NEW RESEARCH

Check for updates

Maternal Prenatal Mood, Pregnancy-Specific Worries, and Early Child Psychopathology: Findings From the DREAM BIG Consortium

Eszter Szekely, PhD, Alexander Neumann, PhD, Hannah Sallis, PhD, Alexia Jolicoeur-Martineau, MSc, Frank C. Verhulst, MD, PhD, Michael J. Meaney, PhD, Rebecca M. Pearson, PhD, Robert D. Levitan, MD, James L. Kennedy, MD, John E. Lydon, PhD, Meir Steiner, MD, PhD, Celia M.T. Greenwood, PhD, Henning Tiemeier, MD, PhD, Jonathan Evans, MD, Ashley Wazana, MD

Objective: Few studies have attempted to identify how distinct dimensions of maternal prenatal affective symptoms relate to offspring psychopathology. We defined latent dimensions of women's prenatal affective symptoms and pregnancy-specific worries to examine their association with early offspring psychopathology in three prenatal cohorts.

Method: Data were used from three cohorts of the DREAM-BIG consortium: Avon Longitudinal Study of Parents and Children (ALSPAC [N = 12,515]), Generation R (N = 6,803), and the Canadian prenatal cohort Maternal Adversity, Vulnerability, and Neurodevelopment (MAVAN [N = 578]). Maternal prenatal affective symptoms and pregnancy-specific worries were assessed using different measures in each cohort. Through confirmatory factor analyses, we determined whether comparable latent dimensions of prenatal maternal affective symptoms existed across the cohorts. We used structural equation models to examine cohort-specific associations between these dimensions and offspring psychopathology at 4 to 8 years of age (general psychopathology, specific internalizing and externalizing previously derived using confirmatory factor analyses). Cohort-based estimates were meta-analyzed using inverse variance-weighing.

Results: Four prenatal maternal factors were similar in all cohorts: a general affective symptoms factor and three specific factors—an anxiety/depression factor, a somatic factor, and a pregnancy-specific worries factor. In meta-analyses, both the general affective symptoms factor and pregnancy-specific worries factor were independently associated with offspring general psychopathology. The general affective symptoms factor was further associated with offspring specific internalizing problems. There were no associations with specific externalizing problems.

Conclusion: These replicated findings of independent and adverse effects for prenatal general affective symptoms and pregnancy-specific worries on child mental health support the need for specific interventions in pregnancy.

Key words: prenatal depression, pregnancy anxiety, child internalizing, child externalizing, *p* factor

J Am Acad Child Adolesc Psychiatry 2021;60(1):186–197.

With a burgeoning of research in prenatal programming, it is now well recognized that maternal affective problems during pregnancy are associated with increased psychopathology in the offspring at any stage of development.[1-4] This association remains following adjustment for potential confounders and is present above and beyond the effects of postnatal maternal affective problems.[5,6] Furthermore, the effects seem to be nonspecific, in that prenatal stress increases the offspring's early risk for both internalizing problems (especially anxiety and depression) and externalizing problems (such as attention-deficit/hyperactivity disorder and conduct disorder).[7,8] These effects persist long term and are also present in low- and middle-income countries.[1,9]

However, the synthesis of research findings is complicated by the diversity of measures used to characterize prenatal maternal affective symptoms, which makes it hard to pinpoint whether there are specific components that are most strongly linked with offspring psychopathology or that might show specific associations with child internalizing or externalizing behavior. Prenatal affective problems include depression and various forms of anxiety, including pregnancy-specific anxiety. Despite the heterogeneity of these symptoms, there is limited work attempting to

distinguish underlying dimensions of prenatal affective problems and their consequences for the offspring. Delineating the specific nature of these associations could inform more individualized and robust prevention strategies during pregnancy, with a greater impact on offspring psychopathology over the lifespan.

Studies that have examined the underlying dimensions of maternal mood problems have focused on the postnatal period and one simple, widely used measure, the Edinburgh Postnatal Depression Scale (EPDS).[10] These studies suggest there are two or three underlying symptom dimensions distinguishing items representing anxiety from items representing anhedonia or depression.[11,12] The recently formed consortium Postpartum Depression: Action Towards Causes and Treatment (PACT, 2015) confirmed the existence of these postnatally identified dimensions for perinatal depression.[13] However, there remain important gaps in the literature. First, most studies have not addressed the high correlation between the symptom dimensions.[14,15] Second, it remains unknown whether the same symptom dimensions would emerge when using measures other than the EPDS. Third, there is only limited evidence that these dimensions can be found in prenatal depression.[11,14] This is an important question, in light of the marked differences between pregnancy and the postpartum period, which might promote different subtypes of depression and modes of transmission.[16]

Anxiety symptoms are also heterogeneous in nature, yet most studies of prenatal maternal anxiety and offspring developmental outcomes have focused on rather general measures of stress and anxiety, with stressful life events and state anxiety being the most common.[1] Thus, it is difficult to determine whether specific components of anxiety are most critical for child outcomes, which would necessitate more targeted interventions. Pregnancy-specific anxiety, for instance, is not captured by general anxiety measures, whereas it has been repeatedly highlighted as a powerful prenatal risk factor for negative child outcomes.[17] Notably, compared to prenatal general anxiety and depression, pregnancy-specific anxiety was found to be more strongly associated with infant cognitive and temperamental problems[18,19] and children's executive function and brain structure at age 6 to 9 years.[20,21] Identifying the underlying dimensions of prenatal affective disorders might also help to delineate distinct clinical phenotypes that are specific to the prenatal period. Previous work in the area, however, is extremely scant. We are aware of only two studies to date that have looked at distinct subtypes of perinatal depression. One study examined 2,783 Chinese women from the general population and identified five distinct subtypes: "no symptoms," "mild physio-somatic symptoms," "severe physio-somatic symptoms and moderate anhedonia," "moderate-to-severe symptoms," and "severe symptoms."[22] The other study was the above-cited PACT study, which included 663 women with a documented perinatal-onset depression.[13] Importantly, the authors used the three underlying dimensions of perinatal depression that they identified based on the EPDS (ie, depressed mood, anhedonia, and anxiety) to delineate five distinct subtypes of perinatal depression: severe and moderate anxious depression, anxious anhedonia, pure anhedonia, and resolved depression. Both studies reported clear differences in symptom quality and time of onset across the subtypes. However, it is unclear what pattern of results would emerge when restricting analyses to prenatal symptoms only. Furthermore, none of the studies examined how the different subtypes associate with child outcomes.

Factor analyses of large population-based cross-sectional samples suggest that generalized anxiety might be more closely linked with depression than other forms of anxiety (eg, panic disorder or specific phobias).[23,24] Unfortunately, large-scale epidemiological studies rarely use identical measures to assess the same constructs. In our own recently formed consortium that encompasses 4 prospective longitudinal pregnancy cohorts, prenatal affective symptoms were assessed using four different measures. Given the importance of reproducibility of research findings in independent samples, it is useful to develop underlying constructs that can be generalized across different cohorts and measures.

Here we examine the latent factor structure of prenatal maternal affective symptoms in three independent pregnancy cohorts, which have all used different measures of assessment. Our main goal is to test whether these latent factors of prenatal affective psychopathology are consistently associated with early offspring psychopathology in all three cohorts.

METHOD

Data for the present analyses were drawn from the Developmental Research in Environmental Adversity, Mental health, BIological susceptibility and Gender (DREAM BIG) consortium of longitudinal pregnancy cohorts formed in 2016 to investigate the association between prenatal adversity and later offspring mental health outcomes.[25] The current study includes data from the following studies: Avon Longitudinal Study of Parents and Children (ALSPAC),[26] Generation R Study,[27] and Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) project.[28] A full description of each cohort can be found in the relevant cohort profiles and in Supplement 1, available online.

