological distress (PPD), in moderate-to-severe form, in the early stages of pregnancy, can have detrimental effects on the offspring's cognitive development at 4 years.
- Overall, prenatal vitamin intake did not ameliorate the effects of PPD.
- Early screening and treatment of prenatal maternal mental illness is crucial.

INTRODUCTION

Depression and anxiety are common mental health problems during pregnancy. About 12–17% of pregnant women experience depression whereas 15–21% experience at least one anxiety disorder.[1–4] Maternal prenatal psychological distress (PPD) refers to depression and/or anxiety experienced during pregnancy, which has not reached the severity of a mental disorder.[5] A growing body of evidence has linked PPD to adverse child neurodevelopmental outcomes, such as cognitive, emotional, and behavioral problems.[6,7] It is posited that PPD results in elevated levels of maternal cortisol, which in turn leads to increased fetal exposure to cortisol. The latter can have profound influences on fetal brain development.[8,9] Fetal and infant brain magnetic resonance imaging (MRI) studies have shown that maternal exposure to PPD is associated with impaired fetal brain structure and biochemistry.[10,11] In general, other plausible mechanisms linking PPD to sub-optimal neurodevelopment in the offspring include: interference with uterine blood supply and nutrient transport in the placenta,[12,13] epigenetic mechanisms,[14,15] and other indirect mechanisms involving PPD's effects on maternal physical health and related behaviors, such as adequate nutrition, sleep, and physical activity.[16]

Despite the growing body of literature on the potential negative effects of PPD on child cognitive development, previous studies have reported conflicting results, and the relevant timing of PPD exposure on cognitive outcomes remains to be elucidated.[7,17] For example, a systematic review with eight studies on the association of PPD and child cognition found a significant inverse association among six studies, a positive association in one study, and no association in the largest study of the eight studies.[17] Another meta-analytic review of 11 studies examined the potential modulating effects of PPD timing by trimester and type of PPD assessment.[6] The review showed that, although the associations with cognitive development were in the same direction

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(i.e., adverse), the magnitude of associations relating to major life events (e.g., catastrophic events like natural disasters) were significantly greater than those derived from pregnancy-related stress or other subjective assessments of stress unrelated to pregnancy.[6] This review also found that there were no significant differences in estimated effect size as a function of the trimester when PPD was assessed.[6] Within the Canadian context, studies from the 1998 Quebec ice storm disaster have shown that the adverse associations of PPD with cognition are more pronounced when exposure occurred during the first or second trimester.[18,19] However, few studies without exposure to major life events examine the influence of different timing of PPD exposure on child cognitive development, which highlights the need to further investigate the relationship of PPD with child cognition.

Also, relatively few studies have assessed factors that could mitigate the risk posed by PPD for poor child cognition.[7,17,20] Maternal intake of prenatal vitamins is among these under-researched factors which may potentially play a beneficial role. Since prenatal vitamins contain a variety of components such as vitamins A, B, C, D, and E, folic acid, niacin, calcium, iron, zinc, etc.,[21] it is challenging to single out which compounds may have an impact on child outcomes. Nonetheless, folate is among the essential nutrients for fetal brain development, owing to its role in supporting cell replication, cell division, nucleotide, and neurotransmitter synthesis.[22] Also, some vitamins (e.g., B-6 and B-12) play critical functions in the growth and development of the fetus, including neurodevelopment.[23,24] Another plausible mechanism through which prenatal vitamin intake may impact cognition in the offspring is through reducing the occurrence of known risk factors for poor neurodevelopment such as infections, improving metabolism, and lowering the risk of low birth weight.[25] Studies have also shown that prenatal vitamin intake prevents neural tube defects and/or congenital anomalies[26] and reduces the risk of autism spectrum disorder[27,28] in the offspring. Previous studies have indicated mixed evidence of the benefits of maternal prenatal vitamin intake on children's neurodevelopmental outcomes (including child cognition).[25,29] No previous study has examined whether the intake of prenatal vitamins could ameliorate the negative impact of PPD on child cognition. Overall, the evidence surrounding the relationship of prenatal vitamin intake with child cognition within the context of maternal exposure to PPD is scarce.

The primary objective of the current study was to investigate the association between PPD (assessed during early and late pregnancy) and prenatal vitamin intake (at both pre-conception and first trimester) as the main exposures and child cognition at 4 years as the main outcome in an ongoing birth cohort. The secondary objective was to investigate whether daily intake of prenatal vitamins modified the association between PPD and child cognitive outcomes. We hypothesized that PPD experienced at each of the gestation periods would be associated with reduced child cognition at 4 years, with stronger associations among offspring who were exposed in the earlier gestation period and to a more severe form of PPD. We also hypothesized that daily prenatal vitamin intake would be positively associated with child cognition and ameliorate the adverse association of PPD on child cognition at 4 years.

