Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Teniola Balogun Date

The Association Between Migraines and Incident Hypertensive Disorders of Pregnancy Among an Obstetric Population at a Large, Urban Safety Net Hospital

By

Teniola Balogun

Degree to be Awarded: Master of Public Health

Department of Epidemiology

Penelope P. Howards, A.B., M.S., PhD.

Committee Chair

Sheree Boulet, B.S., M.P.H, DrPH.

Committee Member

The Association Between Migraines and Incident Hypertensive Disorders of Pregnancy Among an Obstetric Population at a Large, Urban Safety Net Hospital

By

Teniola Balogun

Bachelor of Science

The George Washington University

2019

Thesis Committee Chair: Penelope P. Howards, A.B., M.S., PhD. &

Thesis Committee Member: Sheree Boulet, B.S., M.P.H, DrPH.

An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Public Health
in the Department of Epidemiology

2023

Abstract

The Association Between Migraines and Incident Hypertensive Disorders of Pregnancy Among an Obstetric Population at a Large, Urban Safety Net Hospital

By Teniola Balogun

Introduction: The highest prevalence of migraine attacks typically occurs during a woman's childbearing years. Migraines in pregnancy are also associated with adverse reproductive outcomes such as pre-term birth, placental abruption, and cesarean section delivery. Evidence shows that pregnancy-associated migraines are associated with hypertensive disorders of pregnancy (HDP) – likely due to shared pathophysiological characteristics. There is limited work examining migraine exposure during pregnancy in relation to HDP subtypes. The goal of this study is to examine if physician-diagnosed, pregnancy-associated migraines are associated with the odds of developing a subtype of hypertensive disorders of pregnancy.
Methods: Data was retrieved from the GOGO database, containing electronic medical records of pregnant patients giving birth at Grady Memorial Hospital between July 1, 2016, and October 31, 2022. We used generalized estimating equations for multinomial logistic regression to examine the associations between physician-diagnosed, pregnancy-associated migraines, covariates of interest and HDP diagnoses at delivery.
Results: Our study sample consisted of 10181 deliveries of which 210 reported a physician-diagnosed, pregnancy-associated migraine. The proportion of deliveries to non-Hispanic Black pregnant patients was higher among those with migraines than those without migraines (82.9% vs 70.2%). Among the 210 migraineurs, 73.0% were multiparous (vs. 67.6%), 11.4% had an anxiety diagnosis (vs. 3.1%), 32.4% were obese (vs. 18.6%), and 24.8% had a pre-existing chronic hypertension diagnosis (vs. 11.4%). After adjusting for confounders, patients with a pregnancy-associated migraine had a 29% marginally increased odds of developing any hypertensive disorder of pregnancy (1.29; 95% CI: 0.97,1.73); 14% increased odds of developing preeclampsia with severe features or eclampsia (1.14; 95% CI: 0.63, 2.06), and 33% increased odds of developing pre-eclampsia without severe features or gestational hypertension (1.33; 95% CI: 0.97,1.81).
Conclusion: In this population with co-occurring chronic conditions, physician-diagnosed, pregnancy-associated migraines were weakly associated with hypertensive disorders of pregnancy. Prospective studies are needed to further evaluate the temporality and extent to which migraines and co-occurring conditions are additionally associated with HDP of differing severity presentation.

The Association Between Migraines and Incident Hypertensive Disorders of Pregnancy Among an Obstetric Population at a Large, Urban Safety Net Hospital

By

Teniola Balogun

Bachelor of Science

The George Washington University

2019

Thesis Committee Chair: Penelope P. Howards, A.B., M.S., PhD. &

Thesis Committee Member: Sheree Boulet, B.S., M.P.H, DrPH.

The thesis of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Public Health
in the Department of Epidemiology

2023

Table of Contents

Introduction

Migraine attacks are a neurological condition that causes headache pain lasting from four to 72 hours and are typically associated with nausea, vomiting and light and sound sensitivity. Women are likely to present with more migraine-associated symptoms that worsen with age, compared to men.[1] There is a disproportionately high burden of disease amongst women of the reproductive ages 15-49 years with the highest prevalence of migraines typically occurring during a woman's childbearing years.[2] The correlation between stages of hormonal fluctuations (puberty, pregnancy, menopause) and migraine incidence suggests the influence of the female sex hormones.[3] This is especially true with obstetric populations.