Measures of Maternal Psychopathology

ALSPAC. Edinburgh Postnatal Depression Scale (EPDS). Women rated their depressive symptoms using the EPDS at 18 weeks of pregnancy. The EPDS is a 10-item self-report questionnaire designed to screen for prenatal and postnatal depression in primary care.[10] The scale indicates how the mother felt during the previous week. Items 1, 2, and 4 are scored on a scale from 0 to 3, with higher scores indicating more severe symptoms, whereas the remaining items are reverse coded.

Crown–Crisp Experiential Index (CCEI). At 18 weeks of pregnancy, women also completed a modified questionnaire based on the CCEI.[29] This questionnaire had been reduced from the original 48 items to 23, with responses standardized into four categories ("never," "sometimes," "often," "very often"). The CCEI is divided in a set of six subscales: somatization, depression, free-floating anxiety, phobic anxiety, obsessive-compulsive symptoms, and hysteria, with higher scores indicating more severe symptoms.

Pregnancy-Specific Reactions. Women were asked about their reactions to becoming a parent, at 18 weeks' gestation. The following five items were included in the model: "Were you deliberately trying to get pregnant this time?" "How would you describe your reaction when you first found you were pregnant this time?" "Does being a mother mean giving up something that is important to you?" "Does becoming a mother give you new opportunities and interests?" "How do you feel about your pregnancy now?"

Generation R

Brief Symptom Inventory (BSI). Maternal psychopathology was measured with the BSI[30] at 20 weeks of pregnancy, at 2 months, and at 6 months after delivery. Items covering depressive (six items), anxiety (six items), and somatic symptoms (seven items) were used to estimate prenatal affective factors. Mothers rated each item by indicating whether a symptom occurred in the past 7 days on a scale from "not at all" (0) to "extremely" (4).

Pregnancy-Specific Reactions. Women's reactions to becoming pregnant were assessed using 13 items adapted from the Pregnancy Outcome Questionnaire.[31] Items were rated on a scale from "almost never" (0) to "almost always" (3). Items are listed in Supplement 1, available online.

MAVAN

Center for Epidemiologic Studies Depression Scale (CES-D). Women reported on their depressive symptoms at 24 to 26 weeks' gestation using the CES-D.[32] The CES-D includes 20 items capturing mood-, appetite-, and sleep-related symptoms in community-based populations. Each item was rated on a scale from 0 (rarely or none of the time) to 3 (most or all of the time). With the exception of four positively-worded items, higher scores indicate more severe depressive symptoms. In the present study, we included 14 of the 20 items as recommended by Carleton *et al.* for factor analysis of the CES-D.[32]

Pregnancy-Specific Anxiety Scale. At 24 to 26 weeks of pregnancy, women rated how often they felt (1) anxious, (2) concerned, (3) afraid, or (4) panicky about being pregnant in the past week, using the Pregnancy-Specific Anxiety scale.[33] Ratings on the 4 items were provided on a scale from 0 (never) to 4 (almost always), with higher scores indicating more severe worries.

Measures of Child Psychopathology

Measures relating to psychopathology from 4 to 8 years of age were collated using self-, parental-, teacher-, and observer-rated measures. These are listed in Supplement 1, available online, and described in detail by Sallis *et al.*[25]

Statistical Analysis

Confirmatory factor analyses (CFA) were sequentially used to identify best fitting and parsimonious model(s). We compared a series of increasingly complex models from a simple unifactor model to a bifactor model, in which all symptoms simultaneously load onto a general factor and their corresponding specific factor (ie, depression/anxiety, somatic symptoms, or pregnancy-specific worries). Latent factors of the bifactor model were defined to be uncorrelated. The exact model descriptions are provided in Supplement 1, available online.

Confirmatory factor analyses were performed separately in each cohort using MPlus v.7 in ALSPAC and the lavaan R package in Generation R and MAVAN. Robust maximum likelihood estimators were used in MAVAN and Generation R (all continuous indicator variables), whereas weighted least-square means and variances (WLSMV) were used in ALSPAC (both continuous and dichotomous indicator variables). To maximize the number of observations included in the analyses and to prevent sampling bias, participants with available data on at least one psychopathology subscale were included in analyses. Incomplete indicators were handled using full information maximum likelihood in Generation R and MAVAN. This was not possible in ALSPAC because of dichotomous indicators. Therefore, missing values were estimated using multiple imputation across 40 imputed datasets. Latent variables were standardized in each of the cohorts. Goodness of fit was evaluated using three indices.

Structural equation models (SEM) (lavaan R package) were used to examine whether the latent factors of prenatal maternal affective problems are associated with early-age offspring psychopathology. Analyses were run separately in

each cohort. Predictors (ie, maternal latent factors) were modeled within the SEM according to the best-fitting model identified in confirmatory factor analyses. The SEM models included all latent factors derived in the CFA. However, we decided not to test associations that would be either theoretically questionable (eg, specific factor to specific factor) or clinically less applicable (eg, how to clinically interpret residual anxious/depressive symptoms relative to general affective symptoms, or how to differentiate somatic symptoms of depression/anxiety from those that typically occur during pregnancy). Outcomes included standardized latent factor scores derived previously in all cohorts representing general psychopathology and residual internalizing and externalizing symptoms of the offspring. The exact steps of this process are detailed in Sallis *et al*.[25] Including previously extracted latent factor scores of offspring psychopathology rather than remodeling them within the larger SEM was preferred in order to reduce the number of free parameters to avoid convergence problems.

In addition to the unadjusted model, we examined adjusted models controlling for methodological confounders and basic sociodemographic characteristics that relate to both maternal prenatal stress and offspring psychopathology.[34,35] More specifically, covariates included child sex, maternal age, and education and family income. In Generation R, offspring ethnicity and age at the time of the different psychopathology assessments were further included, as the sample was more heterogeneous in terms of these variables than were the other two cohorts. In MAVAN, study site (Montreal, QC versus Hamilton, ON) was also included as a covariate. Finally, models were also rerun by additionally adjusting for postpartum maternal depressive symptoms to examine whether these could explain any observed prenatal effects. Postnatal depressive symptoms were computed as the average of two assessments spanning the first postpartum year. In ALSPAC, the EPDS was administered at 2 months and 8 months postnatally. In Generation R, the BSI anxiety and depression subscales were administered at 2 months and 6 months, and the somatic symptoms subscale at 2 months. In MAVAN, the CES-D was administered at 6 and 12 months postpartum. Standardized SEM effect estimates from the individual cohorts were meta-analyzed using random-effect inverse variance weighing within the rmeta R package.

RESULTS

A brief description of the cohorts and measures are provided in Table 1. Baseline characteristics of the samples are shown in Table 2.

We compared the final sample used in SEM analyses to those participants who were not included in these analyses because of missing information. These two groups did not differ in terms of distribution of boys and girls ($p < .05$). Mothers were slightly older in all samples included in SEM analyses than those who were not (ALSPAC: $t = -9.94$, df $= 5449$, $p < .001$; Generation R: $t = -12.56$, df $= 5803.3$, $p < .001$; MAVAN: $t = -2.63$, df $= 392.76$, $p < .01$). Furthermore, in ALSPAC and MAVAN, mothers in the SEM analyses were more highly educated (ALSPAC : $\chi^2 = 82.37$, df $= 4$, $p < .001$; MAVAN: $\chi^2 = 12.86$, df $= 2$, $p < .01$) and had a higher family income (ALSPAC: $\chi^2 = 28.11$, df $= 4$, $p < .001$; MAVAN : $\chi^2 = 30.74$, df $= 4$, $p < .001$) than those excluded because of missing data.