METHODS

Study participants

The Ontario Birth Study (OBS) is an ongoing prospective pregnancy cohort study started in 2013.[30] Briefly, pregnant women aged 18 years and older, at less than 17 weeks gestation and able to communicate in English, are recruited during their first ultrasound or antenatal visit at Mount Sinai Hospital Obstetrics clinics. During pregnancy, study participants are asked to complete two self-administered general lifestyle questionnaires during the periods of 12–16 (LSQ1) and 28–32 weeks (LSQ2) gestational age. A detailed description of the contents of the questionnaires is available in a previous publication.[30] A total of 3211 pregnant women have been recruited up to mid-July 2021. The follow-up of children involves 2 home visits (at ages 24 months and 4 years) and 2 telephone follow-up interviews (at ages 8 and 36 months) conducted by trained research assistants. A total of 470 mother–child dyads reached the 4-year follow-up time point by November 2020. The current study includes 418 mother–child dyads from the ongoing cohort with complete data on PPD and child cognition up to age 4 years (from Feb 2018 to Nov 2020) available at the time of the current analysis (see Fig. 1 for details).

Measures

The primary outcome for this study was child cognition at 4 years. Children's cognitive development at 4 years was assessed using the Early Childhood Cognition Battery of the NIH Toolbox.[31] The cognition battery comprises 4 tests (picture sequence memory test, flanker inhibitory control and attention test, picture vocabulary test, dimensional change card sort test) appropriate for children aged 3–6 years,[31] which are combined into a composite cognition score, and was administered using an iPad. The Cognition Battery of the NIH Toolbox was shown to have acceptable test-retest reliability in children aged 3–15 years in North America.[31] The battery is sensitive to different cognitive ability levels in children. A high correlation between the Cognition Battery of the NIH Toolbox and the Wechsler Preschool and Primary Scale of Intelligence has been shown among children aged 3–6 years.[31] We computed *Z*-scores from the age-corrected composite cognition scores and the lowest 10th percentile within the study cohort was defined as *suboptimal cognition*. The use of normative percentiles with values ranging from the 25th percentile to the 10th percentile for evaluating group differences in cognitive and learning disabilities is widely documented. We chose the 10th percentile because it is considered a more restrictive criterion and shown to be close to the reported prevalence of learning/cognitive problems.[32]

The main exposure variables were PPD and maternal prenatal vitamin intake. PPD was assessed separately at 12–16 weeks and 28–32 weeks of gestation using the Patient Health Questionnaire-4 (PHQ-4), which is a four-item composite measure that combines a two-item measure consisting of core criteria for depression (the PHQ–2), and a two-item measure for anxiety (the GAD–2).[33] PHQ–4 total scores range from 0–12, and these were operationally categorized as normal (0–2), mild (3–5), moderate (6–8), and severe PPD (9 –12) based on previous psychometric validation of the PHQ-4.[33] In the present study, we utilized a 3-level ordinal variable to capture variation in magnitude of PPD: women who scored a total of 0-2 on PHQ-4 were defined as *not having experienced PPD*, those who scored 3–5 on PHQ-4 were defined as *having experienced mild PPD*

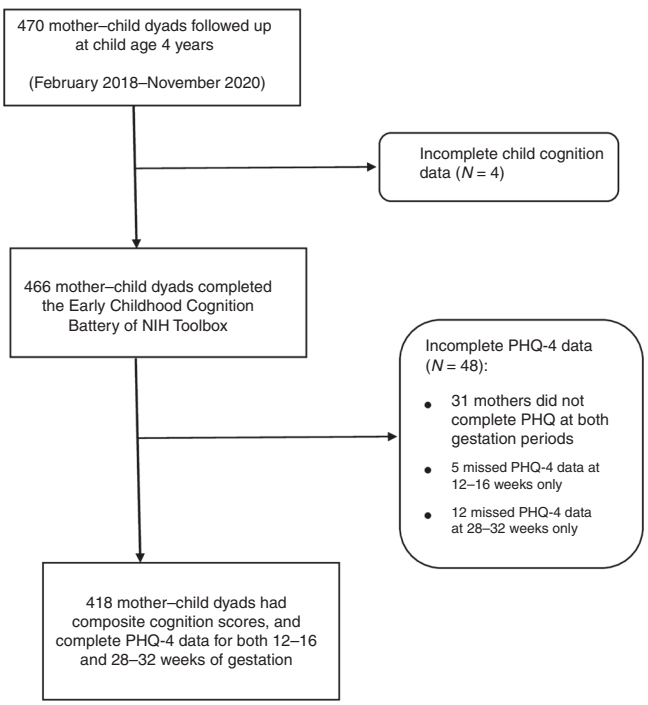

Fig. 1 Study flowchart. Selection process of the mother-child dyads from the OBS Kids follow-up.

