Maternal Anxiety and Infants Birth weight and Length of Gestation. A sibling design.

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Abstract

Objective: To examine the effect of prenatal maternal anxiety on birthweight and preterm birth, controlling for genetic confounding using a sibling comparison design. Design: This is a population-based prospective cohort study with a comparison of a population level analysis and a sibling analysis. Setting: This study is based on the Norwegian Mother, Father and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health (https://www.fhi.no/en/studies/moba/). Sample: Women and their chiold participating in the MoBa (n= 78,117) and women participating with more than one pregnancy (n=12,480). Methods: Associations between prenatal maternal anxiety (measured across the 17th and 30th weeks) and birth outcomes (birthweight and gestational age) were examined using linear regression with adjustment for family-shared confounding in a sibling comparison design. Main outcomes: Birthweight (in grams) and gestational age (ultrasound measure in days) were obtained from the Medical Birth Registry of Norway. Results: The maternal anxiety score during pregnancy was inversely associated with newborn's birthweight (Beta = -112,8 95% CI: –142.7, -83.0) and gestational age (Beta=-1.77, 95% CI: -2.42, -1.13) after adjustment for several covariates. The association of the maternal anxiety score with both newborn's birthweight (Beta=-173.9, 95% CI: -252.3, -95.4) and gestational age (Beta=-1.08, 95% CI: -2.91, -0.75) remained but was largely weakened after further adjusting for the shared-family confounding in the sibling comparison design. Conclusion: The link between maternal prenatal anxiety and birthweight and gestational age remained after adjusting for shared family confounding, yet estimates were weakened after adjusting for environmental covariates.

Introduction

Preterm birth (PTB) and low birthweight (LBW) are related to perinatal mortality, and have been associated with a wide range of adverse developmental outcomes for children.[1] Recently, much focus has been on the potential impact of maternal distress and anxiety on birth outcomes. Studies have reported that the prevalence of maternal anxiety during pregnancy varies from 6.6 to 10.4%.[2,3]Further, maternal anxiety during pregnancy is associated with birthweight and gestational age.[4,5] Prenatal anxiety is recognized as a potential risk factor for PTB and LBW.[6,7,8]

While associations between prenatal maternal anxiety and PTB and LBW have been reported, causal inferences are only tentative. For several reasons, randomization of anxiety or distress during pregnancy cannot be conducted.[9] Thus, in humans, investigations are limited to observational designs. Using this methodology, associations between prenatal maternal anxiety and PTB and LBW have been established. New approaches to estimate the effects of prenatal maternal anxiety on childhood outcomes are crucial in advancing the field.[9,10]

In this study, we estimate the effects of degree (no symptoms, light symptoms and severe symptoms) and

timing of prenatal maternal anxiety on infant birthweight and preterm birth. Timing was accounted for by examining whether symptoms were reported at either or both of the 17th or 30th gestational weeks. We test these associations using a sibling comparison design. The design, which involves studying birth outcomes following differential exposure to anxiety during pregnancy across siblings, has been found to reduce the extent of the impact of family-level confounding factors.[9-11] on examinations of prenatal anxiety effects.

Methods

In MoBa, 78,117 mothers of 91,378 children completed a series of questionnaires in the 17th and 30thweek of gestation of each unique pregnancy (Figure 1). The questionnaires asked the mothers to report their anxiety level, in addition to providing information regarding their age, education, marital status, smoking and drinking habits, and their relationship with their partner. The MoBa cohort[12] was also linked to the Medical Birth Registry of Norway (MBRN), which contains detailed medical information about new-born children (gender, birthweight, and gestational age) as well as their mothers (parity and birth complications).

Among these full data sets, there were 12,480 pairs of siblings. The mean age difference between siblings was 2.77 years. The numbers of pairs dropped slightly after excluding half-siblings who had the same mother but different fathers (Figure 1). We used version eight of the quality-assured data files.

Measures

Measures of maternal general anxiety

Mothers reported symptoms of anxiety using validated short versions of two Hopkins Symptom Checklists, the SCL-5 and SCL-8. Items from the SCL are scored on a Likert scale ranging from 1 (not at all bothered) to 4 (very much bothered) and have been validated at a correlation of 0.92 with the SCL-25[13]. Assessments of anxiety were reported in the 17th and 30thgestational weeks of each pregnancy. Two out of five questions from the SCL-5 and four out of eight questions from the SCL-8 measured anxiety at 17th and 30th gestational week, respectively. The mean score for the 17th and 30thgestational week measure ranged from 1-4. The "week 17" in Table 2-B represents the effect of maternal anxiety score at 17th gestational week on the birth outcomes (birthweight and gestational age), and so does the "week 30" that of maternal anxiety score at 30th week on the birth outcomes. The "Both" represents the additive effect of maternal anxiety score at 17th, 30thgestational week and the interaction.