Modeling the Latent Factor Structure of Prenatal Maternal Affective Symptoms and Pregnancy-Specific Worries

Model fit indices for all tested models are shown in Table 3. Generally, model fit for the single factor and 3-factor models were relatively poor in all cohorts (ie, RMSEA >0.05; CFI and TLI <0.9). Model fit improved considerably for the bifactor model and when also accounting for measurement-related variance, such as item wording. The four positively-worded items of the CESD in MAVAN made up the anhedonia factor; however, in ALSPAC and Generation R, positively worded items were not all anhedonia items (in Generation R, all positively worded items were related to pregnancy reactions, whereas in ALSPAC it was a combination). The best model in ALSPAC also included a positive and negative wording factor in addition to the general and specific affective factors. In Generation R, this model did not converge (possibly because of underidentification). Here, the best model comprised the general and specific affective factors and a positive wording factor. In MAVAN, the best models also included the specific affective factors uncovered in ALSPAC and Generation R (ie, depression, somatic symptoms, and pregnancy-specific worries); however, the positively worded anhedonia items loaded on a specific anhedonia factor, as in previous studies of the CESD,[32] with or without including a general affective factor (ie, bifactor structure). Given that we were interested in disentangling the effects of women's general prenatal affective symptoms (as captured by the general factor) from pregnancy-specific worries, and given that the higher-order solutions clearly offered the best-fitting models in the two larger cohorts, we retained the bifactor model solution for further analysis in MAVAN. Cohort-specific individual factor loadings for the best model solutions are shown Tables S1 to S3, available online. In summary, there were four latent factors present across all cohorts: the general affective symptoms factor, a specific depression/anxiety factor (including general anxiety symptoms where applicable), a specific somatic symptoms

TABLE 1 Description of Cohorts and Measures

	ALSPAC	Generation R	MAVAN
Geographic location	Former county of Avon, UK	Rotterdam area, Netherlands	Montreal (QC) and Hamilton (ON), Canada
Recruitment period	1991–1992	2002–2006	2003–2009
CFA, n	12,515	8,339	578
SEM, n	11,612	6,803	408
Time of assessment of prenatal affective symptoms	18 wk gestation	20 wk gestation	24–26 wk gestation
Measures of prenatal affective symptoms	EPDS	BSI	CES-D
	CCEI	POQ	PSAQ
	Pregnancy-specific reactions		
Assessment of offspring psychopathology (time; rater)	SDQ (7 y; parent, teacher)	SRS (6 y; parent)	SDQ (5, 6 y; mother, father)
	DAWBA (7 y; parent, teacher)	CBCL (6 y; parent)	CBCL (4, 5 y; mother)
	SCDC (7.5 y; parent)	CPRS-R (8 y; parent)	CPRS-R (5, 6 y; mother, father)
	Additional teacher questions (7 y; teacher)	TRF (7 y; teacher)	PAPA (6 y; mother)
	Field worker observations (7 y; field workers)	BPI (6 y; child)	PDQ (6 y; child)

Note: *BPI = Berkeley Puppet Interview; BSI = Brief Symptom Inventory; CBCL = Child Behavioral Checklist; CCEI = Crown-Crips Experiential Index; CES-D = Center for Epidemiologic Studies Depression Scale; CPRS-R = Conners' Parent Rating Scale–Revised: Short Form; DAWBA = Development and Well-being Assessment; EPDS = Edinburgh Postnatal Depression Scale; PAPA = Preschool Age Psychiatric Assessment; PDQ = Pictorial Dominic Questionnaire; POQ = Pregnancy Outcome Questionnaire; PSAQ = Pregnancy-Specific Anxiety Scale; SCDC = Social and Communication Disorders Checklist; SDQ = Strengths and Difficulties Questionnaire; SRS = Social Responsiveness Scale; TRF = Teachers Rating Form.*

TABLE 2 Descriptive Characteristics of the Cohorts

ALSPAC		Generation R		MAVAN	
Characteristic		Characteristic		Characteristic	
Child sex (male)	51.5	Child sex (male)	50	Child sex (male)	49.9
Child ethnicity (White)	94.9	Child ethnicity (European)	62.00%	Child ethnicity (White)	82[a]
Maternal age (y)	27.99 (4.96)	Maternal age (y)	30.24 (5.10)	Maternal age (y)	30.44 (5.07)
Maternal education		Maternal education		Maternal education	
CSE/None	21.8	None or primary	3.5	Low	20.7
Vocational	10.6	Secondary	39.1	Medium	32.8
O-level	37.4	College or higher	57.4	High	46.5
A-level	24.2	Family income (monthly)		Family income (annual)	
University	13.9	<1,600 Euro	16.4	<15,000 CAD	8.8
Family income (quintiles)[b]		< 2,400 Euro	14.1	<30,000 CAD	15.0
First (poorest)	19.9	<3,200 Euro	18.3	<50, 000 CAD	22.2
Second	19.8	<4,800 Euro	27.8	<80,000 CAD	23.3
Third	19.9	≥ 4,800 Euro	23.2	≥80,000 CAD	30.6
Fourth	20.0			Study site	
Fifth (better off)	20.4			Montreal	57.4
				Hamilton	42.6

Note: *Data are mean (SD) or percentage. ALSPAC = Avon Longitudinal Study of Parents and Children; CAD = Canadian dollars; CSE = certificate of secondary education; MAVAN = Canadian prenatal cohort Maternal Adversity, Vulnerability, and Neurodevelopment*

[a]*Cumulative percentage; 30.6% of observations are missing; not included in further analysis.*

[b]*Average weekly household disposable income recorded at age 3 and 4 years, divided into quintiles and re-scaled to account for family size, composition, and estimated housing benefits.*[36] *We do not have exact values that correspond to the quintiles.*

TABLE 3 Model Fit Indices From Confirmatory Factor Analyses Across Cohorts

	ALSPAC			Generation R			MAVAN		
	RMSEA (90% CI)	**CFI**	**TLI**	**RMSEA (90% CI)**	**CFI**	**TLI**	**RMSEA (90% CI)**	**CFI**	**TLI**
Model 1[a]	0.076 (0.077, 0.079)	0.845	0.836	0.070 (0.069, 0.071)	0.735	0.717	0.095 (0.090, 0.101)	0.772	0.751
Model 2[b]	0.079 (0.078, 0.080)	0.833	0.823	0.053 (0.052, 0.054)	0.851	0.839	0.069 (0.064, 0.075)	0.881	0.868
Model 3[c]	0.145 (0.144, 0.146)	0.440	0.408	0.049 (0.048, 0.050)	0.873	0.863	**0.047 (0.038, 0.055)**	**0.964**	**0.957**
Model 4[d]	0.046 (0.045, 0.047)	0.947	0.941	0.047 (0.046, 0.048)	0.890	0.872	**0.049 (0.041, 0.058)**	**0.963**	**0.952**
Model 5[e]	0.038 (0.038, 0.039)	0.900	0.888	**0.037 (0.036, 0.038)**	**0.931**	**0.920**	0.048 (0.040, 0.056)	0.966	0.954[g]
Model 6[f]	**0.038 (0.037, 0.039)**	**0.967**	**0.960**	Model did not converge.			0.045 (0.036, 0.054)	0.974	0.960[h]

Note: Boldface type indicates best-fitting models. ALSPAC = Avon Longitudinal Study of Parents and Children; CFI = comparable fit index; MAVAN = Maternal Adversity, Vulnerability and Neurodevelopment project; RMSEA = root mean square error of approximation; TLI = Tucker Lewis index.

