Moderate prenatal stress may buffer the impact of Superstorm Sandy on placental genes: Stress in Pregnancy (SIP) Study

Wei Zhang1,2*, Jacob Ham3*, Qian Li4, Maya A. Deyssenroth4, Luca Lambertini5,6, Yonglin Huang1,7, Kenji J. Tsuchiya8, Jia Chen4, Yoko Nomura1,3,4,7,8*

1 Department of Psychology, Queens College, CUNY, New York, NY, United States of America, 2 Department of Psychology, New Jersey City University, Jersey City, NJ, United States of America, 3 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, United States of America, 4 Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, United States of America, 5 Department of Medicine, Endocrinology, Diabetes and Bone Disease, Icahn School of Medicine at Mount Sinai, New York, NY, United States of America, 6 Department of Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY, United States of America, 7 Department of Psychology, The Graduate Center, CUNY, New York, NY, United States of America, 8 Research Center for Child Mental Development, Hamamatsu University School of Medicine, Shizuoka, Japan

* These authors contributed equally to this work.
* yoko.nomura@qc.cuny.edu

Abstract

The placenta plays a central role in the epigenetic programming of neurodevelopment by prenatal stress (PS), but this pathway is not fully understood. It difficult to study in humans because the conditions for intense, traumatic PS are almost impossible to create ethically. This study was able to capitalize on a 2012 disaster that hit New York, Superstorm Sandy, to examine the impact of traumatic stress on placental gene expression while also examining normative PS, and compare the two. Of the 303 expectant mothers participating in the Stress in Pregnancy Study, 95 women were pregnant when Superstorm Sandy struck. During their pregnancy, participants completed self-report measures of PS and distress that were combined, using latent profile analysis, into one global indicator of normative PS. Placental tissue was collected at delivery and frozen for storage. RNA expression was assessed for 40 placental genes known to associate with the stress response system and neurodevelopment in offspring. Results showed that normative PS increased expression of MECP2, HSD11B2, and ZNF507, whereas Superstorm Sandy PS decreased expression of CDKL5, CFL1, Dyrk1a, HSD11B2, MAOA, MAOB, NCOR1, and ZNF507. Interaction analyses indicated that Superstorm Sandy PS was associated with decreased gene expression for the low and high PS group for CFL1, Dyrk1a, HSD11B2, MAOA, and NCOR1 and increased expression for the moderate PS group for Foxp1, Nrr3C1, and Nrr3C2. This study supports the idea that a moderate amount of normative PS may buffer the impact of traumatic PS, in this case caused by Superstorm Sandy, on placental gene expression, which suggests that the placenta itself mirrors the organism's ability to develop an epigenetic resilience to, and inoculation from, stress.
Introduction

Prenatal stress (PS) has been shown to impact offspring development over the lifespan [1–5]. Psychiatically, PS increases the risk of behavioral and attentional disorders, autism and schizophrenia in male offspring and later-onset anxiety and affective disorders in females [3,6]. The biological impact of PS can include dysregulation of the hypothalamic pituitary adrenal (HPA) axis, broad alterations in brain growth, size or density, specific alterations to functional brain regions or neural components such as white matter abnormalities and hypomyelination in the hippocampus, prefrontal cortex, amygdala, and hypothalamus [7–13].

One of the biological pathways underlying this fetal programming is through the placenta, a maternal and fetal endocrine organ and the sole transporter and filter for nutrients, waste and teratogens. PS can have a direct impact on the placenta itself by altering its development especially early in pregnancy, changing structures that can lead to vasoconstriction of placental arteries or altering gene expression encoding for important functional proteins [4]. The epigenetic regulation of placental gene expression has been extensively explored in recent research, examining mechanisms such as DNA methylation, microRNA molecules, and histone modification [14–17].

One set of genes of great interest in the placental transmission of PS have been those involved in placental regulation of cortisol, the central stress hormone, and certain stress-related neurotransmitters [18]. The genes with the most substantive human research support are NR3C1, HSD11B2, MAOA, and SLC6A4. HSD11B2 converts cortisol into its inactive form, cortisone. Cortisone is extremely important because fetal over-exposure to cortisol can lead to growth restriction, premature maturation of proliferative neural precursors, pre-term birth and altered HPA-axis development [18,19]. NR3C1 encodes the glucocorticoid receptor that binds to cortisol [20]. In the placenta, it is postulated to be an upstream regulator of placental HSD11B2 [21]. Methylation of NR3C1 has been associated with a reactive, poorly regulated neurobehavioral profile in newborns [22] and behavior disorders in childhood [23]. MAOA metabolizes stress-related neurotransmitters such as serotonin and norepinephrine [24], and SLC6A4 encodes the serotonin transporter [25]: over-exposure to stress-related neurotransmitters can have a significant impact on fetal development, synaptogenesis and neuronal cell division [26,27] and increase the risk for autism [28] and Attention Deficit /Hyperactivity Disorder (ADHD) [29].

PS can have an impact on the expression of placental genes, though the direction of impact varies for different genes and may depend on whether PS is measured as depression, anxiety or stress [2]. For the neurotransmitter genes, MAOA expression was found to decrease with greater maternal depression, whereas, SLC6A4 expression increased with depression and anxiety [30,31]. Research on HPA-axis genes has produced even more complex findings. NR3C1 increased with depression [32] but decreased with war trauma and normative stress [33]. HSD11B2 has generally been found to decrease with normative stress, perceived stress and anxiety [34–36], though there are also a few studies reporting an increase in HSD11B2, but in response to traumatic stress [37,38].

Given the ethical limitations to stress research in humans, researchers have to capitalize where possible on natural disasters as proxies for the experimental introduction of traumatic PS. The largest natural disaster studied is the Quebec Ice Storm in 1998 [39,40]. There, researchers differentiated the objective impact of the storm in terms of loss, injury and physical impact from subjective perceptions of distress. Their results suggest that while objective and subjective PS are correlated, objective PS is associated with subsequent cognitive, linguistic and physical developmental outcomes [41–44], while subjective PS is associated with childhood anxiety, depression and aggression [40]. A study of the 2005 hurricane in New Orleans, Katrina, found that neither objective nor subjective PS predicted difficult infant temperament,
but prenatal maternal mental health did [45]. A study of the 2008 flood in Iowa found that objective and subjective PS were related to cortisol reactivity in female toddlers alone [46]. Of note, none of these disaster studies investigated placental genomics, which we are suggesting may help us to understand the underlying mechanisms.

To advance our understanding of how PS impacts the placenta, we measured normative PS as maternal depression, anxiety, and lifetime histories of negative life events and traumatic Superstorm Sandy PS as prenatal exposure to Superstorm Sandy of 2012—the most destructive hurricane to ever strike New York City and at 50 billion dollars in damages, the second costliest natural disaster in the United States up to that point [47]. The impact in New York included 53 deaths, 305,000 homes destroyed, 250,000 vehicles damaged, massive power outages, flooding, and major disruption to the transit system [48]. We hypothesized that both normative and traumatic PS would impact placental gene expression, though the direction of impact would depend on type of PS and type of gene. We also explored whether normative PS might alter the impact of traumatic Superstorm Sandy PS on placental gene expression.

**Materials and methods**

**Participants**

Participants came from the Stress in Pregnancy (SIP) Study [49]https://paperpile.com/c/rh5zV9/EFym, an ongoing longitudinal study begun in 2009, that examines the impact of PS on child neurodevelopment. Expectant mothers in the second trimester were recruited from obstetrics clinics at Mount Sinai Hospital and New York-Presbyterian/Queens in New York City. Women were excluded based on HIV infection, maternal psychosis, maternal age < 15 years, life-threatening maternal medical complications, and congenital or chromosomal abnormalities in the fetus. Written informed consent was obtained in all cases. The Institutional Review Boards at the City University of New York, Icahn School of Medicine at Mount Sinai, and New York Presbyterian/Queens approved the study.

Superstorm Sandy hit New York City in October 2012, affecting 408 SIP Study families, of which 303 had complete data for this study. These 303 did not differ demographically from the full cohort. Among the 303, 95 dyads experienced the storm during pregnancy.

The mean (±standard deviation) age of mothers was 27 (±6.0) years. The mothers were Hispanic/Latino (53%), Black (24%), White (9%), Asian (8%) and other (6%). Though 58% of mothers attended college, only 18% had completed a bachelor or graduate degree. A small majority of mothers were single (57%), while 40% were married or in a common law marriage. Among offspring, 52% were male.

**Exposure to superstorm sandy**

The specific gestational timing during which Superstorm Sandy occurred was calculated based on the date of birth of the child and the day the storm hit the metropolitan New York area (October 29, 2012), and serves as our primary measure of exposure to Superstorm Sandy. Following the classification, a dichotomous variable was created to categorize mothers as either pregnant during Superstorm Sandy (Exposed, n = 95) or pregnant before or after the storm (Non-Exposed, n = 208). Of the 95 exposed, 66 participants experienced the storm during the first trimester and 29 during the 2nd or 3rd trimesters.