The mean score for the two assessments ranged from 1.2 to 1.4 and included the following items: constantly frightened or anxious; nervous, inner turmoil; tense or stressed; and sudden fear without reason.

Birthweight and Gestational age

Birthweight (measured in grams) was extracted from the MBRN and was treated as a continuous scale producing a mean value of 3,608 (SD 544.8). Gestational age (measured in days) was also treated as a continuous variable and the mean score was 39.5 (SD 1.72). All maternity units in Norway must notify the MBRN of all births and pregnancies terminating after week 12. The MBRN includes information on pre- and post-pregnancy variables including medication, birth complication, and maternal complications.

Assessment of potential confounders

Potential confounding factors were considered based on whether they could influence both prenatal maternal anxiety and child development outcomes, and were included in the adjusted model if associated with the exposure (prenatal maternal anxiety) and one of the two outcome measures. The following variables were considered to be potential confounders: alcohol consumption during pregnancy (coded as 0 for "never" and 1 for "more than once a month"); smoking in pregnancy (coded as 0 for "never", 1 for "sometimes", and 2 for "daily"); marital status (coded as 0 for "married/living together" and 1 for "single"); and maternal education (coded as 0 for "higher university degree, and "1" for +4 years)", 1 for "college/university (3 years), 2 for "college (1-2 years)", and 3 for "secondary school"). The following variables extracted from the MBRN were also controlled for: maternal age as a continuous variable; parity coded as itself, where greater

than or equal to 4 was coded as 4+; birth complications (coded as 1 for "yes" or 0 for "no"); child's sex (coded as 0 for "girl" and 1 for "boy"); and preeclampsia (coded as 0 for "no" and 1 for "yes").

Statistical analyses

Multiple regressions were used to estimate the effects of prenatal maternal anxiety on birthweight and gestational age. In a full cohort where all subjects with the exposures, outcomes and adjusting variables were included, we regressed birthweight and gestational age on maternal anxiety score at 17^{th} and 30^{th}gestational week, their interactions (Crude in Table 2-A and 2-B), and further included adjusting variables step by step. The step1 encompassed maternal smoking and alcohol intake, and the step 2 was those in the step 1 and parity, birth complication, child's sex and preeclampsia. The step 3 was those in the step 2 and maternal age, education and marital status. Regression analyses were performed in R 4.0.0.

In the sibling comparison design, we selected all available sibling pairs (For families participating more than three times, the sibling pairs were randomly selected) and computed the difference values in each variable between a sibling and the other. Similar to the analyses in the full cohort, we regressed the sibling-difference values in the outcomes on those in the exposures, controlling for family shared effects. Here, the three steps of adjustments were made in the same manner as in the full cohort.

We performed multiple imputations to handle the missing data points in the exposures, outcomes and adjusting variables. The mice R package was used; the number of imputations was set to be 5 (m=5), and the imputation method in use was predictive mean matching (method="pmm"). All the analyses in the full cohort and sibling-design were re-run using the imputed data (Supplementary File x).

Results

In the full cohort (Table 1-A), the mean birthweight of infants of mothers reporting severe anxiety symptoms in the 17^{th}gestational week was 85.3 grams lower than that of infants born to mothers with very light anxiety symptoms or none at all. Similarly, the mean birthweight of infants born to mothers reporting severe anxiety symptoms in the 30^{th} gestational week was 94 grams lower than that of infants not exposed to high levels of maternal anxiety. The mean gestational age between light and severe maternal anxiety differed by two days for those reporting maternal anxiety in the 17^{th} gestational week. Between light and severe anxiety symptoms reported in the 30^{th} gestational week, the mean gestational age decreased by three days.

Among the 25,058 siblings (see Table 1-B), a mean birthweight difference between infants born to mothers reporting light anxiety symptoms and infants born to mothers reporting severe anxiety symptoms was also found. However, for the sibling subsample, only a 53.1-gram difference in mean birthweight was recorded for infants exposed to light anxiety or none at all, as reported in the 17^{th} gestational week. Mean birthweight for infants exposed to severe compared to light or no maternal anxiety, as reported in the 30^{th} gestational week, differed by 148.3 grams. Mean gestational age decreased by two days between infants born to mothers reporting severe symptoms and infants born to mothers reporting light symptoms in the 17^{th} gestational week; however, this difference was five days for those reporting symptoms in the 30^{th}gestational week.

Differences in anxiety levels between the two pregnancies were also examined. Of mothers participating twice, a sample of 1,502 mothers (17%) experienced more anxiety during their first pregnancy than during their second pregnancy, while 2,756 mothers (9%) had the opposite experience. The rest of the mothers (74%) experienced the same anxiety levels during their first and second pregnancies. The mean difference between maternal anxiety during first and second pregnancies was small ($\text{mean}_{\text{diff}} = 0.05$).