[a]*Model 1: Single-factor model.*

[b]*Model 2: Three-factor model, correlated: general anxiety and depression combined, somatic symptoms, pregnancy-specific reactions (ALSPAC and Generation R); depression and anhedonia combined, somatic symptoms, pregnancy-specific anxiety (MAVAN).*

[c]*Model 3: Four-factor model, correlated: general anxiety, depression, somatic symptoms, pregnancy-specific reactions (ALSPAC and Generation R); anhedonia, depression, somatic symptoms, pregnancy-specific fears (MAVAN)*

[d]*Model 4: Bifactor model, orthogonal: general affective psychopathology factor, general anxiety and depression combined, somatic symptoms, pregnancy-specific reactions (ALSPAC, Generation R); general affective psychopathology factor, depression, somatic symptoms, anhedonia, pregnancy-specific fears (MAVAN)*

[e]*Model 5: Bifactor-methods model with positive wording, orthogonal: same as model 4 with a positive wording factor added.*

[f]*Model 6: Bifactor-methods model with both positive and negative wording, orthogonal: same as model 5 with a negative wording factor added.*

[g]*Anhedonia items were included with the depression factor but were simultaneously allowed to load on a positive wording factor. Scale loadings on the depression factor of the model are all nonsignificant.*

[h]*Anhedonia items were treated the same way as in model 5, whereas all negatively worded items were additionally loaded on a negative wording factor. Model solution has negative observed variable variances and all nonsignificant item loadings on the depression and somatic symptoms factors.*

factor, and a specific pregnancy worries factor. Although the inclusion of all these specific factors improved model fit, upon inspecting individual factor loadings, the anxiety/depression and somatic symptom factors carried little unique variance, which was not explained by the general factor. This observation renders them unsuitable for examining separately as independent dimensions. Furthermore, the interpretation of the specific anxiety/depression and somatic factors can be challenging, as they represent specific affective symptom variance unrelated to other affective symptoms. In contrast, pregnancy-specific worries can occur in both the presence and absence of general affective problems, which makes this specific factor more readily interpretable. Thus, we report below associations for only the general affective vulnerability factor and the pregnancy-specific worries factor in relation to child psychopathology.

Testing the Associations Between Maternal Prenatal Affective Symptoms, Pregnancy-Specific Worries, and Early Child Psychopathology

Correlation coefficients for offspring psychopathology latent factors and their indicator subscales in each cohort are shown in Tables S4 to S6, available online. Cohort-specific and meta-analytic results are shown for offspring general psychopathology, specific internalizing behavior, and externalizing behavior in Tables 4 and 5. More prenatal general affective symptoms and pregnancy-specific worries were both associated with increased offspring general psychopathology in meta-analyses (Figure 1A and B) and in ALSPAC and Generation R, specifically (Table 4). These associations persisted following adjustment for covariates, including postnatal maternal depression (Table 4).

In addition, prenatal general affective symptoms were also associated with increased specific internalizing behavior in the offspring in both cohort-specific (Table 5) and meta-analyses (Figure 1C). This association remained essentially unchanged after adjusting for postnatal maternal depression (Table 4). Pregnancy-specific worries were not related to offspring specific internalizing difficulties with the exception of Generation R (Table S7, available online). None of the prenatal maternal affective factors were associated with specific externalizing difficulties (Table 5).

Moreover, we reran all SEM analyses by further adjusting for prenatal smoking and alcohol consumption (in ALSPAC and Generation R, as MAVAN had a very high percentage of missing data for these variables) and birthweight, to eliminate the effects of other known prenatal risks on the associations between prenatal affective symptoms and offspring psychopathology. In ALSPAC and MAVAN, all results held, whereas in Generation R, most results remained significant except for the association between pregnancy-specific worries and offspring general psychopathology (standard estimate = 0.025, standard error [SE] = 0.019, $Z = 1.36$, $p = .174$). Nevertheless, the

TABLE 4 Associations Between Prenatal Maternal Latent Factors and Offspring General Psychopathology

	Outcome: early childhood general psychopathology factor (Age 4–8 y)																
	ALSPAC				Generation R				MAVAN				Meta-analysis (random effect)				
	Standard Estimate	SE	*Z*	*p*	Standard Estimate	SE	*Z*	*p*	Standard Estimate	SE	*Z*	*p*	Estimate	SE	*p*	*Q*	*p*
Unadjusted model																	
General prenatal affective symptoms	0.15	0.01	10.61	.000	0.16	0.02	8.27	.000	0.02	0.08	0.29	.769	0.15	0.02	0.000	3.06	.22
Pregnancy–specific worries	0.03	0.01	2.60	.009	0.06	0.02	3.07	.002	0.11	0.08	1.43	.154	0.04	0.01	0.000	1.75	.42
Adjusted model[a]																	
General prenatal affective symptoms	0.14	0.01	9.92	.000	0.12	0.02	5.92	.000	−0.02	0.08	−0.18	.860	0.12	0.02	0.000	4.01	.13
Pregnancy–specific worries	0.03	0.01	2.52	.012	0.04	0.02	2.45	.014	0.11	0.07	1.45	.147	0.04	0.01	0.000	1.19	.55
Adjusted model including postnatal depression[b]																	
General prenatal affective symptoms	0.14	0.01	10.78	.000	0.11	0.02	4.80	.000	−0.12	0.10	−1.28	.202	0.10	0.03	0.002	8.07	0.02
Pregnancy–specific worries	0.03	0.01	2.25	.024	0.04	0.02	−2.45	.014	0.09	0.07	1.29	.197	0.03	0.01	0.001	1.23	.54

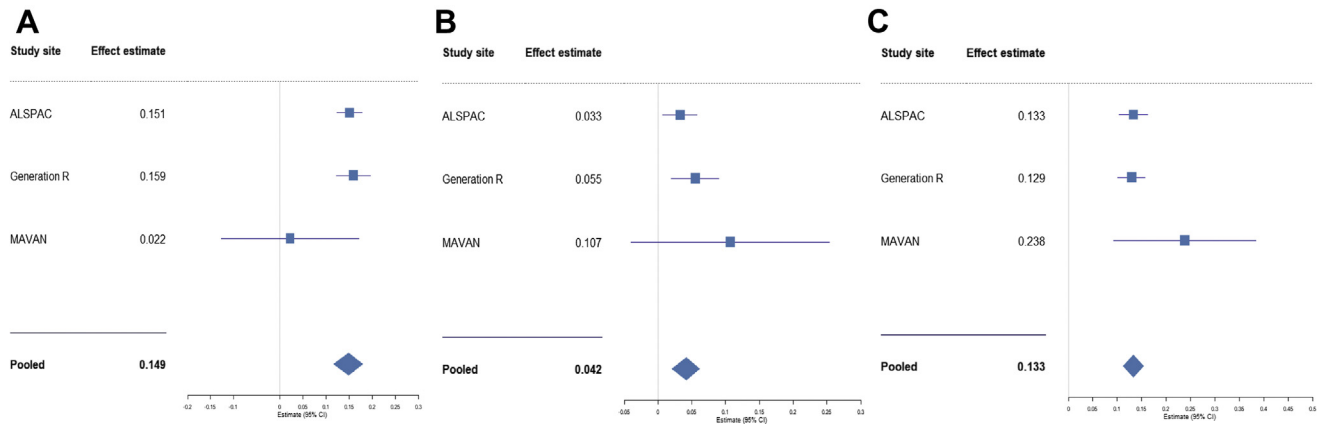
Note: ALSPAC = Avon Longitudinal Study of Parents and Children; Q = Cochran Q; SE = standard error.
[a]*Models were adjusted for child sex (age and ethnicity in Generation R), maternal age, education, and family income (and study site in MAVAN).*
[b]*Models were adjusted for child sex (age and ethnicity in Generation R), maternal age, education, family income (and study site in MAVAN), and postpartum depressive symptoms.*

TABLE 5 Associations Between General Prenatal Affective Symptoms and Specific Offspring Internalizing and Externalizing Difficulties

