Maternal Stress Volatility During Pregnancy on Child Health Outcomes

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Abstract

Pregnancy is one of the most stressful periods in someone's life, and this stress often arrives in inconsistent, fluctuating waves depending on the time, day, and trimester of pregnancy. The concept of stress in pregnant individuals being associated with negative health outcomes in their children is a theory with precedent set by many distinguished clinical trials. This study aims to quantify the volatility of that stress as it appears day to day and within each trimester of pregnancy, to inferentially explore if that stress variability is an adverse fetal exposure associated with infantile health outcomes. Approximately 250 pregnant individuals completed demographic and biological questionnaires, along with self reported stress diaries in the form of ecological momentary assessments (EMA) ten times a day, for four days, roughly every trimester of the pregnancy. No later than one-month post birth, clinician-reported outcome (ClinRO) measures were taken on the newborns including birth weight, body fat %, and telomere length.

Background

There were three studies which are very similar to our current research question. The first two involve the subject of pregnancy stress and newborn health outcomes, while the third delves into the methodological approach of using the RMSSD measure of variability for repeated measures.

The first, "Psychological stress and cortisol during pregnancy: An ecological momentary assessment (EMA)-Based within- and between-person analysis", was a clinical research paper which examined the psychoendocrine covariance at the between and within

person level in pregnancy using ecological momentary assessment (EMA) methods for 152 participants. They assessed maternal perceived stress along 4 days long in early, mid, and late pregnancy to provide stress appraisals. They used a linear mixed effect model (LMM) to identify the source of variance in momentary PSS-EMA and cortisol in different levels. After accounting for the effects of key determinants of variation in cortisol, momentary stress was significantly and positively associated with cortisol at the within- person level (B = 0.30, p = 0.031) (Lazarides et al 2020).

The second study, "Physiological reactions to acute stressors and subjective stress during daily life: A systematic review on ecological momentary assessment (EMA) studies" was a clinical study which aimed to analyze ecological momentary assessment studies as far as their ability to record stress variability and how that impacts physiological responses in the reporting individuals. At the conclusion of the study, approximately 50% of study participants drew an association between collected ecological momentary assessment data and measured physiological responses including, fluctuating cortisol levels, and increased blood pressure and heart rates (Weber J, Angerer P, Apolinário-Hagen J, 2022)

The third study called "Affect fluctuations examined with ecological momentary assessment in patients with current or remitted depression and anxiety disorder" at University of Groningen. They were interested in day-to-day affect fluctuation of patients with depressive and anxiety disorder. They used (EMA) data for 365 participants. For two weeks, five times per day, participants reported items on positive affect (PA) and negative effect (NA) momentary assessments. Affect instability between time lagged collections of PA and NA assessments was calculated as the root mean square of successive difference (RMSSD). This volatility measure is able to assess instability by quantifying both variance and time series dependency in EMA data through means of autocorrelation (Schoevers, et al 2021). Person mean levels of PA and NA and RMSSD of PA and NA were compared group-wise in persons with no reported depression. Patients with reported depression and or anxiety had the largest measured affect instability in both PA and NA, which was then proceeded by remitter patients and then controls. The following conclusion was reported, "Instability differences between groups remained significant when controlling for mean affect levels, but differences between current and remitted were no longer significant. Patients with a current disorder have higher instability of NA and PA than remitted patients and controls. Especially with regard to NA, this could

be interpreted as patients with a current disorder being more sensitive to internal and external stressors and having suboptimal affect regulation" (Schoevers, et al 2021).

Data

The given data was from a 2011 NIH clinical. Four data frames were provided:

- EMA diary data ("EMA")
- Mother demographics and birthed infant characteristics ("StatsProjectData")
- Mother biological characteristics
- Gestational age data ("GA")

Exploratory data analysis

To study maternal stress volatility on physiological fetal measurements, three of the four data sets were used: EMA, StatsProjectData, and GA.