Regression analyses for prenatal maternal anxiety and birthweight

First, as shown in Table 2-A, the maternal anxiety score at the 17^{th} week was associated with birthweight. A stronger association was found for those reporting symptoms in the 30^{th} week. Children exposed to maternal anxiety prenatally, as reported at both the 17^{th} and 30^{th} gestational weeks, were at higher risk of low birthweight compared to those not exposed and those exposed only once during pregnancy. This

association was reduced, but remained, after adjusting for smoking and alcohol consumption. In addition, adjustments for potential confounders at steps 2 and 3 found the association to be weaker but still significant.

Sibling-comparison analyses found maternal anxiety to be associated with low birthweight when reported in only the 17^{th}gestational week and in only the 30^{th} gestational week. Children exposed to maternal anxiety as reported in both the 17^{th} and 30^{th} gestational weeks were at the highest risk of low birthweight, even after shared-family confounding was adjusted for. This association remained robust after adjusting for smoking and alcohol intake during pregnancy. However, the association was no longer significant when the birth-related and socio-demographic variables were controlled for.

Regression analyses for prenatal maternal anxiety and gestational age

We also examined the association between maternal anxiety and gestation (Table 2-B). In the full cohort, a stronger association was found for those reporting symptoms in the 30^{th} week. Children exposed to maternal anxiety prenatally, across both the 17^{th} and 30^{th} gestational weeks, were at higher risk of short gestational age, compared to those not exposed and those exposed only once during pregnancy. This association was only moderately reduced, after adjusting for smoking and alcohol consumption and remained significant. Similarly to the associations for birthweight, these associations was further reduced, but remained robust after adjusting for multiple birth-related and socio-demographic variables in step 2 and 3.

In the sibling-design, we found no significant associations between maternal anxiety and gestational age. The confidence intervals were quite wide and overlapped the corresponding confidence intervals derived from the full cohort. Unlike the case of birthweight, the different set of adjustments did not change the magnitude of the associations.

Supplementary analyses after multiple imputations

Additional supplementary analyses was conducted after multiple imputations. As can be seen in the supplementary files S-Table 2-A and S-Table 2-B, after multiple imputations the width of the confidence intervals was smaller. In addition the association between prenatal maternal anxiety at week 30 and gestational age remained in the sibling cohort, adjusting for shared family effects and control variables in all steps.

Discussion

Main Findings

Infants of mothers reporting severe anxiety symptoms in the 17^{th} gestational week were more likely to have lower birth weight than infants born to mothers with very light anxiety symptoms or none at all. This association was reduced, but remained, after adjusting for shared family factors as well as smoking and alcohol consumption. However, in the sibling subsample, once socio-demographic variables were controlled for, the association was no longer significant. In regard to prenatal anxiety and gestational age, there wass no significant change before and after family adjustment. After multiple imputations, maternal anxiety at week 30 in pregnancy was significantly associated with shorter gestational age.

Strengths and limitations

There are several strengths to this study. First, the prospective nature of this study reflects the direction of effects and enhances the validity of measurements. In addition, the large sample size provided a range of opportunities to adequately control for confounding factors. This enabled examination of the association between maternal anxiety and birthweight and gestation. That is, several confounders could be included at different levels, such as those operating prenatally, as well as those related to birthweight and gestation (e.g. birth complications). Contextual factors such as maternal age and education could also be included. Next, the unique sample included a large sibling population, which allowed adequate control for family variables such as maternal genetic effects. [11] A sibling comparison design using a large cohort study can test whether associations differ between children born after subsequent pregnancies to the same mother. A discordant sibling design could also rule out all environmental differences that may vary between families, which can't be done using a population comparison design.[14] However, although the sibling design is helpful to control

for constant family factors, caution is required as effects could also be a result of unmeasured unshared environmental factors.[15] The women participating with multiple pregnancies might also represent a selection bias: there is a possibility that the first pregnancy influences the second, as has been suggested by Sjölander et al.,[16]and Frisell et al.[17] It should also be noted that important moderators that could influence maternal anxiety have not been examined (for example, genetic x environmental effects). In addition, maternal self-reporting was used to measure maternal anxiety. Social stigma about mental health problems, and especially a desire to appear healthy for the expected baby, could potentially lead to the under-reporting of anxiety symptoms. However, in large-scale cohort studies, the full range of symptoms can be found.