	ALSPAC				Generation R				MAVAN				Meta-analysis (random effect)				
Outcome: specific internalizing factor (4–8 y)	Standard estimate	SE	*Z*	*p*	Standard estimate	SE	*Z*	*p*	Standard estimate	SE	*Z*	*p*	Estimate	*SE*	*p*	*Q*	*p*
General prenatal affective symptoms																	
Unadjusted model	0.13	0.02	8.57	.000	0.13	0.01	9.31	.000	0.24	0.07	3.24	.001	0.13	0.01	.000	2.09	.35
Adjusted model[a]	0.13	0.02	8.46	.000	0.06	0.01	4.15	.000	0.26	0.08	3.40	.001	0.12	0.04	.001	16.97	.00
Adjusted model including postnatal depression[b]	0.13	0.02	8.67	.000	0.05	0.02	3.38	.001	0.22	0.09	2.64	.008	0.11	0.04	.003	15.57	.00
Outcome: specific externalizing factor (4–8 y)																	
General prenatal affective symptoms																	
Unadjusted model	−0.01	0.01	−0.82	.415	0.04	0.01	2.61	.009	0.01	0.08	0.07	.942	0.01	0.02	.543	5.95	.05
Adjusted model[a]	−0.01	0.01	−0.48	.632	0.01	0.02	0.83	.405	0.00	0.07	0.03	.973	0.00	0.01	.872	0.89	.64
Adjusted model including postnatal depression[b]	−0.01	0.01	−0.42	.672	0.01	0.02	0.60	.548	0.02	0.09	0.24	.808	0.00	0.01	.979	0.58	.75

Note: ALSPAC = Avon Longitudinal Study of Parents and Children; Q = Cochran's Q; SE = standard error.
[a]*Models were adjusted for child sex (age and ethnicity in Generation R), maternal age, education, and family income (and study site in MAVAN).*
[b]*Models were adjusted for child sex (age and ethnicity in Generation R), maternal age, education, family income (and study site in MAVAN), and postpartum depressive symptoms.*

FIGURE 1 Maternal Prenatal Affective Symptoms and Offspring Psychopathology



Note: *Forest plots showing unadjusted cohort-specific and pooled effect estimates of the effect of maternal prenatal general affective symptoms on early offspring general psychopathology (A), pregnancy-specific worries on early offspring general psychopathology (B), and maternal prenatal general affective symptoms on early offspring specific internalizing problems (C). ALSPAC = Avon Longitudinal Study of Parents and Children; MAVAN = Maternal Adversity, Vulnerability and Neurodevelopment project. Please note color figures are available online.*

pooled effect remained significant in the meta-analysis (β = 0.029, SE = 0.010, p = .003).

To further eliminate potential effects of prematurity on the results, we also repeated all SEM analyses by excluding children born preterm (<37 weeks' gestation) from ALSPAC (n = 1,246) and Generation R (n = 441). In MAVAN, these children were excluded by study design. ALSPAC results were unaffected, whereas in Generation R, all results held except the association between pregnancy-specific worries and offspring general psychopathology (standard estimate = 0.03, SE = 0.02, Z = 1.60, p = .110). Nevertheless, this association remained significant in the meta-analysis (β = 0.033, SE = 0.011, p = .003).

DISCUSSION

Our study extends the literature on the relationship between prenatal maternal affective problems and early offspring psychopathology in several important ways. First, we defined generalizable latent dimensions of prenatal affective problems that replicated across three prenatal cohorts, which had all used different measures of assessment. These dimensions included a general affective vulnerability factor, a specific anxiety/depression factor, a specific somatic symptoms factor, and a specific pregnancy worries factor. Second, we simultaneously explored the overall effect of prenatal affective psychopathology and the specific effect of pregnancy worries while accounting for the correlation between them. Third, all associations between maternal prenatal affective symptoms and child psychopathology were examined across three cohorts to see whether results would be consistent.

One finding of the present study is the identification of a latent structure of prenatal affective problems that could be generalized across multiple cohorts. This was a bifactor model that included a "general factor" encompassing variance common to all depressive, anxiety, and pregnancy-specific symptoms included. The existence of such a general factor was previously supported for postnatal maternal affective symptoms using only the EPDS.[15] We are not aware of further studies exploring a bifactor structure for describing prenatal affective problems. In addition to the general factor, we also identified specific factors that replicated across cohorts: a combined general anxiety/depression factor; a somatic symptoms factor; and a pregnancy-specific worries factor. Although these specific factors were significant on formal testing, in the case of the first two specific factors, loadings were low to moderate in comparison to the general factor loadings.

These results are consistent with previous literature suggesting that pregnancy anxiety and general prenatal anxiety/depression are only moderately associated.[17] Here, we show how we can study their independent and overlapping effects at the same time. Furthermore, our finding that items load weakly on the specific depression/anxiety factor and somatic symptoms factor when a general factor is included is consistent with Reichenheim *et al.*[15] study findings for postnatal depression. One explanation for this is that the proportion of variance not explained by the general factor might be part of the error term, which is then further partitioned into multiple residual, specific factors.

In the main part of the study, we found that women's prenatal affective symptoms and pregnancy-specific worries uniquely predicted their children's general psychopathology at ages 4 to 8 years. Associations remained after controlling for age, sex, family socioeconomic status and women's postpartum affective symptoms. These observations are

consistent with those in prior literature.[1-3] Associations also remained after controlling for additional confounders, such as maternal prenatal smoking and alcohol consumption and offspring birthweight, as well as when removing preterm-born children from the analyses, although the point estimate for the association between pregnancy-specific anxiety and offspring general psychopathology in Generation R attenuated considerably. However, this latter not surprising, given the solid evidence for the association of prenatal stress—especially, pregnancy-specific anxiety—with birth outcomes,[33,37,38] and the known links between birth outcomes and offspring psychopathology.[39] Consequently, as causal mechanisms are not yet fully understood, one should exercise caution when adjusting for variables that might be part of the causal pathway in order to avoid overadjustment. Individual effect estimates for general prenatal affective symptoms were smaller in MAVAN than in the two larger cohorts and not always consistent. In contrast, effect estimates for pregnancy-specific worries were larger in MAVAN than in the two other cohorts. The reason for this might be that items of the pregnancy-specific worries factor in MAVAN were specifically tapping into pregnancy anxiety (eg, "How often have you felt anxious about being pregnant?"), while in the other 2 cohorts items included more generally negative reactions related to being pregnant (eg, "Does being a mother mean giving up something that is important to you?" "I feel reluctant about making preparations for the baby"). In summary, effect estimates were similar in the two larger cohorts, whereas in the smallest cohort they had wide confidence intervals. The discrepancy in results may therefore also stem from higher sampling variance in smaller cohorts, which makes under- or overestimation of associations more likely. Furthermore, smaller samples might be statistically underpowered to detect associations. This underscores the importance of multi-cohort investigations to reduce sampling variance, to increase power, and to estimate effects that are less dependent on a particular method.

In addition to its effect on general offspring psychopathology, general prenatal affective symptoms were further associated with children's specific internalizing but not externalizing behavior. This is in contrast to previous studies that have reported associations also with children's externalizing difficulties, such as attention-deficit/hyperactivity disorder, conduct problems, and antisocial behavior.[40] However, one should bear in mind that specific factors in a bifactor model represent residual variance that may or may not be meaningful when accounting for their contribution to general psychopathology. Psychiatric symptoms at all ages, including the preschool and early school age, are highly comorbid, and externalizing problems are more prevalent in early childhood than internalizing problems.[41] Nevertheless, specific internalizing problems were the only childhood outcome for which all individual cohort-based effect estimates of the maternal general prenatal affective factor were significant. This suggests that maternal general affective symptoms during pregnancy are associated with children's specific internalizing problems above and beyond an effect on increasing their general vulnerability for developing psychopathology, in general.

