The Effect of Maternal Hypertension and Maternal Mental Illness on Adverse Neonatal Outcomes: A Mediation and Moderation Analysis in a U.S. Cohort of 9 Million Pregnancies

Jason Raina, MD[1]; Guillaume Elgbeili, MSc[2]; Tina Montreuil, MD, OPQ[2]; Tuong-Vi Nguyen, MD, MSc[1,2]; Marc Beltempo, MD[3]; Dian Kusuma, MPH, ScD[4]; Togas Tulandi, MD, MHCM[1]; Natalie Dayan, MD, MSc[1]; Femmy Yunia Bahroen, MD, MHA[1]; Christina Caccese, MSc[5]; Ahmad Badageish, MD, MPH, FRCSC [1]; Eva Suarthana, MD, PhD[1]

[1]Department of Obstetrics and Gynecology, McGill University, Montréal, Québec, Canada;

[2]Department of Psychiatry, McGill University, Montréal, Québec, Canada

[3]Department of Pediatrics, McGill University, Montréal, Québec, Canada

[4]School of Health and Psychological Sciences, City, University of London, UK

[5]McGill University Health Center, Montréal, Québec, Canada

Corresponding author:

Eva Suarthana MD, Ph.D.

Department of Obstetrics and Gynecology

McGill University

1001 Decarie Boulevard

Montréal, Québec, Canada, H4A 3J1

Fax: (514)-843-1496

Email: eva.suarthana@mcgill.ca

Manuscript: 2,729 words

ABSTRACT

Background

While Hypertensive Disorders of Pregnancy (HDP) coexist with maternal anxiety and depression, it is unclear how these conditions affect neonatal outcomes. We evaluated the prevalence as well as associations and potential mechanisms between HDP, maternal anxiety and depression, preterm birth (PTB), and small for gestational age (SGA).

Methods

We conducted a retrospective population-based study using the Healthcare Cost and Utilization Project (HCUP) database from 2004 to 2014. Preterm birth (<37 weeks), SGA (<10th percentile for gestational age and sex), HDP, and mental disorders (anxiety and depression) were extracted using the International Classification of Diseases, Ninth Revision (ICD-9). Mediation and moderation models were constructed separately to evaluate potential mechanisms between maternal anxiety and depression, HDP, and adverse neonatal outcomes. Multivariate logistic regressions were used to determine their associations.

Results

Of 9,097,355 pregnant women, the prevalence of HDP was 6.9%, anxiety 0.91%, depression 0.36%, preterm birth 7.2%, and SGA 2.1%. Anxiety increased the probability of having HDP (OR=1.242, 95% CI 1.235–1.250), and HDP mediated the association between anxiety and preterm birth (mediation effect=0.048, p-value<0.001). Depression significantly moderated the effect of HDP on preterm birth (moderation effect=-0.126, p-value=0.027). HDP also mediated the association between anxiety and SGA (mediation effect=0.042, p-value<0.001), but depression did not moderate the association between HDP and SGA (p-value=0.29).

Conclusion

Our study suggests that women with anxiety are more likely to have HDP, and HDP mediates the associations between anxiety and adverse neonatal outcomes. Depression moderates associations between HDP and preterm birth but not between HDP and SGA.

Keywords: preterm birth, small for gestational age, anxiety, depression, hypertensive disorders of pregnancy

Abstract: 246 words

INTRODUCTION

Globally, 2.4 million neonates and children died within the first month of life in 2019 (World Health Organization, 2020). Adverse neonatal outcomes during pregnancy, namely preterm birth, infant with low birth weight or small for gestation age (SGA), intrapartum-related complications, infections, and birth defects are the driving forces for neonatal deaths (World Health Organization, 2020). The estimated preterm birth rate is 7.8% in Canada and 8.4% in the United States (Ferré et al., 2016; Statistics Canada, 2021). In high-income countries preterm birth rates average around 9.3% (Chawanpaiboon et al., 2019). Infants with SGA in Canada and the United States were estimated to be 8.9% and 8.3% respectively (Martin et al., 2021; Statistics Canada, 2021).

Maternal mental disorders and hypertensive disorders of pregnancy (HDP, including gestational hypertension, preeclampsia, and eclampsia) have each been shown to be independently associated with the development of both preterm birth and SGA (Ding et al., 2014; Mengistu & Kuma, 2020). Research as delved into the associations between depression, anxiety and the risk of developing HDP through prospective longitudinal studies where factors contributing to the former may play a role (comorbid depression and anxiety, BMI) (Jackson et al., 2016). Exploring mediating factors between these variables during a very sensitive period of development (pregnancy) is critical, due to the heightened risk on well-being of mother and baby. Prior mediation and moderation models studies have shown biological determinants as well as physiological immaturity are associated with neonatal mortality with outcomes, namely preterm birth (Brown et al., 2014). However, the interplay between maternal hypertension and anxiety on neonatal outcomes has not been well studied. Our previous publication reported increasing trends of mental disorders including anxiety and depression among hospitalized pregnant women in the

United States. We also demonstrated consistent associations between HDP and anxiety, but not between HDP and depression (Raina et al., 2021). For this reason, we aimed to create models to evaluate HDP as the mediator of the associations between anxiety and adverse neonatal outcomes in a large population dataset. Separately, we evaluated models where depression moderated the associations between HDP and adverse neonatal outcomes.

MATERIALS AND METHODS

Study samples

We evaluated all hospital discharge records in the Healthcare Cost and Utilization (HCUP) – Nationwide Inpatient Sample (NIS) dataset from 2004-2014 using the pregnancy codes based on the International Classification of Diseases, Ninth Revision (ICD-9) codes for pregnancy (validated codes: 634x-679x, V22x, V23x, V27x; or procedure codes: 72x-75x). The HCUP-NIS database is a 20% stratified sample of all discharges from hospitals in the United States with the exclusion of certain facilities, such as long-term care homes and rehabilitation centers. It contains data from an estimated 7 million per year inpatient hospital stays from over 1,000 community hospitals (HCUP, 2021). Information provided through the database is geographically unrestricted. Data obtained for this study is exclusively publicly accessible and anonymous; hence this study requires no Institutional Review Board approval.