Interpretation

Several studies have focused on effects of anxiety on low birthweight and premature birth, both of which have been recognized as important markers for later mental health problems.[5, 18,19] Mean birthweight was lower for infants born to mothers reporting severe symptoms of anxiety, and the lowest birthweight was found for exposure to anxiety symptoms as reported in the 30^{th}gestational week. During the third trimester in a pregnancy, the fetus grows rapidly and triples its weight, and these findings suggest that severe symptoms of anxiety later in pregnancy increase the chance of a lower birthweight. The findings persisted following control for multiple covariates, such as smoking and alcohol exposure, birth complications, and the socio-economic status of the mother. These findings are also in accordance with a meta-analysis performed by Ding et al.[5] which found that maternal anxiety was associated with an increased probability of low birthweight. We also found maternal anxiety in pregnancy to be linked to shortened gestational age in the full cohort, with wider overlapping confidence intervals in the sibling control analyses. After multiple imputations maternal anxiety at week 30 in pregnancy was associated with gestational age, as was found in that earlier meta-analysis[5].

There are several hypotheses regarding the influence of maternal anxiety on fetal growth and gestation. One such mechanism involves changes to maternal hypothalamic-pictuary-adrenal (HPA) axis activity.[20] That is, it is suggested that maternal anxiety during pregnancy increases the production of stress hormones such as cortisol and catecholamines.[21,22] Animal models have found these stress hormones to influence uterine blood flow and immunologic functioning, thus potentially increasing risk of shortened gestational length and lower fetal growth.[23]Another potential explanation for this link, could be through higher risks of infections due to stress. Studies suggests that high levels of stress may be linked to lower immune funcuion[24] , and increased infections during pregnancy that could shorten gestation.[25]

The second aim was to apply a sibling comparison design to compare siblings that differed in exposure to maternal anxiety. This made it possible to estimate associations without the potential confounding by unmeasured constant family effects. Several studies have found individuals high in stress and anxiety to be at risk of poor health outcomes[26,27] and to display higher-risk behaviours.[28] Thus, several confounders needed to be taken into consideration, including shared-family confounding.

We found that exposure to maternal anxiety was associated with lower birthweight, also when family effects were controlled in sibling analyses. The association increased after controlling for smoking and alcohol exposure. However, the effect became non-significant after parity, birth complications, child's sex, and preeclampsia were controlled for. These associations were also examined for gestation age; however unlike the case of birthweight, the different set of adjustments did not change the magnitude of the associations. It is possible that for the sibling analyses, these associations were not significant due to a smaller sample size. In fact, after multiple imputations to account for missing, maternal anxiety at week 30 in pregnancy was significantly associated with shorter gestational age.

Self-reported exposure to maternal anxiety during pregnancy has therefore found to be associated with an increased risk of low birthweight and shorter gestation age. This finding is in accordance with previous studies examining prenatal anxiety and birth outcomes.[29,30,31] However, the association for prenatal anxiety and gestation was not significant in the sibling sub-sample, this could reflect the fact that a low-risk sample, in which few children are born preterm, was used and it could also reflect the fact that perinatal care was provided for these women to reduce the risk of preterm birth. However, it should be noted that the findings

are conflicting and some studies have found only small associations between prenatal maternal anxiety and preterm birth[30] and some have found no such association.[31]

Conclusion

These findings suggest that prenatal anxiety is associated with low birthweight and short gestational age. This association was robust following consideration of controlling for shared family confounding, and exposure to alcohol and smoking during pregnancy. It is therefore important to consider maternal mental health during pregnancy, as these women may need extra psychological attention and support during prenatal care.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors declare that they have no conflict of interest.

The Author Contributions: MB developed the research question and prepared the first draft of the manuscript together with SO, YL, REB and PM. MB have been the main author of all sections of the paper, while REB has written the introduction. YL has conducted all analyses together with SO. All authors has contributed to the interpretation of the data and analyses for the work, and all authors revised the manuscript critically and approved the version to be published.

Ethical approval: The MoBa have approval from the committee for medical research ethics in 2009 (REK-2009/1899-7), and 12$^{\text{th}}$ of October, 2016 (REK-2016/1424).

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References

1. Academy of Medical Sciences (AMS) (2007). *Identifying the environmental causes of disease: how should we decide what to believe and when to take action?* London: Academy of Medical Sciences.

2. Andersson, L., Sundström-Poromaa, I., Bixo, M., Wulff, M., Bondestam, K., & Åström, M. (2003). Point prevalence of psychiatric disorders during the second trimester of pregnancy: a population-based study.*Am J Obstet Gynecol, 189* (1), 148-154.

3. Berle, J., Mykletun, A., Daltveit, A. K., Rasmussen, S., Holsten, F., & Dahl, A. A. (2005). Neonatal outcomes in offspring of women with anxiety and depression during pregnancy. *Arch Womens Ment Health, 8* (3), 181-189.

4. Accortt, E. E., Cheadle, A. C., & Schetter, C. D. (2015). Prenatal depression and adverse birth outcomes: an updated systematic review.*Matern Child Health J, 19* (6), 1306-1337.

