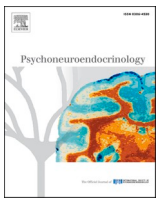
Psychoneuroendocrinology 171 (2025) 107196

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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



Maternal high BMI: Sex-dimorphic alterations in maternal and offspring stress indices

Sameera Abuaish [a,*], Vanessa Babineau [b], Seonjoo Lee [b,c], Benjamin Tycko [d], Frances A. Champagne [e], Elizabeth Werner [b,f], Catherine Monk [b,c,f]

[a] Department of Basic Sciences, College of Medicine, Princess Nourah bint Abdulrahman University, P.O.Box 84428, Riyadh 11671, Saudi Arabia
[b] Department of Obstetrics and Gynecology, Columbia University Irving Medical Center, New York, NY, USA
[c] New York State Psychiatric Institute, New York, NY, USA
[d] Hackensack-Meridian Health Center for Discovery and Innovation, Nutley, NJ 07110, USA
[e] Department of Psychology, University of Texas at Austin, Austin, TX, USA
[f] Department of Psychiatry, Columbia University Medical Center, New York, NY, USA

ARTICLE INFO

Keywords:
High BMI
Pregnancy
Prenatal programming
Fetal heart rate
Heart rate variability
Infant behavior

ABSTRACT

Maternal body mass index (BMI) influences pregnancy and birth outcomes along with child metabolic and neurodevelopmental health and fetal sex may be a moderating factor in these effects. Alternations in autonomic nervous system (ANS) functioning, identified in heart rate (HR) measurements, could present early markers of these prenatal programming effects in both the mother and the developing fetus. This study examines the associations between pre-pregnancy BMI and maternal and fetal ANS functioning and infant postnatal behavioral outcomes stratified by fetal sex. Pregnant women (N=176) were recruited at gestational week (GW) T1: 12–22 and categorized into Normal (BMI< 25) or High BMI (BMI > 25). Women attended laboratory sessions at T2: GW 23–28, and T3: GW 34–36 to assess maternal and fetal HR and HR variability (HRV) at baseline and after a stressor at T3. Infant behavior was assessed at 4 months using the Infant Behavior Questionnaire-Revised. Women with high BMI bearing female fetuses had higher HR and lower HRV at both gestational time points. Later in the third trimester, female fetuses of high BMI women exhibited lower HRV when challenged with a stressor. At 4 months, female infants were rated as having lower scores on the Orienting/Regulatory scale. Our findings provide evidence of female sex-specific programming of maternal pre-pregnancy BMI on maternal ANS regulation and neurodevelopment identified *in-utero* and continuing into early infancy.

1. Introduction

In the United States, nearly a third of pregnant women are obese (Driscoll and Gregory, 2020). Overall, increased maternal body mass index (BMI) is associated with a number of unfavorable maternal and child outcomes (Driscoll and Gregory, 2020) as maternal metabolic status plays an important role in priming future health for both generations (Saben et al., 2016; Sales et al., 2017; Shrestha et al., 2020). To date, early identification of this prenatal programming —maternal BMI affecting maternal and fetal health parameters — has been minimal and rarely simultaneously inclusive of both maternal and child health, yet identification of these early maternal-fetal effects could support mechanistic transmission studies and innovation for pregnancy interventions. Finally, fetal sex is a key moderating variable affecting both maternal physiology (DiPietro et al., 2011; Mitchell et al., 2017; Teulings et al., 2020) and fetal adaptation to prenatal exposures (Joshi et al., 2020; van Duijn et al., 2021); it is an important variable in the advancement of Developmental Origins of Health and Disease (DOHaD) research though only recently reliably included in studies.

An earlier work using a latent profile analysis of several biopsychosocial variables categorized women into either physically or psychologically stressed, with BMI being associated with the physically stressed category (Walsh et al., 2019). BMI is a common parameter included in the allostatic load model measuring the 'wear and tear' on the body of life stress and is highly associated with several stress parameters (Juster et al., 2010) such as autonomic nervous system (ANS) functioning, which maintains body homeostasis and is a key effector of the stress response system.

* Corresponding author.
E-mail address: syabuaish@pnu.edu.sa (S. Abuaish).

https://doi.org/10.1016/j.psyneuen.2024.107196
Received 28 February 2024; Received in revised form 30 July 2024; Accepted 24 September 2024
Available online 25 September 2024

The Function of the ANS can be assessed by measuring heart rate (HR) and HR variability (HRV) parameters. HRV can be measured using primarily two different metrics: time and frequency domains. The quantification of the variation in beat-to-beat time intervals is represented in the time domain indices, such as standard deviation in normal-to-normal R-R intervals (SDNN) and the root mean square of successive RR interval differences (RMSSD). While SDNN is influenced by both the sympathetic (SNS) and parasympathetic nervous systems (PNS), RMSSD is more influenced by the parasympathetic system. The frequency domain represents the distribution of power in either high (HF) or low (LF) frequency bands of oscillatory rhythms in the variability of the RR intervals (Cooley et al., 1998; Kimmel et al., 2021). The ratio of the LF/HF HRV is believed to represent the balance between the SNS and PNS, based on the assumption that LF is generated by the SNS while the HF reflects the parasympathetic activity; however, these assumptions, especially regarding the LF generation by SNS have been challenged and should be interpreted with caution. Findings of these matrices might indicate the dominance of either arm of the ANS.

In people with high BMI (>25), ANS functioning is altered, evidenced in higher resting HR and lower resting HRV (Godfrey et al., 2019; Triggiani et al., 2019; Yadav et al., 2017). In adults and children, lower resting HRV is associated with disease and a diminished capacity for self-regulation and adaptation to challenging environments (Shaffer and Ginsberg, 2017).

During pregnancy, physiological adjustments to support the mother and her fetus are observed with significant changes in maternal hemodynamics, including increased blood volume and cardiac output and reduced vascular resistance (Kodogo et al., 2019). These changes are governed by alternations of the ANS seen in increasing HR and decreasing HRV as pregnancy progresses (Helmreich et al., 2008; Walther et al., 2005). Relatively lower maternal HRV is associated with hypertensive disorders of pregnancy such as pre-eclampsia (Moors et al., 2020) as well as maternal mental health conditions pre and post pregnancy (Kimmel et al., 2021; Solorzano et al., 2022).

For the developing fetus, HR and HRV serve as developmental biomarkers. Fetal HR and HRV reliably decrease and increase, respectively over gestation reflecting greater parasympathetic control in the ANS system (Shuffrey et al., 2019). Intraindividual fetal HR parameters are largely stable prenatally into infancy and childhood, predicting mental and psychomotor development, language abilities, and capacity to regulate emotion and behavior (DiPietro et al., 2007; Werner et al., 2007). Specifically, fetal HRV is positively associated with neurodevelopment and language acquisition (DiPietro et al., 2007) and inversely with aspects of infant reactive temperament (Werner et al., 2007). Recent DOHaD studies have examined maternal BMI in relation to fetal HR outcomes reporting lower fetal HRV in high BMI women and an inverse association between weight or gestational weight gain and fetal HRV (Christifano et al., 2021; Husin et al., 2020).

The hypothalamic-pituitary-adrenal axis and inflammation are both implicated in the regulation of the autonomic nervous system, and are known to be dysregulated in individuals with high body mass index (Friis et al., 2013; Incollingo Rodriguez et al., 2015). This suggests that the HPA axis, inflammation, and ANS are common biological pathways, which are known to influence each other, that could explain the biological dysregulation reported with high BMI. For instance, lower heart rate variability and vagal function have been associated with elevated urinary cortisol levels and proinflammatory cytokines in adults (Thayer and Sternberg, 2006). Additionally, maternal salivary cortisol has been reported to be linked with increased fetal heart rate (Monk et al., 2011a).

Fetal sex appears to influence maternal and infant physiology in the context of prenatal exposures, with effects identified in relation to female sex. For example, some data suggest that carrying a female is associated with higher maternal cortisol levels (DiPietro et al., 2011) and augmented stimulated cytokine production across pregnancy (Mitchell et al., 2017). For children, sex-dimorphic effects are observed in metabolic consequences such that type 2 diabetes development is associated with maternal BMI and waist circumference only in daughters (Talbot and Dolinsky, 2019). In animal models, sex-dimorphic differences in developmental outcomes in relation to maternal obesity are frequently reported, with females particularly affected. For example, in rodent studies, maternal obesity is associated with reduced sociability (Kang et al., 2014), increased anxiety (Sasaki et al., 2013), and altered neonatal ultrasonic vocalization, specifically in female offspring (Abuaish et al., 2020). Animal studies also show sex-dimorphic physiological and molecular responses to maternal obesity in offspring tissues including the brain (Edlow et al., 2016; Sasaki et al., 2013), and placenta (Leon-Garcia et al., 2016; Mandò et al., 2016). To our knowledge, no studies have investigated in humans whether high maternal BMI is associated with sex-specific differences in indices of maternal physiology and fetal and infant development.