and those who scored 6–12 were defined as *having experienced moderate–severe PPD*. A score of 3 or more is considered positive for screening purposes for this measure. Women who scored ≥3 on the sub-scale for depression (PHQ-2) were defined as having experienced depression and those who scored ≥3 on the sub-scale for anxiety (GAD-2) were defined as having experienced anxiety. The PHQ-4 has been shown to be a valid and brief tool for detecting both anxiety and depressive disorders, including among pregnant women.[33,34]

Maternal prenatal vitamin intake was assessed in the questionnaire administered at 12–16 weeks of gestation (LSQ1) by asking the participants how often they took prenatal vitamins in the 3 months before pregnancy and during their first trimester of pregnancy. A binary variable combining both time periods was generated, whereby *daily intake* comprised participants who reported that they took prenatal vitamins every day for both periods and *less than daily intake* included those who reported intake less frequently than daily at either period.

The covariates comprised socio-demographics and birth-related characteristics, including marital status, maternal education, ethnicity, and age at delivery, infant sex, birth weight, and breastfeeding duration as well as child age at assessment. Data on marital status, highest maternal education level, and ethnicity were captured in the LSQ1, whereas maternal age at delivery (in years), infant sex, birth weight, and child date of birth (used to compute age at date of cognition assessment) were extracted from hospital charts and electronic medical records using standardized abstraction forms. Low birth weight was defined as birth weight <2500 g.[35] Breastfeeding duration was assessed during the telephone follow-up interviews.

Statistical analyses

We utilized Poisson regression models with robust error variance,[36] adjusted for infant sex, maternal age at delivery, maternal education, and history of major anxiety or depression for all models. These covariates were selected based on extensive literature supporting their link to child cognition (maternal age)[37] and on the basis of having *P* values of 0.25 or less ($P \leq 0.25$) in the initial bivariate analyses[38] (infant sex and maternal education). History of major anxiety or depression diagnosed by health professionals was included among the covariates to control for the potential influence of mothers' pre-existing conditions on the observed associations.[39] First, we assessed the association between child cognition at 4 years and PPD using the 3-level ordinal variable on PPD in early pregnancy (12–16 weeks gestation), late pregnancy (28–32 weeks gestation), and either period. Second, we investigated the association between maternal prenatal vitamin intake and child cognition at 4 years. Third, to evaluate the potential effect modification of pre-natal vitamin, we conducted stratified analysis by prenatal vitamin intake for PPD and tested for interaction between PPD and prenatal vitamin intake. The interaction analysis was based on a binary (instead of 3-level) variable of mild–severe PPD (scored 3–12 on PHQ-4) vs. none to ensure sufficient sample size given that the occurrence of moderate/severe PPD is low. Finally, Kernel density plots were generated to visualize the distribution of age-corrected composite cognition scores across the sub-categories of the mild–severe PPD and prenatal vitamin intake status for each of the time periods (early pregnancy, late pregnancy, and either time period). The Kernel density plots were generated using a combinational variable to capture both PPD and prenatal vitamin intake; that is, (i) women who did not experience mild–severe PPD and reported daily intake of prenatal vitamins (reference category), (ii) women who experienced mild–severe PPD and reported daily intake of prenatal vitamins, (iii) women who did not experience mild–severe PPD and reported less than daily intake of prenatal vitamins, and (iv) women who experienced mild–severe PPD and reported less than daily intake of prenatal vitamins. All statistical analyses were performed using STATA (Version 15; StataCorp) and *P* values ≤0.05 were considered to be statistically significant. All tests are two-sided.

RESULTS

The socio-demographic, prenatal vitamin intake, and maternal and infant characteristics of the 418 mother–child dyads are summarized both according to the total sample and across the two child cognition groups (Table 1). The mean age of the children was

Table 1. Socio-demographic, maternal, and infant characteristics of the study participants across the child cognition categories ($N = 418$).