5. Ding, X.-X., Wu, Y.-L., Xu, S.-J., Zhu, R.-P., Jia, X.-M., Zhang, S.-F., . . . Tao, F.-B. (2014). Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. *J Affective Disorders, 159* , 103-110.

6. Loomans, E. M., Van Dijk, A. E., Vrijkotte, T. G., Van Eijsden, M., Stronks, K., Gemke, R. J., & Van den Bergh, B. R. (2012). Psychosocial stress during pregnancy is related to adverse birth outcomes: results from a large multi-ethnic community-based birth cohort. *Eur J Environ Public Health, 23* (3), 485-491.

7. Nasreen, H. E., Kabir, Z. N., Forsell, Y., & Edhborg, M. (2010). Low birth weight in offspring of women with depressive and anxiety symptoms during pregnancy: results from a population based study in Bangladesh.*BMC Public Health, 10* (1), 515.

8.Sanchez, S. E., Puente, G. C., Atencio, G., Qiu, C., Yanez, D., Gelaye, B., & Williams, M. A. (2013). Risk of spontaneous preterm birth in relation to maternal depressive, anxiety and stress symptoms. *J Reprod Med, 58* , 25.

9. Lewis, S.J., Relton, C., Zammit, S. and Smith, G.D. (2013), Approaches for strengthening causal inference regarding prenatal risk factors for childhood behavioural and psychiatric disorders. *J Child Psychol Psychiatry, 54* : 1095-1108. doi:10.1111/jcpp.12127

10. Smith, G. D. (2008). Assessing intrauterine influences on offspring health outcomes: can epidemiological studies yield robust findings?*Basic Clin Pharmacol Toxicol, 102* (2), 245-256.

11. D'onofrio, B. M., Lahey, B. B., Turkheimer, E., & Lichtenstein, P. (2013). Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. *Am J Public Health, 103* (S1), S46-S55.

12. Magnus, P., Birke, C., Vejrup, K., Haugan, A., Alsaker, E., Daltveit, A. K., . . . Knudsen, G. P. (2016). Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol* , 45 (2)382-8. doi: 10.1093/ije/dyw02.

13. Tambs, K., & Moum, T. (1993). How well can a few questionnaire items indicate anxiety and depression? *Acta Psychiatr Scand, 87* (5), 364-367.

14. Lahey, B. B., & D'Onofrio, B. M. (2010). All in the Family: Comparing Siblings to Test Causal Hypotheses Regarding Environmental Influences on Behavior. *Curr Dir Psychol Sci* , *19* (5), 319–323. doi:10.1177/0963721410383977

15. Kendler KS. Causal Inference in Psychiatric Epidemiology. *JAMA Psychiatry* . 2017;74(6):561–562. doi:10.1001/jamapsychiatry.2017.0502

16. Sjölander, A. (2016). A cautionary note on the use of attributable fractions in cohort studies. *Stat Methods Med Res, 25* (6), 2434-2443. doi:10.1177/0962280214523953

17. Frisell, T., Oberg, S., Kuja-Halkola, R., & Sjolander, A. (2012). Sibling comparison designs: bias from non-shared confounders and measurement error. *Epidemiol, 23* (5), 713-720. doi:10.1097/EDE.0b013e31825fa230

18. Schlotz, W. Phillips, D. I.W., (2009). Fetal origins of mental health: Evidence and mechanisms. *Brain, Behav Immun* , 23 (7). 905-916. https://doi.org/10.1016/j.bbi.2009.02.001.

19. Wojcik, W., Lee, W., Colman, I., Hardy, R., Hotopf, M. (2013). Foetal origins of depression? A systematic review and meta-analysis of low birth weight and later depression. *Psychol Med* , 43, 1-12.

20. Weaver, I.C.G. et al. (2017). Stress and the emerging roles of chromatin remodeling in signal intergration and stable transmission of reversible phenotypes. *Frontiers in Behav Neurosci, 11. 41* https://doi.org/10.3389/fnbeh.2017.00041.

21. Coussons-Read, M. E., Lobel, M., Carey, J. C., Kreither, M. O., D'Anna, K., Argys, L., ... Cole, S. (2012). The occurrence of preterm delivery is linked to pregnancy-specific distress and elevated inflammatory markers across gestation. *Brain, Behav Immun* , *26* (4), 650–659. doi:10.1016/j.bbi.2012.02.009

22. Dunkel Schetter, C., & Tanner, L. (2012). Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice. *Curr Opin Psychiatry* *25* (2), 141–148. doi:10.1097/YCO.0b013e3283503680

23. Wadhwa PD, Entringer S, Buss C, Lu MC. The contribution of maternal stress to preterm birth: issues and considerations. *Clin Perinatol* . 2011;38(3):351–384. doi:10.1016/j.clp.2011.06.007