EMA

The "EMA" (Ecological Momentary Assessment) data set was the largest of the three with 57859 observations of 114 variables. The data was a mix of numeric and categorical formats. Some columns were replicates of other variables as a different type. For ease of analysis, any of these repeat categorical variables were dropped. This data set was used to record subjects' answers each time they were alerted to fill out their questionnaire. These entries looked at how individuals were feeling, what they were eating or drinking, if they had pregnancy symptoms, and how they were sleeping. The majority of this data set was pared down to focus exclusively on variables that dealt with stress. These included "StressedNumeric," "PerceivedStressScore," "PositiveMoodScore," and "NegativeMoodScore." "StressedNumeric" was a self-reported number on a scale of 0 to 4 as an indicator of low to high stress. "PerceivedStressScore" used an amalgamation of different self-reported questionnaire answers to create a singular score representing what someone's stress-level should be. The positive and negative mood score variables look at specific groupings of self-reported emotions to create their respective values.

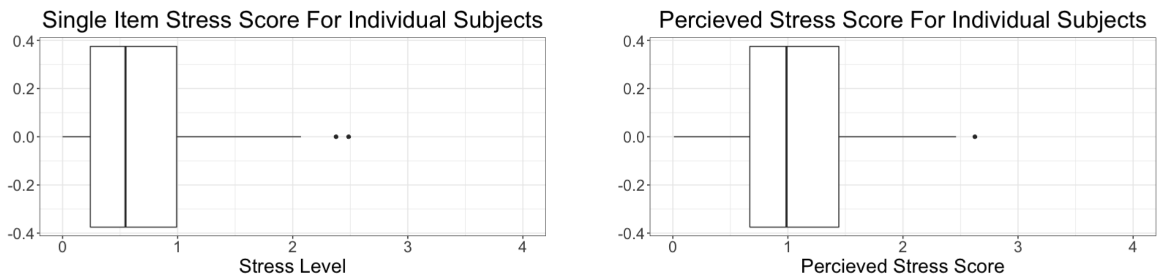


Figure 1: Individual Averaged Single Item Stress Score ("StressedNumeric") vs Perceived Stress Score

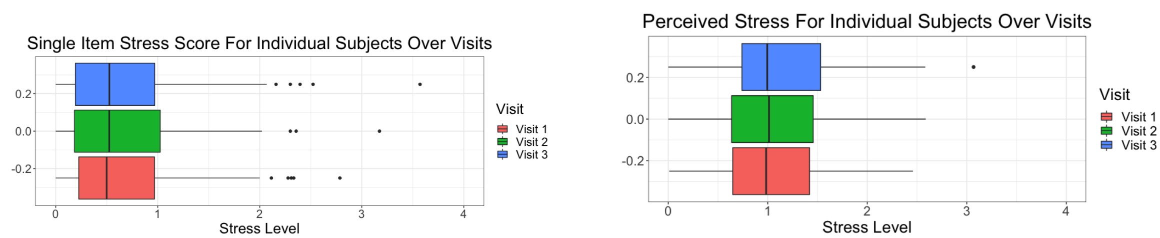


Figure 2: Individual Averaged Single Item Stress Score ("StressedNumeric") vs Perceived Stress Score Over Visits

"StressedNumeric" and "PerceivedStressScore" were compared against each other and it was found that often "PerceivedStressScore" would be at a higher value than "Stressed-Numeric" both on their own and when comparing through visits. Additionally, looking at visits also revealed that, while people's single item stress remained fairly consistent, the perceived stress value increased as the pregnancy moved along.

	RMSSD Difference
Visit 1 and 2, Stress Numeric	7.5635916
Visit 1 and 3, Stress Numeric	0.4365593
Visit 2 and 3, Stress Numeric	-9.8197050
Visit 1 and 2, PSS	7.0509829
Visit 1 and 3, PSS	15.2092810
Visit 2 and 3, PSS	6.3114177
Visit 1 and 2, Postive Mood Score	6.6749889
Visit 1 and 3, Postive Mood Score	10.2651725
Visit 2 and 3, Postive Mood Score	2.3465619
Visit 1 and 2, Negative Mood Score	3.5999631
Visit 1 and 3, Negative Mood Score	3.5999631
Visit 2 and 3, Negative Mood Score	-3.0166448

Figure 3: The average difference in RMSSD was taken for each pairwise visit between stress score groups.