Pregnancy is a critical window that uniquely influences the health of the pregnant individual. Over the course of pregnancy, individuals undergo significant changes in hormone levels and immune system function.[3,4] These physiological changes can serve as a common trigger for migraine attacks among pregnant persons. Migraines tend to be most active during the first trimester of pregnancy as estrogen levels fluctuate more between low and high levels than at any other time over the female life course.[4] Migraines in pregnancy are also associated with an increased risk for several adverse reproductive outcomes such as preterm birth, placental abruption, cesarean section delivery, and particularly hypertensive disorders of pregnancy (HDP)[5-9] – likely due to shared pathophysiological characteristics such as inflammation,[10,11] and endothelial dysfunction.[12,13]

Migraine attacks adversely affect a patient's quality of life and are associated with anxiety about the next migraine attack. Migraine attacks additionally cause concern over their effect on future pregnancy plans. Of the 607 women enrolled in the American Registry for Migraine Research observational study, 19.9% stated they avoided pregnancy because of migraine attacks. Women who avoided pregnancy believed that their migraine attacks would worsen during pregnancy (72.5%), that the disability caused by migraine attacks would make pregnancy difficult (68.3%), or that migraine attacks would cause the baby to have abnormalities

at birth (14.0%).[14] Women who avoided pregnancy had fewer children than those who did not avoid pregnancy (0.8±1.1 vs 1.5±1.5; *P*<0.001).

The severity and symptom presentation of migraine attacks differs by three main subtypes. Migraine with aura gradually develops with an “aura” presentation related to visual, sensory, speech, and motor phenomenon. This subtype occurs on one side of the body or in one visual field. The “aura” symptoms last for a few minutes in duration and are followed by a headache.[15,16] The most common subtype of a migraine attack is migraine without aura. Migraine without aura is defined by recurrent headaches with symptoms lasting from four to 72 hours in duration with at least a pulsating presentation on one side of the body. This migraine subtype is additionally defined by its severe intensity enough to limit daily activity.[15] Chronic migraines are a subtype of migraine attacks that occur for ≥ 15 days per month for more than three months with symptom presentation similar to other subtypes.[15]

A minority of patients experience a first migraine attack onset during pregnancy or in the postpartum period.[17] Pregnancy can also reduce the severity of migraine symptoms.[3,18,19] Many patients rank their symptoms to have improved by 80% by the second trimester. A large, prospective study showed that by the third trimester, 89% of patients had either no migraine attacks or fewer attacks.[20] A prospective, observational study of 49 patients with migraine reported an 11%, 53%, and 79% reduction in migraine attacks in the first, second, and third trimesters respectively.[19] While the sample size of the mentioned studies affects study precision, the prospective nature of the studies speaks to the accuracy of the temporality of migraine attack reduction as pregnancy progresses.

Migraines and hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HDP) complicates 5 to 10% of all pregnancies in the U.S.[21,22] Despite advances in obstetric care, HDPs remain a major pregnancy-related health problem. The occurrence of migraines during pregnancy is associated with an increased risk of HDPs (OR range, 1.05-6.8).[23-27] HDPs are conditions that cause elevated blood pressure in

pregnant patients. The defined categories of HDPs are chronic hypertension, gestational hypertension, preeclampsia-eclampsia, and chronic hypertension with superimposed preeclampsia. Chronic hypertension during pregnancy is defined as hypertension before conception, elevated blood pressure before 20 weeks of gestation, or hypertension continuing beyond 12 weeks postpartum.[28] Gestational hypertension is a transitional diagnosis detailed as new-onset hypertension after 20 weeks of gestation in the absence of diagnostic criteria for preeclampsia. This diagnosis can change to chronic hypertension if elevated blood pressure remains beyond 12 weeks postpartum. Preeclampsia is defined as new hypertension that develops after 20 weeks of gestation with accompanying elevated levels of protein in urine (proteinuria) or end-organ dysfunction. In patients with preeclampsia, a secondary condition, eclampsia, is defined by the additional presence of seizures. Chronic hypertension with superimposed preeclampsia is defined as the development of preeclampsia in a patient with existing chronic hypertension after 20 weeks of gestation. Each categorical diagnosis of HDP details its severity and potential consequence for adverse outcomes.

The diagnosis of any HDP subtype is more common among Black women.[29] During a 40-year period, the preeclampsia-eclampsia-related maternal mortality rate (MMR) reduced by 300%, while chronic-hypertension-related MMR increased by 15 times the previous rate.[30] Additionally during the 40-year period, chronic hypertension–related MMR showed a sharp linear increase with advancing age, with MMRs being higher among Black women (9.4%) compared with White women (9.1%). Black women were also more likely to develop early preeclampsia (OR: 3.64; 95% CI: 1.84-7.21) and late preeclampsia (OR: 2.97; 95% CI: 1.98-4.26) compared to the White women.[31] Working closely with healthcare providers during obstetric care visits can assist with close monitoring of blood pressure levels, or adherence to medications, potentially reducing the risk of pregnancy-related hypertension.