24. Cohen S, Miller GE, Rabin BS. Psychological stress and antibody response to immunization: a critical review of the human literature.*Psychosom Med* . 2001 Jan-Feb; 63(1):7-18. 10.1097/00006842-200101000-00002

27. Madianos PN, Lieff S, Murtha AP, et al. Maternal periodontitis and prematurity. Part II: Maternal infection and fetal exposure. *Ann Periodontol* . 2001;6(1):175-182. doi:10.1902/annals.2001.6.1.175

26. Felitti VJ,Anda RF,Nordenberg D,et al. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences(ACE) study.*Am J Prev Med* , 14(4):245-258.doi:10. 1016/S0749-3797(98)00017-8

27. Schneiderman, N., Ironson, G., & Siegel, S. D. (2005). Stress and health: psychological, behavioral, and biological determinants.*Annu Rev Clin Psychol* , *1* , 607–628. doi:10.1146/annurev.clinpsy.1.102803.144141

28. Kendler, K. S., Gardner, C. O., Fiske, A., & Gatz, M. (2009). Major depression and coronary artery disease in the Swedish twin registry: phenotypic, genetic, and environmental sources of comorbidity. *Arch Gen Psychiatry* , *66* (8), 857–863. doi:10.1001/archgenpsychiatry.2009.94

29. Grigoriadis S, Graves S, Peer M, Mamisashvili, MSW, Tomlison G,. . . . . Richter, M. (2018). Maternal anxiety during pregnancy and association with adverse perinatal outcomes: Systematic review and meta-analyses. *J Clin Psychiatry* , 79 (5) 17r12011

30. Wadhwa PD, Sandman CA, Porto M, Dunkel-Schetter C, Garite TJ. (1993). The association between prenatal stress and infant birth weight and gestational age at birth: A prospective investigation. *Am J Obstet Gynecol* , 169 (4) 858-865.

31. Staneva, A, Bogossian F, Pritchard M, Wittkowski A. (2015). The effects of maternal depression, anxiety and precieved stress during pregnancy on preterm birth: A systematic review. *Women Birth* , 28, 179-93.

30. Psonen, A-K, Lahti M, Kuusinen T, Tuovinen S, Villa P, Hämäläinen E. . . . . ..Räikkönen K. (2016). Maternal prenatal positive affect, depressive and anxiety symptoms and birth outcomes:The PREDO Study. *Plus One* , 11(2): e0150058.doi.10.1371/journal.pone.0150058

31. Dayan, J.,, Creveuil, C., Marks, M., Conroy, S., Herlicoviez, M., Dreyfus, M., Tordjman, S., (2006). Prenatal depression, prenatal anxiety, and spontaneous preterm birth: A prospective cohort study among women with early and regular care. *Psychosom Med,* 68 (6), 938-946. doi: 10.1097/01.psy.0000244025.20549.bd

Table 1-A. Characteristics of full cohort.

Table 1-A. Characteristics of full cohort.

				Birthweight (in grams)	Birthweight (in grams)	Gestational age (in days)	Gestational age (in days)
		Count n=91,165	Mean μ=3,610.3	Mean μ=3,610.3	SD s=542.3	Mean μ=279.7	SD s=11.7
Maternal anxiety	1-2, Light	80,233	3,615.1	3,615.1	540.2	279.8	11.7
at week 17 (score)	2-3	8,022	3,581.1	3,581.1	554.3	279.1	12.1
	3-4, Severe	1,362	3,529.9	3,529.9	573.0	277.6	12.9
	NA	1,548	3,583.5	3,583.5	545.7	279.0	12.0
Maternal anxiety	1-2, Light	85,064	3,615.0	3,615.0	537.3	279.9	11.5
at week 30 (score)	2-3	4,690	3,559.4	3,559.4	572.9	278.5	13.2
	3-4, Severe	639	3,519.8	3,519.8	643.1	276.5	15.6
	NA	772	3,470.6	3,470.6	728.9	275.5	20.1
Maternal age	<25	9,862	3,552.4	3,552.4	547.6	279.0	12.3
	25-29	30,223	3,592.8	3,592.8	533.2	279.7	11.6
	30-34	35,280	3,631.6	3,631.6	536.4	279.9	11.4