In this study we aim to examine the effects of pre-pregnancy BMI on prenatal maternal and fetal ANS function and postnatal infant behavior with a special focus on sex-dimorphic differences. Based on prior work in adults, we hypothesized that high BMI would be associated with reduced HRV in mothers; given the minimal research to date, we explored sex differences without an *a priori* hypothesis. Based on prior animal and human studies (Abuaish et al., 2020; Kang et al., 2014; Sasaki et al., 2013; Werner et al., 2007), we hypothesized that high pre-pregnancy BMI would be associated with altered fetal ANS regulation such that female fetuses exhibit reduced HRV and that the offspring *in-utero* alteration would be paralleled postnatally in infant behavior with reduced behavioral regulation.

2. Materials and methods

2.1. Participants and procedures

This is a secondary analysis of an already existing data set including participants who were part of a longitudinal study examining maternal stress in relation to maternal and fetal epigenetic modifications (Jensen Peña et al., 2012; Walsh et al., 2019). A total of N=187 healthy pregnant women ages 18–45 years were recruited between 2011 and 2016 from the Department of Obstetrics and Gynecology at Columbia University Medical Centre during either their first or second trimester. Only women with singleton pregnancies fluent in English and who were not actively smoking or taking psychiatric drugs were included in this study. All participants provided written informed consent, and all procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute. Eleven women withdrew from the study after their first visit (N= 176). Pre-pregnancy BMI was used to assess maternal BMI as it is a predictor of adverse maternal and offspring outcomes (Voerman et al., 2019). Participants were recruited at gestation weeks (GW) 12–22 (T1) and their pre-pregnancy weight was self-reported, and BMIs were calculated using their pre-pregnancy weights and categorized based on the Centers of Disease Control and Prevention classifications: Underweight (BMI < 18.5) (N= 9), Normal BMI (BMI < 25) (N= 77), Overweight (BMI 25–29) (N= 55), or Obese (BMI ≥30) (N= 33). Two groups were created: Normal BMI (N= 77) and High BMI (N= 88), which includes both Overweight and Obese women. Maternal weights were collected at each visit and they showed significant positive correlation with reported pre-pregnancy BMI (Supplementary Table 1). Women attended laboratory sessions for HR assessment sessions in their second trimester (T2: GW 23–28) and third trimester (T3: GW 34–36). During laboratory sessions participants' blood were collected and later analyzed for leptin levels (Supplementary methods), which were also positively correlated with pre-pregnancy BMI (Supplementary Table 1). In addition, leptin levels were significantly higher in High BMI compared to Normal BMI women (Supplementary Figure 1). A total of eleven women were excluded from the analyses including the 9 underweight women and 2 who had missing pre-pregnancy weights, resulting in a sample of N=165. Demographics, perceived stress, and depression

(Supplementary methods) data were collected and updated at both sessions. Medical records were accessed to collect birth outcomes.

2.2. Maternal and fetal heart rate assessments

At T2, participants laid comfortably for a 20-min baseline session in a semi-recumbent position during the acquisition of both maternal and fetal HR. At T3, the 20-min session was followed by stressor paradigms: participants were presented with two different 5-minute tasks, Stroop and paced breathing, after an additional 5-minute resting baseline; tasks were separated by a 5-minute recovery period as previously described (Monk et al., 2011b). The order of the two tasks was counterbalanced among the participants.

Maternal electrocardiogram (ECG) and respiration impedance were acquired and digitized at 500 Hz and 50 Hz, respectively, by a 16-bit A/D conversion board (National Instruments, Austin, TX). ECG analysis was done as described in (Monk et al., 2000; Sloan et al., 2007). Waveforms were analyzed using costume developed software to detect R waves and calculate RR intervals and later visually inspected to correct mislabeled waves. Mean HR (bpm) and HRV time domain indices including standard deviation of RR intervals (SDNN) and the root mean squared successive difference (RMSSD) were calculated for each period. To obtain HRV frequency domain indices, spectral power in the low (0.04–0.15 Hz (LF)) and high (0.15–0.40 Hz (HF)) frequency bands were computed by subjecting 300-sec epochs to an interval method for computing Fourier transforms of calculated spectra. Before computing Fourier transforms, the mean of the RR interval series was subtracted from each value in the series and the series was then filtered using a Hanning window and the power, i.e., variance (in msec2), over the LF and HF bands was summed. Estimates of spectral power were adjusted to account for attenuation produced by this filter. The ratio of LF/HF HRV was calculated as a possible estimate of HRV reflecting the sympathetic and parasympathetic balance (Shaffer and Ginsberg, 2017). Respiration measured as average breaths per minute was calculated after identifying the peaks of respiratory impedance waveform via a custom-developed software and later visually inspected for accuracy and used as a covariate in analyses. A total of T2: N= 139, T3: N= 133 participants provided HR and HRV data for analysis (T2: N= 23 participants did not have enough data collected, N= 4 participants joined the study at T3, N= 4 participants did not complete the session; T3: N= 6 participants withdrew from the study after T2, N= 4 participants did not enough data collected, N= 22 participants did not complete the session).

Fetal HR was obtained using Toitu MT 325 fetal actocardiograph (Toitu Co.) via a single transabdominal Doppler transducer and later processed through filters removing movement associated with HR and maternal somatic activity. The output data from Toitu was digitized at 50 Hz using a 16-bit A/D card (National Instruments 16XE50) and data were later analyzed offline using a MATLAB software developed for this assessment. Average fetal HR were calculated as described in (Doyle et al., 2015). When 4-minute recoded segments did not meet the criteria as described elsewhere (Doyle et al., 2015), these individuals were excluded (T2: N= 28, T3: N= 8) from the analysis. HRV was calculated as the standard deviation of HR. There were no significant differences in the missing fetal heart rate data between the two different groups (missing: Normal BMI N= 14 (9.9 %), High BMI N= 17(11.6 %), X (1288)= 0.239, p= 0.6).

2.3. Mother reported infant behavior

At 4 months postpartum, a subset of participants (N= 91) completed the Infant Behavior Questionnaire-Revised (IBQ-R). The IBQ-R assesses infant behavior between 2 and 12 months, consists of 191 items divided into 14 subscales, and is scored on a 7-point Likert scale ranging from "Always" to "Never". A three-factor structure is constructed: 1) Surgency/Positive Emotionality (subscales: Activity Level, Vocal Reactivity, Approach, Smiling and Laughter, High-Intensity Pleasure, and Perceptual Sensitivity), 2) Negative Affect (Distress to Limitation, Sadness, Fear, and Falling Reactivity), and 3) Orienting/Regulatory (Duration of Orienting, Soothability, Low Intensity Pleasure, and Cuddliness) (Gartstein and Rothbart, 2003).

2.4. Statistical analysis

Demographic data was analyzed using chi-square and Fisher exact test. Maternal HRV variables were skewed and were log-transformed for normalization. Values that were 3X the interquartile range of the data were considered extreme outliers and removed (Maternal variables: LF/HF HRV N= 2; Fetal variables: HR N= 4, 20-minute baseline HRV N= 5, stressor task HRV N= 9). There were no group differences Normal versus High BMI in maternal age, education, and ethnicity. However, annual income was significantly different (p = 0.05; Table 1) indicating that women with lower income were more likely to have high BMI; it was added as a covariate in all analyses. There were no group differences in parity, gestational diabetes, infant sex, gestational age at birth, birth weight or birth weight adjusted to gestational age at birth (calculated as the residuals of a regression analysis of birth weight on gestational age at birth). Women with high BMI, however, were more likely to deliver with C-section (p = 0.07; Table 1), which was added as a covariate in all analyses. We did not find any significant differences in weight gain between Normal and High BMI women. High BMI was associated with higher depression scores measured by Hamilton Depression Rating Scale (HAMD; Supplementary material) and was used in sensitivity analyses for all variables and it did not change the findings for any of the variables except for the fetal HRV during the stress task (see results).

Baseline maternal and fetal HR parameters were analyzed using factorial Linear Mixed Models (LMM) (2 BMI X 2 trimester) using AR1 covariate matrix with trimester as the repeated measures and subject ID as a random factor and were stratified by fetal sex. Fetal HR parameters during the stress challenge were analysed using factorial LMM (2 BMI X 5 periods) using AR covariate matrix and period as the repeated measures. Average HR and HRV are presented across the stress period. A factorial univariate ANOVA (2 BMI X 2 sex) was used to analyse infant behavior. Spearman correlation was used to examine the relationship between fetal HRV and infant behavior. Maternal ethnicity, maternal age, and birth weight adjusted to gestational age at birth were related to some maternal and fetal HR parameters and were added in all HR models as covariates. Maternal physical activity (Supplementary material) is shown to be associated with maternal HR parameters (Doyle et al., 2015) and therefore was included as a covariate in the analysis. For maternal HF-HRV, maternal respiration during the assessment was also included as a covariate similar to other reports (Sloan et al., 2007). The order of stressor tasks, whether Stroop task or paced breathing were presented first, were added as covariates in the model assessing the differences in fetal HR parameters during the stress challenge. Maternal reports of infant behavior were related to maternal age, gestational age at birth, parity, and ethnicity. Previous studies have indicated that maternal stress is associated with maternal reports of infant temperaments (Pesonen et al., 2008, 2005), therefore maternal perceived stress collected at 4 months (supplementary material) was added to the analysis as a covariate. Bonferroni post hoc test was used for all multiple comparisons reported.