The overall trend in positive values in figure 3 indicates a higher prior RMSSD volatility in visits, or that stress volatility decreases throughout the pregnancy in most stress scores.

There is an exception with visit 2 and 3 for both the single item stress score numeric and negative mood score, whose negative values indicate an increase in stress volatility. Stress score based RMSSD differences between visits is a good exploratory indicator of how we may expect affect size to differ between visits. I would expect, preliminarily, that there would be more significant effects in earlier visits as opposed to later visits, with greatest magnitude in effect belonging to all the first visit RMSSD stress measures.

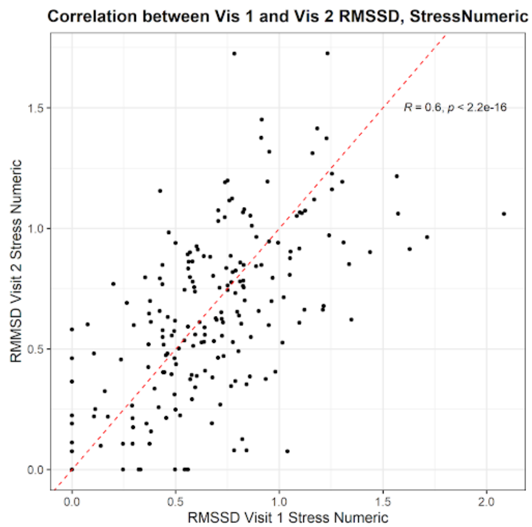


Figure 4: Scatter Plot of RMSSD's for visit 1 and visit 2 single item stress scores, each point is a single participant. Spearman's correlation coefficient shown.

The majority of the points are below the y = x line on red dashes which is consistent with the findings in the first row of figure 3. The range of pairwise spearman correlation coefficients between stress score visits in relation to figure 3 is between 53% and 68%, which is fairly strong given the bounds of the RMSSD measurement as always positive.

StatsProjectData

This data set included 250 observations of 37 numeric variables. These variables contained demographic information on the pregnant individuals and biological assessments of the newborns. The majority of variables in this data set were used as predictors of interest or response variables throughout the modeling process. The response variables focused on certain physiological measurements of the newborns such as their body fat composition, birth weight, telomere length, gray/white matter volume, or hippocampal volume. In order to make assertions on the impact of stress on these variables, certain potential predictor variables were used such as socioeconomic status, race/ethnicity, parity, obstetric risk, pre-pregnancy BMI, sex of the baby, etc..

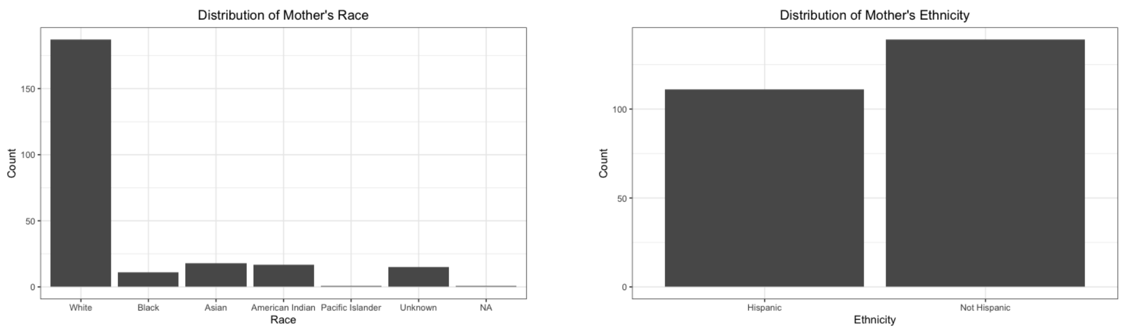


Figure 5: Bar plots depicting maternal race and ethnicity

One potential predictor of interest that got eliminated was "race_mom" since there is not an even distribution of individuals. Instead, the "ethnicity_mom" (Hispanic/not Hispanic) variable was used as a substitute. Additionally, "t0_parity" was changed from a continuous numeric variable to binary that determined if a subject had given birth previously or not.