**Normative prenatal stress**

Mothers completed the following five self-report scales of normative PS during the second trimester. The 10-item Edinburgh Postnatal Depression Scale (EPDS) rates the severity of
depressive symptoms from 0 to 3. Items were summed, with scores above 13 suggesting clinical levels of depression [50]. The inventory is well-validated in different languages and has acceptable reliability, sensitivity and specificity [51]. The 10-item Pregnancy Related Anxieties Questionnaire-Revised (PRAQ-R) measures pregnancy related fears and worries, rated from 1 (definitely not true) to 5 (definitely true) [52], with three subscales: fear of giving birth, fear of bearing a handicapped child, and concerns about changes in appearance. Subscale scores are an average of item scores, and the total score, ranging from 3 to 15, is the sum of subscale scores. PRAQ-R has good reliability and validity in predicting adverse child behaviors and developmental delays [53]. The 40-item State-Trait Anxiety Inventory (STAI) assesses temporary “state anxiety” and long-standing, characterological “trait anxiety” [54]. Each subscale consists of 20 items rated from 1 to 4, summed to produce subscale scores ranging from 20 to 80. In one normative sample, working females aged 19–39 reported average subscale scores of 36.17 (SD = 10.96) [55]. A meta-analysis found the STAI to have very good internal consistency [56]. The 14-item Perceived Stress Scale (PSS-14) assesses how often raters appraise situations in the past month as stressful from 0 to 4 [57]. The total score was computed by reverse scoring positively stated items and then summing the scores. Total scores ranged from 0 to 56. PSS-14 has adequate internal consistency and test-retest reliability [57,58]. The 23-item Psychiatric Epidemiology Research Interview Life Events Scale (PERI LES) [59] has widely been used to study the effects of adverse life events during pregnancy [60–62]. PERI LES assesses five major areas of life: relationships, health, legal matters, work and finances, and friendships. Participants further categorize the stressors as either a “good” or “bad” experience, the total number of which represents the positive and negative scales. The LES has been validated against narrative reports of life events [63].

The six PS measures were amalgamated into one normative PS scale, because (1) they were all significantly correlated (r’s = .18 to .83; p < .01; S1 Table), (2) they were always correlated in the same direction with individual gene expression levels (S1 Table), and (3) other researchers have amalgamated maternal distress variables in prior research [64–66]. The amalgamated PS scale was created using latent profile analysis (LPA) with MPlus. Missing data were negligible (EPDS, 2.3%; PRAQ-R, 3%; PSS-14, 0.7%; STAI, 2.3%; and negative PERI LES, 1%), and were imputed using full maximum likelihood estimation. LPA produced models with two to four levels. The three-level model, representing Low, Moderate, and High PS, best fit the data based on Bayesian Information Criteria [67], adjusted BIC [68], Lo-Mendell-Rubin test [69] and entropy values (S2 Table). Sample sizes for each PS group were 116 for Low, 132 for Moderate and 55 for High PS.

Placenta collection and gene expression profiling

At delivery, research staff gathered medical birth records and collected placentas. Placenta biopsies, free of maternal decidua, were collected from each quadrant midway between the cord insertion and the placenta rim within one hour of delivery to prevent RNA degradation. The placentas were snap-frozen in liquid nitrogen and stored at -80°C. RNA was extracted with the Maxwell 16 automated DNA/RNA extraction equipment (Promega: Madison, WI) using the proprietary extraction kits following the manufacturer’s protocol. RNA was quantified with Nanodrop spectrophotometer (Thermo Electron North America: Madison, WI).

Forty candidate genes were identified a priori for their involvement in HPA-axis functioning and neurodevelopment, based on an extensive literature search and using the Ingenuity Knowledge Base (http://www.ingenuity.com). Placental RNA was profiled using nCounter by nanoString Technologies (Seattle, WA) as described elsewhere [70,71]. Nanostring data were normalized using the NanoString Norm package [72]. First, raw code counts were normalized
against the geometric mean of spike-in controls to account for differences in hybridization and recovery. Differences in sample content were accounted for by normalizing the data against the geometric mean of housekeeping genes (GAPDH, RPL19, and RPLP0). The background threshold was set to the limit of detection divided by the square root of two to maintain sample variability. Thirteen genes were considered unexpressed and omitted from analysis because more than 50% of the sample fell below the limit of detection. Of the remaining 27 genes, 14 genes were related to HPA-axis function, and 13 genes were related to neurodevelopment (S3 Table).

**Statistical analyses and covariates**

Differences across demographic variables among the PS groups were examined using ANOVA for continuous variables and Chi-square/Fisher’s exact tests for categorical variables. The impact of normative and traumatic PS, and their interaction, on placental gene expression was assessed using a general linear model (GLM), controlling for infant gender, maternal race and education, and delivery mode, selected based on prior research [24,73,74] (significance set at \( p < 0.05 \)). In order to control for Type I errors due to multiple testing, we made an adjustment using the Benjamini–Hochberg procedure [75,76].

**Results**

**Descriptive analyses**

Differences between PS groups were examined using descriptive analyses on demographic and stress variables. As shown in Table 1, the PS groups did not differ on maternal demographic characteristics, but there were relatively more female infants in the Moderate PS group \( (p = 0.008) \). Table 2 shows the differences between Superstorm Sandy and the control groups in birthweight, race, marital status, and education levels. Means and SDs for all stress measures by PS groups are listed in Table 3. Based on commonly used clinical norms available for the EPDS and STAI, the High PS group was above the clinical cutoff for depression on the EPDS and in the Moderate Anxiety range for State Anxiety, which provides an informal validation of the classification.

**Associations between Superstorm Sandy exposure and placental gene expression**

Table 4 shows genes that were significantly or marginally significantly associated with the main effects of normative, Superstorm Sandy PS, or their interactions. Prenatal storm exposure significantly or marginally significantly predicted decreased expression of CDKL5 \( (p = 0.053) \), CFL1 \( (p = 0.046) \), DYRK1A \( (p = 0.002) \), HSD11B2 \( (p < 0.001) \), MAOA \( (p = 0.002) \), MAOB \( (p < 0.001) \), MECP2 \( (p = 0.056) \), NCOR1 \( (p = 0.052) \), and ZNF507 \( (p < 0.001) \). The one exception, DBH was related to a marginally significant increase in expression with storm exposure \( (p = 0.076) \). Graphs of the mean expression levels of each gene are presented in Fig 1A–1J. The results were calculated using the GLM models. Not all genes expressed in the sample. In the sections regarding PS and placental gene expression, we did not describe all non-significant associations. Reported p-values are FDR-adjusted.

**Association between PS and placental gene expression**

The overall group difference in normative PS levels was shown to be marginally significantly and positively related to MECP2 \( (p = 0.090) \) using GLM. Pairwise comparisons of means showed mean gene expression levels for Moderate PS were marginally greater than for Low PS
(p = .073). A similar, though only marginally significant, pattern in overall group differences was found for HSD11B2 (p = .099) and ZNF507 (p = .092). Pairwise comparisons showed that the mean expression level of HSD11B2 and ZNF507 was marginally greater for high PS versus low PS (p = .099, .099 respectively). Graphs of the means of gene expression are presented in Fig 2A–2C.

One gene, CRHBP, was significantly related to PS (p = .007) in a curvilinear, inverted-U shape, when analyzing overall group differences. The marginal mean of CRHBP expression was significantly smaller for high PS compared to moderate PS (p = .011). FOXP1 and NR3C1 also showed similar, though only marginally significant, curvilinear patterns (p = .077 and .077 respectively). Fig 3A–3C shows the means for these curvilinear patterns.

Differential impact of superstorm sandy PS by normative PS

To assess whether normative PS might moderate the impact of prenatal storm exposure, an interaction term for the two was included in the original GLM with normative PS, traumatic PS and the noted covariates. The most prevalent pattern of findings was where Superstorm Sandy PS was associated with decreased gene expression for the low and high PS groups but not Moderate PS. This pattern was significant or marginally significant for CFL1 (p = .053),...
Table 2. Demographic characteristics of participants by sandy prenatal stress groups.

|                       | No Sandy | Sandy | p value |
|-----------------------|----------|-------|---------|
|                       | (n = 208) | (n = 95) |         |
| Infant sex            |          |       | 0.542   |
| Males                 | 106 (51%) | 52 (55%) |         |
| Females               | 102 (49%) | 43 (45%) |         |
| Gestational age (wks) | 39.05 (2.23) | 39.22 (1.69) | 0.5     |
| Birthweight (g)       | 3202.44 (620.78) | 3408.69 (507.09) | 0.003   |
| Maternal race         |          |       | 0.015   |
| White                 | 15 (7%)  | 12 (13%) |         |
| Black                 | 58 (28%) | 16 (17%) |         |
| Hispanic/Latino       | 111 (53%) | 48 (51%) |         |
| Asian                 | 10 (5%)  | 13 (14%) |         |
| Others                | 13 (6%)  | 5 (5%)  |         |
| Missing               | 1 (~0%)  | 1 (1%)  |         |
| Maternal education    |          |       | <.001   |
| Primary school        | 5 (2%)   | 1 (1%)  |         |
| Some high school      | 47 (23%) | 6 (6%)  |         |
| High school graduate  | 48 (23%) | 20 (21%) |         |
| Some college          | 66 (32%) | 25 (26%) |         |
| Associate degree      | 16 (8%)  | 14 (15%) |         |
| Bachelor’s degree     | 14 (7%)  | 16 (17%) |         |
| Graduate degree       | 12 (6%)  | 13 (14%) |         |
| Marital status        |          |       | <.001   |
| Married               | 50 (24%) | 51 (54%) |         |
| Common law            | 14 (7%)  | 7 (7%)  |         |
| Single                | 140 (67%) | 34 (36%) |         |
| Widowed               | 2 (1%)   | 0 (0%)  |         |
| Divorced/separated    | 1 (~0%)  | 2 (2%)  |         |
| Missing               | 1 (~0%)  | 1 (1%)  |         |
| Normative Stress      | 1.8 (0.74) | 1.79 (0.70) | 0.882   |

Discussion

In this study, we examined whether traumatic and/or normative PS impacted the expression of placental genes related to HPA-axis function and neurodevelopment. Further, we examined whether the impact of Superstorm Sandy PS depended on the level of normative PS. Normative PS was defined as depression, anxiety, pregnancy-related stress, and negative life events. Superstorm Sandy PS was defined as prenatal exposure to Superstorm Sandy.