Table 1-A. Characteristics of full cohort.	**Table 1-A.** Characteristics of full cohort.			Birthweight (in grams)	Birthweight (in grams)	Gestational age (in days)	Gestational age (in days)
	>=35	15,800	3,632.0	3,632.0	564.9	279.6	12.2
Partner harmony (score)	1-2, Good	64,618	3,602.6	3,602.6	540.2	279.8	11.8
	2-3	19,726	3,638.9	3,638.9	538.4	279.8	11.4
	3-4	3,977	3,646.6	3,646.6	537.8	279.6	11.2
	4-5	919	3,637.1	3,637.1	581.1	278.8	12.1
	5-6, Bad	359	3,518.4	3,518.4	570.4	278.8	11.5
	NA	1,566	3,476.8	3,476.8	617.3	278.0	14.8
Education	University 4y+	20,406	3,602.9	3,602.9	525.4	280.3	11.3
	College/University 3y	35,732	3,620.1	3,620.1	534.3	279.8	11.6
	College 1-2y	12,684	3,623.4	3,623.4	555.7	279.7	12.0
	Secondary school	17,720	3,595.2	3,595.2	566.3	278.8	12.3
	NA	4,623	3,588.3	3,588.3	542.6	279.8	12.0
Marital status	Married/Partner	87,656	3,613.7	3,613.7	540.9	279.7	11.7
	Single	3,509	3,523.1	3,523.1	568.3	279.1	12.3
Parity	0	41,316	3,505.5	3,505.5	535.4	279.9	12.5
	1	32,276	3,683.5	3,683.5	523.1	279.8	10.8
	2	13,754	3,725.8	3,725.8	541.4	279.4	11.1
	3	2,912	3,723.1	3,723.1	562.3	278.7	11.8
	4	907	3,661.1	3,661.1	601.8	276.5	13.1
Alcohol consumption during pregnancy	Never	74,786	3,611.1	3,611.1	541.7	279.7	11.8
	1+/month	533	3,567.4	3,567.4	537.9	280.4	12.1
	NA	15,846	3,607.6	3,607.6	545.1	279.8	11.7
Smoking during pregnancy	None	81,879	3,621.6	3,621.6	538.9	279.8	11.6
	Sometimes	4,018	3,570.9	3,570.9	554.5	279.9	12.3
	Daily	3,746	3,420.1	3,420.1	553.4	278.5	12.4
	NA	1,522	3,571.3	3,571.3	566.9	279.2	13.2
Birth complication	No	66,220	3,627.8	3,627.8	546.0	280.1	11.9
	Yes	24,945	3,563.6	3,563.6	529.3	278.6	11.3
Child sex	Girl	44,450	3,546.2	3,546.2	524.6	279.2	11.5
	Boy	46,715	3,671.2	3,671.2	551.7	280.2	12.0
	NA	87,792	3,624.7	3,624.7	524.6	280.1	11.2
Preeclampsia	Yes	3,373	3,234.0	3,234.0	799.2	270.2	19.2
	No	80,233	3,615.1	3,615.1	540.2	279.8	11.7

Table 1-B. Characteristics of sibling sub-sample.

				Birthweight (in grams)	Birthweight (in grams
		Count	Mean	Mean	SD
		n=24,960	μ=3,639.5	μ=3,639.5	s=523.0
Maternal anxiety	1-2, Light	22,888	3,642.9	3,642.9	521.4
at week 17 (score)	2-3	1,571	3,602.7	3,602.7	538.5
	3-4, Severe	219	3,598.8	3,598.8	510.1
	NA	282	3,596.6	3,596.6	563.2
Maternal anxiety	1-2, Light	23,836	3,642.5	3,642.5	519.2
at week 30 (score)	2-3	890	3,605.8	3,605.8	562.6
	3-4, Severe	104	3,489.5	3,489.5	575.4
	NA	130	3,444.3	3,444.3	767.5
Maternal age	<25	2,306	3,598.8	3,598.8	540.8
	25-29	8,883	3,623.9	3,623.9	521.0
	30-34	10,265	3,655.6	3,655.6	517.1
	>=35	3,506	3,658.4	3,658.4	530.4
Partner harmony (score)	1-2, Good	18,030	3,628.7	3,628.7	522.6
	2-3	5,497	3,669.9	3,669.9	516.2
	3-4	984	3,686.4	3,686.4	518.7
	4-5	198	3,698.8	3,698.8	549.8
	5-6, Bad	47	3,577.9	3,577.9	470.7
	NA	204	3,501.4	3,501.4	660.7
Education	University 4y+	6,432	3,634.1	3,634.1	507.0
	College/University 3y	10,958	3,641.6	3,641.6	523.6
	College 1-2y	2,945	3,647.4	3,647.4	528.8
	Secondary school	3,572	3,635.8	3,635.8	541.7
	NA	1,053	3,640.2	3,640.2	531.7
Marital status	Married/Partner	24,420	3,640.4	3,640.4	522.3
	Single	540	3,596.7	3,596.7	548.9
Parity	0	9,425	3,535.0	3,535.0	528.3
	1	11,388	3,692.1	3,692.1	505.2
	2	3,279	3,739.1	3,739.1	513.3
	3	654	3,736.3	3,736.3	514.2
	4	214	3,619.2	3,619.2	616.9
Alcohol consumption	Never	21,072	3,641.0	3,641.0	521.0
during pregnancy	1+/month	97	3,602.8	3,602.8	559.2
	NA	3,791	3,632.0	3,632.0	532.8
Smoking	None	23,251	3,646.5	3,646.5	521.3
during pregnancy	Sometimes	743	3,577.1	3,577.1	533.9
	Daily	589	3,442.7	3,442.7	528.1
	NA	377	3,637.3	3,637.3	529.2
Birth complication	No	17,519	3,662.7	3,662.7	528.6
	Yes	7,441	3,584.8	3,584.8	505.3
Child sex	Girl	12,172	3,579.4	3,579.4	504.2
	Boy	12,788	3,696.7	3,696.7	534.0
	NA	24,164	3,650.9	3,650.9	507.5
Preeclampsia	Yes	796	3,292.1	3,292.1	796.2
	No	22,888	3,642.9	3,642.9	521.4