	Low (N=119)	Medium (N=71)	High (N=59)
SES			
High	17 (14.3%)	14 (19.7%)	7 (11.9%)
Low	35 (29.4%)	25 (35.2%)	18 (30.5%)
Medium	67 (56.3%)	32 (45.1%)	34 (57.6%)
Maternal Ethnicity			
Hispanic	53 (44.5%)	31 (43.7%)	27 (45.8%)
Not_Hispanic	66 (55.5%)	40 (56.3%)	32 (54.2%)
Pre-pregnancy Maternal BMI			
Mean (SD)	27.1 (6.92)	26.1 (5.78)	25.6 (5.78)
Median [Min, Max]	25.3 [17.6, 48.5]	24.9 [18.0, 46.0]	24.1 [17.4, 44.2]
Missing	3 (2.5%)	2 (2.8%)	1 (1.7%)

Figure 6: Table comparing predictors of interest against low, medium, and high stress levels

The table above provided a preliminary look into the interactions between three of the predictor variables. Their impact on the averaged stress level of participants throughout the study is shown.

GA

The "GA" (Gestational Age) data set is focused on tracking the gestational age of the child throughout doctor visits. This data consisted of 4393 observations of 4 numeric variables. Besides gestational age ("GA"), trimester ("Trimester"), and day ("Day") were also recorded. For the purposes of this study, the trimester variable needs to be regarded as a visit counter since there is no guarantee that doctor visits occurred during the actual time ranges of the three trimesters. The day variable corresponds to the four sampling days within each visit period.

NA data

In addition to a preliminary analysis of the data, NA data was also looked into. Evaluating the missingness of the various stress scores across visits from the EMA data set revealed consistency of NA data across all stress scores and a jump in missing responses for the second visit.

	Visit 1 <int>	Visit 2 <int>	Visit 3 <int>
Stress Numeric	5460	14266	8501
Perceived Stress Score	5459	14262	8495
Positive Mood Score	5461	14266	8502
Negative Mood Score	5460	14266	8501

Figure 7: Table comparing NA data across stress scores and visits

Methods

In order to analyze the data properly, linear modeling was chosen. An initial model with over 20 predictors was cut down to one with only eight (maternal age, maternal ethnicity, parity, obstetric risk, pre-pregnancy BMI, natal sex, RMSSD, and mean stress).

$$\hat{Y} = \beta_0 + \beta_1\, RMSSD + \beta_2\, Mean\ Score + \bar{z_\iota}\, \bar{\gamma}$$

Figure 8: Equation for the new linear model

This new model not only reduced predictors but also lessened co-dependence and overfitting while simultaneously improving interpretability. Additionally, the predictors chosen allowed for score means to be accounted for so they are not treated the same if they have identical RMSSDs. These linear models were used to measure three clinical outcomes: birth weight, body fat percentage, and telomere length of newborns. For this study, 72 models were created. 36 of these models used RMSSD as their measure of volatility while the other 36 used variance. Within the 36 RMSSD models, 12 models were created for each of the three clinical outcomes. These 12 models consisted of four models per each visit. These four models were based on the four stress scores used (single-unit stress score, perceived stress score, positive mood score, and negative mood score). This same structure was also applied to the 36 variance models. The assumptions used for the models followed those of a linear model. There was an assumption that data was linear. This was checked using fitted vs residuals plotting.

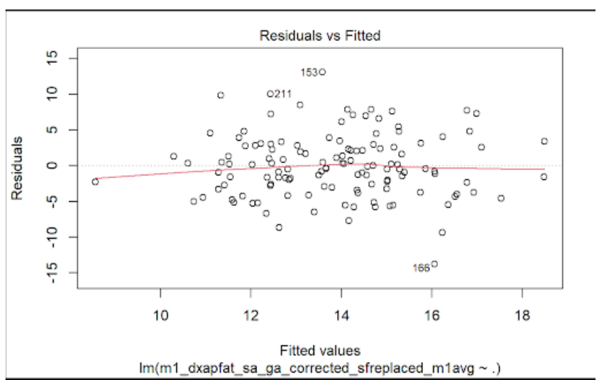


Figure 9: Graph of residual vs. fitted values

Additionally, the normality of residuals was confirmed using a normal Q-Q plot. Homoskedasticity in variance was assumed for all clinical outcomes except body fat percentage. Similarly, homogeneity of the residual variance was presumed for all clinical outcomes except body fat percentage which required usage of the robust variance estimator. Finally, independence of the residual error terms was assumed.