Adverse neonatal outcomes, HDP, maternal mental disorders, and potential confounders

We incorporated ICD-9 codes for gestational hypertension (642.3x), preeclampsia (642.4x, 642.5x), and eclampsia (642.6x), preterm birth (644.2x), and SGA (76x). We also extracted anxiety disorder (300.0x, 300.2x, 300.3x, 309.8x) and depression (296.2x, 296.3x, 300.4x, 311x). Covariates relevant to this study including those related to maternal demographics with or

without preterm birth and SGA were extracted from the dataset. Baseline characteristics included age, race, and insurance plan type. Potential cofounders included both maternal and pregnant co-morbidities such as smoking during pregnancy, substance abuse, obesity, thyroid disease, underlying chronic hypertension, pregestational diabetes mellitus, gestational diabetes mellitus, and multiple gestations. Parity and advanced maternal age pregnancy (maternal age >35 years) were also considered.

Statistical methods

Initial analysis consisted of determining the annual rates for the adverse neonatal outcomes in the presence or absence of either anxiety and/or HDP. Sociodemographic and clinical characteristics of the pregnant women as well as the adverse neonatal outcomes were stratified by the presence or absence of anxiety and/or HDP (i.e., no HDP, no anxiety; no HDP, had anxiety; had HDP, no anxiety; had HDP and anxiety) and compared using Chi-square test. The same applies to depression and/or HDP. Statistical significance was set at $p<0.05$

To examine potential associations between HDP and mental disorders on adverse neonatal outcomes, we used mediation and moderated models separately using a series of logistic regression. A mediation model was constructed to observe a potential relationship between anxiety and preterm birth or SGA using HDP as the mediator. The moderation model was constructed to determine if depression affects the association between HDP on preterm birth or SGA. We reported odds ratios (ORs) and 95 % confidence intervals (CIs) adjusted for sociodemographic characteristics and comorbidities (covariates: age, race, income, insurance type, hospital setting, smoking in pregnancy, substance use, obesity, thyroid disease, chronic hypertension, pregestational diabetes mellitus, gestational diabetes mellitus, and advanced maternal age (primigravida and multigravida). To test the mediation model, the analysis was

done through R4.0.1 version with RStudio (R Core Team, 2021). Statistical significance was set at $p<0.05$. R was also used to test the mediation model, using the lavaan package, creating a path analysis and computing the A*B effect and testing the significance of that effect with a Wald test.

RESULTS

Of 9,097,355 pregnant women evaluated, 628,140 (6.9%) had HDP; 82,629 (0.91%) had anxiety; 33,016 (0.36%) had depression; 653,895 (7.2%) had preterm birth; and 198,070 (2.1%) had SGA. Among women with any HDP, 95,507 had preterm birth and 30,070 had SGA (Fig. S1). Rates of preterm birth among pregnant women in the absence of anxiety, regardless of the presence of HDP, showed a decreasing trend during the study period (Fig. 1a). On the contrary, the rates of SGA among women without anxiety, showed increasing trend regardless the presence of HDP (Fig. 1b). Similar pattern was seen for the rates of preterm birth and SGA in the absence of depression, regardless of the presence of HDP during the same time period (Figure 2a and 2b, respectively).

Table 1 shows that in comparison to those without anxiety, women who experienced anxiety presented with more co-morbidities such as smoking during pregnancy, obesity, thyroid disease, pregestational DM and depression. Similar distributions were found in depressed women than those without (Table 2).

Table S1 presents baseline characteristics of pregnant women stratified by the presence or absence of adverse neonatal outcomes (i.e., preterm birth and SGA). In comparison to those with uneventful deliveries, women who experienced preterm delivery and SGA were younger, Caucasians, and had low-income profiles and had more comorbidities such as smoking during

pregnancy, substance abuse, chronic hypertension, anxiety, preeclampsia, and elderly primigravida.

Mediation and moderation model for the association between Anxiety and Preterm Birth

Anxiety on PTB Mediated by HDP; HDP on PTB Moderated by Depression

Figure 3a shows that women with anxiety were more likely of having HDP (OR: 1.242, 95% CI: 1.226-1.257) and PTB (OR=1.098, 95% CI: 1.084-1.113). The effect of anxiety on preterm birth was significantly mediated by HDP (mediation effect=0.048, p-value<0.001). Women with HDP were at greater likelihood of having PTB (OR=1.249, 95% CI: 1.247-1.252). Depression significantly moderated the associations between HDP and preterm birth (moderation effect=-0.126, p-value=0.027). Figure 3a also demonstrates that women with both HDP and depression had the highest predicted probability of having PTB (13.7%), while those without these two conditions had the lowest probability (5.0%). Among women without depression, those with HDP were 2.355 (95% CI: 2.345 – 2.365) more likely to have PTB than those without HDP, while among women with depression were 2.076 (95% CI: 1.961 – 2.197) times more likely. Among women without HDP, those with depression were 1.444 (95% CI: 1.413 – 1.476) times more likely to have PTB than those without depression, while among women with HDP, those with depression were 1.273 (95% CI: 1.208 – 1.342) times more likely.

Mediation and moderation model for the association between Anxiety and SGA

Anxiety on SGA Mediated by HDP; HDP on SGA Moderated by Depression

Figure 3b displays the same association between anxiety and risk of HDP (OR: 1.242, 95% CI: 1.235-1.250). Anxiety increased the probability of SGA (OR: 1.100, 95% CI 1.081-1.120). HDP also mediated the association between anxiety and SGA (mediation effect=0.042, p-value<0.001.

Women with HDP had greater odds of having SGA (OR=1.216, 95% CI 1.212-1.220). However, depression did not moderate the association between HDP and SGA (p-value=0.29).