Migraine diagnoses and HDPs are both risk factors for postpartum hospital readmission.[32-34] Postpartum readmission, defined as readmission to the birth facility for any

reason within 42 days after discharge from birth hospitalization, disrupts the postpartum recovery time. Maternal, delivery, and hospital characteristics are common indicators for the likelihood of hospital readmission. Migraines are regarded as a potential risk marker for adverse vascular events such as ischemic stroke during pregnancy and general obstetric complications extended to the postpartum period.[35] The Women's Health Study presented an increased risk for hemorrhagic stroke in women with active migraine with aura (aOR 2.25, 95% CI 1.11-4.54).[36] In a systematic review of 17 articles, investigators found an increased risk of maternal stroke in pregnancy among patients with overall active migraine diagnoses (OR range, 7.9-30.7).[24] Postpartum readmission can also represent poor hypertensive control that can predispose women to medical complications such as stroke, seizures, and renal failure.[34] Persistent postpartum hypertension was identified as an independent risk factor for readmission in a multivariable analysis. Patients with a single blood pressure reading of ≥ 140/90 mmHg had increased odds of readmission (aOR: 1.98; 95% CI: 1.37–2.87), and additionally, 2 or more elevated BP readings further increased the odds of readmission (aOR: 3.14; 95% CI: 2.33–4.24).[34]

Risk factors

Large-scale research studies have identified several common risk factors for migraine attacks and HDPs, including reaction to stress and anxiety disorders. The identification of hormonal factors as associated with migraine attacks is strongly supported by the shared pathophysiology basis and the physiological response caused by hormone imbalances in the body.[37,38] The physiological stress response is examined by changes in cortisol levels and the subsequent elevation in a patient's blood pressure.[37] The anxiety disorders commonly associated with migraine attacks are panic disorder (PD), generalized anxiety disorder (GAD), and obsessive-compulsive disorder (OCD).[39] Rubertsson and colleagues have shown that 16% of pregnant patients presented with clinically anxious symptoms during their first trimester[40]. Additionally, in a cross-sectional analysis of women receiving care at a university obstetric clinic,

84% of women reported some form of psychosocial stress during pregnancy.[41] Patients with a panic disorder had an increased association with high psychosocial stress disorder (OR: 6.8; 95% CI: 2.9 –16.2). Patients with ≥ 2 medical comorbidities had an increased association with high psychosocial stress (OR: 3.1; 95% CI: 1.8 –5.5). Among the populations experiencing social and economic vulnerabilities, the root cause of anxiety could be ongoing health conditions, economic stability, or access to adequate health services. These experienced stressors can trigger the onset of neurological symptoms synonymous with migraine attacks, especially during pregnancy.

Obesity is a well-defined risk factor for migraine attacks and HDPs.[26,42-47] In a case-control study conducted at the Swedish Medical Center and Tacoma General Hospital, overweight women with migraines had the highest risk of preeclampsia (aOR: 12.3; 95 CI: 5.8 – 25.7), compared with the lean control participants.[26] In a high-risk pregnancy cohort (assessed by cardiovascular risk profile), compared with women without obesity, women with obesity had a greater risk of incident preeclampsia (unadjusted risk ratio RR: 2.2; 95% CI:1.1–4.5).[47]

Knowledge gap

Despite the accumulating evidence of the elevated risk of HDPs among pregnant patients with migraines, none of these studies feature HDP subtypes as a three-level severity variable. Previous studies examining the association between migraines and HDP excluded preeclampsia without severe features and gestational hypertension as subtypes in analyses.[48,49] Studies that combine overall subtypes of HDPs for analyses overlook the opportunity to explore the complexities of the severity of hypertension presentation. Therefore, these studies may not accurately reflect the risk of migraines on HDP subtypes. Existing research on migraines and HDP primarily included White patients. Those research findings may not be generalizable to other study participants with differing baseline characteristics. Black pregnant patients, for instance, bear a disproportionate burden of hypertension and pregnancy-related morbidity and mortality.

The goal of our study was to investigate the relationship between migraines during pregnancy and HDP (overall and by subtype) in a predominately publicly-insured non-Hispanic Black population. We also compared postpartum readmission rates among patients with migraines and HDP. Analyses considered the role of race and ethnicity, co-morbid conditions, maternal age, and number of prenatal visits as potential covariates.[50]

Methods

Data

This project used data from the Grady Obstetric and Gynecologic Outcomes (GOGO) database. The database is an automated data extraction system drawing from electronic medical record information for patients giving birth at Grady Memorial Hospital in Atlanta, Georgia. We obtained de-identified data from all deliveries that occurred between July 1, 2016, to October 31, 2022. Prenatal care encounters were captured in the nine months prior to delivery and deliveries were followed for 42 days post-delivery to ascertain readmissions. Data were extracted from the GOGO database by hospital encounter. The extracted data was aggregated by delivery resulting in data available for 10297 deliveries. All information that would potentially expose a patient's identification was removed. The confidentiality of the data abides by the data regulations of Grady Memorial Hospital and the Emory University School of Medicine's Department of Gynecology and Obstetrics. Emory University's institutional review board approved this study.