Results

To show the significance of the four stress score point estimates per visit, along with the effect size and direction, a forest plot was constructed and stratified by clinical outcome.

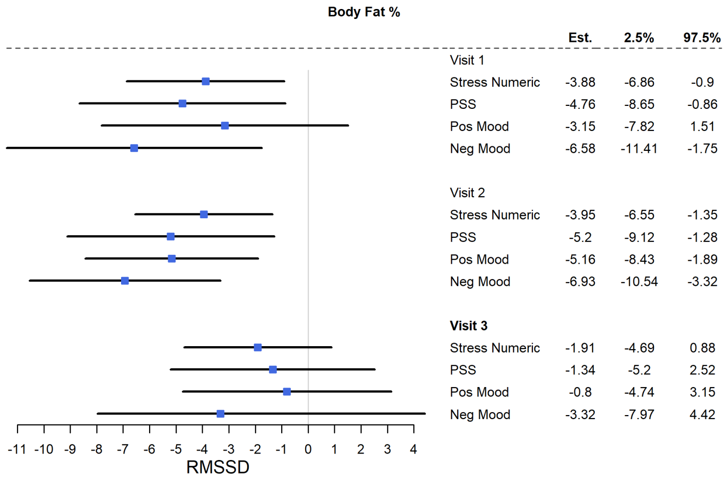


Figure 10: Body fat percentage had the greatest number of significant effects with respect to visit stress score RMSSD's, with 7 significant effects of the same direction but in varying degrees of magnitude.

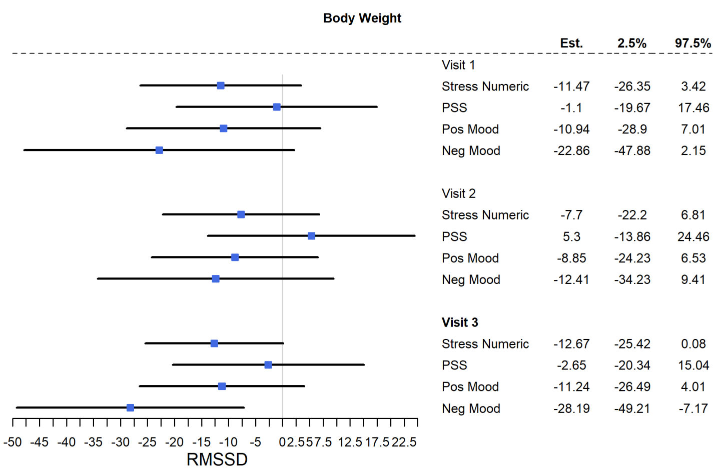


Figure 11: Negative mood score RMSSD in visit 3 was measured to have a significant effect on body weight. With 72 linear models, type I error inflation is a very real possibility to explain this seemingly random significant effect. A bonferroni correction or less conservative type I error reduction method may be considered.