Our findings presented a complex narrative for how normative and Superstorm Sandy PS might impact expression patterns of some, but not all, placental genes. Our result runs counter to other studies that found an increase in expression in response to PS [36]. First, in terms of main effects, Superstorm Sandy PS generally downregulated placental gene expression.
CDKL5, CFL1, DYRK1A, HSD11B2, MAOA, MAOB, NCOR1, and ZNF507). Their downregulation suggests one pathway through which expression of other genes might be altered by stress from extreme events such as disasters.

The most interesting of these impacted genes is HSD11B2, which is centrally involved in prenatal stress because it buffers fetal exposure to cortisol. MAOA metabolizes stress-related neurotransmitters such as serotonin and norepinephrine [24]. MAOB regulates the stress-related neurotransmitter, dopamine, but is minimally present in the placenta [77]. CFL1 and DYRK1A are involved in cell division and proliferation. DYRK1A has been linked to the memory and learning deficits associated with Down syndrome [78,79]. The remaining four genes (CDKL5, MECP2, NCOR1, and ZNF507) are transcription regulators. CDKL5 and MECP2 have been associated with Rett’s Disorder [80–82]. ZNF507 has been implicated in schizophrenia [83].

In contrast to the large impact of Superstorm Sandy PS, normative PS alone only marginally impacted expression of MECP2, ZNF507 and HSD11B2, all in the direction of increased expression, which is opposite to the impact of Superstorm Sandy PS. Notably, the upregulation

### Table 3. Mean scores on individual normative prenatal stress (PS) measures among total sample and PS levels identified through latent profile analysis.

|                          | Total (N = 303) | Low PS (n = 116) | Moderate PS (n = 132) | High PS (n = 55) |
|--------------------------|----------------|-----------------|----------------------|-----------------|
| **Prenatal depression (EPDS)** | M (SD)         | M (SD)          | M (SD)               | M (SD)          |
|                          | 7.36 (5.40)    | 3.02 (3.13)     | 7.87 (3.43)          | 15.09 (3.22)    |
| **Pregnancy-related anxiety (PRAQ-R)** | 5.86 (2.29)    | 4.69 (1.65)     | 6.03 (1.95)          | 7.94 (2.65)     |
| **Perceived prenatal stress (PSS-14)** | 36.39 (7.38)   | 31.07 (6.35)    | 37.85 (5.32)         | 44.02 (4.93)    |
| **State anxiety (STAI-S)** | 37.94 (11.59)  | 27.13 (4.97)    | 40.94 (6.72)         | 53.65 (7.88)    |
| **Trait anxiety (STAI-T)** | 38.39 (10.76)  | 27.97 (4.74)    | 41.03 (4.98)         | 54.13 (5.83)    |
| **Number of negative stressful life event (LES)** | 1.57 (2.02)    | 0.91 (1.50)     | 1.39 (1.54)          | 3.38 (2.81)     |

https://doi.org/10.1371/journal.pone.0226605.t003

### Table 4. Significant p-values (FDR-adjusted p-values) in the Prediction of Gene Expression using Normative Prenatal Stress (PS), Superstorm Sandy PS and their Interaction: GLM Model.

| Gene   | Normative PS Main Effect | Normative PS Quadratic | Superstorm Sandy PS Main Effect | Normative x Superstorm Sandy |
|--------|--------------------------|------------------------|--------------------------------|-----------------------------|
| CDKL5  | 0.042 (0.053)            |                        | 0.095 (0.10)                   |                             |
| CFL1   | 0.028 (0.046)            | 0.026 (0.053)          |                                |                             |
| CRHBP  | 0.014 (0.04)             | 0.007 (0.007)          |                                |                             |
| DBH    | 0.001 (0.002)            |                        | 0.012 (.042)                   |                             |
| DYRK1A | 0.071 (0.077)            | 0.011 (.042)           |                                |                             |
| FOXP1  |                          |                        |                                |                             |
| HSD11B2| 0.099 (0.099)            | 0.001 (<0.001)         | 0.049 (0.057)                   |                             |
| MAOA   | 0.001 (0.002)            |                        | 0.085 (0.095)                   |                             |
| MAOB   | 0.001 (<0.001)           |                        |                                |                             |
| MECP2  | 0.046 (0.090)            | 0.051 (0.056)          | 0.09 (0.095)                   |                             |
| NCOR1  | 0.039 (0.052)            | 0.083 (0.095)          |                                |                             |
| NR3C1  | 0.077 (0.077)            |                        | 0.036 (0.076)                   |                             |
| NR3C2  |                          |                        | 0.038 (0.076)                   |                             |
| ZNF507 | 0.068 (0.092)            |                        |                                | 0.001 (<.001)                |

Note: P-values are calculated based on GLM controlling for infant gender, maternal race and education, and delivery mode. Values in the parentheses are the FDR-adjusted p-values

https://doi.org/10.1371/journal.pone.0226605.t004
of HSD11B2 is opposite to the results of prior studies that showed PS downregulating HSD11B2 expression [34,36,84]. It may be that our definition of Superstorm Sandy PS was too general, in contrast to, for example, a very discrete event like an amniocentesis [85]. A natural disaster, especially including an extended aftermath, might be better be defined as an intense normative stressor. However, this explanation does not account for why the natural disaster would impact gene expression in the opposite direction to normative PS as we defined it in this study. Perhaps, the best conclusion is to be left wondering at the complex and dynamic ways in which stress in all its forms appears to impact the placenta rather than drawing simple, unidirectional and reductionistic conclusions.

Fig 1. Marginal Mean (SE) Gene Expression Level (represented on the Y axis) by Traumatic Prenatal Stress (yes = Storm Exposure, no = No Storm Exposure). (A) CDKL5 gene expression by traumatic prenatal stress. (B) CFL1 gene expression by traumatic prenatal stress. (C) DBH gene expression by traumatic prenatal stress. (D) DYRK1A gene expression by traumatic prenatal stress. (E) HSD11B2 gene expression by traumatic prenatal stress. (F) MAOA gene expression by traumatic prenatal stress. (G) MAOB gene expression by traumatic prenatal stress. (H) MECP2 gene expression by traumatic prenatal stress. (I) NCOR1 gene expression by traumatic prenatal stress. (J) ZNF507 gene expression by traumatic prenatal stress.

https://doi.org/10.1371/journal.pone.0226605.g001
Results from our interaction analysis suggest a framework of dynamic complexity. For five of the eight genes downregulated by Superstorm Sandy PS alone (\textit{CFL1}, \textit{DYRK1A}, \textit{HSD11B2}, \textit{MAOA}, and \textit{NCOR1}), moderate normative PS appeared to nullify the effect of Superstorm Sandy PS such that only the Low or High normative PS groups showed significant reductions in gene expression associated with traumatic PS. \textit{CDKL5} and \textit{MECP2} showed a similar result though only the High or the Low normative PS group, respectively, showed significantly different estimated marginal means in gene expression. \textit{FOXP1}, \textit{NR3C1} and \textit{NR3C2} showed a variant of the pattern in which the Moderate normative PS group showed a significant or marginally significant increase in gene expression. \textit{FOXP1} is a transcription repressor involved in brain function and neurodevelopment [86]. Altered levels of \textit{FOXP1} expression have been linked to abnormal neurodevelopment and autism [87–89]. \textit{NR3C1} and \textit{NR3C2} produce the glucocorticoid and mineralocorticoid receptors, which bind to cortisol, and may increase sensitivity to glucocorticoids [18] and regulate expression of \textit{HSD11B2} [21]. They are some of the most widely studied genes and generally have been found to decrease in expression in response to prenatal stress [90].

Finally, \textit{CRHBP}, which regulates the stress response by binding to corticotropin-releasing hormone [91–94], was the one gene that produced a divergent but related pattern to the others. It was downregulated in response to normative PS but appeared to follow a curvilinear, inverted-U shaped pattern, resulting in the moderate normative PS group having the highest
Fig 4. Marginal Mean (SE) Gene Expression Levels (represented on the Y axis) by Normative Prenatal Stress X Superstorm Sandy Prenatal Stress (Storm Exposure) (Solid Line = No Storm Exposure; Dotted Line = Storm Exposure) (Low = low PS; Mod = moderate PS; High = high PS). (A) CDKL5 by normative prenatal stress X Superstorm Sandy prenatal stress. (B) CFL1 by normative prenatal stress X Superstorm Sandy prenatal stress. (C) DYRK1A by normative prenatal stress X Superstorm Sandy prenatal stress. (D) FOXP1 by normative prenatal stress X Superstorm Sandy prenatal stress. (E) HSD11B2 by normative prenatal stress X Superstorm Sandy prenatal stress. (F) MAOA by normative prenatal stress X Superstorm Sandy prenatal stress. (G) MECP2 by normative prenatal stress X Superstorm Sandy prenatal stress. (H) NCOR1 by normative prenatal stress X Superstorm Sandy prenatal stress. (I) NR3C1 by normative prenatal stress X Superstorm Sandy prenatal stress. (J) NR3C2 by normative prenatal stress X Superstorm Sandy prenatal stress.
average gene expression levels. However, neither main effect of Superstorm Sandy PS nor the interaction with normative PS altered its expression.