Sample characteristics	Overall sample, *n* (%)	Cognition[a], *n* (%)		
		Normal ($n = 373$)	Suboptimal cognition ($n = 45$)	*P* value
Categorical variables				
Infant sex				0.01
Males	213 (50.6)	182 (48.8)	31 (68.9)	
Females	205 (49.4)	191 (51.2)	14 (31.1)	
Maternal education				0.15
Below Bachelor degree	58 (14.1)	49 (13.3)	9 (20.5)	
Bachelor degree or higher	354 (85.9)	319 (86.7)	31 (79.5)	
Marital status				0.25
Married	366 (87.6)	328 (87.9)	38 (84.4)	
Living with a partner	40 (9.6)	36 (9.7)	4 (8.9)	
Other	12 (2.9)	9 (2.4)	3 (6.7)	
Low birth weight (yes)	24 (5.7)	20 (5.4)	4 (8.9)	0.31
History of major anxiety or depression (yes)[b]	54 (12.9)	47 (12.6)	7 (15.6)	0.64
Prenatal vitamin intake[c]				0.36
Daily intake	195 (51.7)	178 (52.5)	17 (44.7)	
Less than daily intake	182 (48.3)	161 (47.5)	21 (55.3)	
Continuous variables	Mean (SD)			
Child age (months)	55.6 (±2.5)	55.6 (±2.5)	55.6 (±2.5)	0.90
Maternal age at delivery (years)	34.5 (±3.7)	34.4 (±3.7)	34.9 (±4.4)	0.42
Breastfeeding period (months)	13.1 (±8.5)	13.1 (±8.4)	13.1 (±9.8)	0.97

Child age and maternal age at delivery are presented in mean (standard deviation).
[a]Cut-off for cognition is based on *Z*-scores (below 10th percentile is defined as suboptimal).
[b]Participants asked if they have ever been told by a doctor that they have major depression or anxiety disorder.
[c]Reference period for prenatal vitamin intake is 3 months before pregnancy and during first trimester ($n = 377$).

55.6 months, without significant differences across the cognition groups. A greater proportion of boys than girls (69 vs. 31%) were in the suboptimal cognition group ($P = 0.01$). On average, children were breastfed for 13 months and a very small proportion of children (6%) were born with low birth weight. Most (78%) of the mothers were of European descent, 15% were Asian (East, South, or South East) and the rest (7%) identified as Aboriginal, Black, Arab, or other racial/ethnic groups. The majority (86%) had a bachelor's degree or higher, were currently married or living with their partner (97%) and the mothers were an average of 35 years of age at delivery.

Of the 418 pregnant women, 382 had data on prenatal vitamin intake during the first trimester. Almost all (97.6%) of them reported that they had taken prenatal vitamins in the first trimester and 82.2% of the 382 reported daily intake of prenatal vitamins during this period. For the 3-month pre-conception period, 75.2% reported that they took prenatal vitamins in this period and 55.4% reported daily intake. The majority (98.9%) of the women who had taken prenatal vitamins during the pre-conception period continued in the first trimester. Of the 418 women in this study, 3.4% ($n = 14$), 3.1% ($n = 13$), and 5.5% ($n = 23$) experienced moderate–severe PPD in early pregnancy (12–16 weeks gestation), late pregnancy (12–16 weeks), and in either gestation period, respectively. Mild–severe PPD was experienced among 19.6% ($n = 82$) in early pregnancy, 16.8% ($n = 70$) in late pregnancy, and in 26.6% ($n = 111$) during either gestation period. Furthermore, 5.7, 6.0, and 8.6% had experienced anxiety during early pregnancy, late pregnancy, and at either gestation period (i.e., overall), respectively, while 6.9% of the pregnant women had experienced depression at either gestation period (4.3% in early and 3.4% in late pregnancy).

The results from multivariable Poisson regression for the association between PPD (at 12–16 weeks, 28–32 weeks and either gestation period) and child cognition at 4 years are summarized in Table 2. A statistically significant association between moderate–severe PPD and suboptimal child cognition was observed when PPD occurred during 12–16 weeks, but not for the 28–32 weeks period. Specifically, children born to mothers who experienced moderate–severe PPD during early pregnancy (12–16 weeks gestation) had over 3.5-fold increased risk of suboptimal cognition compared to those born to mothers who did not experience PPD during the same gestation period (Adjusted incident rate ratio (IRR_{adj}) = 3.71, 95% CI: 1.57–8.77). The relationship was also statistically significant when moderate–severe PPD in either period was considered (IRR_{adj} = 3.32, 95% CI: 1.57–6.99).