Table 2-A. Effect of maternal anxiety on birth weight.

Full cohort	Crude	Step1*	Step2**	Step3***
	Beta [95% CI]	Beta [95% CI]	Beta [95% CI]	Beta [95% CI]
No Anxiety	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Week 17	**-55.8 [-78.3, -33.2]**	**-53.8 [-79.3, -28.3]**	**-28.5 [-53.3, -3.8]**	**-26.9 [-52.7, -1.2]**
Week 30	**-78.8 [-102.5, -55.1]**	**-63.9 [-90.9, -36.9]**	**-38 [-64.2, -11.8]**	**-34.5 [-61.7, -7.3]**
Both	**-112.8 [-142.7, -83]**	**-95.1 [-128.9, -61.2]**	**-56.3 [-89.1, -23.4]**	**-54.2 [-88.4, -20.1]**
Sample size	88,904	73,014	73,014	69,430
Sibling cohort				
No Anxiety	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Week 17	**-92.1 [-150.8, -33.5]**	**-102.5 [-173.4, -31.6]**	-0.4 [-68.5, 67.7]	-3.7 [-75.6, 68.3]
Week 30	**-115.1 [-175.8, -54.3]**	**-118.8 [-193.5, -44]**	-13 [-84.9, 58.9]	-14.1 [-90.1, 62]
Both	**-173.9 [-252.3, -95.4]**	**-185.4 [-281.1, -89.7]**	-24.2 [-116.5, 68]	-31.1 [-128.5, 66.3]
Sample size[1]	12,080	8,937	8,937	8,298

*Adjusted for smoking and alcohol intake.

**Adjusted for smoking, alcohol intake, parity, birth complication, child's sex and preeclampsia.

***Adjusted for smoking, alcohol intake, parity, birth complication, child's sex, preeclampsia, maternal age, education and marital status.

[1] Number of sibling "pairs".

Table 2-B. Effect of maternal anxiety on gestational age.

Full cohort	Crude	Step1*	Step2**	Step3***
	Beta [95% CI]	Beta [95% CI]	Beta [95% CI]	Beta [95% CI]
No Anxiety	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Week 17	**-0.61 [-1.1, -0.13]**	**-0.71 [-1.26, -0.16]**	**-0.66 [-1.2, -0.11]**	-0.5 [-1.07, 0.06]
Week 30	**-1.28 [-1.79, -0.77]**	**-1.27 [-1.86, -0.69]**	**-1.16 [-1.74, -0.58]**	**-0.94 [-1.54, -0.34]**
Both	**-1.77 [-2.42, -1.13]**	**-1.83 [-2.57, -1.1]**	**-1.72 [-2.44, -0.99]**	**-1.43 [-2.19, -0.68]**
Sample size	88,596	72,769	72,769	69,192
Sibling cohort				
No Anxiety	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Week 17	0.14 [-1.22, 1.51]	0.41 [-1.24, 2.05]	0.55 [-1.09, 2.19]	0.34 [-1.39, 2.08]
Week 30	-1.32 [-2.74, 0.1]	-1.45 [-3.18, 0.29]	-1.32 [-3.06, 0.41]	-1.39 [-3.22, 0.45]
Both	-1.08 [-2.91, 0.75]	-1.08 [-3.31, 1.14]	-0.89 [-3.12, 1.33]	-1.08 [-3.42, 1.27]
Sample size[1]	12,017	8,883	8,883	8,249

*Adjusted for smoking and alcohol intake.

**Adjusted for smoking, alcohol intake, parity, birth complication, child's sex and preeclampsia.

***Adjusted for smoking, alcohol intake, parity, birth complication, child's sex, preeclampsia, maternal age, education and marital status.

[1] Number of sibling "pairs".

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