The interaction analyses suggest that moderate, normative PS may protect the placenta from Superstorm Sandy PS; whereas, low normative PS left the placenta unprepared, and high normative PS may have overwhelmed the placenta’s tolerance for stress. The possibility that moderate normative PS might buffer the placenta from Superstorm Sandy PS was anticipated by various theories encapsulated under the Developmental Origins of Health and Disease hypothesis (DOHaD) [95], such as Allostatic Load [96], Predictive Adaptive Response [97] and the three-hit concept of vulnerability and resilience [98], which generally conceptualize epigenetic responses as anticipatory adaptations to an environment such as the one the mother experiences during pregnancy. In these models, PS signals an environment that is either impoverished or dangerous and thus programs offspring, especially male offspring, to grow to become smaller (to need less energy), slower in metabolism (to better conserve it), faster to mature and more vigilant, impulsive, aggressive and unemotional (to better fend off competitors and predators) [99]. Additionally, these DOHaD theories can be viewed as consonant with a stress inoculation model [100] in which moderate stress exposure protects the organism from future stress—a model consistent with our results.

Limitations and future research

First, our hypotheses about how changes in gene expression operate in the placenta must be recognized mostly as speculation since the level of variance explained by normative and/or traumatic PS on placental gene expression was minimal (Fig 1). Several genes, especially HSD11B2 and SCL6A4, have been extensively studied as they regulate maternal neurotransmitters, thus consequently affecting the developing fetus more directly, whereas a gene such as MAOA is less studied, requiring the present findings to be replicated in different studies. While our findings wait for replication and validation in other studies, we are planning to evaluate subsequent neurobehavioral outcomes in the offspring in relation to the current, complex findings of PS and placenta genes. It is our belief that this will further aid understanding the DOHaD hypotheses that involve genes censoring the prenatal environment and adaptation to the predicted postnatal environment for the best survival trajectory. These hypotheses need to be substantiated through more research including longitudinal studies on child development looking at epigenetic mechanisms. Our hypotheses are based on the known functions of the various genes in question and the function of the proteins they program. Further, although our total sample was relatively large, especially for an opportunistic study that capitalized on a natural disaster, the size of the high normative PS group was much smaller than the others (n = 55 for the High PS as compared to 132 for Moderate PS and 116 for Low). These sample size differences are unavoidable when looking for extremes of distress in a normative sample. Future studies with different community and clinical samples would help substantiate our findings. Another limitation of a natural disaster study is limited control of the timing of storm exposure—66 of the 95 storm-exposed pregnancies came during the first trimester. Our current understanding, through previous studies such as the Dutch Cold Winter Study, broadly suggests that stress exposure across different trimesters give rise to different programming outcomes [101–103]. It is generally believed that exposure to stress during early pregnancy is often associated with greater risk for disrupted developmental programming and increased risk for neurodevelopmental disorders in offspring. Also, much of our original
baseline data were collected during the second trimester, so storm exposure may have impacted ratings of normative PS before we measured normative PS. However, we found a very small correlation between storm exposure and normative PS classification. Further, although normative PS was measured primarily in the 2nd trimester, current research suggests that normative PS ratings are highly consistent throughout pregnancy [32,104,105]. We are aware that we are examining placental gene expression at term, and therefore we are examining how PS throughout pregnancy interacts with a traumatic Superstorm Sandy stressor that may have occurred early in pregnancy, but whose residual impact may have continued for much longer. Recent research on the 2011 Queensland Flood revealed placental glucocorticoid and glucose systems gene expression were associated with natural disaster-related PS (i.e., objective hardship and subjective distress) [106].

One limitation of our study is that we only assessed exposure to the storm and not the more nuanced physical or psychological impact of the storm such as objective hardship, measured by Storm32 and developed by King and Laplante [107, 108] or subjective distress, measured by the Impact of Event Scale-Revised [109]. In order to explore whether the degree of traumatic exposure to Superstorm Sandy (either subjectively or objectively) was associated with gene expression levels in a dose response fashion, we conducted a post-hoc analysis using the placentas of the exposed (N = 95). In this post-hoc analysis, we found no notable associations between either objective hardship or subjective distress, with the exception of SRD5A3. SRD5A3 was upregulated as the degree of objective hardship (p = .03) and subjective distress (p = .04) increased. As our sample size for this subsample analysis was relatively low, future studies with a larger sample size should include a more elaborate measure of the subjective or objective impact of the storm, such as Project Ice Storm [39] managed, and the duration of impact. In addition, we did not investigated the role of pregnancy diseases such as endometriosis, pre-eclampsia, and intrauterine growth restriction, which may affect both reported stress and placenta epigenetics [16,110–113]. The restriction of our analyses on placentas from healthy pregnancies may have constrained variances in the stress impacts and placental gene expression. However, the addition of HPA axis functioning measures (e.g., maternal cortisol) would strengthen the present findings with the placental glucocorticoid genes.

The most important question is whether and how specific alterations in placental gene expression shape the lifelong development and functioning of the offspring and perhaps future generations. The adaption of placental gene expression in response to PS may be seen as mediating between PS and an increased propensity for future neurobehavioral dysregulation and disorders. This can be investigated by combing neurodevelopmental and biological assessments (e.g., brain imaging and cortisol measures) in the offspring. The pathway is certainly complex, nonlinear, and dynamic, and further shaped by interacting endogenous, exogenous, and epigenetic factors. In this study we focused on mRNA expression and did not measure epigenetic mechanisms that regulate gene expression (e.g., miRNAs, DNA methylation) [1,17,114]. Though the research has focused on the impact of placental genes on fetal programming, we recognize that the placenta plays a central role in priming maternal behavior as well [115] and acknowledge the existing research on the epigenetics of early child-rearing [1,4,88,98]. So far we believe that stress during early pregnancy may begin to shape the mother, the fetus and the placenta itself both phenotypically and epigenetically, which then primes but does not predestine the adaptation of the maternal-offspring complex to future environments and lead to further alterations in phenotypic and epigenetic function.

**Conclusion**

Though DOHaD researchers have applied theories of predictive adaptability and stress inoculation to explain the impact of PS on fetal programming (96–98), to our knowledge this is the
first study to document evidence in support of these theories in relation to the life of the placenta itself. Our results suggest that the life of the placenta may represent a fractal of the life of the organism in its attempt to manage and prepare for the vicissitudes of life. With further longitudinal follow-up, it may become possible to use genetic analysis of the placenta to anticipate the risks for stress-related developmental psychopathology and identify children and families who might benefit from psychosocial prevention programs.

Supporting information
S1 Table. Correlations of all variables.
(DOCX)

S2 Table. Fit statistics for latent classes determining normative prenatal stress.
(DOCX)

S3 Table. The 40 candidate genes.
(DOCX)

S1 Data.
(XLS)

Acknowledgments
This work was supported by the NIMH grants K01 MH080062, ARRA supplement K01 MH080062S and R01MH102729 (to YN). None of the authors have any conflict of interests.

Author Contributions
Conceptualization: Yoko Nomura.
Formal analysis: Wei Zhang, Jacob Ham, Luca Lambertini, Yoko Nomura.
Funding acquisition: Yoko Nomura.
Investigation: Wei Zhang, Jacob Ham.
Methodology: Wei Zhang, Jacob Ham, Qian Li, Maya A. Deyssenroth, Jia Chen.
Project administration: Yoko Nomura.
Validation: Luca Lambertini.
Writing – original draft: Wei Zhang, Jacob Ham, Qian Li, Maya A. Deyssenroth, Yonglin Huang, Kenji J. Tsuchiya, Yoko Nomura.
Writing – review & editing: Wei Zhang, Jacob Ham, Qian Li, Maya A. Deyssenroth, Yonglin Huang, Kenji J. Tsuchiya, Jia Chen, Yoko Nomura.

References
1. Babenko O, Kovalchuk I, Metz GAS. Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. Neurosci Biobehav Rev [Internet]. 2015 [cited 2017 Jan 9]; 48:70–91. Available from: https://doi.org/10.1016/j.neubiorev.2014.11.013 PMID: 25464029

2. Graignic-Philippe R, Dayan J, Chokron S, Jacquet A-Y, Tordjman S. Effects of prenatal stress on fetal and child development: A critical literature review. Neurosci Biobehav Rev [Internet]. 2014 Jun 1 [cited 2019 Jan 14]; 43:137–62. Available from: https://www.sciencedirect.com/science/article/pii/S0149763414000797 https://doi.org/10.1016/j.neubiorev.2014.03.022 PMID: 24747487
3. Faas G, Manchia M, Pintus R, Gerosa C, Marcialis MA, Fanos V. Fetal programming of neuropsychiatric disorders. Birth Defects Res Part C Embryo Today Rev [Internet]. 2016 Sep 1 [cited 2019 Jan 14]; 108(3):207–23. Available from: http://doi.wiley.com/10.1002/bdrc.21139

4. Hocher B. More than genes: the advanced fetal programming hypothesis. J Reprod Immunol [Internet]. 2014 Oct 1 [cited 2019 Jan 14]; 104–105(C):8–11. Available from: https://www.sciencedirect.com/science/article/pii/S0165037814000308

5. Bock J, Wainstock T, Braun K, Segal M. Stress In Utero: Prenatal Programming of Brain Plasticity and Cognition. Biol Psychiatry [Internet]. 2015 Sep 1 [cited 2019 Jan 14]; 78(5):315–26. Available from: https://www.sciencedirect.com/science/article/pii/S0006322315001626 https://doi.org/10.1016/j.biopsych.2015.02.036 PMID: 25863359

6. Davis EP, Pfaff D. Sexually dimorphic responses to early adversity: Implications for affective problems and autism spectrum disorder. Psychoneuroendocrinology [Internet]. 2014 Nov 1 [cited 2019 Jan 14]; 49:11–25. Available from: https://www.sciencedirect.com/science/article/pii/S0306453014002212 https://doi.org/10.1016/j.psyneuen.2014.06.014 PMID: 25038479

7. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci [Internet]. 2009 Jun 29 [cited 2019 Jan 14]; 10(6):434–45. Available from: http://www.nature.com/articles/nrn2639 PMID: 19401723

8. 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 [Internet]. 2016 Jan 1 [cited 2019 Jan 14]; 65:133–47. Available from: https://www.sciencedirect.com/science/article/pii/S0306453015000466 https://doi.org/10.1016/j.psyneuen.2015.02.043 PMID: 25863360

9. Lou HC, Hansen D, Nordentoft M, Pryds O, Jensen F, Nim J, et al. Prenatal stressors of human life affect fetal brain development. Dev Med Child Neurol [Internet]. 1994 Nov 12 [cited 2018 Jun 21]; 36 (9):826–32. Available from: https://doi.org/10.1111/j.1469-8749.1994.tb08192.x PMID: 7926332

10. Qiu A, Rifkin-Grabin A, Chen H, Chong Y-S, Kwek K, Gluckman PD, et al. Maternal anxiety and cortisols is inversely associated with fetal brain growth. Neurosci Biobehav Rev [Internet]. 2012 Mar 1 [cited 2019 Jan 14]; 36(3):1085–92. Available from: https://www.sciencedirect.com/science/article/pii/S0149763411002123 https://doi.org/10.1016/j.neubiorev.2011.12.006 PMID: 22269902

11. Lou HC, Hansen D, Nordentoft M, Pryds O, Jensen F, Nir J, et al. Prenatal stressors of human life affect fetal brain development. Dev Med Child Neurol [Internet]. 1994 Nov 12 [cited 2018 Jun 21]; 36(9):826–32. Available from: https://doi.org/10.1111/j.1469-8749.1994.tb08192.x PMID: 7926332

12. Qiu A, Rifkin-Grabin A, Chen H, Chong Y-S, Kwek K, Gluckman PD, et al. Maternal anxiety and infants’ hippocampal development: timing matters. Transl Psychiatry [Internet]. 2013 Sep 24 [cited 2019 Jan 14]; 3(9):e306–e306. Available from: http://www.nature.com/articles/tp201379

13. Qiu A, Anh TT, Li Y, Chen H, Rifkin-Grabin A, Broekman BFP, et al. Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. Transl Psychiatry [Internet]. 2015 Feb 17 [cited 2019 Jan 14]; 5(November 2014):e508. Available from: http://www.nature.com/articles/tp20153

14. Palma-Gudiel H, Ordova-Palomera AC, Eixarch E, Deuschle M, Fañan As L, Córdova-Palomera A, et al. Maternal psychosocial stress during pregnancy alters the epigenetic signature of the glucocorticoid receptor gene promoter in their offspring: A meta-analysis. Epigenetics [Internet]. 2015 Oct 3 [cited 2016 Dec 13]; 10(10):893–902. Available from: http://www.nature.com/articles/tp2014172

15. Manchia M, Pintus R, Gerosa C, Marcialis MA, Fanos V. Fetal programming of neuropsychiatric disorders. Birth Defects Res Part C Embryo Today Rev [Internet]. 2016 Sep 1 [cited 2019 Jan 14]; 108(3):207–23. Available from: http://doi.wiley.com/10.1002/bdrc.21139

16. Hofer S, Hranickova M, Monti G, Pelosi F, Sambataro F, Hennig J, et al. Prenatal stress and placental genes. Placenta [Internet]. 2012 Apr 1 [cited 2019 Jan 14]; 33(4):327–33. Available from: https://www.sciencedirect.com/science/article/pii/S0143400412000384 https://doi.org/10.1016/j.placenta.2012.04.005 PMID: 22466013

17. Vaiman D. Genes, epigenetics and miRNA regulation in the placenta. Placenta [Internet]. 2017 Apr 1 [cited 2019 Aug 27]; 52:127–33. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0143400416308604?via%3Dihub https://doi.org/10.1016/j.placenta.2017.02.026 PMID: 28043658

18. Seckl JR, Holmes MC. Mechanisms of disease: Glucocorticoids, their placental metabolism and fetal “programming” of adult pathophysiology. Nat Clin Pract Endocrinol Metab [Internet]. 2007 Jun 1 [cited 2017 Jan 10]; 3(6):479–88. Available from: http://www.nature.com/articles/ncpendmet0515 https://doi.org/10.1038/ncpendmet0515 PMID: 17515892
19. Shams M, Kilby MD, Somerset DA, Howie AJ, Gupta A, Wood PJ, et al. 11Beta-hydroxysteroid dehydrogenase type 2 in human pregnancy and reduced expression in intrauterine growth restriction. Hum Reprod [Internet]. 1998 Apr 1 [cited 2019 Jan 14]; 13(4):799–804. Available from: https://academic.oup.com/humrep/article-lookup doi/10.1093/humrep/13.4.799 PMID: 9619527

20. Palma-Gudiel H, Córdova-Palomera A, Leza JC, Fañanás L. Glucocorticoid receptor gene (NR3C1) methylation processes as mediators of early adversity in stress-related disorders causality: A critical review. Neurosci Biobehav Rev [Internet]. 2015 Aug 1 [cited 2019 Jan 14]; 55:520–35. Available from: https://www.sciencedirect.com/science/article/pii/S014763415001517 https://doi.org/10.1016/j.neubiorev.2015.05.016 PMID: 26073068

21. Garbrecht MR, Schmidt TJ. Expression and Regulation of 11-β Hydroxysteroid Dehydrogenase Type 2 Enzyme Activity in the Glucocorticoid-Sensitive CEM-C7 Human Leukemic Cell Line. ISRN OncoI [Internet]. 2013 Mar 17 [cited 2019 Jan 14]; 2013:245246. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23762608 PMID: 23762608

22. Paquette AG, Lester BM, Lesser C, Armstrong DA, Guerin DJ, Appleton AA, et al. Placental epigenetic patterning of glucocorticoid response genes is associated with infant neurodevelopment. Epigenomics [Internet], 2015 Aug; 7(5):767–79. Available from: http://www.futuremedicine.com doi/10.2217/epi.15.28 PMID: 26343289

23. Janssen AB, Kertes DA, McNamara GI, Braithwaite EC, Creeth HDJ, Glover VI, et al. A Role for the Placenta in Programming Maternal Mood and Childhood Behavioural Disorders [Internet]. Journal of Neuroendocrinology Wiley-Blackwell; Aug, 2016 p. n/a. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26836228

24. Bronson SL, Bale TL. The Placenta as a Mediator of Stress Effects on Neurodevelopmental Reprogramming [Internet]. Vol. 41, Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. Nature Publishing Group; 2016 [cited 2017 Jul 20]. 207–18 p. Available from: http://dx.doi.org/10.1038/npp.2015.231

25. Oberlander TF. Fetal serotonin signaling: Setting pathways for early childhood development and behavior. J Adolesc Heal [Internet]. 2012; 51(2 SUPPL.):S9–16. Available from: http://dx.doi.org/10.1016/j.jadoheal.2012.04.009

26. Gaspar P, Cases O, Maroteaux L. The developmental role of serotonin: news from mouse molecular genetics. Nat Rev Neurosci [Internet]. 2003 Dec 1 [cited 2019 Jan 14]; 4(12):1002–12. Available from: http://www.nature.com/articles/nrn1256 PMID: 14618156

27. Salichon N, Gaspar P, Upton AL, Picaud S, Hanoun N, Hamon M, et al. Excessive activation of serotonin (5-HT) 1B receptors disrupts the formation of sensory maps in monoamine oxidase a and 5-ht transporter knock-out mice. J Neurosci [Internet]. 2001 Feb 1 [cited 2019 Jan 14]; 21(3):884–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11157075 PMID: 11157075

28. Sjaarda CP, Hecht P, McNaughton AJM, Zhou A, Hudson ML, Will MJ, et al. Interplay between maternal SLC6A4 mutation and prenatal stress: a possible mechanism for autistic behavior development. Sci Rep [Internet]. 2017 Dec 18 [cited 2019 Jan 14]; 7(1):8735. Available from: http://www.nature.com/articles/s41598-017-07405-3 https://doi.org/10.1038/s41598-017-07405-3 PMID: 28821725

29. Park S, Lee J-M, Kim J-W, Cho D-Y, Yun HJ, Han DH, et al. Associations between serotonin transporter gene (SLC6A4) methylation and clinical characteristics and cortical thickness in children with ADHD. Psychol Med [Internet]. 2015 Oct 28 [cited 2019 Jan 14]; 45(14):3009–17. Available from: http://www.journals.cambridge.org/abstract_S003329171500094X https://doi.org/10.1017/S003329171500094X PMID: 26017091

30. Blakeley PM, Capron LE, Jensen AB, O’Donnell KJ, Glover V. Maternal prenatal symptoms of depression and down regulation of placental monoamine oxidase A expression. J Psychosom Res [Internet]. 2013 Oct 1 [cited 2017 Mar 17]; 75(4):341–5. Available from: https://www.sciencedirect.com/science/article/pii/S0022399913002687 https://doi.org/10.1016/j.jpsychores.2013.07.002 PMID: 24119940

31. Ponder KL, Salisbury A, McGonigal B, Laliberte A, Lester B, Padbury JF. Maternal depression and down regulation of placental monoamine oxidase A expression. J Psychosom Res [Internet]. 2013 Dec 1 [cited 2017 Mar 17]; 75(4):341–5. Available from: https://www.sciencedirect.com/science/article/pii/S0022399913002687 https://doi.org/10.1016/j.jpsychores.2013.07.002 PMID: 24119940