COMMENT

Principle Findings and Results in the Context of What is Known

Our study showed decreasing trends of preterm birth in pregnant women with no anxiety or HDP. *Ferré et al* (Ferré et al., 2016) also found that the rate for spontaneous preterm birth decreased from 10.41% to 9.54% from 2007 to 2014. In agreement with another study (Sarkar et al., 2017), we found that women with preterm birth or SGA were less likely to be older or with higher income levels. Furthermore, when we stratified age less than 25 years, women who experienced SGA/preterm birth were had a higher percentage among those with HDP than without.

Our moderated model suggested the presence of depression plays a role in the development of PTB. The probability of PTB in patients with HDP compared to those without is dependent on the presence or absence of depression. The negative moderation effect represents a lower probability of PTB due to combination of HDP and depression compared to having HDP or depression independently. Li et al conducted a population prospective cohort showing that pregnant women with depression were at risk for preterm delivery. The severity of the depression also dictated the risk of preterm delivery (Li et al., 2009). It suggests that depression management might reduce the risk of preterm birth. This may explain the negative moderation effect of depression we found on the association between HDP and preterm birth. Another study has shown an increased risk of SGA in pregnant women with depressive symptoms (Babu et al., 2018).

The results of our mediation and moderation models showed that women with anxiety are at an increased likelihood of having HDP. A prospective cohort study from Alberta, Canada suggested that anxiety and depression may contribute to increased risk of SGA associated with HDP (Horsley et al., 2019). The origins of psychosocial stress and anxiety in women can be a factor in downstream neonatal complications. *Hoffman et al* (Hoffman et al., 2016) used cortisol levels measured through maternal hair follicles as an index of stress. Higher stress levels as indicated in increased cortisol levels were found in the second trimester of pregnancy and in those with preterm birth. It has been advocated those pregnant women with stimulation of cortisol through cortisol-releasing hormones may complicate the endocrine function of the placenta which further complicates chronic hypertension and hypertensive states (Warren et al., 1995). In addition, alterations in the maternal vascular system have been shown to alter stress patterns in pregnancy. Evidence has shown that uterine artery blood flow increased in the last trimester, enhancing maternal distress and anxiety though measurable parameters, such as K10 test (Vythilingum et al., 2010). As seen in our study, the effect of anxiety on preterm birth or SGA was significantly mediated by HDP. HDP, such as preeclampsia, have been shown to augment cortisol metabolism through various enzymes (Kosicka et al., 2018). Similar studies have found that the enzyme involved in cortisol metabolism, the placental 11β-hydroxysteroid dehydrogenase type 2, has decreased activity in a preeclampsia state, leading to cortisol elevation, and subsequent association with prematurity and low birth weight (Aufdenblatten et al., 2009).

Growth pathologies or prematurity can also be attributed to abnormal blood flow in the uteroplacental circulation. This can lead to insufficient blood supply to the fetus leading to early delivery, or pathological growth (Hüneke & Ude, 2002). McCubbin et al reported that a

substantial maternal diastolic blood pressure response to stress resulted in infants with low birth weights (McCubbin et al., 1996). This explains the role HDP plays during stress and the effect on a growing fetus.

Strengths and Limitations

The strength of our study was the use of a large population-based database. This allowed for extensive analysis of maternal psychopathologies with neonatal outcomes in the course of a decade. A large dataset over an extended period of time is vital to establish trends and determine associations. However, HCUP-NIS is a medico-administrative database, and hence lacks of clinical details. By using this database, it is not possible to ascertain if the diagnosis of interest was made during hospitalization or if the patient had been diagnosed previously. In addition, the validity of the diagnostic codes in HCUP-NIS might contribute to lower rates as seen in other types of administrative databases. This can explain the lower-than-expected preterm birth and SGA rates compared to the national average in developed countries such as the Canada and the United States. HCUP displays data in a cross-sectional manner, thereby providing no link between years to observe temporal trends. In terms of diagnosis, maternal hypertensive disorders like HDP, are diagnosed beyond 20 weeks gestation while anxiety has no specific timing diagnostic parameters in pregnancy. Therefore, based on the data structure, we assumed most anxiety disorders were diagnosed before HDP, but we acknowledge that this has limitations. In addition, it does not provide any information on pharmacological history or any treatments used during the hospital stay. *Avalos et al* examined the role anti-depressants play in the development of preeclampsia. The timing of anti-depressant medication use was determined to be an important factor in the development of preeclampsia. There was a significant increase in the risk of preeclampsia, especially if medications were taken during the second trimester of pregnancy.

In addition, a significant relationship arose between the duration of the antidepressant use and preeclampsia (Avalos et al., 2015).

Research/Clinical Implications and Recommendations

Our findings support the need of early screening of maternal mental disorders such as anxiety and depression and prompt management of pregnancy hypertensive disorders to reduce the risk of developing neonatal complications. Screening of maternal mental disorders should be done early in the first trimester of the pregnancy if it is to be used prospectively to prevent HDP and mental health disorders in the postpartum period. In addition, while many clinicians and researchers have lumped in anxiety and depression, the results of our study suggest that these disorders should be screened for and treated separately with extensive follow-ups. Mental health professionals and obstetricians play an important role in identifying and treating both psychological and hypertensive disorders. Early mental health surveillance is vital through the use of counselling, and screening tools which can be conducted in a resourceful manner. Simple scales such as Pregnancy-Related Anxiety Questionnaire (PRAQ), and Generalized Anxiety Disorder-7 (GAD-7), are efficient as brief screening measures for anxiety in pregnant women and to establish a mental picture of an individual prior to pursing additional investigations. Having these screening tests provides a quick assessment of an individual's mental health which can be done quickly and in the office setting by any practician. However, there is a need to implement better and more routine screening measures during the prenatal period to improve the general well-being of women. The implementation of both systematic screening guidelines and mental health consultation on site has been shown to be an effective way to pinpoint women with higher risk without incorporating further burden on the medical care providers (Johnson et al., 2021). A recent systematic review by Verbeke et al. also showed that mental health intervention

during and after pregnancy was cost-effective (Verbeke et al., 2022). In addition, hypertensive disorders in the mother can have significant associations with the development of mental and behavioural problems in the offspring. *Robinson et al* conducted a metanalysis which showed significant associations between both these the disorders and the outcomes (Robinson et al., 2021). Evidence in this field provides implications for future research and development into effects of maternal conditions on the mental development of the offspring into childhood.