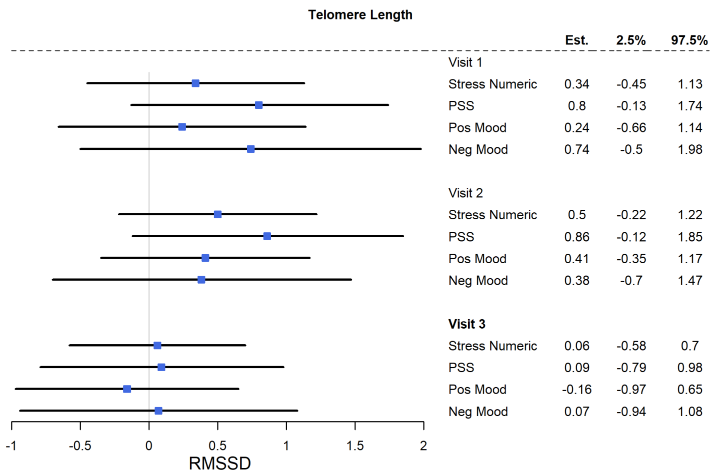
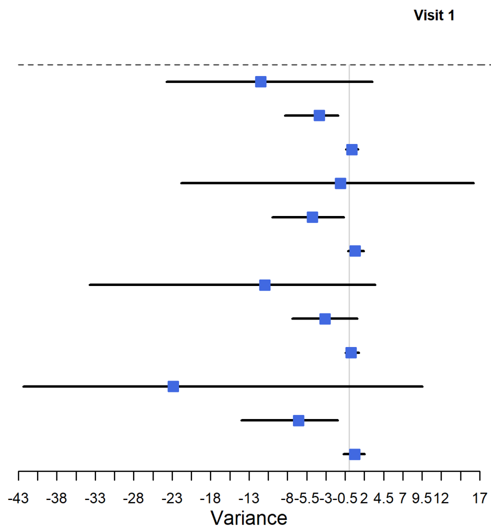


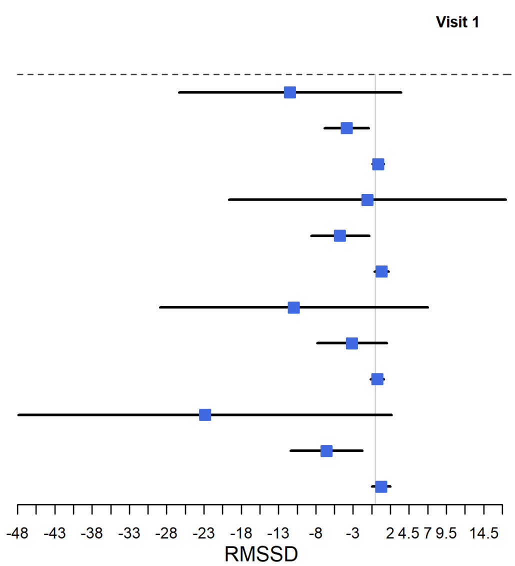
Figure 12: No stress score RMSSD at any visit was shown to have a significant effect on telomere length of the newborn.

From preliminary and pre robust variance estimate analysis, the linear regression using RMSSD and variance volatility measures had identical point estimates and very similar confidence bands. RMSSD was chosen as our main and final model volatility measure due to the auto-correlation we expect to experience in our data. The RMSSD volatility measure is a composite measure of variance and auto-correlation, in which we did not observe a significant difference in confidence intervals. RMSSD was still chosen to be the volatility measure of choice, as the degree of correlation between demographic and biological predictors was determined to be non-zero, and thus deemed important to account for in this lagged measures model.



Stress Type	Mean	CI Lower	CI Upper
Strs Num BW	-11.47	-23.75	3.06
Strs Num BF%	-3.88	-8.32	-1.41
Strs Num TL	0.34	-0.38	1.16
PSS BW	-1.1	-21.85	16.23
PSS BF %	-4.76	-9.99	-0.66
PSS TL	0.8	-0.13	1.91
Pos M BW	-10.94	-33.72	3.41
Pos M BF %	-3.15	-7.4	1.07
Pos M TL	0.24	-0.47	1.3
Neg M BW	-22.86	-42.38	9.56
Neg M BF %	-6.58	-13.99	-1.47
Neg M TL	0.74	-0.74	2.03

Figure 13: Variance volatility measure



Stress Type	Mean	CI Lower	CI Upper
Strs Num BW	-11.47	-26.35	3.42
Strs Num BF%	-3.88	-6.86	-0.9
Strs Num TL	0.34	-0.45	1.13
PSS BW	-1.1	-19.67	17.46
PSS BF %	-4.76	-8.65	-0.86
PSS TL	0.8	-0.13	1.74
Pos M BW	-10.94	-28.9	7.01
Pos M BF %	-3.15	-7.82	1.51
Pos M TL	0.24	-0.66	1.14
Neg M BW	-22.86	-47.88	2.15
Neg M BF %	-6.58	-11.41	-1.75
Neg M TL	0.74	-0.5	1.98

Figure 14: RMSSD volatility measure

The following forest plots (figures 15, 16, and 17) are stratified by visit, rather than clinical outcome to show overall effect changes throughout the pregnancy. Telomere point estimates and confidence bands appear to have smaller magnitude of effects due to overall scaling compared to body weight and body fat %. For scaled analysis of stress measure effects on telomere length, refer to figure 12.