Assessment of Exposure

Migraine diagnoses were extracted from electronic medical records based on the International Classification of Diseases, Tenth Revision (ICD-10), Clinical Modification codes reported during outpatient prenatal visits, at delivery, or within the postpartum period were included. According to the ICD-10-CM, six subgroups of migraine were defined: Migraine without aura, codes G43.009 and G43.019; Migraine with aura, code G43.109; chronic migraine

without aura, codes G43.709; other migraine, codes G43.809; migraine unspecified, codes G43.909 and G43.919, and ophthalmoplegic migraine, code G43.B0. The timing of the migraine diagnosis was determined by days elapsed from a patient's hospital admission until the end of the study observation period. This definition depicts a patient's recent history of pregnancy-associated migraines. Based on frequencies and ICD-CM code definitions of the migraine subtypes, we decided to classify migraine status as a dichotomous indicator of any reported migraine or no reported migraine. In a validation study, the accuracy of migraine diagnosis codes in large integrated healthcare system's electronic health records was stronger compared to identifying migraine diagnoses with pharmacy codes.[51]

Assessment of Outcome

The main outcome of HDP was defined as a delivery hospitalization with a report of ICD-10-CM codes for HDP. According to the ICD-10-CM codes, six subgroups of hypertensive disorders of pregnancy were defined: gestational hypertension, codes O13.2 - O13.9; mild to moderate preeclampsia, codes O14.00 - O14.05; unspecified preeclampsia, codes O14.90, O14.93 - O14.95; preeclampsia with severe features, codes O14.10, O14.12 - O14.15; HELLP syndrome, codes O14.22 - O14.25, and Eclampsia, codes O15.1 - O15.2. We assessed HDP subtypes and classified outcome status as a nominal indicator variable with three levels of increasing severity: no HDP, preeclampsia without severe features/gestational hypertension, and preeclampsia with severe features/eclampsia based on the severity of presentation defined by the ICD-10-CM codes. We also considered a binomial indicator of any HDP (gestational hypertension, pre-eclampsia without severe features, pre-eclampsia with severe features and eclampsia) versus no HDP given sample size limitations for the subtypes. As a secondary outcome, we additionally examined postpartum readmissions and ED visits that occurred up to 42 days after delivery, regardless of reason.

Assessment of Covariates

We additionally extracted self-reported data for patient race and ethnicity (Hispanic, Black or African American, White or Caucasian, Asian, Alaskan Indian/Alaskan Native, Hawaiian/Pacific Islander, Multi-Race, Other, Unknown), age at admission (years), gestational length at admission (weeks), mode of delivery (cesarean, vaginal, and operative), outpatient and inpatient medications orders during pregnancy by pharmaceutical class ("Analgesics-Nonnarcotic", and "Migraine Products"). Additional data was extracted for insurance status (Medicaid/Medicare, Commercial, Self-Pay), tobacco use during pregnancy (dichotomized), and parity (Nulliparous/Multiparous).

We extracted data for anxiety disorders diagnoses based on ICD-10-CM codes (F31-F34, F39-F44, F50-F51 and F53); and reaction to stress disorder (F43). Select delivery comorbidities were extracted using ICD-10-CM codes from the validated and expanded Leonard comorbidity index developed for obstetric populations.[50] Diagnostic indicator categories were extracted included Gestational diabetes, (O24.4); Preexisting diabetes mellitus (E08-E13, O24.0- O24.3, O24.8, O24.9, and Z79.4); Obesity (E66 and O99.210-O99.215), Chronic hypertension (O10, O11, and I10), and Anemia, preexisting (O99.01, O99.02, D50, D55, D56, D57.1, D57.20, D57.3, D57.40, D57.80, D58, and D59).

Statistical Analysis

We examined the descriptive statistics for the distributions of patients' demographic, pregnancy, and delivery characteristics, according to migraine exposure status. Our final analytic dataset represented 10181 deliveries to 8759 patients, after excluding 78 deliveries with missing data on race/ethnicity and 38 deliveries with missing data on parity. We utilized Chi-square tests, two-sample t-tests, and sign tests to examine if there were differences in the distribution of demographic and clinical characteristics by migraine status.

Pregnant patients had multiple deliveries reported and represented during the observation period. To assess the correlation of repeated observations for the same pregnant patient, we estimated crude and adjusted odds ratios and 95% confidence intervals for a

multinomial HDP and a binary HDP outcome (any HDP vs no HDP). We used generalized estimating equations for both multinomial logistic regression and binomial logistic regression.