Our study is the first attempt to harmonize latent constructs of prenatal maternal affective problems and pregnancy-specific worries across large, independent cohorts that had used different measures to assess these problems. We benefited from the inclusion of the two largest prenatal cohorts to date, namely, the inclusion of a wide range of measures and, in the case of the child outcome, the inclusion of repeated assessments and multiple informants. The present study thus fully exploited the benefits that a consortium of large observational cohorts can provide. Nevertheless, we were faced with several limitations. We did not assess general anxiety symptoms prenatally in MAVAN, and, as such, the specific depression factor in MAVAN is not fully comparable to the combined depression and general anxiety factor in the other two cohorts. The pregnancy-specific items in ALSPAC and Generation R were more general reactions related to pregnancy, whereas in MAVAN these items were specifically tapping into anxiety about the pregnancy itself. Such discrepancies are, however, inevitable when working with existing cohorts. Our factor scores represent latent traits of prenatal affective and pregnancy-specific symptoms. An important question concerns the use of raw scores as proxies for these latent traits in applied research.[15] Using structural equation models, it is possible to assess only linear associations; as such, we may have missed or mischaracterized important nonlinear relationships between the maternal latent factors and offspring psychopathology outcomes. Although analyses were adjusted for postnatal maternal depression, other aspects of maternal affective psychopathology were not included postnatally in two of the three cohorts. This may have resulted in less precise estimates of the effect of postnatal maternal affective symptoms on offspring psychopathology. However, most evidence supports the role of postnatal maternal depression in the risk for offspring psychopathology.[8,42–44] As maternal affective symptoms were not measured before conception in the participating cohorts, women with prenatal symptoms might have had chronic affective problems that continued into the prenatal period. We could not test the hypothesis that the observed effects were due to the offspring's exposure to maternal affective symptoms in utero. Nevertheless, in addition to the findings of this study,

there is good evidence for the presence of direct and persisting prenatal effects when adjusting for postnatal maternal depressive symptoms[5,35,45–47] and for specific sex-dimorphic transmission mechanisms through the placenta.[37,48–50] These findings support the in utero programming hypothesis and the consideration of potential sensitive periods. Indeed, previous work applying a life-course perspective found that the prenatal period is a sensitive one for the effect of maternal depression on child outcome.[51] Unfortunately, data on preconceptional affective symptoms are not commonly available in most pregnancy cohorts. However, they are increasingly being collected in newly designed cohort studies (eg, the Healthy Life Trajectories Initiative, Generation R *Next).* Maternal prenatal affective symptoms are known to be associated with a host of child outcomes, from neurobiological to cognitive and behavioral outcomes. This study focused on offspring psychopathology; however, the other outcomes are of equal importance and deserve their due attention. Our other research activities, for example, specifically address cognitive outcomes related to executive function and ADHD, in a model that harmonizes three levels of outcome, from clinical phenotype to cognition to neurobiology.

Common questionnaires assessing general depressive symptoms, such as those included in this study (ie, EPDS, CES-D), may be used to derive scores representing underlying dimensions of depressed mood, anxiety, and anhedonia, as shown previously.[11,32] However, these measures do not tap into symptoms of pregnancy-specific anxiety. Therefore, we suggest that clinicians complement these measures for screening purposes with a brief, validated questionnaire of pregnancy-specific anxiety (eg, the Pregnancy-Specific Anxiety Scale or the abbreviated version of the Pregnancy Related Anxieties Questionnaire).

The findings presented here underscore the importance of intervening in the prenatal period, including for pregnancy-specific worries. Currently, there are few prenatal interventions to reduce maternal depression, anxiety, or stress, and few studies that track the long-term developmental outcomes of the offspring whose mothers receive such interventions.[52] Psychological interventions (eg, cognitive-behavioral therapy, interpersonal therapy, massage therapy, or relaxation techniques) and/or antidepressant medication have proved effective in reducing perinatal anxiety and depression.[52–54] A meta-analysis of interventions in pregnancy for mental health problems found beneficial effects of cognitive-behavioral therapy and interpersonal psychotherapy for depression, but limited trials on other mental health problems including anxiety.[55] One study has investigated the feasibility of a randomized controlled trial using a group-based intervention for anxiety in pregnancy.[56] There is some evidence on short-term maternal and fetal/newborn outcomes (eg, fetal heart rate, prematurity, and low birthweight),[53] but even less on the longer-term impact on child outcomes of prenatally treating anxiety and depression. Furthermore, women experiencing intense fears and worries relating to the pregnancy might benefit from a more targeted approach, one that specifically addresses the negative thoughts and emotions related to the pregnancy itself. Group therapy for anxiety run jointly by a midwife and psychological treatment practitioner would be one model to address this. Although pregnancy-specific anxiety is distinct from generalized anxiety and depression, no clinical guidelines currently exist for establishing clinically relevant thresholds for these symptoms. For women showing more severe signs of pregnancy-related anxiety, specialized interventions may be necessary; however those with milder symptoms might already benefit from more widely accessible mobile applications targeting negative assumptions related to their pregnancy.

Regarding research implications, our study adds further support to hypotheses (eg, the Developmental Origins of Health and Disease hypothesis, fetal programming, and prenatal programming of early postnatal plasticity) contending that adversity during the prenatal period may have long-term consequences for the future health of the offspring.[57] The evidence is considerable for prenatal programming effects. A previous study using the ALSPAC sample showed direct and persisting effects of prenatal mood problems on offspring psychiatric symptoms (ages 4−13 years) above and beyond psychosocial and obstetric risk, postnatal maternal mood, pre- and postnatal paternal mood, and parenting.[46] Similar findings were also obtained by an Australian group for prenatal depressive, anxious, and stress symptoms relating to adolescent internalizing problems (age 14 years) following adjustment for a number of prenatal confounders, concurrent maternal depressive and anxious symptoms, paternal history of mental problems, and mother−infant relationship.[45] However, a previous cross-cohort examination of the Generation R and ALSPAC samples, specifically focusing on attentional problems in very young children (ages 3−4 years), reported that much of the effects of prenatal anxiety and depression could be explained by postnatal maternal mood, at least in one of the cohorts (Generation R).[58] The authors suggested that the apparent intrauterine effect of maternal affective problems on offspring attention problems may be partly explained by residual confounding and genetic mechanisms rather than fetal programming. In contrast, an independent Finnish cohort study found that prenatal maternal depressive symptoms predicted offspring ADHD symptoms from 3 to 6 years, above and beyond maternal depressive symptoms after pregnancy.[47]

Future research could benefit from applying a study design similar to ours for further examining parameters that

can moderate the impact of prenatal adversity on the offspring, such as genetic susceptibility, the sex and gender of the offspring, and the early postnatal rearing environment.

Accepted March 11, 2020.

Drs. Szekely, Meaney, Greenwood, Lydon, and Wazana are with McGill University Faculty of Medicine, Montreal, Quebec, Canada. Drs. Szekely, Neumann, Jolicoeur-Martineau, Greenwood, and Wazana are with Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada. Dr. Wazana is also with the Centre for Child Development and Mental Health, Jewish General Hospital, Montreal, Quebec, Canada. Drs. Neumann, Verhulst, and Tiemeier are with Erasmus University Medical Center-Sophia Children's Hospital, Rotterdam, The Netherlands. Drs. Evans, Sallis, and Pearson are with the Centre for Academic Mental Health, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, United Kingdom. Dr. Sallis is also with MRC Integrative Epidemiology Unit, University of Bristol, Bristol, United Kingdom. Dr. Verhulst is also with the Child and Adolescent Mental Health Center, Mental Health Services, Capital Region of Denmark, Copenhagen, Denmark, and the Faculty of Health and Medical Sciences, University of Copenhagen, Denmark. Dr. Meaney is also with the Douglas Mental Health Institute, Montreal, Quebec, Canada, and Singapore Institute for Clinical Sciences, Singapore City, Singapore. Drs. Levitan and Kennedy are with the Centre for Addiction and Mental Health, Toronto, Ontario, Canada. Dr. Levitan is also with the University of Toronto, Toronto, Ontario, Canada. Dr. Steiner is with McMaster University, Hamilton, Ontario, Canada. Dr. Tiemeier is with Harvard T. H. Chan School of Public Health, Boston, Massachusetts.

This research was made possible by the Canadian Institutes of Health Research (CIHR; grants 359912, 365309, and 231614), the Fonds de la recherche en santé du Québec (FRSQ; grant 22418), and the March of Dimes Foundation (grant 12-FY12-198). The UK Medical Research Council (grant reference74882), the Wellcome Trust (grant reference 076467), and the University of Bristol provide core support for the Avon Longitudinal Study of Parents and Children (ALSPAC).