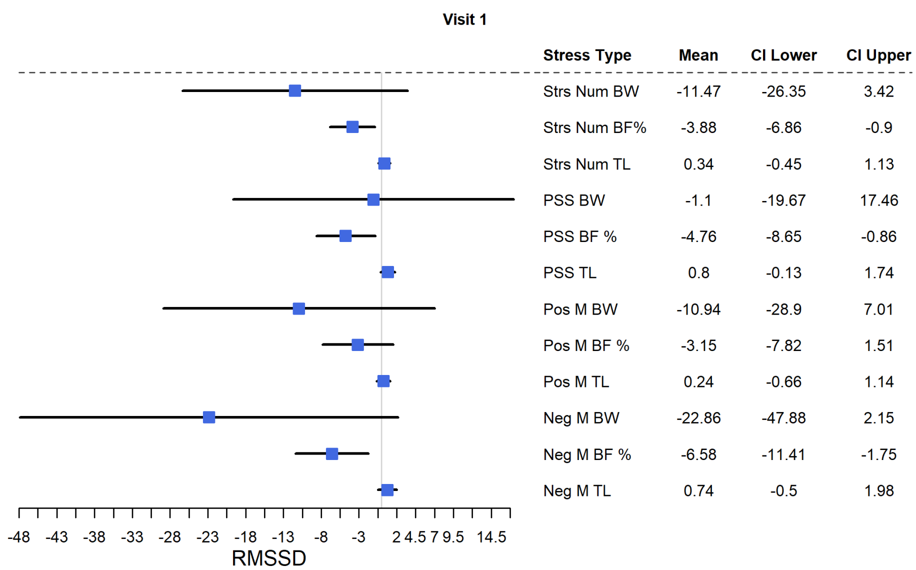


Figure 15: Visit 1

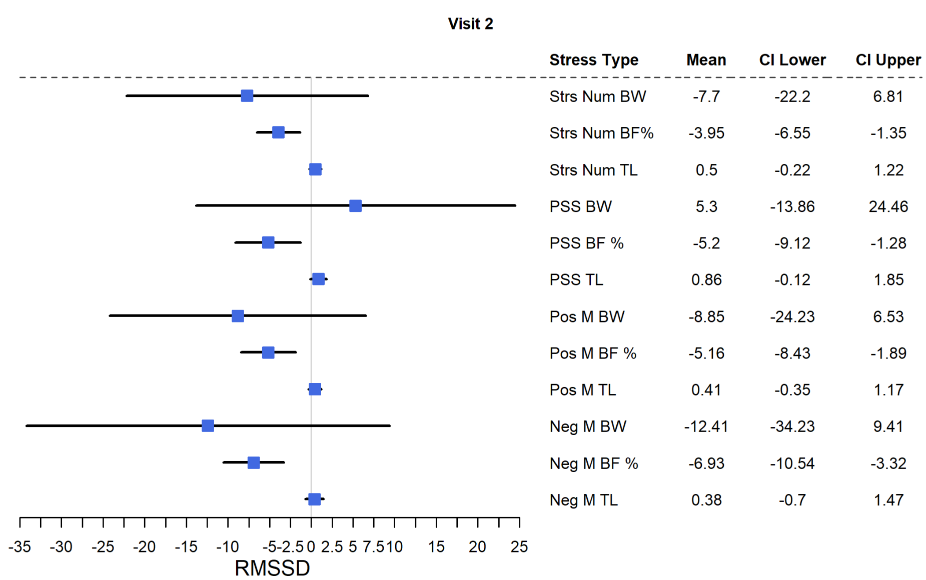
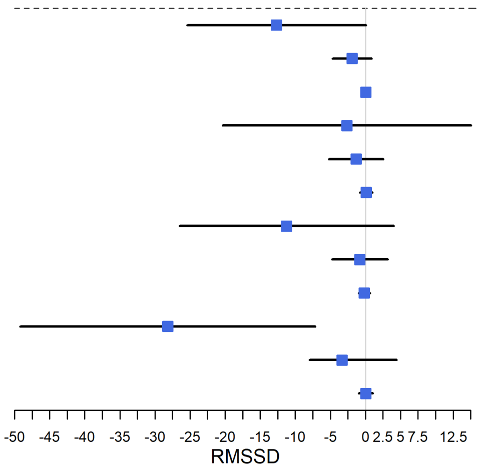