A collinearity assessment examined which variables might be highly correlated with each other. We determined a multicollinearity problem by variables that had condition indices >15 and variance decomposition proportions > 0.5. We assessed the effects of retaining or keeping them in the models. Effect modification was assessed for the variables insurance (Medicaid/Medicare, Commercial, self-pay) and age at hospital admission (continuous and categorical at the median value in years). We drafted directed acyclic graphs and compared the goodness of fit of the full and reduced multinomial logistic regression models using a likelihood ratio test. Chronic hypertension, age at admission (dichotomized by the median value, years), parity, race/ethnicity, obesity, and anemia were characteristics amongst deliveries jointly associated with a migraine diagnosis. Multiplicative interaction was additionally used to assess joint interaction for the variables age at admission (≤ 27/ >27 years), anemia (dichotomized), chronic hypertension (dichotomized), obesity (dichotomized), parity (nulliparous/multiparous), race/ethnicity (non-Hispanic Black/non-Hispanic White/Other), and reaction to stress disorder (dichotomized). Adjusted odds ratios with 95% confidence intervals were obtained for these stratified models.

Identified from the literature, the potential covariates identified were age, race/ethnicity, anxiety disorder, reaction to stress disorder, obesity disorder, parity, and tobacco use. Based on the study population characteristics, potential covariates were anemia disorder, insurance status, gestational age at first prenatal visit, and chronic hypertension. For the confounding assessment, models with various combinations of covariates were examined to detect meaningful changes in the odds ratios when one or more variables were removed from the model. The following covariates did not appear to be meaningful confounders: tobacco use, and age at first prenatal visit.

The final adjusted model included confounders, as well as those covariates of a priori interest: reaction to stress (dichotomized), age at admission (continuous, years), anxiety disorder (dichotomized), obesity disorder (dichotomized), chronic hypertension (dichotomized), race/ethnicity (non-Hispanic Black, non-Hispanic White, Hispanic, and Other), parity (nulliparous/multiparous), and insurance (Medicaid/Medicare, commercial, self-pay)

Cumulative incidence was defined as the proportion of any new inpatient admissions and emergency department visits in the population at risk during observed the postpartum period. All analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Sensitivity Analysis

Due to small count sizes, the third level preeclampsia with severe features category was combined with eclampsia for the main analysis. However, we conducted a sensitivity analysis using four-level response variable for HDP to examine the consistency of findings. To explore the effect of prenatal care use as a confounder, we conducted an analysis among deliveries with non-missing data (n=8,597).

The American College of Obstetricians and Gynecologists and the United States Preventative Services Task Force currently suggest administering low-dose aspirin as a preventative measure for preeclampsia in at-risk pregnant persons.[52,53] As aspirin may be commonly used in an obstetric population, we planned to assess the variable as a potential confounder or effect modifier on the exposure-outcome relationship. However, 13.8% of deliveries reported using aspirin prenatally, at delivery or postpartum. About 0.07% of deliveries reported using any form of migraine medications prenatally, at delivery, or postpartum.

Results

Demographic and hospital characteristics of the 10181 deliveries that took place at Grady Memorial Hospital during the study observation period from July 1, 2016, and October 31, 2022, are presented in Table 1. Approximately, 1422 pregnant patients had multiple

deliveries represented. Figure 1 shows how we achieved our final sample size from the initial population of 10297 deliveries.

Of the 10181 deliveries included for analysis, 210 (2.06%) deliveries had an associated migraine diagnosis during the study observation period (Table 2). The average age at admission was 27.6 years (+/- 6.4) and did not differ by migraine status. The proportion of deliveries to non-Hispanic Black pregnant patients was higher among those with migraines compared to pregnant patients without migraines (82.9% vs 70.2%, p-value<0.001). Deliveries with an associated migraine diagnosis presented to prenatal care earlier than those deliveries without a migraine diagnosis (14 weeks vs. 17 weeks, p-value<0.001). The gestational age at hospital admission (in weeks) did not differ by migraine status.

There was a higher proportion of multiparity among deliveries with a reported migraine compared to those without a reported migraine (73.0% vs. 67.6%). Approximately, 3.3% of the total population had an anxiety diagnosis, which was more common among those with a migraine diagnosis (11.4%) versus those without a migraine diagnosis (3.1%). Approximately, 18.9% of the total population had an obesity diagnosis, which was more common among those with a migraine diagnosis (32.4%) versus those without a migraine (18.6%). Deliveries with a migraine diagnosis had a higher proportion of pre-existing chronic hypertension compared to those without a reported migraine diagnosis (24.8% vs. 11.4%).