32. Reynolds RM, Pesonen A-K, O'Reilly JR, Tuovinen S, Lahti M, Kajantie E, et al. Maternal depressive symptoms throughout pregnancy are associated with increased placental glucocorticoid sensitivity. Psychol Med [Internet]. 2015 Jul 28; 45(10):2023–30. Available from: http://www.journals.cambridge.org/abstract_S003329171400316X

33. Kertes DA, Kamin HS, Hughes DA, Rodney NC, Bhatt S, Mulligan CJ. Prenatal Maternal Stress Predicts Methylation of Genes Regulating the Hypothalamic-Pituitary-Adrenocortical System in Mothers and Newborns in the Democratic Republic of Congo. Child Dev [Internet]. 2016 Jan 1 [cited 2017 Jul
16; 87(1):61–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26822443 https://doi.org/10.1111/cdev.12487 PMID: 26822443

34. 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(6):818–26. https://doi.org/10.1016/j.psyneuen.2011.09.014 PMID: 22000100

35. Jensen Peña C, Monk C, Champagne FA, Peña CJ, Monk C, Champagne FA. Epigenetic Effects of Prenatal Stress on 11β-Hydroxysteroid Dehydrogenase-2 in the Placenta and Fetal Brain. Sun K, editor. PLoS One [Internet]. 2012 Jun 26 [cited 2016 Sep 14]; 7(6):e39791. Available from: http://dx.plos.org/10.1371/journal.pone.0039791 https://doi.org/10.1371/journal.pone.0039791 PMID: 22761903

36. Togher KL, Togher KL, O’Keeffe MM, O’Keeffe MM, Khashan AS, Khashan AS, et al. Epigenetic regulation of the placental HSD11B2 barrier and its role as a critical regulator of fetal development. Epigenetics [Internet]. 2014 Jun 12 [cited 2019 Jan 14]; 9(6):816–22. Available from: http://www.tandfonline.com/doi/abs/10.4161/epi.28703 PMID: 24717516

37. Welberg LAM, Thrivikraman K V, Plootsky PM. Chronic maternal stress inhibits the capacity to up-regulate placental 11β-hydroxysteroid dehydrogenase type 2 activity. J Endocrinol. 2005; 186(3):7–12.

38. Mairesse J, Lesage J, Breton C, Bérent B, Hahn T, Darnaudery M, et al. Maternal stress alters endocrine function of the feto-placental unit in rats. Am J Physiol Metab [Internet]. 2007 Jun [cited 2019 Jan 15]; 292(6):E1526–33. Available from: http://www.physiology.org/doi/10.1152/ajpemet.00574.2006

39. Cao-Lei L, Laplante DP, King S. Prenatal Maternal Stress and Epigenetics: Review of the Human Research. Curr Mol Biol Reports [Internet]. 2016 Mar 17 [cited 2019 Jan 15]; 2(1):16–25. Available from: http://link.springer.com/10.1007/s40610-016-0030-x

40. King S, Dancause K, Turcotte-Tremblay A-M, Veru F, Laplante DP. Using Natural Disasters to Study the Effects of Prenatal Maternal Stress on Child Health and Development. Birth Defects Res Part C Embryo Today Rev [Internet]. 2012; 96(4):273–88. Available from: http://wiley.com/10.1002/bdrc.21026

41. Dancause KN, Laplante DP, Oremus C, Fraser S, Brunet A, King S. Disaster-related prenatal maternal stress influences birth outcomes: Project Ice Storm. Early Hum Dev [Internet]. 2011 Dec 1 [cited 2019 Jan 15]; 87(12):813–20. Available from: https://www.sciencedirect.com/science/article/pii/S0378378211002106 https://doi.org/10.1016/j.earhumdev.2011.06.007 PMID: 21784587

42. Dancause KN, Veru F, Andersen RE, Laplante DP, King S. Prenatal stress due to a natural disaster predicts insulin secretion in adolescence. Early Hum Dev [Internet]. 2013 Sep 1 [cited 2019 Jan 15]; 89(9):773–6. Available from: https://www.sciencedirect.com/science/article/pii/S0378378213001448 https://doi.org/10.1016/j.earhumdev.2013.06.006 PMID: 23830724

43. Cao-Lei L, Massart R, Suderman MJM, Machnes Z, Elgebei G, Laplante DPĐ, et al. DNA methylation signatures triggered by prenatal maternal stress exposure to a natural disaster. Project Ice storm. Iwamoto K, editor. PLoS One [Internet]. 2014 Sep 19 [cited 2016 Dec 1]; 9(9):e107653. Available from: http://dx.plos.org/10.1371/journal.pone.0107653 https://doi.org/10.1371/journal.pone.0107653 PMID: 25238154

44. Laplante DP, Brunet A, Schmitz N, Ciampi A, King S. Project Ice Storm: Prenatal maternal stress affects cognitive and linguistic functioning in 5½-year-old children. J Am Acad Child Adolesc Psychiatry. 2008; 47(9):1063–72. https://doi.org/10.1097/CHI.0b013e31817ee80 PMID: 18665002

45. Tees MT, Harville EW, Xiong X, Buekens P, Prdijian G, Elkind-Hirsch K. Hurricane Katrina-related stress, maternal mental health, and early infant temperament. Matern Child Health J [Internet]. 2010 Jul 25 [cited 2017 Feb 17]; 14(4):511–8. Available from: https://doi.org/10.1007/s10995-009-0486-x PMID: 19554438

46. Yong Ping E, Laplante DP, Elgebei G, Hillerer KM, Brunet A, O’Hara MW, et al. Prenatal maternal stress predicts stress reactivity at 2½ years of age: The Iowa Flood Study. Psychoneuroendocrinology [Internet]. 2015 Jun 1 [cited 2019 Jan 15]; 56:62–78. https://doi.org/10.1016/j.psyneuen.2015.02.015 PMID: 25800150

47. Blake ES, Kimberlain TB, Berg RJ, Cangialosi JP, Beven II JL. Tropical Cyclone Report Hurricane Sandy Rep. AL182012: National Hurricane Center. 2013;

48. MMWR. Deaths Associated with Hurricane Sandy—October—November 2012. Centers Dis Control Prev. 2013; 62(20):2010–3.

49. Fink J, Nomura Y. Cohort Profile: Stress in Pregnancy (SIP) Study. Int J Epidemiol [Internet]. 2017 Jan 15;dyw264. Available from: https://academic.oup.com/ije/article-lookup/doi/10.1093/ije/dyw264

50. Murray L, Carothers AD. The validation of the Edinburgh Post-natal Depression Scale on a community sample. Br J Psychiatry [Internet]. 1990 Aug 1 [cited 2016 Dec 27]; 157(2):288–90. Available from: https://www.cambridge.org/core/product/identifier/S0007125000062516/type/journal_article
51. Kheirabadi GR, Maracy MR, Akbaripour S, Masaeil N. Psychometric properties and diagnostic accuracy of the edinburgh postnatal depression scale in a sample of Iranian women. Iran J Med Sci [Internet]. 2012 Mar [cited 2016 Dec 30]; 37(1):32–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23115428 PMID: 23115428

52. Huizink AC, Mulder EJHH, Robles De Medina PG, Visser GHAA, Buïtelaar JK. Is pregnancy anxiety a distinctive syndrome? Early Hum Dev [Internet]. 2004 Sep 1 [cited 2017 Oct 31]; 79(2):81–91. Available from: https://www.sciencedirect.com/science/article/pii/S037837820400074X https://doi.org/10.1016/j.earlhumdev.2004.04.014 PMID: 15324989

53. Huizink A, Delforterie M, Scheinin N, Tolvanen M, Karlsson L, Karlsson H. Pregnancy-Related Anxiety Questionnaire—Revised; Modified Version. PsychTESTS Dataset. 2016;

54. Spielberger CD. State-trait anxiety inventory: A comprehensive bibliography. Consulting Psychologists Press; 1989.

55. Spielberger C, Gorsuch R, Lushene R, Vagg P, Jacob G. Manual for the State-Trait Anxiety Inventory (Form Y1 –Y2). (Vol. IV). CA: Consulting Psychologists Press; 1983.

56. Barnes LLB, Harp D, Jung WS. Reliability generalization of Scores on the Spielberg er State-Trait Anxiety Inventory. Educ Psychol Meas [Internet]. 2002 Aug 2 [cited 2017 Oct 31]; 62(4):603–18. Available from: http://journals.sagepub.com/doi/10.1177/0013164402062004005

57. Cohen S, Kamarck T, Mermelstein R. A Global Measure of Perceived Stress. J Health Soc Behav [Internet]. 1983 Dec [cited 2017 Apr 4]; 24(4):385. Available from: http://www.jstor.org/stable/2136404?origin=crossref PMID: 6668417

58. Andreou E, Alexopoulos EC, Lionis C, Varvogli L, Gnardellis C, Chrousos GP, et al. Perceived Stress Scale: Reliability and Validity Study in Greece. Int J Environ Res Public Health [Internet]. 2011 Aug 11 [cited 2019 Jan 17]; 8(8):3287–98. Available from: http://www.mdpi.com/1660-4601/8/8/3287 https://doi.org/10.3390/ijerph8083287 PMID: 21909307

59. Dohrenwend BPBS, Askenasy AR, Krasnoff L, Dohrenwend BPBS. Exemplification of a Method for Scaling Life Events: The PERI Life Events Scale. J Health Soc Behav [Internet]. 1978 Jun [cited 2017 Jul 18]; 19(2):205. Available from: http://www.jstor.org/stable/21365367?origin=crossref PMID: 681735

60. Barrett ES, Redmon JB, Wang C, Sparks A, Swan SH. Exposure to prenatal life events stress is associated with masculinized play behavior in girls. Neurotoxicology [Internet]. 2014 Mar 1 [cited 2019 Jan 15]; 41:20–7. Available from: https://www.sciencedirect.com/science/article/pii/S0161813X13001927 https://doi.org/10.1016/j.neuro.2013.12.011 PMID: 24406375

61. Barrett ES, Parlett LE, Sathyanarayana S, Redmon JB, Nguyen RHN, Swan SH. Prenatal Stress as a Modifier of Associations between Phthalate Exposure and Reproductive Development: results from a Multicentre Pregnancy Cohort Study. Paediatr Perinat Epidemiol [Internet]. 2016 Mar 1 [cited 2019 Jan 17]; 30(2):105–14. Available from: http://doi.wiley.com/10.1111/ppe.12264 PMID: 26576028

62. Hoffman S, Hatch MC. Depressive symptomatology during pregnancy: Evidence for an association with decreased fetal growth in pregnancies of lower social class women. Heal Psychol. 2000; 19 (6):535–43.