Conclusions

Our study demonstrates potential mechanisms and associations between mental disorders, HDP and adverse neonatal outcomes in pregnant women. HDP mediates the associations between anxiety and preterm birth while depression moderates the effect of HDP on preterm birth. HDP also mediates the association between anxiety and SGA, but depression does not moderate the association between HDP and SGA. Based on our findings, we recommend clinicians screen pregnant women for anxiety and depression in the first trimester of pregnancy as early as possible. This would allow for timely surveillance, management, and treatment to avoid adverse downstream detrimental neonatal complications and possible subsequent mental and development problems in childhood.

REFERENCES

Aufdenblatten, M., Baumann, M., Raio, L., Dick, B., Frey, B. M., Schneider, H., Surbek, D., Hocher, B., & Mohaupt, M. G. (2009). Prematurity Is Related to High Placental Cortisol in Preeclampsia. *Pediatric Research*, *65*(2), 198-202. https://doi.org/10.1203/PDR.0b013e31818d6c24

Avalos, L. A., Chen, H., & Li, D. K. (2015). Antidepressant medication use, depression, and the risk of preeclampsia. *CNS Spectr*, *20*(1), 39-47. https://doi.org/10.1017/s1092852915000024

Babu, G. R., Murthy, G. V. S., Reddy, Y., Deepa, R., Yamuna, A., Prafulla, S., Krishnan, A., Lobo, E., Rathnaiah, M., & Kinra, S. (2018). Small for gestational age babies and depressive symptoms of mothers during pregnancy: Results from a birth cohort in India. *Wellcome Open Res*, *3*, 76. https://doi.org/10.12688/wellcomeopenres.14618.3

Brown, H. K., Speechley, K. N., Macnab, J., Natale, R., & Campbell, M. K. (2014). Neonatal morbidity associated with late preterm and early term birth: the roles of gestational age and biological determinants of preterm birth. *Int J Epidemiol*, *43*(3), 802-814. https://doi.org/10.1093/ije/dyt251

Chawanpaiboon, S., Vogel, J. P., Moller, A.-B., Lumbiganon, P., Petzold, M., Hogan, D., Landoulsi, S., Jampathong, N., Kongwattanakul, K., Laopaiboon, M., Lewis, C., Rattanakanokchai, S., Teng, D. N., Thinkhamrop, J., Watananirun, K., Zhang, J., Zhou, W., & Gülmezoglu, A. M. (2019). Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *The Lancet Global Health*, *7*(1), e37-e46. https://doi.org/10.1016/S2214-109X(18)30451-0

Ding, X. X., Wu, Y. L., Xu, S. J., Zhu, R. P., Jia, X. M., Zhang, S. F., Huang, K., Zhu, P., Hao, J. H., & Tao, F. B. (2014). Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. *J Affect Disord*, *159*, 103-110. https://doi.org/10.1016/j.jad.2014.02.027

Ferré, C., Callaghan, W., Olson, C., Sharma, A., & Barfield, W. (2016). Effects of Maternal Age and Age-Specific Preterm Birth Rates on Overall Preterm Birth Rates - United States, 2007 and 2014. *MMWR Morb Mortal Wkly Rep*, *65*(43), 1181-1184. https://doi.org/10.15585/mmwr.mm6543a1

HCUP, N. D. d. (2021). *HCUP, NIS Database documentation*. Retrieved February 10 from https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp

Hoffman, M. C., Mazzoni, S. E., Wagner, B. D., Laudenslager, M. L., & Ross, R. G. (2016). Measures of Maternal Stress and Mood in Relation to Preterm Birth. *Obstet Gynecol*, *127*(3), 545-552. https://doi.org/10.1097/aog.0000000000001287

Horsley, K. J., Tomfohr-Madsen, L. M., Ditto, B., & Tough, S. C. (2019). Hypertensive Disorders of Pregnancy and Symptoms of Depression and Anxiety as Related to Gestational Age at Birth: Findings From the All Our Families Study. *Psychosom Med*, *81*(5), 458-463. https://doi.org/10.1097/psy.0000000000000695

Hüneke, B., & Ude, C. (2002). [Uteroplacental and fetal arterial Ultrasound Doppler Flow Velocity measurements in unselected pregnancies as a screening test at 32 to 34 gestational weeks]. *Z Geburtshilfe Neonatol*, *206*(2), 57-64. https://doi.org/10.1055/s-2002-30138 (Dopplersonographische Blutflussmessungen in uterinen und fetalen arteriellen Gefässen als Screeninguntersuchung in der 32. - 34. Schwangerschaftswoche.)

Jackson, C. A., Pathirana, T., & Gardiner, P. A. (2016). Depression, anxiety and risk of hypertension in mid-aged women: a prospective longitudinal study. *J Hypertens*, *34*(10), 1959-1966. https://doi.org/10.1097/hjh.0000000000001030

Johnson, A., Stevenson, E., Moeller, L., & McMillian-Bohler, J. (2021). Systematic Screening for Perinatal Mood and Anxiety Disorders to Promote Onsite Mental Health Consultations: A Quality Improvement Report. *J Midwifery Womens Health*, *66*(4), 534-539. https://doi.org/10.1111/jmwh.13215

Kosicka, K., Siemiątkowska, A., Szpera-Goździewicz, A., Krzyścin, M., Bręborowicz, G. H., & Główka, F. K. (2018). Increased cortisol metabolism in women with pregnancy-related hypertension. *Endocrine*, *61*(1), 125-133. https://doi.org/10.1007/s12020-018-1586-4

Li, D., Liu, L., & Odouli, R. (2009). Presence of depressive symptoms during early pregnancy and the risk of preterm delivery: a prospective cohort study. *Hum Reprod*, *24*(1), 146-153. https://doi.org/10.1093/humrep/den342

Martin, J. A., Hamilton, B. E., Osterman, M. J. K., & Driscoll, A. K. (2021). Births: Final Data for 2019. *Natl Vital Stat Rep*, *70*(2), 1-51.