An estimated 86.1% of deliveries had Medicaid/Medicare insurance, 8.9% had commercial insurance, and 4.9% paid for care out of pocket. Among those who had a migraine diagnosis, 88.6% were privately insured, 11.0% were publicly insured, and 0.5% paid for care out of pocket. Deliveries with an associated migraine diagnosis attended more prenatal care visits than those deliveries without a migraine diagnosis (8 visits vs. 6 visits, p-value<0.001). The proportion of pregnant patients who had a cesarean delivery was higher among those with migraines compared to pregnant patients without (41.2% vs 29.4%, p-value<0.001)

A total of 3427 (33.7%) deliveries had an HDP diagnosis. Patients were more likely to have developed pre-eclampsia without severe features or gestational hypertension during pregnancy (26.9% vs 6.8%) compared to pre-eclampsia with severe features or eclampsia (Table 3). The frequency of any HDP representing the four diagnoses levels was 36.7% among deliveries with an associated migraine and 33.6% among deliveries without a migraine.

Crude and adjusted odds ratios and 95% confidence intervals for odds of HDP and migraine are shown in Table 4. The multi-collinearity assessment showed that our variables depicted weak evidence of collinearity. The interaction assessment showed that the product term for age at admission and insurance status was not statistically significant, so the product term was dropped from the model (p-value = 0.18). Using a multinomial analysis adjusting for confounders, migraineur patients had 33% increased odds of developing pre-eclampsia without severe features or gestational hypertension (1.33; 95% CI: 0.97,1.81). Compared to deliveries without a migraine diagnosis, patients with a migraine had 14% increased odds of developing pre-eclampsia with severe features or eclampsia (1.14; 95% CI: 0.64, 2.06). In a binomial analysis adjusting for confounders, patients with a pregnancy-associated migraine had 29% increased odds of developing any HDP (1.29; 95% CI: 0.96,1.73).

Among all deliveries, 4.12% patients had a postpartum readmission. Of those deliveries that resulted in postpartum readmission, 96.9% were not associated with a migraine diagnosis and 3.1% of deliveries were (Table 5). The cumulative incidence of postpartum readmission among those without a reported migraine diagnosis was 4.07% and was 6.2% for those with a recent history of pregnancy-associated migraine (Table 5).

Table 6 shows results from a multiplicative interaction analysis on the effects of combinations of chronic hypertension (dichotomized), anemia (dichotomized), reaction to stress disorder (dichotomized), parity (Nulliparous/Multiparous), median age at admission (≤ 27/ >27 years), and race/ethnicity (non-Hispanic Black/non-Hispanic White/Hispanic/Other) and recent history of physician-diagnosed migraine (dichotomized) on the odds of any HDP. Pregnant

patients older than 27 years old at admission with a positive for a history of migraines had 65% increased odds of any HDP compared with younger patients without a migraine diagnosis (1.65; 95% CI: 1.1, 2.45). Pregnant patients who were both non-Hispanic Black and had a migraine diagnosis had 34% increased odds of any HDP compared with patients who were non-Hispanic Black with no migraine diagnosis (1.34; 95% CI: 0.98, 1.83).

The measures of effect using the new three-level variable for HDP were similar to the initial analysis with a four-level variable for HDP for all reported regression models. In investigating the impact of prenatal care utilization in a confounding variable, we ultimately removed the covariate from the final models due to the high proportion of missing data.

Discussion

In this observational study, we used health record data to assess the relationship between pregnancy-associated migraines and the odds of HDP among patients seeking care at Grady Memorial Hospital in Downtown Atlanta, Georgia. Given the type of study design used and the magnitude of measures of effect, these results suggest that a recent history of physician-diagnosed, pregnancy- associated migraine was weakly associated with the odds of HDP among a predominately non-Hispanic Black and publicly-insured population. However, we did find evidence of multiplicative interactions among covariates. Compared to those who were younger than age 27 and had no reported pregnancy-associated migraine, older patients with a migraine were more likely to develop a hypertensive disorder. Additionally, the cumulative incidence was 6.2% for postpartum readmission among those who had a history of migraines. The cumulative incidence for postpartum readmission was 4.07% for those without a history of migraines. Notably, 3427 (33.7%) patients in this study cohort developed a form of HDP, which is remarkably higher than the national estimate of 13.0% and suggests a higher baseline risk in this study population.[54] Among our study population, gestational hypertension/preeclampsia without severe features diagnoses were the most reported hypertensive disorder (26.8%), compared to the US prevalence of gestational hypertension (6.5%).[55]