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the Erasmus University Rotterdam, Faculty of Social Sciences, the Municipal Health Service Rotterdam area, and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond (STAR), Rotterdam. The Generation R Study is made possible by financial support from Erasmus Medical Center, Rotterdam, and the Netherlands Organization for Health Research and Development (ZonMw).

A. Neumann and H. Tiemeier are supported by a grant of the Dutch Ministry of Education, Culture, and Science and the Netherlands Organization for Scientific Research (NOW; grant no. 024.001.003, Consortium on Individual Development). The work of H. Tiemeier is supported by NWO-VICI grant (NWO-ZonMW: 016.VICI.170.200). R.D. Levitan has acknowledged support from the Cameron Parker Holcombe Wilson Chair in Depression Studies, University of Toronto and the Centre for Addiction and Mental Health (CAMH).

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing the report. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

Ms. Jolicoeur-Martineau and Dr. Greenwood served as the statistical experts for this research.

Author Contributions

Conceptualization: Szekely, Neumann, Jolicoeur-Martineau, Verhulst, Meaney, Pearson, Kennedy, Lydon, Steiner, Greenwood, Tiemeier, Evans, Wazana
Data curation: Szekely, Neumann, Sallis, Jolicoeur-Martineau, Verhulst, Meaney, Lydon, Steiner, Tiemeier, Evans, Wazana
Formal analysis: Szekely, Neumann, Sallis, Jolicoeur-Martineau, Meaney, Pearson, Kennedy, Greenwood, Tiemeier, Evans, Wazana
Funding acquisition: Szekely, Verhulst, Meaney, Levitan, Kennedy, Lydon, Steiner, Greenwood, Tiemeier, Evans, Wazana
Investigation: Szekely, Meaney, Levitan, Lydon, Steiner, Tiemeier, Evans, Wazana
Methodology: Szekely, Neumann, Sallis, Jolicoeur-Martineau, Verhulst, Meaney, Pearson, Levitan, Kennedy, Lydon, Steiner, Greenwood, Tiemeier, Evans, Wazana
Project administration: Szekely, Meaney, Levitan, Steiner, Tiemeier, Evans, Wazana
Software: Jolicoeur-Martineau, Wazana
Supervision: Pearson, Steiner, Greenwood, Tiemeier, Evans, Wazana
Validation: Wazana
Visualization: Wazana
Writing — original draft: Szekely, Neumann, Sallis, Jolicoeur-Martineau, Verhulst, Meaney, Levitan, Kennedy, Lydon, Steiner, Greenwood, Tiemeier, Evans, Wazana
Writing — review and editing: Szekely, Neumann, Sallis, Jolicoeur-Martineau, Greenwood, Tiemeier, Evans, Wazana

ORCID
Alexander Neumann, PhD: https://orcid.org/0000-0001-6653-3203
Hannah Sallis PhD: https://orcid.org/0000-0002-4793-6290
Alexia Jolicoeur-Martineau, MSc: https://orcid.org/0000-0003-2169-4008
Robert D. Levitan, MD: https://orcid.org/0000-0003-1306-3847
Celia M.T. Greenwood, PhD: https://orcid.org/0000-0002-2427-5696
Henning Tiemeier, MD, PhD: https://orcid.org/0000-0002-4395-1397
Jonathan Evans, MD: https://orcid.org/0000-0003-3171-640X
Ashley Wazana, MD: https://orcid.org/0000-0002-4964-5163

The authors gratefully acknowledge the contribution of general practitioners, hospitals, midwives, and pharmacies in Rotterdam.

Disclosure: Dr. Verhulst is a contributing author of the Achenbach System of Empirically Based Assessment (ASEBA), from which he has received remuneration. Drs. Szekely, Neumann, Sallis, Meaney, Pearson, Levitan, Kennedy, Lydon, Steiner, Greenwood, Tiemeier, Evans, and Wazana and Ms. Jolicoeur-Martineau have reported no biomedical financial interests or potential conflicts of interest.

Correspondence to Ashley Wazana, MD, Centre for Child Development and Mental Health, Jewish General Hospital, 4335 Saint Catherine Road, Montreal, QC H3T 1E4, Canada; e-mail: ashley.wazana@mcgill.ca

https://doi.org/10.1016/j.jaac.2020.02.017

REFERENCES

1. Madigan S, Oatley H, Racine N, *et al*. A meta-analysis of maternal prenatal depression and anxiety on child socioemotional development. J Am Acad Child Adolesc Psychiatry. 2018;57:645-657.
2. Rees S, Channon S, Waters CS. The impact of maternal prenatal and postnatal anxiety on children's emotional problems: a systematic review. Eur Child Adolesc Psychiatry. 2019;28:257-280.
3. Robinson R, Lahti-Pulkkinen M, Heinonen K, Reynolds RM, Räikkönen K. Fetal programming of neuropsychiatric disorders by maternal pregnancy depression: a systematic mini review. Pediatr Res. 2019;85:134-145.
4. Van den Bergh BRH, van den Heuvel MI, Lahti M, *et al*. Prenatal developmental origins of behavior and mental health: the influence of maternal stress in pregnancy. Neurosci Biobehav Rev. July 2017 [Epub ahead of print.
5. Lahti M, Savolainen K, Tuovinen S, *et al*. Maternal depressive symptoms during and after pregnancy and psychiatric problems in children. J Am Acad Child Adolesc Psychiatry. 2017;56:30-39.
6. Pearson RM, Evans J, Kounali D, *et al*. Maternal depression during pregnancy and the postnatal period. JAMA Psychiatry. 2013;70:1312-1319.
7. Glover V. Annual research review: Rrenatal stress and the origins of psychopathology: An evolutionary perspective. J Child Psychol Psychiatry Allied Discip. 2011;52:356-367.
8. Goodman SH, Rouse MH, Connell AM, Broth MR, Hall CM, Heyward D. Maternal depression and child psychopathology: a meta-analytic review. Clin Child Fam Psychol Rev. 2011;14:1-27.
9. Buffa G, Dahan S, Sinclair I, *et al*. Prenatal stress and child development: a scoping review of research in low- and middle-income countries. PLoS One. 2018;13:e0207235.
10. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150:782-786.
11. Coates R, Ayers S, de Visser R. Factor structure of the Edinburgh Postnatal Depression Scale in a population-based sample. Psychol Assess. 2017;29:1016-1027.