McCubbin, J. A., Lawson, E. J., Cox, S., Sherman, J. J., Norton, J. A., & Read, J. A. (1996). Prenatal maternal blood pressure response to stress predicts birth weight and gestational age: a preliminary study. *Am J Obstet Gynecol*, *175*(3 Pt 1), 706-712. https://doi.org/10.1053/ob.1996.v175.a74286

Mengistu, M. D., & Kuma, T. (2020). Feto-maternal outcomes of hypertensive disorders of pregnancy in Yekatit-12 Teaching Hospital, Addis Ababa: a retrospective study. *BMC Cardiovasc Disord*, *20*(1), 173. https://doi.org/10.1186/s12872-020-01399-z

Raina, J., El-Messidi, A., Badeghiesh, A., Tulandi, T., Nguyen, T. V., & Suarthana, E. (2021). Pregnancy hypertension and its association with maternal anxiety and mood disorders: A population-based study of 9 million pregnancies. *J Affect Disord, 281*, 533-538. https://doi.org/10.1016/j.jad.2020.10.058

Robinson, R., Lähdepuro, A., Tuovinen, S., Girchenko, P., Rantalainen, V., Heinonen, K., Lahti, J., Räikkönen, K., & Lahti-Pulkkinen, M. (2021). Maternal Hypertensive Pregnancy Disorders and Mental and Behavioral Disorders in the Offspring: a Review. *Current Hypertension Reports, 23*(5), 30. https://doi.org/10.1007/s11906-021-01141-w

Sarkar, K., Das, G., Chowdhury, R., Shahbabu, B., Sarkar, P., Maiti, S., & Dasgupta, P. A. (2017). Screening antenatal anxiety: Predicting its effect on fetal growth. *Journal of Family Medicine and Primary Care, 6*, 131. https://doi.org/10.4103/2249-4863.214956

Statistics Canada. (2021). *Birth-related indicators (low and high birth weight, small and large for gestational age, pre-term births), by sex, five-year period, Canada and Inuit regions*. Retrieved April 19, 2021 from https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310006401

Verbeke, E., Bogaerts, A., Nuyts, T., Crombag, N., & Luyten, J. (2022). Cost-effectiveness of mental health interventions during and after pregnancy: A systematic review. *Birth, 49*(3), 364-402. https://doi.org/10.1111/birt.12623

Vythilingum, B., Geerts, L., Fincham, D., Roos, A., Faure, S., Jonkers, J., & Stein, D. J. (2010). Association between antenatal distress and uterine artery pulsatility index. *Arch Womens Ment Health, 13*(4), 359-364. https://doi.org/10.1007/s00737-010-0144-8

Warren, W. B., Gurewitsch, E. D., & Goland, R. S. (1995). Corticotropin-releasing hormone and pituitary-adrenal hormones in pregnancies complicated by chronic hypertension. *Am J Obstet Gynecol*, *172*(2 Pt 1), 661-666. https://doi.org/10.1016/0002-9378(95)90589-8

World Health Organization. (2020). *Newborns: improving survival and well-being*. Retrieved February 24 from https://www.who.int/news-room/fact-sheets/detail/newborns-reducing-mortality

FIGURE LEGENDS

Figure 1a

Title: Prevalence of hospitalized pregnant women with preterm birth (PTB) with and without hypertensive disorders of pregnancy (HDP) and/or anxiety in the United States from the year 2004 to 2014

Figure 1b

Title: Prevalence of hospitalized pregnant women with small for gestational age (SGA) with and without hypertensive disorders of pregnancy (HDP) and/or anxiety in the United States from the year 2004 to 2014

Figure 2a

Title: Prevalence of hospitalized pregnant women with preterm birth (PTB) with and without hypertensive disorders of pregnancy (HDP) and/or depression in the United States from the year 2004 to 2014

Figure 2b

Title: Prevalence of hospitalized pregnant women with small for gestational age (SGA) with and without hypertensive disorders of pregnancy (HDP) and/or depression in the United States from the year 2004 to 2014

Figure 3a. Mediation and moderation models for preterm birth (PTB) using HDP as the mediator and depression as the moderator. HDP: Hypertensive Disorders of Pregnancy; PTB: Preterm Birth. The numbers represent odds ratio (OR); *: $p<0.05$.

Figure 3b. Mediation and moderation models for small for gestational age (SGA) using HDP as the mediator and depression as the moderator. HDP: Hypertensive Disorders of Pregnancy; SGA: small for gestational age. The numbers represent odds ratio (OR); *: $p<0.05$.