Our findings of an association between migraine and HDP are consistent with some existing literature. Existing studies examining the association of the exposure-outcome relationship have an OR ranging from 1.05 to 6.8.[6,23-27,33] There is heterogeneity in the assessment of migraine status among previous studies which may explain the wide range of effect estimates. In one case-control study among 714 pregnant patients, the assessment of migraine exposure was self-reported.[26] Another case-control study among 676 pregnant patients assessed exposure using an adapted genetic migraine questionnaire.[27] A prospective cohort study conducted among 685 pregnant patients assessed migraine exposure by conducting interviews based on the International Society of Headache criteria.[33] Differing exposure assessments can affect prevalence estimates likely due to selection bias or measurement bias. A study that relies on self-reported diagnoses of migraine may exclude patients who do not perceive their symptoms as severe enough to warrant a diagnosis. In contrast, a study that utilizes a clinical evaluation of well-defined headache criteria may be biased towards patients with more severe or persistent symptoms. Clinic-based measures may be affected by presentation to care bias while self-reported measures may be affected due to recall bias. Additionally, measurement bias can arise when there are differences in the interpretation of patient symptoms. The interviewer may find it difficult to differentiate the migraine subtypes from each other. The vernacular of migraine ICD-10-CM codes such as “not intractable” or “without status migrainosus” may be hard to explain on both the part of the interviewer and the patient. Different measurement tools for migraine exposure may introduce bias and ultimately affect validity of results, but the association between migraine and HDP may still be present.

Given that a majority of pregnancies are unplanned, it is imperative to discuss options for migraine management and treatment during routine obstetrics and gynecology visits in an effort to reduce the burden of HDPs and other associated adverse health events. Previous literature has noted other conditions that co-occur with migraine attacks may explain the

increased odds for hypertension in pregnancy. These co-occurring conditions among patients with migraines in pregnancy are obesity, hypertension, anxiety and stress.[24,26] Due to shared pathophysiology traits, these co-existing conditions may affect the associational relationship to a degree. However, it is important to acknowledge that the presence of co-occurring conditions alone does not conclusively indicate interaction between covariates. In a study population of 1,175 pregnant women, an estimated 15.6% reported to have anxiety symptoms.[40] Women under age 25 years had an increased risk of anxiety symptoms during pregnancy or fear of birth (OR 2.6; 95% CI: 1.7-4.0). Additionally, a cohort study found an increased risk of preeclampsia among pregnant women with mood or anxiety disorders (2.12; 95% CI: 1.02-4.45).[56] Additional research is needed to investigate potential causal pathways underlying the relationship between migraines and adverse health events in pregnancy.

Since our study population of migraineurs has a higher prevalence of stress and anxiety disorder compared to patients without migraines, it is important to examine the relationship between those existing conditions, its risk factors, and migraine status especially during significant periods such as pregnancy. Pregnancy itself can be a stressful and demanding period for patients, which could trigger or worsen migraines and other co-occurring conditions. Understanding the role of existing conditions with migraines during pregnancy can help healthcare providers develop effective management plans for this vulnerable population. Additionally, the type of assessment or scale measure used to assess an outcome is important. In some literature, stress and anxiety disorders are self-reported, which may have underestimated the true rates in those observed populations. Misclassification of these co-occurring conditions could bias results towards or away from the null value.

Like migraines, the pathophysiology of obesity and hypertension are associated with inflammation, oxidative stress and elevated blood pressure.[10,13] Among migraineurs in our study population, 32.4% of deliveries reported an obesity diagnosis, compared to 18.6% of deliveries without a migraine diagnosis. Approximately, 24.8% of deliveries additionally reported a chronic

hypertension diagnosis, compared to the 11.4% of deliveries without a migraine diagnosis. Similar findings of co-occurring conditions among the migraine cohorts were seen in the literature. Adeney and colleagues observed a higher proportion of a medical diagnoses of migraine headache among preeclampsia cases compared to controls (23.8% vs 16.2%).[26] An observed 14.75% of the preeclamptic cases reported having a migraine diagnosis and having a pre-pregnancy BMI ≥ 25 kg/m^2. In another study of 1028 patients identifying risk factors for recurrent preeclampsia, Bijl and colleagues found patients with chronic hypertension to have 82% increased odds of recurrent preeclampsia (OR 1.82; 95% CI: 1.11-2.98).[57] To accurately reflect the co-occurrence of migraines, hypertension and obesity among patients, we retained these co-occurring conditions as covariates in the final model after confounding assessment as they were associated with both migraines and HDP.

Another theory related to the co-occurrence of obesity and hypertension with migraines is that those co-occurring conditions may be commonly documented by clinicians in obstetric settings. Pregnant patients are prone to pregnancy weight gain as well as elevated blood pressure over the course of pregnancy. The early diagnosis or management of co-occurring conditions aids in preventing pregnancy and delivery complications. Patients with these co-occurring risk factors may also attend their prenatal appointments more regularly because of their familiarity with the healthcare system in the context of having those existing conditions. The failure to diagnose migraines in patients who do not have these co-existing conditions could increase the odds of complications during pregnancy and delivery. Understanding the potential reasons for the co-occurrence of the mentioned conditions is important to provide effective care.