12. Martin CR, Redshaw M. Establishing a coherent and replicable measurement model of the Edinburgh Postnatal Depression Scale. Psychiatry Res. 2018;264:182-191.
13. Putnam KT, Wilcox M, Robertson-Blackmore E, *et al*. Clinical phenotypes of perinatal depression and time of symptom onset: analysis of data from an international consortium. Lancet Psychiatry. 2017;4:477-485.
14. Phua DY, Kee MKZL, Koh DXP, *et al*. Positive maternal mental health during pregnancy associated with specific forms of adaptive development in early childhood: Evidence from a longitudinal study. Dev Psychopathol. 2017;29:1573-1587.
15. Reichenheim ME, Moraes CL, Oliveira AS, Lobato G. Revisiting the dimensional structure of the Edinburgh Postnatal Depression Scale (EPDS): empirical evidence for a general factor. BMC Med Res Methodol. 2011;11:93.
16. Altemus M, Neeb CC, Davis A, Occhiogrosso M, Nguyen T, Bleiberg KL. Phenotypic differences between pregnancy-onset and postpartum-onset major depressive disorder. J Clin Psychiatry. 2012;73:e1485-e1491.
17. Huizink AC, Mulder EJH, Robles de Medina PG, Visser GHA, Buitelaar JK. Is pregnancy anxiety a distinctive syndrome? Early Hum Dev. 2004;79:81-91.
18. Huizink AC, Robles de Medina PG, Mulder EJH, Visser GHA, Buitelaar JK. Psychological measures of prenatal stress as predictors of infant temperament. J Am Acad Child Adolesc Psychiatry. 2002;41:1078-1085.
19. Huizink AC, Robles de Medina PG, Mulder EJH, Visser GHA, Buitelaar JK. Stress during pregnancy is associated with developmental outcome in infancy. J Child Psychol Psychiatry. 2003;44:810-818.
20. Buss C, Davis EP, Hobel CJ, Sandman CA. Maternal pregnancy-specific anxiety is associated with child executive function at 6-9 years age. Stress. 2011;14:665-676.
21. Buss C, Davis EP, Muftuler LT, Head K, Sandman CA. High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6-9-year-old children. Psychoneuroendocrinology. 2010;35:141-153.
22. Sun JW, Cao DF, Li JH, *et al*. Profiles and characteristics of clinical subtypes of perinatal depressive symptoms: a latent class analysis. J Adv Nurs. 2019;75:2753-2765.
23. Davies SJC, Pearson RM, Stapinski L, *et al*. Symptoms of generalized anxiety disorder but not panic disorder at age 15 years increase the risk of depression at 18 years in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study. Psychol Med. 2016;46:73-85.
24. Vollebergh WA, Iedema J, Bijl RV, de Graaf R, Smit F, Ormel J. The structure and stability of common mental disorders: the NEMESIS study. Arch Gen Psychiatry. 2001; 58:597-603.
25. Sallis H, Szekely E, Neumann A, *et al*. General psychopathology, internalising and externalising in children and functional outcomes in late adolescence. J Child Psychol Psychiatry. 2019;60:1183-1190.
26. Boyd A, Golding J, Macleod J, *et al*. Cohort profile: the 'children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. Int J Epidemiol. 2013;42:111-127.
27. Kooijman MN, Kruithof CJ, van Duijn CM, *et al*. The Generation R Study: design and cohort update 2017. Eur J Epidemiol. 2016;31:1243-1264.
28. O'Donnell KA, Gaudreau H, Colalillo S, *et al*. The maternal adversity, vulnerability and neurodevelopment project: theory and methodology. Can J Psychiatry. 2014;59: 497-508.
29. Crown S, Crisp AH. Manual of the Crown-Crisp Experimental Index. London: Hodder and Stoughton; 1979.
30. De Beurs E. The Brief Symptom Inventory; Manual. Leiden, Netherlands: Pits Publisher; 2004.
31. Theut SK, Pedersen FA, Zaslow MJ, Rabinovich BA. Pregnancy subsequent to perinatal loss: parental anxiety and depression. J Am Acad Child Adolesc Psychiatry. 1988;27:289-292.
32. Carleton RN, Thibodeau MA, Teale MJN, *et al*. The Center for Epidemiologic Studies Depression Scale: a review with a theoretical and empirical examination of item content and factor structure. PLoS One. 2013;8:e58067.
33. Roesch SC, Schetter CD, Woo G, Hobel CJ. Modeling the types and timing of stress in pregnancy. Anxiety, Stress Coping. 2004;17:87-102.
34. Lovejoy MC, Graczyk PA, O'Hare E, Neuman G. Maternal depression and parenting behavior: a meta-analytic review. Clin Psychol Rev. 2000;20:561-592.
35. Quarini C, Pearson RM, Stein A, Ramchandani PG, Lewis G, Evans J. Are female children more vulnerable to the long-term effects of maternal depression during pregnancy? J Affect Disord. 2016;189:329-335.
36. Gregg P, Propper C, Washbrook E. Understanding the relationship between parental income and multiple child outcomes: a decomposition analysis. LSE STICERD Research Paper No. CASE129. Accessed May 5, 2020. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=1159360.
37. Glover V, O'Connor TG. Effects of antenatal stress and anxiety. Implications for development and psychiatry. Br J Psychiatry. 2002;180:389-391.
38. Wadhwa PD, Sandman CA, Porto M, Dunkel-Schetter C, Garite TJ. The association between prenatal stress and infant birth weight and gestational age at birth: a prospective investigation. Am J Obstet Gynecol. 1993;169:858-865.
39. O'Donnell KJ, Meaney MJ. Fetal origins of mental health: the developmental origins of health and disease hypothesis. Am J Psychiatry. 2017;174:319-328.
40. Rice F, Harold GT, Boivin J, van den Bree M, Hay DF, Thapar A. The links between prenatal stress and offspring development and psychopathology: disentangling environmental and inherited influences. Psychol Med. 2010;40:335-345.
41. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry. 2003;60: 837-844.
42. Gelfand DM, Teti DM. The effects of maternal depression on children. Clin Psychol Rev. 1990;10:329-353.
43. Murray L, Arteche A, Fearon P, Halligan S, Goodyer I, Cooper P. Maternal postnatal depression and the development of depression in offspring up to 16 years of age. J Am Acad Child Adolesc Psychiatry. 2011;50:460-470.
44. Verbeek T, Bockting CLH, Van Pampus MG, *et al*. Postpartum depression predicts offspring mental health problems in adolescence independently of parental lifetime psychopathology. J Affect Disord. 2012;136:948-954.
45. Betts KS, Williams GM, Najman JM, Alati R. Maternal depressive, anxious, and stress symptoms during pregnancy predict internalizing problems in adolescence. Depress Anxiety. 2014;31:9-18.
46. O'Donnell KJ, Glover V, Barker ED, O'Connor TG. The persisting effect of maternal mood in pregnancy on childhood psychopathology. Dev Psychopathol. 2014;26: 393-403.
47. Wolford E, Lahti M, Tuovinen S, *et al*. Maternal depressive symptoms during and after pregnancy are associated with attention-deficit/hyperactivity disorder symptoms in their 3- to 6-year-old children. PLoS One. 2017;12:e0190248.
48. Bale TL. The placenta and neurodevelopment: sex differences in prenatal vulnerability. Dialogues Clin Neurosci. 2016;18:459-464.
49. O'Donnell KJ, Bugge Jensen A, Freeman L, Khalife N, O'Connor TG, Glover V. Maternal prenatal anxiety and downregulation of placental 11β-HSD2. Psychoneuroendocrinology. 2012;37:818-826.
50. Monk C, Feng T, Lee S, Krupska I, Champagne FA, Tycko B. Distress during pregnancy: epigenetic regulation of placenta glucocorticoid-related genes and fetal neurobehavior. Am J Psychiatry. 2016;173:705-713.
51. Evans J, Melotti R, Heron J, *et al*. The timing of maternal depressive symptoms and child cognitive development: a longitudinal study. J Child Psychol Psychiatry Allied Discip. 2012;53:632-640.
52. Glover V. Maternal depression, anxiety and stress during pregnancy and child outcome; what needs to be done. Best Pract Res Clin Obstet Gynaecol. 2014;28:25-35.
53. Field T, Diego M, Hernandez-Reif M. Prenatal depression effects and interventions: a review. Infant Behav Dev. 2010;33:409-418.
54. O'Connor TG, Monk C, Fitelson EM. Practitioner review: maternal mood in pregnancy and child development—implications for child psychology and psychiatry. J Child Psychol Psychiatry. 2014;55:99-111.
55. Ravesteyn LMV, Berg MPL Van Den, Hoogendijk WJG, Kamperman AM. Interventions to treat mental disorders during pregnancy: a systematic review and multiple treatment meta-analysis. PLoS One. 2017;12:e0173397.
56. Wilkinson EL, O'Mahen HA, Fearon P, *et al*. Adapting and testing a brief intervention to reduce maternal anxiety during pregnancy (ACORN): study protocol for a randomised controlled trial. Trials. 2016;17:156.
57. Hartman S, Belsky J. Prenatal programming of postnatal plasticity revisited—and extended. Dev Psychopathol. 2018;30:825-842.
58. Van Batenburg-Eddes T, Brion MJ, Henrichs J, *et al*. Parental depressive and anxiety symptoms during pregnancy and attention problems in children: a cross-cohort consistency study. J Child Psychol Psychiatry Allied Discip. 2013;54:591-600.