Table 1. Characteristics of Pregnant Women with and without Anxiety and Hypertensive Disorders of Pregnancy derived from Healthcare Costs and Utilization Project Nationwide Inpatient Sample data (2004-2014)

	No HDP, no anxiety N=8,395,028	No HDP, had anxiety, N=73,620	Had HDP, no anxiety N=619,131	Had HDP and anxiety N=9,009	*p*-value
Age (years)					
<25	37.9	30.1	41.0	30.1	<0.001
25-34	47.5	51.9	44.0	51.4	
≥35	14.7	18.0	15.0	18.5	
Race					
White	51.9	77.8	53.9	78.1	<0.001
Black	13.5	7.6	17.7	8.2	
Hispanic	23.6	9.7	20.3	9.1	
Asian or Pacific Islander	5.3	1.6	3.1	1.4	
Native American	0.8	0.6	0.9	0.6	
Other					
Income Quartiles					
1st Quartile (lowest income)	27.1	22.7	29.9	23.1	
2nd Quartile	25.4	25.6	25.9	26.2	
3rd Quartile	24.9	27.1	24.6	27.1	
4th Quartile (highest income)	22.6	24.6	19.6	23.7	
Plan Type					
Medicare	0.6	2.5	0.7	2.4	<0.001
Medicaid	42.7	40.3	24.1	35.8	
Private	50.5	52.5	51.7	57.3	
Self-pay	3.2	1.5	2.6	1.3	
No charge	0.2	0.1	0.2	0.1	
Other	2.7	3.1	2.8	3.2	
Co-morbidities					
Smoking during pregnancy	4.8	17.2	4.3	13.0	<0.001
Substance use	1.3	7.2	1.3	5.6	<0.001
Obesity	3.2	8.9	8.1	15.2	<0.001
Thyroid disease	2.4	5.8	3.1	7.0	<0.001
Chronic hypertension	1.9	5.1	0.8	1.5	<0.001
Pregestational diabetes mellitus	0.8	1.5	2.0	2.7	<0.001
Depression	0.3	3.3	0.5	3.0	<0.001
Pregnancy condition					
Gestational hypertension	n/a	n/a	48.0	47.1	<0.001

Preeclampsia	n/a	n/a	52.1	53.3	<0.001
Gestational diabetes mellitus	5.5	7.2	8.8	10.1	<0.001
Elderly multigravida	9.4	12.2	8.5	11.4	<0.001
Elderly primigravida	1.6	2.4	2.6	3.9	<0.001
Multiple gestations	1.3	1.9	3.7	4.8	<0.001
Outcomes					
Preterm birth	6.6	9.3	15.2	17.3	<0.001
SGA	2.0	3.2	4.8	6.5	<0.001

Table 2. Characteristics of Pregnant Women with and without Depression and Hypertensive Disorders of Pregnancy derived from Healthcare Costs and Utilization Project Nationwide Inpatient Sample data (2004-2014)

	No HDP, no depression N=8,438,718	No HDP, had depression, N=29,930	Had HDP, no depression N=625,054	Had HDP and depression N=3,086	*p*-value
Age (years)					
<25	37.8	31.5	40.9	31.7	<0.001
25-34	47.5	50.1	44.1	48.3	
≥35	14.7	18.4	15.1	20.0	
Race					
White	52.1	73.7	51.1	75.0	<0.001
Black	13.4	9.2	17.6	9.5	
Hispanic	23.5	12.2	20.2	10.7	
Asian or Pacific Islander	5.3	1.6	3.1	1.4	
Native American	0.8	0.6	0.9	0.8	
Other	4.9	2.8	4.2	2.5	
Income Quartiles					
1st Quartile (lowest income)	27.1	23.7	29.8	22.5	<0.001
2nd Quartile	25.4	26.5	25.9	27.3	
3rd Quartile	24.9	27.0	24.7	28.0	
4th Quartile (highest income)	22.6	22.8	19.6	22.2	
Plan Type					
Medicare	0.6	2.5	0.7	2.7	<0.001
Medicaid	42.7	43.9	42.0	38.5	
Private	50.6	48.8	51.8	54.8	
Self-pay	3.2	1.7	2.5	1.6	
No charge	0.2	0.1	0.2	0.0	
Other	2.7	2.9	2.8	2.4	
Co-morbidities					
Smoking during pregnancy	4.9	18.4	4.4	13.8	<0.001
Substance use	1.4	8.5	1.4	6.4	<0.001
Obesity	3.2	8.7	8.2	15.2	<0.001
Thyroid disease	2.4	5.6	3.1	6.7	<0.001
Chronic hypertension	1.9	4.8	0.8	1.0	<0.001
Pregestational diabetes mellitus	0.8	1.9	2.0	3.6	<0.001
Anxiety	0.8	8.2	1.4	8.7	<0.001
Pregnancy condition					

Gestational hypertension	n/a	n/a	48.0	45.7	<0.001
Preeclampsia	n/a	n/a	52.1	55.1	<0.001
Gestational diabetes mellitus	5.5	7.0	8.8	10.9	<0.001
Elderly multigravida	9.4	12.5	8.6	12.4	<0.001
Elderly primigravida	1.6	2.2	2.6	4.1	<0.001
Multiple gestations	1.3	1.8	3.7	4.3	<0.001
Outcomes					
Preterm birth	6.6	10.6	15.2	19.4	<0.001
SGA	2.0	3.0	4.8	6.1	<0.001

AUTHOR STATEMENT

CONTRIBUTION TO AUTHORSHIP

ES, TM, TVN designed the project. JR and AB took part in the acquisition and management of HCUP data. JR and GE performed the analysis under the supervision of ES and with assistance of CC. JR and ES drafted the manuscript. MB, DK, TM, TVN, TT, ND, FY, CC critically reviewed the manuscript.

FUNDING: ES was supported by the Academic Enrichment Fund of the Department of Obstetrics and Gynecology, McGill University, Montreal, QC, Canada.

ACKNOWLEDGEMENT

None

CONFLICT OF INTERESTS

The authors report no conflict of interest

HIGHLIGHTS:

- We used the HCUP-NIS database containing 9 million records of hospitalized pregnant women in the United States between 2004 and 2014 to analyze the prevalence as well as associations and potential mechanisms between maternal mental disorders (anxiety and depression), hypertensive disorders of pregnancy (HDP), and adverse neonatal outcomes (preterm birth and small for gestational age (SGA)).
- Mediation and moderation modeling were used to separately evaluate potential mechanisms between maternal mental disorders, HDP, and adverse neonatal outcomes.
- We found that associations between anxiety and adverse neonatal outcomes (preterm birth and SGA) were mediated by HDP. Depression was shown to moderate the association between HDP and preterm birth but not between HDP and SGA.
- Early screening in pregnant women for anxiety and depression is strongly recommended for clinicians and mental health professionals to reduce downstream complications in the newborn.