3. Results

3.1. Maternal HR parameters

Women pregnant with females showed the expected increase in HR across pregnancy (Time effect: F(1, 63.97)= 14.95, $p\leq$ 0.001; Fig. 1A; Supplementary Table 5). Pre-pregnancy BMI was associated with higher HR at both time points in women pregnant with females (BMI effect: F(1, 69.15)= 9.33, p = 0.003; High BMI vs. Normal BMI: $p\leq$ 0.01). Women pregnant with males also showed the expected increase in HR (Time

Table 1
Cohort demographics.

Variable	N	Overall, N = 165[a]	High, N = 88[a]	Normal, N = 77[a]	*p*-value[b]
Age	165	29.96 (19.55–44.91)	30.20 (20.26–43.21)	29.69 (19.55–44.91)	0.6
Pre-pregnancy weight	165	155.52 (100.00–310.00)	178.75 (130.00–310.00)	128.97 (100.00–165.00)	<0.001
Pre-pregnancy BMI	165	26.55 (18.70–43.23)	30.50 (25.09–43.23)	22.04 (18.70–24.96)	<0.001
Weight gain[c]	113	29.08 (26.94–31.41)	29.17 (27.07–31.41)	28.99 (26.94–30.11)	0.2
Education	165				0.5
High school		62 (37.6 %)	31 (35.2 %)	31 (40.3 %)	
GED		12 (7.3 %)	9 (10.2 %)	3 (3.9 %)	
Vocational		4 (2.4 %)	3 (3.4 %)	1 (1.3 %)	
Associates		10 (6.1 %)	6 (6.8 %)	4 (5.2 %)	
Bachelors		46 (27.9 %)	26 (29.5 %)	20 (26 %)	
Masters		16 (9.7 %)	8 (9.1 %)	8 (10.4 %)	
PhD		7 (4.2 %)	3 (3.4 %)	4 (5.2 %)	
Other		8 (4.8 %)	2 (2.3 %)	6 (7.8 %)	
Ethnicity	164				0.1
Hispanic/Latina		111 (67.7 %)	64 (73 %)	47 (62 %)	
Income	165				0.05
$0-$15,000		22 (13 %)	16 (18 %)	6 (8 %)	
$16,000-$25,000		32 (19 %)	16 (18 %)	16 (21 %)	
$26,000-$50,000		34 (23 %)	19 (22 %)	15 (19 %)	
$51,000-$100,000		42 (25 %)	25 (28 %)	17 (22 %)	
$101,000-$250,000		28 (17 %)	11 (12 %)	17 (22 %)	
Above $250,000		7 (4 %)	1 (1 %)	6 (8 %)	
Parity	161	0.84 (0–6)	0.92 (0–6)	0.76 (0–4)	0.2
Gestational Diabetes	164	5 (3 %)	4 (4.6 %)	1 (1.3 %)	0.3
Gestational age	156	39.13 (30–41)	39.22 (30–41)	39.15 (34–41)	>0.9
Sex	160				0.3
Female		78 (49 %)	44 (52 %)	33 (45 %)	
Birth weight	159	3314.58 (1310.00–4470.00)	3356.56 (1470.00–4470.00)	3302.12 (1310.00–4395.00)	0.7
Delivery	159				0.07
C-section		56 (35 %)	35 (42 %)	21 (28 %)	
Vaginal		103 (65 %)	48 (58 %)	55 (72 %)	

[a] Mean (Minimum-Maximum); n (%)
[b] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test
[c] Adjusted to gestational week at 3rd trimester

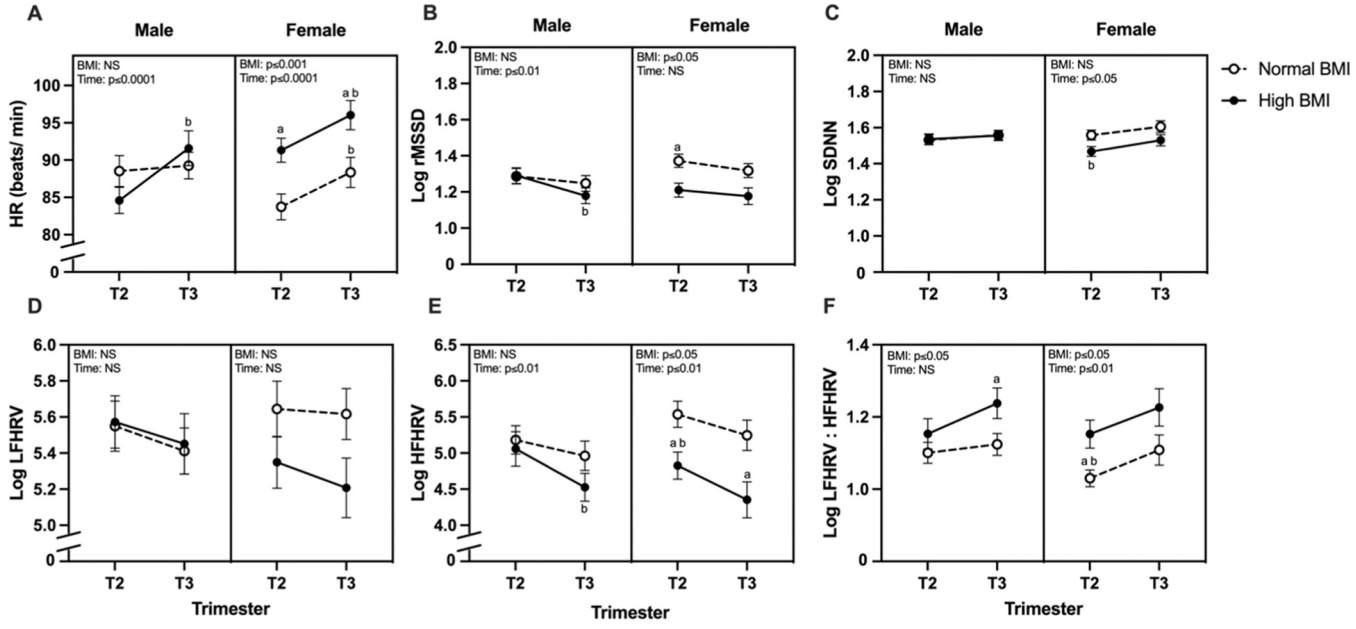


Fig. 1. Heart rate (HR) baseline measurements of pregnant women with Normal or High BMI during a 20-min recording session at gestation weeks 23–28 and 34–36 visits stratified by fetal sex. (A) HR. (B) Log transformed root mean square of the successive differences (RMSSD). (C) Log transformed standard deviation of the NN (R-R) intervals (SDNN). (D) Log transformed low frequency HR variability (LFHRV). (E) Log transformed high frequency HR variability (HFHRV). (F) Ratio of log LFHRV to HFHRV. Data presented are means ± standard error. Bonferroni Post hoc comparisons; a= High BMI vs. Normal BMI, b= T2 vs. T3.

effect: $F(1, 60.71)= 10.74$, $p = 0.002$; Fig. 1A) but this change was only significant in High BMI women (High BMI: T2 vs. T3: $p\leq 0.001$), with no main effect of pre-pregnancy BMI (BMI effect: $F(1, 68.22)= 0.36$, $p = 0.6$).

With respect to the time domains of HRV, RMSSD and SDRR, in women pregnant with females, RMSSD (Fig. 1B; Supplementary Table 5) did not change across pregnancy (Time effect: $F(1, 63.13)= 1.92$, $p = 0.17$), yet it was overall lower across pregnancy in High BMI women

(BMI effect: $F(1, 68.34) = 4.53$, $p = 0.04$). RMSSD levels were significantly lower at T2 (High BMI vs. Normal BMI: $p = 0.04$) and showed a non-significant trend of a decrease at T3 (High BMI vs. normal BMI: $p = 0.09$). In women pregnant with males, RMSSD changed across pregnancy (Time effect: $F(1, 64.22) = 6.04$, $p = 0.01$), with a significant decrease observed only in High BMI women from T2 to T3 ($p = 0.01$). SDNN (Fig. 1C; Supplementary Table 5) exhibited a significant increase across pregnancy only in women carrying female fetuses (Time effect: $F(1, 60.33) = 6.53$, $p = 0.01$). Pairwise comparison analysis revealed that this increase was only significant in High BMI women (T2 vs. T3: $p = 0.02$). In women pregnant with males, SDNN did not change across pregnancy (Time effect: $F(1, 64.22) = 0.63$, $p = 0.4$) nor did it differ by pre-pregnancy BMI (BMI effect: $F(1, 70) = 0.01$, $p = 0.99$).