63. Dohrenwend BP. Inventorying Stressful Life Events as Risk Factors for Psychopathology: Toward Resolution of the Problem of Intracategory Variability. Psychol Bull [Internet]. 2006 May [cited 2017 Jul 18]; 132(3):477–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16719570 https://doi.org/10.1037/0033-2909.132.3.477 PMID: 16719570

64. DiPietro JA, Novak MFSX, Costigan KA, Atella LD, Reusing SP. Maternal Psychological Distress During Pregnancy in Relation to Child Development at Age Two. Child Dev [Internet]. 2006 May [cited 2017 Apr 6]; 77(3):573–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16686789 https://doi.org/10.1111/j.1467-8624.2006.00891.x PMID: 16686789

65. Monk C, Spicer J, Champagne FA. Linking prenatal maternal adversity to developmental outcomes in infants: The role of epigenetic pathways. Dev Psychopathol [Internet]. 2012 Nov 15 [cited 2019 Jan 17]; 24(04):1361–76. Available from: http://www.journals.cambridge.org/abstract_ S0954579412000764

66. Goldenberg RL, Hickey CA, Cliver SP, Gotlieb S, Woolley TW, Hoffman HJ. Abbreviated scale for the assessment of psychosocial status in pregnancy: development and evaluation. Acta Obstet Gynecol Scand Suppl [Internet]. 1997 [cited 2019 Jan 17]: 165:19–29. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9219452 PMID: 9219452

67. Schwarz G. Estimating the Dimension of a Model. Ann Stat [Internet]. 1978 Mar; 6(2):461–4. Available from: http://projecteuclid.org/euclid.aos/1176344136

68. Sclove SL. Application of model-selection criteria to some problems in multivariate analysis. Psychometrika [Internet]. 1987 Sep; 52(3):333–43. Available from: http://link.springer.com/10.1007/BF02294360
Lo Y, Mendell NR, Rubin DB. Testing the number of components in a normal mixture. Biometrika [Internet]. 2001 Oct 1 [cited 2017 Apr 4]; 88(3):767–78. Available from: https://academic.oup.com/biomet/article-lookup/doi/10.1093/biomet/88.3.767

Kappil MA, Green BB, Armstrong DA, Sharp AJ, Lambertini L, Marsit CJ, et al. Placental expression profile of imprinted genes impacts birth weight. Epigenetics. 2015; 10(9):842–9. https://doi.org/10.1089/epi.2015.1073881 PMID: 26186239

Zhang W, Qian L, Deyssenroth M, Lambertini L, Finik J, Ham J, et al. Timing of Prenatal Exposure to Trauma and Altered Placental Expressions of HPA-Axis Genes and Genes Driving Neurodevelopment. J Neuroendocrinol [Internet]. 2018 Feb 9 [cited 2018 Mar 13];(September 2017):e12581. Available from: http://doi.wiley.com/10.1111/jne.12581

Waggott D, Chu K, Yin S, Wouters BG, Liu F-F, Boutros PC. NanoStringNorm: An extensible R package for the pre-processing of NanoString mRNA and miRNA data. Bioinformatics [Internet]. 2012 Jun 1; 28(11):1546–8. Available from: https://academic.oup.com/bioinformatics/article-lookup/doi/10.1093/bioinformatics/bts186 PMID: 22513995

Räikkönen K, O'Reilly JR, Pesonen AK, Kajantie E, Villa P, Laivuori H, et al. Associations between maternal level of education and occupational status with placental glucocorticoid regulation and sensitivity. Clin Endocrinol (Oxf). 2014; 81(2):175–82.

Capron LE, Ramcharndani PG, Glover V. Maternal prenatal stress and placental gene expression of NR3C1 and HSD11B2: The effects of maternal ethnicity. Psychoneuroendocrinology [Internet]. 2018 Jan 1 [cited 2019 Jan 17]; 87:166–72. Available from: https://www.sciencedirect.com/science/article/pii/S0306453017302603 https://doi.org/10.1016/j.psyneuen.2017.10.019 PMID: 29100173

Benjamini Y, Yekutieli D (2001) The Control of the False Discovery Rate in Multiple Testing under Dependenc y. Ann Stat 29:1165–1188

Benjamini Y, Hochberg Y (1995) Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J R Stat Soc Ser B Methodol 57:289–300

Riley LA, Waguespack MA, Denney RM. Characterization and quantitation of monoamine oxidases A and B in mitochondria from human placenta. Mol Pharmacol [Internet]. 1989 [cited 2017 Jul 19]; 36(1). Available from: http://molpharm.aspetjournals.org/content/36/1/54.short

Park J, Song WJ, Chung KC. Function and regulation of Dyrk1A: towards understanding Down syndrome. Cell Mol Life Sci. 2009; 66(20):3235–40. https://doi.org/10.1007/s00018-009-0123-2 PMID: 19685005

Ahn K-J, Jeong HK, Choi H-S, Ryoo S-R, Kim YJ, Goo J-S, et al. DYRK 1A BAC transgenic mice show altered synaptic plasticity with learning and memory defects. Neurobiol Dis [Internet]. 2006 Jun 1 [cited 2019 Jan 17]; 22(3):463–72. Available from: https://www.sciencedirect.com/science/article/pii/S0969996105003426 https://doi.org/10.1016/j.nbd.2005.12.006 PMID: 16455265

Itoh M, Tahimic CGT, Ide S, Otsuki A, Sasaoka T, Noguchi S, et al. Methyl CpG-binding protein isoform MeCP2_e2 is dispensable for Rett syndrome phenotypes but essential for embryo viability and placenta development. J Biol Chem [Internet]. 2012 Apr 20 [cited 2019 Jan 17]; 287(17):13859–67. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22375006 https://doi.org/10.1074/jbc.M111.309864 PMID: 22375006

Nagarajan R, Hogart A, Gwey Y, Martin MR, LaSalle JM. Reduced MeCP2 Expression is Frequent in Autism Frontal Cortex and Correlates with Aberrant MECP2 Promoter Methylation. Epigenetics [Internet]. 2006 Oct 23 [cited 2019 Jan 17]; 1(4):172–82. Available from: http://www.tandfonline.com/doi/abs/10.4161/epi.1.4.3514

Mari F, Azimonti S, Bertani I, Bolognes e F, Colombo E, Caselli R, et al. CDKL5 belongs to the same molecular pathway of MeCP2 and it is responsible for the early-onset seizure variant of Rett syndrome. Hum Mol Genet [Internet]. 2005 Jul 15 [cited 2019 Jan 17]; 14(14):1935–46. Available from: http://academic.oup.com/hmg/article/14/14/1935/608343/CDKL5-belongs-to-the-same-molecular-pathway-of https://doi.org/10.1093/hmg/ddi198 PMID: 15917271

Vachev TI, Popov T, Krasteva Stoyanova V, Ivanov HY, Minchev DS. Down Regulation of MIR-320 Gene Family Members in the Peripheral Blood of Schizophrenia Patients. Int J Curr Microbiol App Sci [Internet]. 2016 [cited 2019 Jan 17]; 5(1):221–30. Available from: http://dx.doi.org/10.20546/ijcms.2016.501.020

Seth S, Lewis A, Saffery R, Lappas M, Galtbally M, Seth S, et al. Maternal Prenatal Mental Health and Placental 11β-HSD2 Gene Expression: Initial Findings from the Mercy Pregnancy and Emotional Wellbeing Study. Int J Mol Sci [Internet]. 2015 Nov 17 [cited 2019 Jan 17]; 16(11):27482–96. Available from: http://www.mdpi.com/1422-0067/16/11/26034 https://doi.org/10.3390/ijms161126034 PMID: 26593902

Ghaemmaghami P, Dainese SM, La Marca R, Zimmermann R, Ehlert U. The association between the acute psychobiological stress response in second trimester pregnant women, amniotic fluid
glucocorticoids, and neonatal birth outcome. Dev Psychobiol [Internet]. 2014 May 1 [cited 2019 Jan 17]; 56(4):734–47. Available from: http://doi.wiley.com/10.1002/dev.21142 PMID: 23775363

86. Ferland RJ, Cherry TJ, Preware PO, Morrissey EE, Walsh CA. Characterization of Foxp2 and Foxp1 mRNA and protein in the developing and mature brain. J Comp Neurol [Internet]. 2003 May 26 [cited 2017 Apr 7]; 460(2):266–79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12687690 https://doi.org/10.1002/cne.10654 PMID: 12687690