Less than daily intake of prenatal vitamins was not significantly associated with child cognition at 4 years ($IRR_{adj} = 1.34$, 95% CI: 0.73–2.46) in the multivariable analysis (Table 3) compared to daily intake. The Kernel density plots to visualize the distribution of age-corrected composite cognition scores across the sub-categories of the combined PPD–prenatal vitamin intake variable is presented in Fig. 2a–c. All the three plots generally show that children from the reference group (no mild–severe PPD and daily prenatal vitamin intake) had the highest cognition distribution among the 4 categories of mild–severe PPD and prenatal vitamin intake.

We further investigated if there was an effect modification by maternal prenatal vitamin intake on the association between PPD and child cognition using the adjusted model for the association between mild–severe PPD and child cognition at 4 years (Table 4). The interaction terms specific to the group which experienced mild–severe PPD and with a daily intake of prenatal vitamins were statistically significant in early pregnancy ($P = 0.03$) and either period ($P = 0.02$). Compared to children born to mothers who did not experience PPD and had daily prenatal vitamin intake, the children born to mothers who experienced PPD and reported daily intake of prenatal vitamins had a higher incidence rate for suboptimal cognition. This was statistically significant in early

Table 2. Adjusted Poisson regression analyses of the association between maternal prenatal psychological distress (PPD) across gestation periods and child cognition at 4 years ($N = 411$).

Variables	Early pregnancy (12–16 weeks of gestation)				Late pregnancy (28–32 weeks of gestation)				Either gestation period (overall)			
	Normal cognition (*n*, %)	Suboptimal cognition (*n*, %)	IRR (95% CI)	*P* value	Normal cognition (*n*, %)	Suboptimal cognition (*n*, %)	IRR (95% CI)	*P* value	Normal cognition (*n*, %)	Suboptimal cognition (*n*, %)	IRR (95% CI)	*P* value
No PPD	300 (81.7)	31 (70.5)	Reference		309 (84.2)	35 (79.6)	Reference		275 (74.9)	28 (63.6)	Reference	
With PPD (mild–severe)	67 (18.3)	13 (29.5)	1.86 (1.03, 3.36)	**0.04**	58 (15.8)	9 (20.5)	1.33 (0.69, 2.57)	0.40	92 (25.1)	16 (36.4)	1.71 (0.97, 3.00)	0.06
Mild PPD	59 (16.1)	9 (20.4)	1.48 (0.74, 2.98)	0.27	49 (13.4)	6 (13.6)	1.03 (0.46, 2.27)	0.95	77 (21.0)	10 (22.7)	1.29 (0.65, 2.57)	0.46
Moderate–severe PPD	8 (2.2)	4 (9.1)	3.71 (1.57, 8.77)	**0.003**	9 (2.4)	3 (6.8)	2.48 (0.91, 6.77)	0.08	15 (4.1)	6 (13.7)	3.32 (1.57, 6.99)	**0.002**

This is a Poisson regression model with robust error variance and was adjusted for infant sex, maternal education level, maternal age at delivery, and history of major depression or anxiety disorder. The reference group for cognition is the normal group.
IRR incidence rate ratio, *CI* confidence interval.

Table 3. Adjusted Poisson regression analyses of the association between maternal prenatal vitamin intake and child cognition at 4 years ($N = 373$).

Variables	Normal cognition, *n* (%)	Suboptimal cognition, *n* (%)	IRR (95% CI)	*P* value
Prenatal vitamin intake				
Daily intake	176 (52.5)	17 (44.7)	Reference	
Less than daily intake	159 (47.5)	21 (55.3)	1.34 (0.73, 2.46)	0.34

Poisson regression models with robust error variance were adjusted for infant sex, maternal education level, maternal age at delivery, history of major anxiety, or depression. The reference group for cognition is the normal group.
IRR incidence rate ratio, *CI* confidence interval.

pregnancy ($IRR_{adj} = 2.88$, 95% CI: 1.12–7.39) and either gestation period ($IRR_{adj} = 2.88$, 95% CI: 1.23–6.71). There was no increase in suboptimal cognition in children of mothers with or without PPD in pregnancy and who did not take daily prenatal vitamins. There were no significant associations in late pregnancy (Table 4). In further analysis, we did not find any significant correlations between prenatal vitamin intake and PPD.

DISCUSSION

This study showed that mild–severe PPD is commonly experienced by pregnant women in the OBS cohort. The experience of moderate–severe PPD during early pregnancy (12–16 weeks), but not in late pregnancy (28–32 weeks), was significantly associated with suboptimal cognitive outcomes in the offspring at 4 years. The daily intake of prenatal vitamins was not associated with child cognitive outcomes on its own and prenatal vitamin intake did not ameliorate the negative effects of PPD on child cognition.