For frequency domains of HRV, LF-HRV levels (Fig. 1D; Supplementary Table 5) did not change across time nor was it associated with pre-pregnancy BMI in either male and female pregnancies. HF-HRV (Fig. 1E), however, decreased overall across time in women pregnant with females (Time effect: $F(1, 62.05) = 7.68$, $p = 0.007$). This decrease was only significant in High BMI women (T2 vs. T3: $p = 0.04$). High BMI was associated with lower HF-HRV at both time points in women carrying female fetuses (BMI effect: $F(1, 68.54) = 5.14$, $p = 0.03$; High BMI vs. Normal BMI: $p \leq 0.05$). Women pregnant with males also exhibited a change in their HF-HRV across pregnancy (Time effect: $F(1, 59.10) = 5.05$, $p = 0.03$), with only High BMI women exhibiting a significant decrease across time (T2 vs. T3: $p = 0.03$). Finally, the ratio of LF:HF HRV (Fig. 1F; Supplementary Table 5) significantly increased across pregnancy in women carrying female fetuses (Time effect: $F(1, 61.72) = 6.59$, $p = 0.01$). This increase was only significant in Normal BMI women (T2 vs. T3: $p = 0.04$). High BMI was associated with high LF:HF HRV ratio in female pregnancies (BMI effect: $F(1,65.35) = 4.26$, $p = 0.04$), which was significant specifically at T2 (High BMI vs. Normal BMI: $p = 0.04$). Male pregnancies on the other hand did not exhibit any change in the ratio of LF:HF HRV across time (Time effect: $F(1, 52.29) = 2.39$, $p = 0.1$), but it was affected by pre-pregnancy BMI (BMI effect: $F(1, 58.03) = 5.13$, $p = 0.03$). Specifically, High BMI women pregnant with males had significantly higher ratio of LF:HF HRV at T3 only compared to Normal BMI women ($p = 0.01$).

3.2. Fetal HR parameters

Fetal HR was lower (Fig. 1A; Supplementary Table 6) across time for both sexes of both BMI groups (Time effect: female; $F(1,59.91) = 29.76$, $p \leq 0.001$; male: $F(1,62.16) = 28.00$, $p \leq 0.001$; T2 vs. T3: $p \leq 0.001$), with no association with maternal BMI (BMI effect: female; $F(1,60.08) = 1.30$, $p = 0.2$; male: $F(1,62.81) = 0.36$, $p = 0.5$). Additionally, there was an overall increase in fetal HRV (Fig. 1B; Supplementary Table 6) across pregnancy (Time effect: female: $F(1,48.01) = 12.59$, $p \leq 0.001$; male: $F(1,70.96) = 11.94$, $p \leq 0.001$; T2 vs. T3: $p \leq 0.05$), with no association with maternal BMI (BMI effect: female; $F(1,53.70) = 0.84$, $p = 0.3$; male: $F(1,65.83) = 0.27$, $p = 0.6$).

During the maternal stressor task in the 3rd trimester, HR (Fig. 2D; Supplementary Table 7) changed in male but only showed trend result in female fetuses (Time effect: female: $F(4186.54) = 2.17$, $p = 0.07$; male: $F(4183.50) = 3.10$, $p = 0.01$). No associations between maternal BMI and fetal HR during the stressor tasks were found (BMI effect: female: $F(1,49.14) = 0.73$, $p = 0.4$; male: $F(1,50.71) = 0.54$, $p = 0.5$). HRV

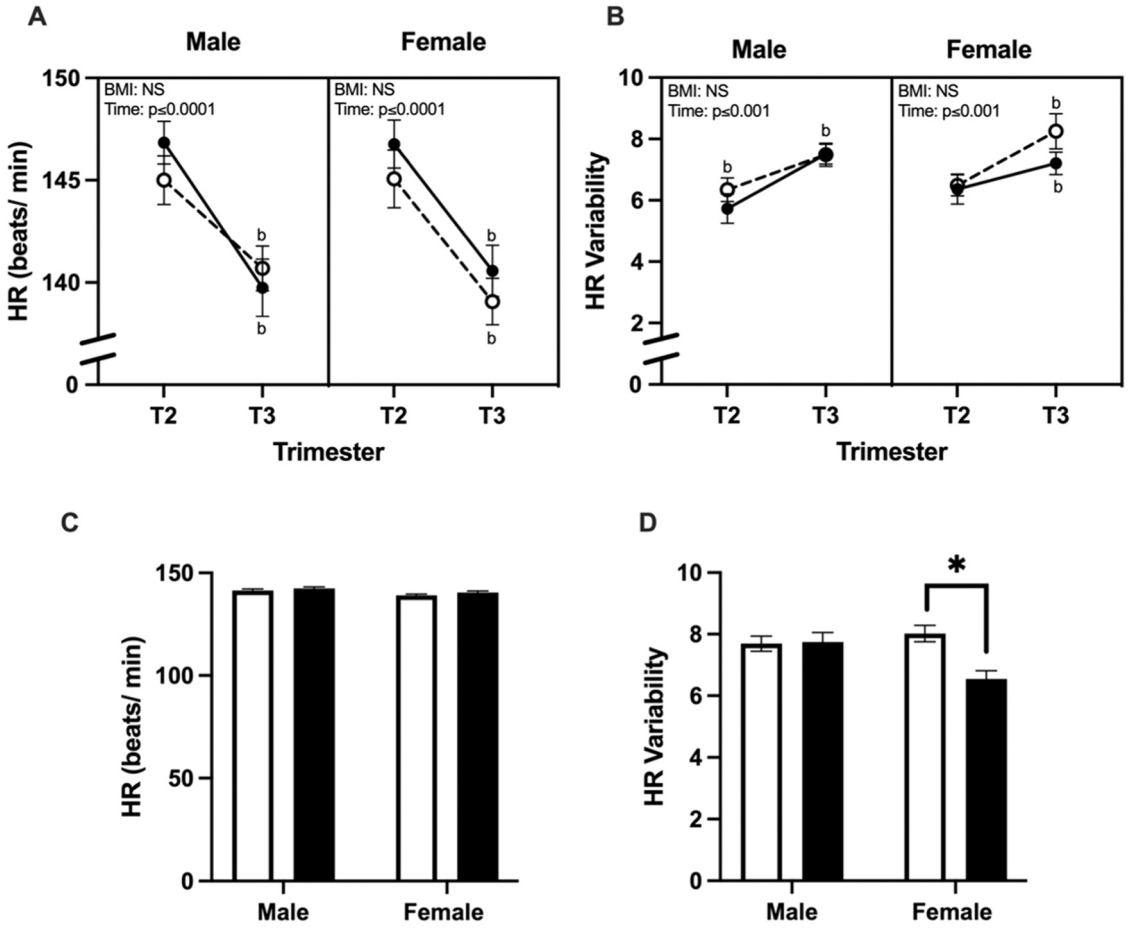


Fig. 2. Heart rate (HR) parameters of male and female infants of women with Normal or High BMI. Baseline HR parameters measured during a 20-min recording session at gestation weeks 23–28 and 34–36 visits. (A) HR. (B) HR variability. Parameters measured during a stress challenge session at gestation weeks 34–36 visit. (C) HR. (D) HR variability. Data presented are means ± standard error.Bonferroni Post hoc comparisons; a= High BMI vs. Normal BMI, b= T2 vs. T3.

(Fig. 2E; Supplementary Table 7) did not change during the stressor periods in either sex (Time effect: female: $F(4128.64) = 1.01$, $p = 0.4$; male: $F(4101.31) = 0.30$, $p = 0.9$). Overall, during this period, HRV was significantly reduced in female fetuses of women with High BMI only (BMI effect: $F(1,67.46) = 5.35$, $p = 0.02$), with no differences observed in male fetuses (BMI effect: $F(1,76.17) = 0.13$, $p = 0.7$). When adjusting for maternal depression using HAMD scores, the reduced HRV levels in High BMI female fetuses were not significant ($F(1, 53.74) = 2.66$, $p = 0.1$; Supplementary Table 7).