87. Chien W-H, Gau SS-F, Chen C-H, Tsai W-C, Wu Y-Y, Chen P-H, et al. Increased gene expression of FOXP1 in patients with autism spectrum disorders. Mol Autism [Internet]. 2013 Nov 6; 4(1):23. Available from: http://peditrics.aappublications.org/cgi/doi/10.1542/peds.2009-1522 PMID: 23815876

88. Bacon C, Schneider M, Le Magueresse C, Froehlich H, Sticht C, Gluch C, et al. Brain-specific Foxp1 deletion impairs neuronal development and causes autistic-like behaviour. Mol Psychiatry [Internet]. 2015 May 30 [cited 2019 Jan 17]; 20(5):632–9. Available from: http://www.nature.com/articles/mp2014116 https://doi.org/10.1038/mp.2014.116 PMID: 25266127

89. Taillkowsk ME, Rosenfeld JA, Blumenthal I, Pillialamarri V, Chiang C, Heilbut A, et al. Sequencing chromosomal abnormalities reveals neurodevelopmental loci that confer risk across diagnostic boundaries. Cell [Internet]. 2012; 149(3):525–37. Available from: https://doi.org/10.1016/j.cell.2012.03.028 PMID: 22521361

90. Vinkers CH, Kalafatelli AL, Rutten BP, Kas MJ, Kaminsky Z, Turner JD, et al. Traumatic stress and human DNA methylation: a critical review. Epigenomics [Internet]. 2015 Jun [cited 2016 Dec 1]; 7 (4):593–608. Available from: http://www.futuremedicine.com/doi/10.2217/epi.15.11 PMID: 26111031

91. Chari A, Laplante DP, Vailancourt C, King S. Prenatal stress and brain development. Brain Res Rev. 2010; 65:65–79. https://doi.org/10.1016/j.brainresrev.2010.06.002 PMID: 20550850

92. Glover V, O’Connor TG, O’Donnell K. Prenatal stress and the programming of the HPA axis. Neurosci Biobehav Rev [Internet]. 2010 Sep [cited 2017 Feb 22]; 35(1):17–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19914282 https://doi.org/10.1016/j.neubiorev.2009.11.008 PMID: 19914282

93. Van Den Bergh BRHH, Mulder EJHH, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: Links and possible mechanisms. A review. Neurosci Biobehav Rev [Internet]. 2005 Apr 1 [cited 2016 Oct 9]; 29(2):237–58. Available from: http://www.sciencedirect.com/science/article/pii/S0306453016307345

94. Ketchesin KD, Stinnett GS, Seasholtz AF. Corticotropin-releasing hormone-binding protein and stress: from invertebrates to humans. Stress [Internet]. 2017 Sep 3 [cited 2019 Jan 17]; 20(5):449–64. Available from: https://doi.org/10.1080/10253890.2017.1322575 PMID: 28436309

95. Van den Bergh BRH, van den Heuvel MI, Lahti M, Braeken M, de Rooij SR, Entringer S, et al. Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. Neurosci Biobehav Rev [Internet]. 2017 Jul 28 [cited 2017 Oct 19];(April). Available from: http://linkinghub.elsevier.com/retrieve/pii/S0149763416307345

96. McEWEN BS. Stress, Adaptation, and Disease; Allostasis and Allostatic Load. Ann N Y Acad Sci [Internet]. 1998 May 1 [cited 2019 Jan 17]; 840(1):33–44. Available from: http://doi.wiley.com/10.1111/j.1749-6632.1998.tb09546.x

97. Gluckman P, Beedle A, Buklijas T, Low F, Hanson M. An Evolutionary Framework for Understanding Human Health and Disease. In: Principles of Evolutionary Medicine. 2nd ed. Oxford: Oxford University Press; 2016.

98. Daskalakis NP, Bagot RC, Parker KJ, Vinkers CH, de Kloet ER. The three-hit concept of vulnerability and resilience: Toward understanding adaptation to early-life adversity outcome. Psychoneuroendocrinology [Internet]. 2013 Sep 1 [cited 2019 Jan 17]; 38(9):1858–73. Available from: https://www.sciencedirect.com/science/article/pii/S0306453013002254 https://doi.org/10.1016/j.psyneu.2013.06.008 PMID: 23838101

99. Glover V. Annual research review: Prenatal stress and the origins of psychopathology: An evolutionary perspective. J Child Psychol Psychiatry Allied Discip. 2011; 52(4):356–67.

100. Bock J, Rether K, Gröger N, Xie L, Braun K. Perinatal programming of emotional brain circuits: an integrative view from systems to molecules. Front Neurosci [Internet]. 2014 Feb 5 [cited 2019 Jan 17]; 8:11. Available from: http://journal.frontiersin.org/article/10.3389/fnsne.2014.00011/abstract https://doi.org/10.3389/fnsne.2014.00011 PMID: 24550772

101. King S, Laplante DP. The effects of prenatal maternal stress on children’s cognitive development: Project Ice Storm. Stress [Internet]. 2005 Mar 7 [cited 2017 Feb 17]; 8(1):35–45. Available from: http://www.tandfonline.com/doi/full/10.1080/10253890500108391 PMID: 16019596

102. Susser ES, Lin SP. Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944–1945. Arch Gen Psychiatry [Internet]. 1992 Dec 1 [cited 2017 Sep 5]; 49(12):983–8. Available from: http://
103. Beversdorf DQ, Manning SE, Hillier A, Anderson SL, Nordgren RE, Walters SE, et al. Timing of Prenatal Stressors and Autism. J Autism Dev Disord [Internet]. 2005 Aug [cited 2017 Feb 28]; 35(4):471–8. Available from: https://pdfs.semanticscholar.org/ac59/503663e07f6a1747647d7d78d56d40c4e9c.pdf https://doi.org/10.1007/s10803-005-5037-8 PMID: 16134032

104. O’Connor TG, Heron J, Golding J, Beveridge M, Glover V. Maternal antenatal anxiety and children’s behavioural/emotional problems at 4 years. Br J Psychiatry. 2002; 180(6).

105. Davis EP, Glynn LM, Waffarn F, Sandman CA. Prenatal maternal stress programs infant stress regulation. J Child Psychol Psychiatry [Internet]. 2011 Feb; 52(2):119–29. Available from: http://doi.wiley.com/10.1111/j.1469-7610.2010.02314.x PMID: 20854366

106. St-Pierre J, Laurent L, King S, Vaillancourt C. Effects of prenatal maternal stress on serotonin and fetal development. Placenta [Internet]. 2016 Dec 1 [cited 2017 Jul 20]; 48 Suppl 1:S66–71. Available from: https://www.researchgate.net/profile/Cathy_Vaillancourt/publication/285672955_Effects_of_prenatal_maternal_stress_on_serotonin_and_fetal_development/links/5665a0708ae192bbf9255d3/Effects-of-prenatal-maternal-stress-on-serotonin-and-fetal-development.pdf?

107. Laplante DP., Zelazo PR, Brunet A., & King S. (2007). Functional play at 2 years of age: Effects of prenatal maternal stress. Infancy 12(1), 69–93. https://doi.org/10.1111/j.1532-7078.2007.tb00234.x

108. Bromet E, Dew M (1995) Review of Psychiatric Epidemiologic Research on Disasters | Epidemiologic Reviews | Oxford Academic. Epidemiol Rev 17:113–119 https://doi.org/10.1093/oxfordjournals.epirev.a036166 PMID: 8521929

109. Weiss D, Marmar C (1997) The Impact of Event Scale-Revised. In: Assessing psychological trauma and PTSD. Guilford Press, New York, NY, pp 399–411

110. Laganà AS, La Rosa VL, Rapisarda AMC, Valenti G, Sapia F, Chiofalo B, et al. Anxiety and depression in patients with endometriosis: impact and management challenges. Int J Womens Health [Internet]. 2017 [cited 2019 Aug 27]; 9:323–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28553145 https://doi.org/10.2147/IJWH.S119729 PMID: 28553145

111. Baggio S, Pomini P, Zecchin A, Garzon S, Bonin C, Santi L, et al. Delivery and pregnancy outcome in women with bowel resection for deep endometriosis: a retrospective cohort study. Gynecol Surg [Internet], 2015 Nov 20 [cited 2019 Aug 27]; 12(4):279–85. Available from: http://link.springer.com/10.1007/s10397-015-0901-9

112. Vitale SG, Petrosino B, La Rosa VL, Rapisarda AMC, Laganà AS. A Systematic Review of the Association Between Psychiatric Disturbances and Endometriosis. J Obstet Gynaecol Canada [Internet]. 2016 Dec 1 [cited 2019 Aug 27]; 38(12):1079–80. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1701216316396153?via%3Dihub

113. Vitale SG, La Rosa VL, Rapisarda AMC, Laganà AS. Impact of endometriosis on quality of life and psychological well-being. J Psychosom Obstet Gynaecol [Internet]. 2017 Oct 2 [cited 2019 Aug 27]; 38 (4):317–9. Available from: https://www.tandfonline.com/doi/full/10.1080/0167482X.2016.1241165

114. Zucchi FCR, Yao Y, Ward ID, Ilnytskyy Y, Olson DM, Benzies K, et al. Maternal stress induces epigenetic signatures of psychiatric and neurological diseases in the offspring. PLoS One [Internet]; 2013 [cited 2017 May 12]; 8(2):e56967. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23451123 https://doi.org/10.1371/journal.pone.0056967 PMID: 23451123

115. Mann PE, Bridges RS. Chapter 18 Lactogenic hormone regulation of maternal behavior. Prog Brain Res [Internet]. 2001 Jan [cited 2019 Jan 17]; 133:251–62. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0079612301330194?via%3Dihub https://doi.org/10.1016/s0079-6123(01)33019-4 PMID: 11589135