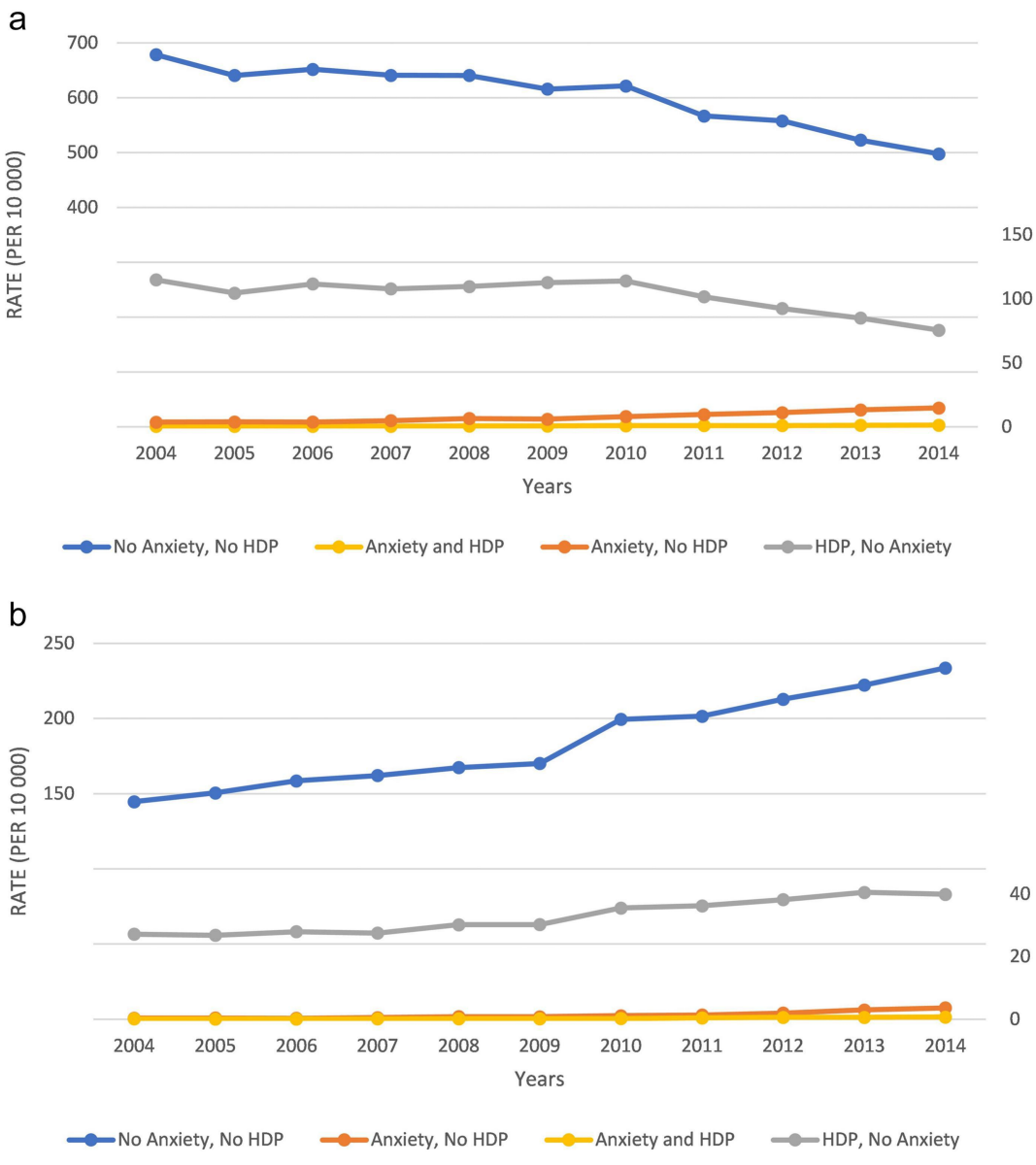
a
700
600
500
400
150
100
50
0
RATE (PER 10 000)
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Years
No Anxiety, No HDP
Anxiety and HDP
Anxiety, No HDP
HDP, No Anxiety
b
250
200
150
40
20
0
RATE (PER 10 000)
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Years
No Anxiety, No HDP
Anxiety, No HDP
Anxiety and HDP
HDP, No Anxiety