3.3. Infant behavior

At 4 months old, only the Orienting/Regulatory factor (Fig. 3A; Supplementary Table 8) differed by maternal BMI ($F(1,78) = 5.49$, $p = 0.02$), but this effect was only significant in female infants, where female infants of high BMI women exhibited significantly lower scores than those of normal BMI women (High BMI vs. Normal BMI: $p = 0.01$). Of the subscales in this factor, the Soothability subscale (Fig. 3B; Supplementary Table 8) was significantly lower only in female infants of High BMI women (High BMI vs. Normal BMI: $p = 0.05$) with no differences observed in male infants. Moreover, the Duration of Orienting subscale (Fig. 3C; Supplementary Table 8) was related to maternal BMI ($F(1,78) = 4.01$, $p = 0.05$), with no effects in males and effects only in females of High BMI women exhibiting significantly lower scores than those of Normal BMI women (High BMI vs. Normal BMI: $p = 0.04$). There were no associations with the Surgency/Positive Emotionality or Negative Affect factors of the IBQ-R.

Spearman correlation analysis revealed a positive relationship between female infant Orienting/Regulatory factor and HRV levels in response to the stress challenge in the 3rd trimester ($r = 0.48$, $p = 0.02$) with no association observed in the male infants.

4. Discussion

In this study, we examined three different outcomes of maternal pre-pregnancy BMI: 1- maternal ANS regulation during pregnancy, 2- fetal ANS development, and 3- infant postnatal behaviors. High maternal BMI was related to behavioral outcomes in infants with potential origins of modification initiated *in utero* through the developing ANS. Interestingly, these effects were sex-specific, with mainly female fetuses and infants exhibiting alteration in their biology and behavior in relation to exposure to high maternal BMI.

High BMI in non-pregnant individuals is associated with a dysregulated ANS, with an increase in HR and alterations in HRV parameters. Specifically, high BMI is associated with an increase in HR and a reduction in parasympathetic HRV markers including RMSSD and HF-HRV (Yadav et al., 2017). Visceral adiposity is also negatively associated with HF-HRV levels (Triggiani et al., 2019). These effects can be normalized after lifestyle or surgical interventions (Sinha et al., 2022). In our study, these reported ANS characteristics in High BMI individuals

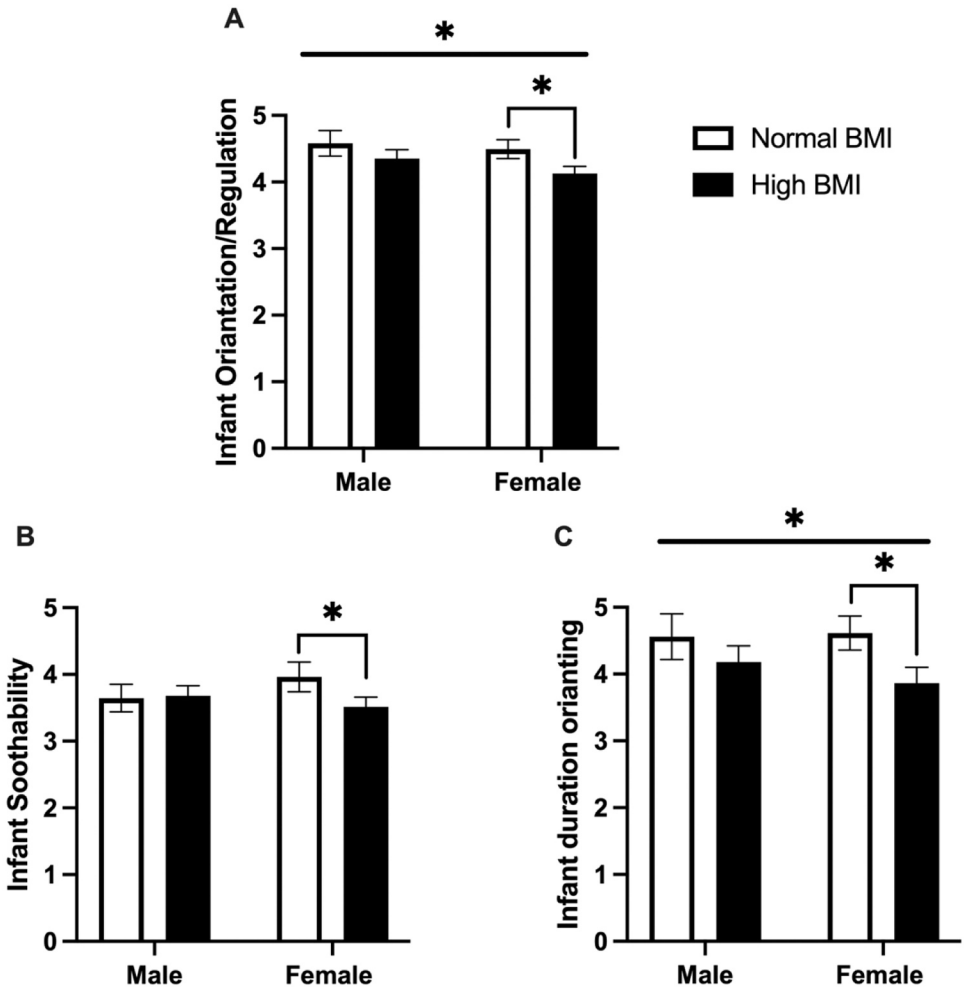


Fig. 3. Maternal reported infant behavior of male and female infants based on the infant behavior questionnaire (IBQ). (A) Infant Orientation/Regulation factor of the IBQ-R. (B) Infant Soothability scale. (C) Infant Duration of Orienting scale. Data presented are means ± standard error. BMI effect: *P ≤ 0.05. Bonferroni Post hoc comparisons: *P ≤ 0.05.

were replicated in pregnant women, but only in women carrying female fetuses. The reduced parasympathetic control as an effect of high BMI was indicated by lower RMSSD, HF-HRV levels, and high LH:HF HRV ratio. Interestingly, this alteration in ANS was not exhibited by High-BMI women carrying males, potentially suggesting that fetal sex modifies maternal physiology. For example, fetal sex is associated with pregnancy outcomes including hypertension and pre-eclampsia (Broere-Brown et al., 2020). Moreover, women carrying female fetuses were found to exhibit augmented stimulated cytokine production across pregnancy (Mitchell et al., 2017) and higher salivary cortisol levels (DiPietro et al., 2011). Another study, reported sex-moderated association between prenatal depression and maternal C-reactive protein (CRP) and hair cortisol levels (Freedman et al., 2021). Specifically, in female pregnancies, maternal depression was associated with higher maternal hair cortisol levels, while depressed women carrying males had higher CRP serum levels (Freedman et al., 2021). These female-specific HPA axis and inflammatory differences might make pregnant female pregnancies even more susceptible to the already augmented inflammatory milieu and dysregulated HPA axis reported with high BMI (Friis et al., 2013; Incollingo Rodriguez et al., 2015). Additionally, these sex-specific effects could be mediated through the placenta, which exhibits significant transcriptome differences between sexes driven by genes escaping X-chromosome inactivation affecting the maternal serum metabolome (Gong et al., 2018). Our results suggest that carrying a male fetus might alter physiological factors in mothers, normalizing the effects of high BMI on maternal ANS characteristics during pregnancy.

These sex-dimorphic responses to high maternal BMI were also observed in fetal ASN development, consistent with our hypotheses. When challenged by a stressor, the differences in HRV of female fetuses between the two BMI groups emerged. Others have reported that maternal high BMI was associated with an increase in fetal HR and a decrease in HRV measured as SDNN (Christifano et al., 2021; Husin et al., 2020), however, these studies controlled for fetal sex as a covariate. At baseline, we did not observe any differences in HR or HRV in either sex. It is only when female fetuses are challenged by a stressor that they exhibit compromised HRV responses, indicating that they may have reduced capacity to adapt to stressors. Our results expand on the initial findings to address the sex-specific effects of maternal BMI that have been reported, particularly using animal models showing stronger effects of maternal obesity on female offspring's physiological, molecular, and behavioral outcomes (Abuaish et al., 2020; Edlow et al., 2016; Kang et al., 2014; Sasaki et al., 2013). Maternal high BMI is a metabolic stressor to the growing fetus and our data, consistent with other studies (Rosenfeld, 2015), indicate that male and female fetuses may adapt differently to this challenge. For example, these sex-dimorphic effects are seen in the placenta morphological and pathological outcomes, where female placentae from High BMI women have higher weight, lower efficiency and higher prevalence of chronic villitis (Leon-Garcia et al., 2016; Mandò et al., 2016). In addition, several variables had higher incidence of preterm births of male fetuses and not females (Walsh et al., 2019).