Figure 16: Visit 2

Visit 3



Stress Type	Mean	CI Lower	CI Upper
Strs Num BW	-12.67	-25.42	0.08
Strs Num BF%	-1.91	-4.69	0.88
Strs Num TL	0.06	-0.58	0.7
PSS BW	-2.65	-20.34	15.04
PSS BF %	-1.34	-5.2	2.52
PSS TL	0.09	-0.79	0.98
Pos M BW	-11.24	-26.49	4.01
Pos M BF %	-0.8	-4.74	3.15
Pos M TL	-0.16	-0.97	0.65
Neg M BW	-28.19	-49.21	-7.17
Neg M BF %	-3.32	-7.97	4.42
Neg M TL	0.07	-0.94	1.08

Figure 17: Visit 3

From figures 15, 16, and 17. The association between stress scores are similar across visits, with exceptional homogeneity between visit 1 and visit 2. This would indicate that we may be able to pool our data together with no regard to visit, as there does not appear to be a difference in random effects between visits. Positive mood score and negative mood score have the same effect which is counter intuitive to what was originally hypothesized (they move in the same direction as one another) this would indicate that spikes in mood, no matter the underlying positive or negativeness, is indicative of the same health outcomes.

Discussion and conclusion

Summary of findings

- Maternal stress appeared to have had a statistically significant negative effect on fetal body fat percentage primarily for early and middle pregnancy.
- The affect direction of positive mood score and negative mood score is unidirectional, indicating that spikes of psychological arousal in any sense have the same association with newborn health

outcomes.

- Stress affect direction and magnitude seemed to have little correlation to visit, implying the ability to pool the data rather than implementing visit and trimester stratification.
- The negative relation between stress and body weight also appeared to be statistically significant during the late stages of pregnancy. At no point in time during the pregnancy did telomere length appear to be significantly affected by stress levels or stress volatility.

Limitations and future remedies

- Insufficient time to explore additional response variables. Future work should focus on gray and white matter, hippocampal, intracranial, amygdala, and hypothalamic volumes.
- There was a considerable amount of missing data. The consistency of the missing data seems to imply that among the pool of participants there was a cohort of mothers that was more readily available to participate, and a group of mothers unable to fully participate. The reasons for either scenario, even though we could speculate, are ultimately unknown and may be considered MAR or MNAR. However, for future work, there needs to be a much more supportive infrastructure to ensure the participation of all mothers in order to accommodate for any underlying reason.
- The attrition rate is considered undesirable. If possible, for future related studies, a dropout rate of 10% or less would be optimal. It would, in fact, be more desirable to have a smaller yet more consistent pool of participants rather than a power maintaining inflated sample size with inconsistent participants.
- Body fat percentage may be more appropriate to be analyzed in a logistic regression model, being that the clinical outcome is a transformed function with a constricted range from 0 to 1.
- We would like to build a model to explore and quantify the change in body fat percentage and change in weight as a clinical outcome in relationship to stress volatility.
- There were 72 total linear models conducted for this report, 36 of them for RMSSD measures at various visits for our four stress scores. A high quantity of linear models being run on the same stochastically dependent data is concerning for the possible inflation of type I error. A Bonferroni correction or the usage of a false discovery rate (FDR) controlling procedure as a way to preserve the statistical power may be considered for future analysis. Possibly, making visit and stress score a factor covariate at the expense of increasing dimensionality, would allow us to reduce the number of total linear models needed to be run. Our linear model as it currently sits, is in less than 10 dimensions, so the AIC or other methods to assess our model fit to our data is not inherently needed, but could be if this increase of dimensionality is considered.

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