The overall prevalence of mild–severe PPD, anxiety, and depression in our study is similar to the findings from another prospective study of pregnant women residing in USA and Canada, which had a prevalence of PPD of 21.2%, 5.4% for depression, and 9.8% for anxiety during their second trimester of pregnancy.[40] Although the burden of these mental illnesses (depression and anxiety) in our cohort was generally lower than what has been reported in systematic reviews,[2,4] it is important to note that when left unattended, mild forms of mental illness can worsen to more adverse psychiatric conditions which can have more lasting adverse health and socio-economic impacts on the women (during pregnancy and in post-natal period), their offspring and their families at large.[41,42] Evidently, there is an urgent need to improve early screening and treatment of prenatal maternal mental illness. A key challenge is that there is still a general lack of consensus on when and how prenatal and postpartum mental illness screening should occur.[43] One possible approach to address PPD could be the use of cognitive behavioral therapy for which there is growing evidence to support its effectiveness as a treatment and preventive intervention for prenatal mental illness, although other alternative approaches can also be considered.[44,45]

The present study showed that PPD experienced during the early stages of pregnancy increased the risk for suboptimal cognitive outcomes in children at 4 years. Moreover, the severity of PPD was associated with an increased magnitude of risk for suboptimal cognition. This finding of a significant association between PPD and suboptimal cognition is compatible with reports from previous studies.[19,46–50] A Dutch study found that stress attributable to life events measured during the early pregnancy period (15–17 weeks), but not later in pregnancy, was adversely associated with learning and memory outcomes of the offspring at 6 years of age.[46] Also, studies on outcomes following prenatal exposure to the Quebec ice storm have found significant adverse associations of PPD with child cognition (at 2 and 5 years) and shown that these were most significant when the exposure happened during the early stages of pregnancy, that is, in the first or second trimester.[18,19,49] The present study expands on previous work, by examining how varying levels of PPD severity across different stages of pregnancy relate to child cognitive outcomes. Importantly, our findings highlight that the severity of PPD during pregnancy matters, however, even in a moderate form, PPD especially when experienced in the early stages of pregnancy, could have detrimental effects on the offspring's cognitive development. It is plausible that vulnerability to the effects of PPD is heightened during early gestation due to increased fetal sensitivity to cortisol.[51] It is known that the neurogenesis and migration, which occurs relatively early in gestation, is highly sensitive to stress.[52]

Our findings on prenatal vitamin intake during the pre-conception and first trimester periods indicate a higher intake of prenatal vitamins compared to findings from other Canadian studies.[53,54] Masih and colleagues found that 60% of Canadian women used B vitamin-containing supplements in pre-conception and this increased to 93% in early pregnancy.[53] Similarly, data from the Maternity Experience Survey indicated that about 58% of women reported intake of a multivitamin containing folic acid or a folic acid supplement in the three months before conception and 90% during the first trimester.[54] We, however, did not verify the specific nutritional components of the prenatal vitamins taken by our study participants. The Canadian guidelines recommend the daily intake of over-the-counter prenatal multivitamins containing 0.4–1.0 mg of folic acid (for the low-moderate risk group for neural tube defect or other folic acid congenital anomaly) or prescription daily multivitamins containing 5.0 mg of folic acid (for high-risk groups) at least 3 months pre-conception and throughout pregnancy, in addition to a diet of folate-rich foods.[26] Based on our findings which indicate that there was much lower prenatal vitamin intake in the first trimester as compared to the pre-conception period, there is need for more public health intervention to improve prenatal vitamin intake during the pre-conception period as recommended in Canadian guidelines.

Our findings suggest that there was no association between prenatal vitamin intake and child cognitive development overall. Prenatal vitamin intake did not ameliorate the deleterious effects of PPD. Nonetheless, with further visual inspection using Kernel density plots, the distribution patterns of the cognition scores indicated a higher distribution of cognitive scores for the group of children born to women who reported daily intake of prenatal vitamins and with no episode of PPD, but with general overlap across the sub-groups. Our sample size may not have been sufficient to robustly detect these associations and interaction effects or there was some loss of information due to collation of the different prenatal vitamin intake sub-categories into binary format. It is plausible that there could have been some element of social desirability bias when participants responded to prenatal vitamin intake items during data collection; however, it should be noted that vitamin intake information was collected prior to the outcome, avoiding recall bias. These findings are preliminary and more research with a larger sample size and more detailed classification of prenatal vitamins is needed to further explore the potential benefits of prenatal vitamin intake for child cognitive development in the context of PPD.