The sex-dimorphic *in-utero* ANS alterations were paralleled in maternal reports of postnatal infant behavior. Female infants of High BMI mothers had decreased capacity to regulate behavioral affect at 4 months of age (i.e., the Orienting/Regulatory factor) with no changes in positive or negative reactivity patterns (i.e., the Surgency/Positive Emotionality and Negative Affect factors). Specifically, mothers perceived female infants as being more difficult to soothe, and as having decreased capacity in the duration of orienting behavior. These findings are consistent with an earlier meta-analysis on associations between maternal pre-pregnancy obesity and child neurobehavioral development showing increased risk for early childhood attention, mood, and behavior problems, difficulties with executive function, lower academic achievement, developmental delays, and autism spectrum disorder (Sanchez et al., 2018). The continuity of compromised capacity of regulation in females starting from *in-utero* measured by HRV as a biomarker into infancy are supported by the positive correlation between HRV levels in response to stress in the 3rd trimester and infant behavioral regulation capacity. Future work should test the mediation of HRV of the BMI effects on infant behavior.

While combining both overweight and obese women into one group might have limited our differentiation of the effects of obesity from overweight, we show that overall deviation from normal BMI influences maternal and fetal physiology. Replicating our findings in a study with a larger sample size to examine these within high BMI subgroup differences is necessary to better inform expecting mothers and health care providers. Yet our study replicates other reports of associations between maternal BMI and fetal ANS function (Triggiani et al., 2019; Yadav et al., 2017) and it expands on that by addressing fetal sex as an important moderator supporting findings in other outcomes related to high maternal BMI. Relying solely on BMI is a limitation in our study, as it not an accurate measurement of adiposity and it does not distinguish between lean and fat mass nor does it indicate fat distribution. However, to circumvent this limitation, as a measure of adiposity, we determined leptin levels during the 2nd and 3rd trimesters, and they were strongly positively correlated with pre-pregnancy BMI and weights during pregnancy. In addition, leptin levels were significantly higher in High BMI compared to Normal BMI women (Supplementary Figure 1). These findings provide a biological metric that is highly correlated with self-reported pre-pregnancy BMI, which corroborates using maternal pre-pregnancy BMI in this study. Despite the known limitations of using pre-pregnancy BMI, it is an easily accessible measure clinically and most guidelines use it to inform clinical practice. Therefore, we have used pre-pregnancy BMI as our independent variable due to its applicability in different settings both clinical and research. We recognize that other measurements related to BMI, such as weight gain and body composition, could provide more practical implications compared to BMI alone. Others have reported reduced fetal HRV in women who gained more than the recommended weight gain ranges within the context of normal pre-pregnancy BMI (Husin et al., 2020). Examining the sex moderation of other BMI related measures in future studies would be useful. We acknowledge the importance of gestational weight gain during pregnancy and our preliminary analysis have calculated the weight gain from pre-pregnancy weight until the 3rd trimester while controlling for gestational weeks at the 3rd trimester. We did not find any significant differences in weight gain between Normal and High BMI women nor when classifying women into Normal, Overweight, or Obese. While we acknowledge that gestational weight gain during pregnancy is an important factor affecting gestational biology and pregnancy outcomes, there are meta-analyses of over million pregnancies reporting that weight gain has low to moderate predictive value compared to pre-pregnancy BMI on pregnancy outcomes (McDermott and Brubaker, 2019; Voerman et al., 2019). Additionally, others show that pre-pregnancy BMI is an important factor determining weight gain during pregnancy and that it may minimize the benefits of weight control during pregnancy (Zhang et al., 2023). Nevertheless, we believe that future studies should expand on our novel findings to assess other metabolic measures and their associations with maternal and fetal autonomic function and infant behavior in a sex-specific manner.

BMI is also tightly correlated with other psychosocial factors; we cannot rule out their contribution to the reported findings. For example, we found that women with high BMI had also high prenatal depression scores. The inclusion of prenatal depression as a covariate, maternal BMI was no longer associated with fetal HRV during stress, suggesting that maternal psychological state also contributes to the regulation of the fetal autonomic nervous system, which is in line with earlier reports of the association between maternal mood and fetal ANS functioning (Kinsella and Monk, 2009). High BMI and depression are known comorbidities and have a very dynamic and reciprocal relationship yet most studies have examined their effects separately. There are limited investigations on the combined effects of these two maternal conditions on child outcomes. One study reports that the concurrent presence of

maternal overweight/obesity and depression appears to pose the highest risk of adverse birth outcomes (McDonald et al., 2015). Future studies should examine both exposures in shaping the development of the ANS and related behavioral outcomes.

Moreover, High-BMI women were more likely to have lower incomes, a variable that we have controlled for in our analysis. Lower income might contribute to food insecurity and consumption of high-caloric and highly processed foods with low nutritional value. During pregnancy micronutrient deficiency, for example zinc, is associated with a reduction in fetal HRV (Spann et al., 2015). More research examining the contribution of nutrients on both maternal and fetal ANS functioning is needed.

Strengths of this study include the diverse participant make up, with a majority identifying as Latinx. Latina compared to White women are reported to have poor diet quality due to food insecurity, less physical activity, and subsequently higher rates of obesity (Kominiarek et al., 2021). Our results provide insights into a population often excluded from research that comprise the largest ethnic minority group with one of the highest fertility rates in the US (Osterman et al., 2021). We also examined mother and child pairs as there are limited studies assessing dyadic measures of mother and child despite evidence suggesting that measures obtained from either might not be sufficient in ensuring a healthy dyad (Handley et al., 2023).

Our work highlights the impact of fetal sex in moderating the BMI effects on fetal and infant outcomes. Our findings also suggest the possible influence of fetal sex on maternal physiology, which is rarely addressed in the literature. Moreover, this study illustrates the ongoing effects of maternal High BMI on child neurodevelopmental outcomes, with effects in infancy concordant with those from the *in-utero* fetal period. To our knowledge, this study is the first in humans to highlight the possible programming effects of high pre-pregnancy BMI on both fetal and infant neurobehavioral outcomes in a sex-specific manner.

5. Conclusion

Our study identifies possible prenatal programming effects of maternal high BMI during fetal development with sequelae out to infancy, as well as sex-specific effects on maternal ANS regulation. In a time of increasing obesity world-wide, the two-generation impact of maternal BMI is an important research area and one with direct implications for clinical care.

Funding

This work is supported by an NIH Grant (R01MH092580) to C.M., F. A.C, B.T. and by Princess Nourah bint Abdulrahman University Researchers Supporting Project (PNURSP2024R338), Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia to SA.

CRediT authorship contribution statement

Seonjoo Lee: Formal analysis, Data curation. **Sameera Abuaish:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. **Vanessa Babineau:** Writing – review & editing. **Elizabeth Werner:** Project administration, Investigation. **Catherine Monk:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Benjamin Tycko:** Resources, Investigation, Funding acquisition. **Frances A Champagne:** Resources, Funding acquisition, Conceptualization.

Declaration of Competing Interest

EW is a consultant for the medical company Philips for an application about pregnancy called Pregnancy + and has received payment from Philips. We confirm that there are no other known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome for other authors.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2024.107196.

References

Abuaish, S., Tse, E.K., McGowan, P.O., 2020. Perinatal high-fat diet impairs pup retrieval and induces sex-specific changes in ultrasonic vocalization characteristics of rat pups. Dev. Psychobiol. 62, 436–445. https://doi.org/10.1002/dev.21923.

Broere-Brown, Z.A., Adank, M.C., Benschop, L., Tielemans, M., Muka, T., Gonçalves, R., Bramer, W.M., Schoufour, J.D., Voortman, T., Steegers, E.A.P., Franco, O.H., Schalekamp-Timmermans, S., 2020. Fetal sex and maternal pregnancy outcomes: a systematic review and meta-analysis. Biol. Sex. Differ. 11, 26. https://doi.org/10.1186/s13293-020-00299-3.

Christifano, D.N., Taylor, M.K., Carlson, S.E., Colombo, J., Gustafson, K.M., 2021a. Higher maternal weight is related to poorer fetal autonomic function. J. Dev. Orig. Health Dis. 12, 354–356. https://doi.org/10.1017/S2040174420000653.

Cooley, R.L., Montano, N., Cogliati, C., van de Borne, P., Richenbacher, W., Oren, R., Somers, V.K., 1998. Evidence for a central origin of the low-frequency oscillation in RR-interval variability. Circulation 98, 556–561. https://doi.org/10.1161/01.CIR.98.6.556.

DiPietro, J.A., Bornstein, M.H., Hahn, C.-S., Costigan, K., Achy-Brou, A., 2007. Fetal heart rate and variability: stability and prediction to developmental outcomes in early childhood. Child Dev. 78, 1788–1798. https://doi.org/10.1111/j.1467-8624.2007.01099.x.

DiPietro, J.A., Costigan, K.A., Kivlighan, K.T., Chen, P., Laudenslager, M.L., 2011. Maternal salivary cortisol differs by fetal sex during the second half of pregnancy. Psychoneuroendocrinology 36, 588–591. https://doi.org/10.1016/j.psyneuen.2010.09.005.