Figure 1

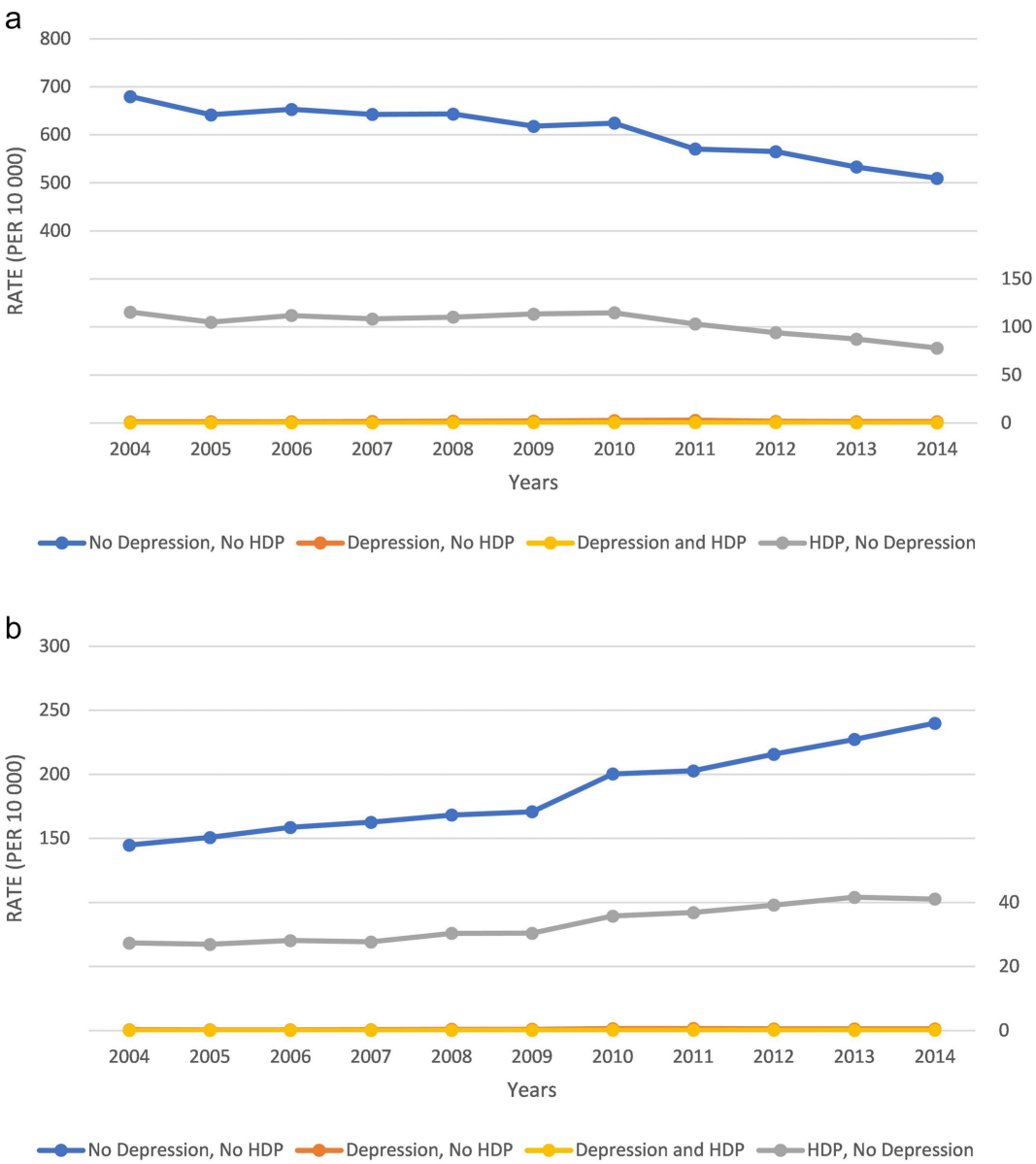
a
800
700
600
500
400
150
100
50
0
RATE (PER 10 000)
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Years
No Depression, No HDP
Depression, No HDP
Depression and HDP
HDP, No Depression
b
300
250
200
150
40
20
0
RATE (PER 10 000)
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Years
No Depression, No HDP
Depression, No HDP
Depression and HDP
HDP, No Depression

Figure 2

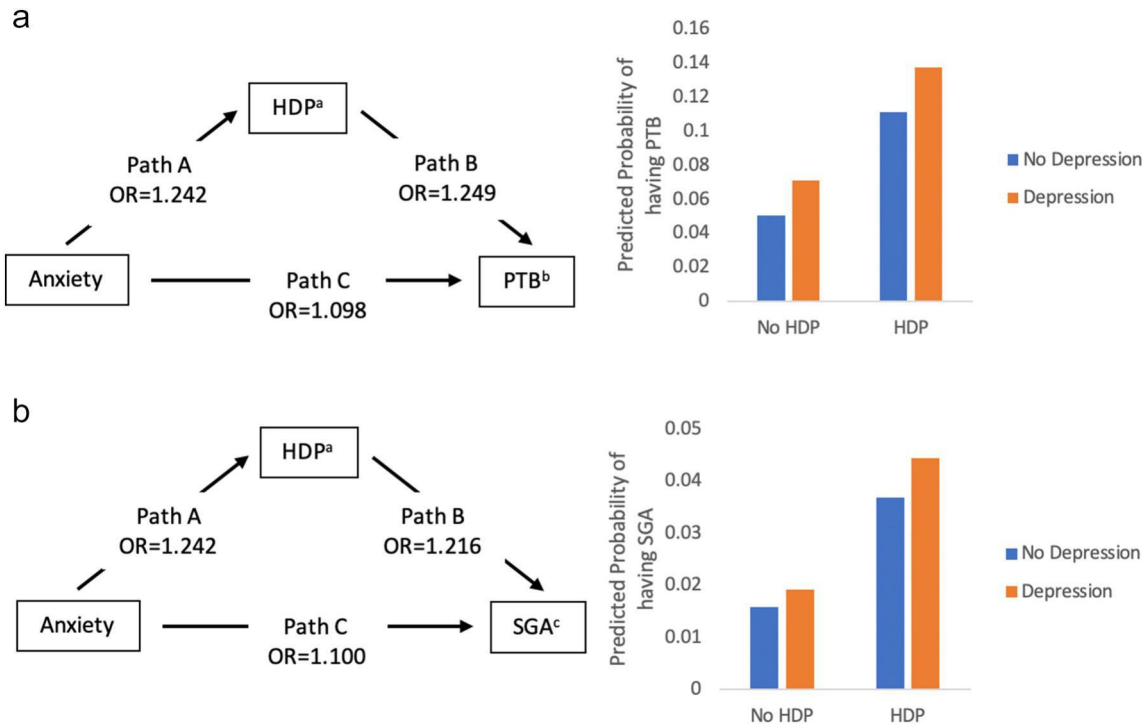
a
HDP[a]
Path A
OR=1.242
Path B
OR=1.249
Anxiety
Path C
OR=1.098
PTB[b]
Predicted Probability of having PTB
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
No HDP
HDP
No Depression
Depression
b
HDP[a]
Path A
OR=1.242
Path B
OR=1.216
Anxiety
Path C
OR=1.100
SGA[c]
Predicted Probability of having SGA
0.05
0.04
0.03
0.02
0.01
0
No HDP
HDP
No Depression
Depression

Figure 3