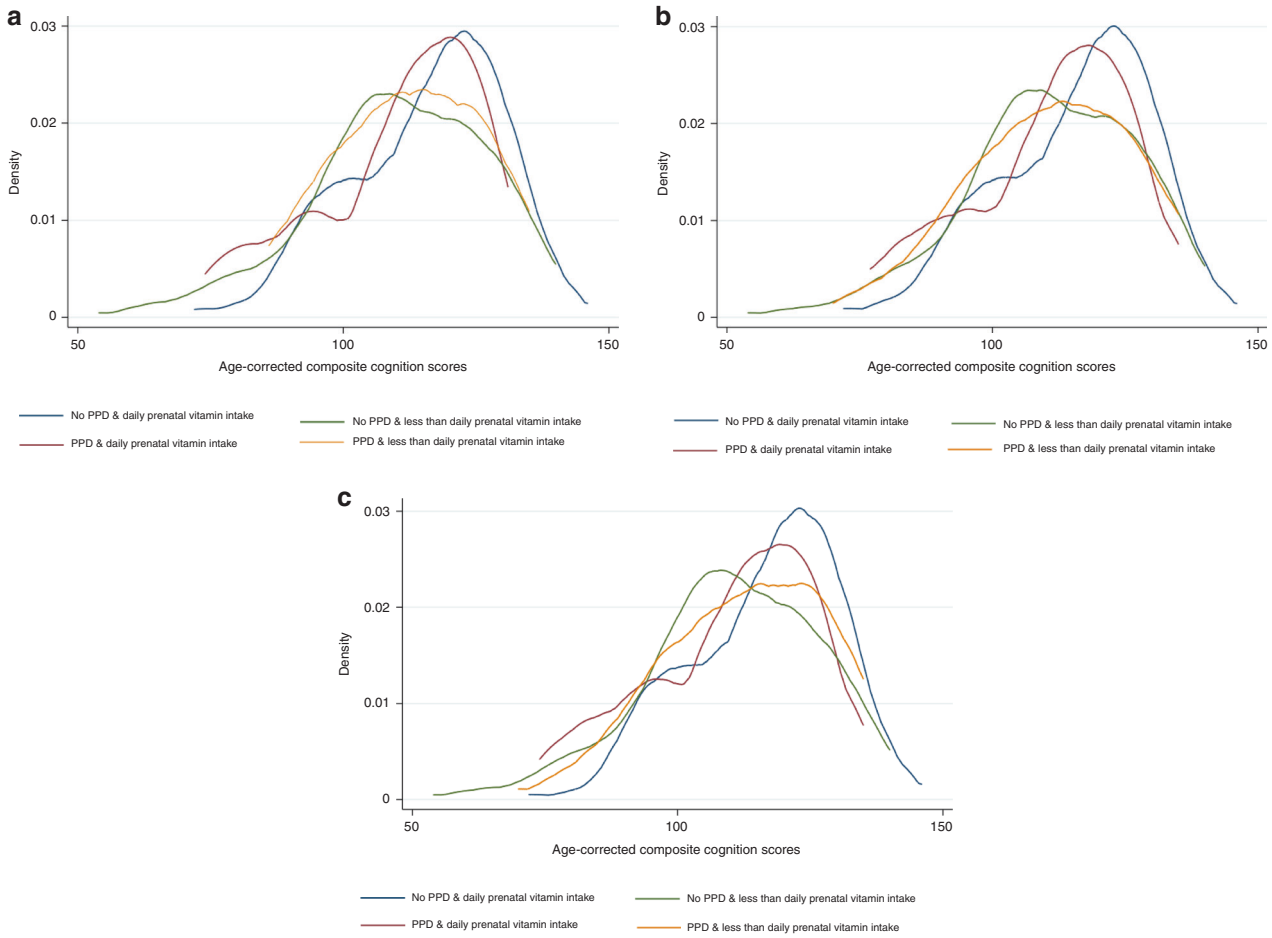

Fig. 2 Kernel density plot of child cognition at 4.5 years across sub-categories of maternal prenatal vitamin intake and psychological distress. a During early pregnancy (12–16 weeks of gestation). **b** During late pregnancy (28–32 weeks of gestation). **c** During either gestation period.

Noteworthy, cognitive development in the offspring is linked to a variety of other factors besides PPD such as maternal alcohol, tobacco and other drug use during pregnancy,[55] neonatal insults like preterm birth, metabolic conditions and infections,[56,57] quality of nurturing care, and social support.[58,59] While we acknowledge that such factors may partly explain the observed differences in child cognition in our study, it was not feasible to include additional factors in our current study for a number of reasons. First, the prevalence of some factors such as substance use during pregnancy is very low in our cohort with only 0.5% who smoked and 4.6% who drank alcohol during pregnancy. In addition, some of the other factors, such as the quality of nurturing care were not assessed in this cohort. Given that we were only able to conduct analysis based on those with a complete 4-year follow-up assessment, which limited the sample size, we focused on a core set of the potential confounders.