Doyle, C., Werner, E., Feng, T., Lee, S., Altemus, M., Isler, J.R., Monk, C., 2015. Pregnancy distress gets under fetal skin: Maternal ambulatory assessment & sex differences in prenatal development. Dev. Psychobiol. 57, 607–625. https://doi.org/10.1002/dev.21317.

Driscoll, A.K., Gregory, E.C.W., 2020. Increases in prepregnancy obesity: United States, 2016-2019. NCHS Data Brief. 1–8.

van Duijn, L., Rousian, M., Laven, J.S.E., Steegers-Theunissen, R.P.M., 2021. Periconceptional maternal body mass index and the impact on post-implantation (sex-specific) embryonic growth and morphological development. Int J. Obes. 45, 2369–2376. https://doi.org/10.1038/s41366-021-00901-7.

Edlow, A.G., Guedj, F., Pennings, J.L.A., Sverdlov, D., Neri, C., Bianchi, D.W., 2016. Males are from Mars, and females are from Venus: sex-specific fetal brain gene expression signatures in a mouse model of maternal diet-induced obesity. Am. J. Obstet. Gynecol. 214, 623.e1–623.e10. https://doi.org/10.1016/J.AJOG.2016.02.054.

Freedman, R., Hunter, S.K., Noonan, K., Wyrwa, A., Christians, U., Law, A.J., Hoffman, M.C., 2021. Maternal prenatal depression in pregnancies with female and male fetuses and developmental associations with C-reactive protein and cortisol. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 6, 310–320. https://doi.org/10.1016/j.bpsc.2020.08.003.

Friis, C.M., Paasche Roland, M.C., Godang, K., Ueland, T., Tanbo, T., Bollerslev, J., Henriksen, T., 2013. Adiposity-related inflammation: effects of pregnancy. Obesity 21, E124–E130. https://doi.org/10.1002/oby.20120.

Gartstein, M.A., Rothbart, M.K., 2003. Studying infant temperament via the revised infant behavior questionnaire. Infant Behav. Dev. 26, 64–86. https://doi.org/10.1016/S0163-6383(02)00169-8.

Godfrey, K.M., Juarascio, A., Manasse, S., Minassian, A., Risbrough, V., Afari, N., 2019. Heart rate variability and emotion regulation among individuals with obesity and loss of control eating. Physiol. Behav. 199, 73–78. https://doi.org/10.1016/J.PHYSBEH.2018.11.009.

Gong, S., Sovio, U., Aye, I.L.M.H., Gaccioli, F., Dopierala, J., Johnson, M.D., Wood, A.M., Cook, E., Jenkins, B.J., Koulman, A., Casero, R.A., Constância, M., Charnock-Jones, D.S., Smith, G.C.S., 2018. Placental polyamine metabolism differs by fetal sex, fetal growth restriction, and preeclampsia. JCI Insight 3. https://doi.org/10.1172/jci.insight.120723.

Handley, S.C., Formanowski, B., Passarella, M., Kozhimannil, K.B., Leonard, S.A., Main, E.K., Phibbs, C.S., Lorch, S.A., 2023. Perinatal care measures are incomplete if they do not assess the birth parent–infant dyad as a whole. Health Aff. 42, 1266–1274. https://doi.org/10.1377/hlthaff.2023.00398.

Helmreich, R.J., Hundley, V., Varvel, P., 2008. The effect of obesity on heart rate (heart period) and physiologic parameters during pregnancy. Biol. Res Nurs. 10, 63–78. https://doi.org/10.1177/1099800408321077.

Husin, H., Schleger, F., Bauer, I., Fehlert, E., Kiefer-Schmidt, I., Weiss, M., Kagan, K.O., Brucker, S., Pauluschke-Fröhlich, J., Eswaran, H., Häring, H., Fritsche, A., Preissl, H., 2020. Maternal weight, weight gain, and metabolism are associated with changes in fetal heart rate and variability. Obesity 28, 114–121. https://doi.org/10.1002/oby.22664.

Incollingo Rodriguez, A.C., Epel, E.S., White, M.L., Standen, E.C., Seckl, J.R., Tomiyama, A.J., 2015. Hypothalamic-pituitary-adrenal axis dysregulation and cortisol activity in obesity: a systematic review. Psychoneuroendocrinology 62, 301–318. https://doi.org/10.1016/J.PSYNEUEN.2015.08.014.

Jensen Peña, C., Monk, C., Champagne, F. a, 2012. Epigenetic effects of prenatal stress on 11β-hydroxysteroid dehydrogenase-2 in the placenta and fetal brain. PLoS One 7, e39791. https://doi.org/10.1371/journal.pone.0039791.

Joshi, A., Azuma, R., Akumuo, R., Goetzl, L., Pinney, S.E., 2020. Gestational diabetes and maternal obesity are associated with sex-specific changes in miRNA and target gene expression in the fetus. Int J. Obes. 44, 1497–1507. https://doi.org/10.1038/s41366-019-0485-y.

Juster, R.-P., McEwen, B.S., Lupien, S.J., 2010. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci. Biobehav Rev. 35, 2–16. https://doi.org/10.1016/j.neubiorev.2009.10.002.

Kang, S.S., Kurti, A., Fair, D. a, Fryer, J.D., 2014. Dietary intervention rescues maternal obesity induced behavior deficits and neuroinflammation in offspring. J. Neuroinflamm. 11, 156. https://doi.org/10.1186/s12974-014-0156-9.

Kimmel, M.C., Fransson, E., Cunningham, J.L., Brann, E., Grewen, K., Boschiero, D., Chrousos, G.P., Meltzer-Brody, S., Skalkidou, A., 2021. Heart rate variability in late pregnancy: exploration of distinctive patterns in relation to maternal mental health. Transl. Psychiatry 11, 286. https://doi.org/10.1038/s41398-021-01401-y.

Kinsella, M.T., Monk, C., 2009. Impact of maternal stress, depression and anxiety on fetal neurobehavioral development. Clin. Obstet. Gynecol. 52, 425–440. https://doi.org/10.1097/GRF.0b013e3181b52df1.

Kodogo, V., Azibani, F., Sliwa, K., 2019. Role of pregnancy hormones and hormonal interaction on the maternal cardiovascular system: a literature review. Clin. Res. Cardiol. 108, 831–846. https://doi.org/10.1007/s00392-019-01441-x.

Kominiarek, M.A., Cordero, C., Stuebe, A.M., Simon, M., Evenson, K.R., Perreira, K.M., Gallo, L.C., Castañeda, S.F., Potter, J.E., Wu, D., Isasi, C.R., Daviglus, M.L., 2021. Pre-pregnancy health behaviors and gestational weight gain among hispanic/latino women: hispanic community health study/study of latinos. Matern Child Health J. 25, 2002–2013. https://doi.org/10.1007/s10995-021-03252-x.

Leon-Garcia, S.M., Roeder, H.A., Nelson, K.K., Liao, X., Pizzo, D.P., Laurent, L.C., Parast, M.M., LaCoursiere, D.Y., 2016. Maternal obesity and sex-specific differences in placental pathology. Placenta 38, 33–40. https://doi.org/10.1016/j.placenta.2015.12.006.

Mandò, C., Calabrese, S., Mazzocco, M.I., Novielli, C., Anelli, G.M., Antonazzo, P., Cetin, I., 2016. Sex specific adaptations in placental biometry of overweight and obese women. Placenta 38, 1–7. https://doi.org/10.1016/j.placenta.2015.12.008.

McDermott, M.M., Brubaker, L., 2019. Prepregnancy body mass index, weight gain during pregnancy, and health outcomes. JAMA 321, 1715. https://doi.org/10.1001/jama.2019.3821.

McDonald, S.D., McKinney, B., Foster, G., Taylor, V., Lutsiv, O., Pullenayegum, E., 2015. The combined effects of maternal depression and excess weight on neonatal outcomes. Int. J. Obes. 39, 1033–1040. https://doi.org/10.1038/ijo.2015.44.

Mitchell, A.M., Palettas, M., Christian, L.M., 2017. Fetal sex is associated with maternal stimulated cytokine production, but not serum cytokine levels, in human pregnancy. Brain Behav. Immun. 60, 32–37. https://doi.org/10.1016/j.bbi.2016.06.015.

Monk, C., Fifer, W.P., Myers, M.M., Sloan, R.P., Trien, L., Hurtado, A., 2000. Maternal stress responses and anxiety during pregnancy: effects on fetal heart rate. Dev. Psychobiol. 36, 67–77. https://doi.org/10.1002/(SICI)1098-2302(200001)36:1<67::AID-DEV7>3.0.CO;2-C.

Monk, C., Fifer, W.P., Myers, M.M., Bagiella, E., Duong, J.K., Chen, I.S., Leotti, L., Altincatal, A., 2011a. Effects of maternal breathing rate, psychiatric status, and cortisol on fetal heart rate. Dev. Psychobiol. 53, 221–233. https://doi.org/10.1002/dev.20513.

Moors, S., Staaks, K.J.J., Westerhuis, M.E.M.H., Dekker, L.R.C., Verdurmen, K.M.J., Oei, S.G., van Laar, J.O.E.H., 2020. Heart rate variability in hypertensive pregnancy disorders: a systematic review. Pregnancy Hypertens. 20, 56–68. https://doi.org/10.1016/j.preghy.2020.03.003.

Osterman, M., Hamilton, B., Martin, J.A., Driscoll, A.K., Valenzuela, C.P., 2021. Births: final data for 2020. Natl. Vital.-. Stat. Rep. 70, 1–50.

Pesonen, A., Räikkönen, K., Heinonen, K., Komsi, N., Järvenpää, A., Strandberg, T., 2008. A transactional model of temperamental development: evidence of a relationship between child temperament and maternal stress over five years. Soc. Dev. 17, 326–340. https://doi.org/10.1111/j.1467-9507.2007.00427.x.

Rosenfeld, C.S., 2015. Sex-specific placental responses in fetal development. Endocrinology 156, 3422–3434. https://doi.org/10.1210/en.2015-1227.

Saben, J.L., Boudoures, A.L., Asghar, Z., Thompson, A., Drury, A., Zhang, W., Chi, M., Cusumano, A., Scheaffer, S., Moley, K.H., 2016. Maternal metabolic syndrome programs mitochondrial dysfunction via germline changes across three generations. Cell Rep. 16, 1–8. https://doi.org/10.1016/j.celrep.2016.05.065.

Sales, V.M., Ferguson-Smith, A.C., Patti, M.-E., 2017. Epigenetic mechanisms of transmission of metabolic disease across generations. Cell Metab. 25, 559–571. https://doi.org/10.1016/j.cmet.2017.02.016.

Sanchez, C.E., Barry, C., Sabhlok, A., Russell, K., Majors, A., Kollins, S.H., Fuemmeler, B. F., 2018. Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: a meta-analysis. Obes. Rev. 19, 464–484. https://doi.org/10.1111/obr.12643.

Sasaki, A., de Vega, W.C., St-Cyr, S., Pan, P., McGowan, P.O., 2013. Perinatal high fat diet alters glucocorticoid signaling and anxiety behavior in adulthood. Neuroscience 240, 1–12.

Shaffer, F., Ginsberg, J.P., 2017. An overview of heart rate variability metrics and norms. Front Public Health 5, 258. https://doi.org/10.3389/fpubh.2017.00258.

Shrestha, N., Ezechukwu, H.C., Holland, O.J., Hryciw, D.H., 2020. Developmental programming of peripheral diseases in offspring exposed to maternal obesity during pregnancy. Am. J. Physiol. - Regul. Integr. Comp. Physiol. 319, R507–R516. https://doi.org/10.1152/ajpregu.00214.2020.

Shuffrey, L.C., Myers, M.M., Odendaal, H.J., Elliott, A.J., du Plessis, C., Groenewald, C., Burd, L., Angal, J., Nugent, J.D., Isler, J.R., Fifer, W.P., 2019. Fetal heart rate, heart rate variability, and heart rate/movement coupling in the safe passage study. J. Perinatol. 39, 608–618. https://doi.org/10.1038/s41372-019-0342-9.

Sinha, M.K., Maiya, G.A., Moga, A.M., K N, S., Shankar, N., R., K., V., 2022. Exercise dose–response relationship with heart rate variability in individuals with overweight and obesity: protocol for a systematic review and meta-analysis of randomised controlled trials. BMJ Open 12, e047821. https://doi.org/10.1136/bmjopen-2020-047821.

Sloan, R.P., McCreath, H., Tracey, K.J., Sidney, S., Liu, K., Seeman, T., 2007. Rr interval variability is inversely related to inflammatory markers: the CARDIA study. Mol. Med. 13, 178–184. https://doi.org/10.2119/2006-00112.Sloan.

Solorzano, C.S., Violani, C., Grano, C., 2022. Pre-partum HRV as a predictor of postpartum depression: The potential use of a smartphone application for physiological recordings. J. Affect Disord. 319, 172–180. https://doi.org/10.1016/j.jad.2022.09.056.

Spann, M.N., Smerling, J., Gustafsson, H., Foss, S., Altemus, M., Monk, C., 2015. Deficient maternal zinc intake—but not folate—is associated with lower fetal heart rate variability. Early Hum. Dev. 91, 169–172. https://doi.org/10.1016/j.earlhumdev.2015.01.007.

Talbot, C.P.J., Dolinsky, V.W., 2019. Sex differences in the developmental origins of cardiometabolic disease following exposure to maternal obesity and gestational diabetes. Appl. Physiol., Nutr., Metab. 44, 687–695. https://doi.org/10.1139/apnm-2018-0667.

Teulings, N.E.W.D., Wood, A.M., Sovio, U., Ozanne, S.E., Smith, G.C.S., Aiken, C.E., 2020. Independent influences of maternal obesity and fetal sex on maternal cardiovascular adaptation to pregnancy: a prospective cohort study. Int. J. Obes. 44, 2246–2255. https://doi.org/10.1038/s41366-020-0627-2.

Thayer, J.F., Sternberg, E., 2006. Beyond heart rate variability. Ann. N. Y Acad. Sci. 1088, 361–372. https://doi.org/10.1196/annals.1366.014.

Triggiani, A.I., Valenzano, A., Trimigno, V., Di Palma, A., Moscatelli, F., Cibelli, G., Messina, G., 2019a. Heart rate variability reduction is related to a high amount of visceral adiposity in healthy young women. PLoS One 14, e0223058. https://doi.org/10.1371/journal.pone.0223058.

Voerman, E., Santos, S., Inskip, H., Amiano, P., Barros, H., Charles, M.-A., Chatzi, L., Chrousos, G.P., Corpeleijn, E., Crozier, S., Doyon, M., Eggesbø, M., Fantini, M.P., Farchi, S., Forastiere, F., Georgiu, V., Gori, D., Hanke, W., Hertz-Picciotto, I., Heude, B., Hivert, M.-F., Hryhorczuk, D., Iñiguez, C., Karvonen, A.M., Küpers, L.K., Lagström, H., Lawlor, D.A., Lehmann, I., Magnus, P., Majewska, R., Mäkelä, J., Manios, Y., Mommers, M., Morgen, C.S., Moschonis, G., Nohr, E.A., Nybo Andersen, A.-M., Oken, E., Pac, A., Papadopoulou, E., Pekkanen, J., Pizzi, C., Polanska, K., Porta, D., Richiardi, L., Rifas-Shiman, S.L., Roeleveld, N., Ronfani, L., Santos, A.C., Standl, M., Stigum, H., Stoltenberg, C., Thiering, E., Thijs, C., Torrent, M., Trnovec, T., van Gelder, M.M.H.J., van Rossem, L., von Berg, A., Vrijheid, M., Wijga, A., Zvinchuk, O., Sørensen, T.I.A., Godfrey, K., Jaddoe, V.W.V., Gaillard, R., 2019. Association of gestational weight gain with adverse maternal and infant outcomes. JAMA 321, 1702. https://doi.org/10.1001/jama.2019.3820.

Walsh, K., McCormack, C.A., Webster, R., Pinto, A., Lee, S., Feng, T., Krakovsky, H.S., O'Grady, S.M., Tycko, B., Champagne, F.A., Werner, E.A., Liu, G., Monk, C., 2019. Maternal prenatal stress phenotypes associate with fetal neurodevelopment and birth outcomes. Proc. Natl. Acad. Sci. 116, 23996–24005. https://doi.org/10.1073/pnas.1905890116.

Walther, T., Wessel, N., Baumert, M., Stepan, H., Voss, A., Faber, R., 2005. Longitudinal analysis of heart rate variability in chronic hypertensive pregnancy. Hypertens. Res. 28, 113–118. https://doi.org/10.1291/hypres.28.113.

Werner, E.A., Myers, M.M., Fifer, W.P., Cheng, B., Fang, Y., Allen, R., Monk, C., 2007. Prenatal predictors of infant temperament. Dev. Psychobiol. 49, 474–484. https://doi.org/10.1002/dev.20232.

Yadav, R.L., Yadav, P.K., Yadav, L.K., Agrawal, K., Sah, S.K., Islam, M.N., 2017a. Association between obesity and heart rate variability indices. Intuit. Card. Auton. Alter. - a risk Cvd. Diabetes Metab. Syndr. Obes. 10, 57–64. https://doi.org/10.2147/DMSO.S123935.

Zhang, J., Zhang, R., Chi, J., Li, Y., Bai, W., 2023. Pre-pregnancy body mass index has greater influence on newborn weight and perinatal outcome than weight control during pregnancy in obese women. Arch. Public Health 81, 5. https://doi.org/10.1186/s13690-023-01025-2.