Although we utilized a well validated measure of PPD (PHQ-4), this is a subjective measure of distress and may not necessarily capture pregnancy-specific distress. It is therefore important to start examining screening measures that are specifically validated for perinatal populations, such as the Perinatal Anxiety Screening Scale.[60] Some researchers have also suggested that measures in which core features of the full spectrum of a mental health disorder are assessed hold the promise for providing higher level screening accuracy.[61] Our sample was largely comprised of participants with European ancestry who were highly educated and, therefore, our findings may not entirely represent the burden of PPD in pregnancy and/or its influence on child cognition among under-represented sub-populations and racial groups. There is a need for more research on this issue in order to inform better planning and delivery of maternal and child health services. Another study limitation is that prenatal vitamin use was assessed for the pre-conception and first trimester periods only. Nonetheless, the longitudinal assessment of PPD at different gestational periods, use of robust validated measures of cognition (NIH Toolbox) and PPD, and inclusion of prenatal vitamin intake (which is an important public health intervention) are major strengths of the present study.

CONCLUSION

Moderate-to-severe PPD is associated with poorer cognitive outcomes in offspring at 4 years, and the association is most significant when PPD is experienced in early pregnancy. There is a need to promote prenatal vitamin intake, especially during the pre-conception, as the intake was lowest during this period. Prenatal vitamin intake did not ameliorate the detrimental impact of PPD on child cognition; the adverse association between mild–severe PPD and child cognition at 4 years persisted for children born to mothers who had daily prenatal vitamin intake but not those with less than daily intake. It is not clear why there was no association in the latter group. This finding is preliminary and requires replication in larger studies.

Table 4. Adjusted Poisson regression analyses of the association between mild–severe prenatal psychological distress (PPD) across gestation periods and child cognition at 4 years, stratified by prenatal vitamin intake ($N = 373$).

Variables	Early pregnancy (12–16 weeks of gestation)				Late pregnancy (28–32 weeks of gestation)				Either gestation period (overall)			
	Normal cognition (*n*, %)	Suboptimal cognition (*n*, %)	IRR (95% CI)	*P* value	Normal cognition (*n*, %)	Suboptimal cognition (*n*, %)	IRR (95% CI)	*P* value	Normal cognition (*n*, %)	Suboptimal cognition (*n*, %)	IRR (95% CI)	*P* value
Daily prenatal vitamin Intake ($n = 193$)												
No PPD	151 (85.8)	11 (64.7)	Reference		152 (86.4)	13 (76.5)	Reference		139 (79.0)	9 (52.9)	Reference	
Mild–severe PPD	25 (14.2)	6 (35.3)	2.88 (1.12, 7.39)	0.03	24 (13.6)	4 (23.5)	1.82 (0.69, 4.81)	0.23	37 (21.0)	8 (47.1)	2.88 (1.23, 6.71)	0.01
Less than daily prenatal vitamin intake ($n = 180$)												
No PPD	121 (76.1)	17 (80.9)	Reference		130 (81.8)	17 (80.9)	Reference		113 (71.1)	16 (76.2)	Reference	
Mild–severe PPD	38 (23.9)	4 (19.1)	0.78 (0.29, 2.08)	0.62	29 (18.2)	4 (19.1)	0.99 (0.39, 2.56)	0.99	46 (28.9)	5 (23.8)	0.79 (0.32, 1.96)	0.61

Poisson regression models with robust error variance were adjusted for infant sex, maternal education level, maternal age at delivery, and history of major anxiety or depression. The reference group for cognition is the normal group.
IRR incidence rate ratio, *CI* confidence interval.

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AUTHOR CONTRIBUTIONS

R.J.H., J.A.K., S.J.L., and S.G.M. conceptualized and designed the study. D.S. analyzed the data, interpreted the data, and drafted the initial manuscript. N.A.K., J.L., K.F., J.W., and J.O. contributed to the data collection and study coordination roles. R.J.H. and J. A.K. guided the data analysis process and the result interpretations. S.J.L. and S.G.M. provided support for the interpretation of the data. All authors provided critical feedback and approved the final version.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The OBS and OBS Kids follow-up were approved by the Mount Sinai Hospital Research Ethics Board, Toronto, Ontario. All study participants provided written informed consent for their participation in both study components and access to their data for research. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

ADDITIONAL INFORMATION

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