The readmission characteristics from this study population suggest there is a higher baseline risk in this community. The cumulative incidence of postpartum readmission among those with a reported migraine was 1.52 times the cumulative incidence among those without a reported migraine (6.2% vs 4.07%). This suggests that a migraine diagnosis may be contributing to postpartum complications among this study population. The already high

prevalence of existing co-existing conditions may have residual confounding leading to the depicted marginal association with migraines and HDP. Previous literature was conducted in less diverse populations, and among patients accessing care for more severe cases of migraine attacks. The majority of patients included in our study population were non-Hispanic Black and were publicly insured. Healthcare disparities based on race can lead to delayed diagnoses or underdiagnosis of migraines or HDPs. We need more policies aimed at improving access to care for minority populations.

This study has some limitations. Migraine and HDP case ascertainment were assessed by ICD-10-CM codes. ICD codes vary in their ability to accurately diagnose. Diagnosed conditions range in symptoms presentation and are dependent on whether an individual seeks medical care for their condition. If misdiagnosed or undiagnosed cases were misclassified, the true measure of effect could introduce bias. However, a recent study conducted among this population found the validity of ICD-10-CM codes for HDP to be high (with sensitivity > 80% and specificity >90%).[58] Additionally, our study was limited by missing data regarding gestational age of first prenatal care visit. Timing of entry into prenatal care may influence the likelihood of receiving a migraine and HDP diagnosis. This missing data could impact our scope in capturing complete medical history for pregnant persons who deliver in the Grady Health Systems.

The subtypes of hypertensive disorders of pregnancy resulted in small count sizes which made it difficult to evaluate the association between migraines and HDP subtypes. In addition, the majority of migraines reported during the study period were diagnosed in the postpartum period, so we were unable to examine associations between timing of migraine diagnosis and HDP risk. Given that migraine attacks are chronic conditions that additionally can be triggered by physiological changes, it is likely that a reported postpartum migraine was also present over the course of the pregnancy. However, we cannot eliminate the possibility of reverse causality. Additionally, the Other and Hispanic racial categories were underrepresented in this study causing the measures of effects among these groups to be limited by small sample size.

This study's examination of subtypes of HDP is a strength because it allows for a more detailed analysis of the association between migraines and HDP severity. This approach allows the researchers to consider distinct clinical outcomes, providing a more nuanced understanding of the relationship with severity of HDP presentation. This approach allows for comparison to groups without the outcome of interest. Another strength of this study is its large sample size improving statistical power. Additionally, non-Hispanic Black patients were adequately represented in study which typically is not the case in research studies. Our study's representation of an understudied demographic group allows for the generalization of findings amongst individuals accessing other public hospital systems. non-Hispanic Black individuals and public hospital patients are largely underrepresented in prior studies assessing migraines and the odds of HDP. Thus, our study population can contribute to building the foundation for targeted community-based approaches for public health and obstetric care.

Conclusions

Our study revealed a weak association between migraines and HDP, an increased rate of postpartum readmission among migraineur patients, which findings suggest that migraines may not be the most important risk factor for HDP in a population that is already burdened with a co-occuring conditions. These results may help us identify pregnant patients at higher risk for complications associated with migraine diagnoses or HDP subtypes of differing severity, depedendent on their pre-pregnancy chronic conditions. Pregnancy offers a unique time for intervention due to the increased interaction with the healthcare system. These research findings could have implications for future screening recommendations and emphasize areas for public health interventions aimed at reducing the burden of migraines in pregnancy and its associated conditions. A more specified definition for migraine subtypes could allow for targeted screening to increase identification of migraine attacks in pregnant patients. This proposition could lead to enhanced knowledge about the trajectory of migraine in pregnancy, and the component causes leading to the odds of hypertension development, and rates of postpartum

readmission. Future directions include investigating the genetic or biomedical connection between migraines and hypertension. We could also expand this analysis to other health systems to evaluate the temporality of co-occuring conditions and the improvement of migraine symptoms across pregnancy and the resolution of hypertensive symptoms in the postpartum period.

References

1. Buse DC, Loder E, Gorman JA, et al. Sex Differences in the Prevalence, Symptoms, and Associated Features of Migraine, Probable Migraine and Other Severe Headache: Results of the American Migraine Prevalence and Prevention (AMPP) Study. H*eadache: The Journal of Head and Face Pain*. 2013;53(8):1278-1299.

2. Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: figures and trends from government health studies. *Headache: The Journal of Head and Face Pain* 2018;58(4):496-505.

3. Borsook D, Erpelding N, Lebel A, et al. Sex and the migraine brain. N*eurobiology of disease*. 2014;68:200-214.

4. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and Infection2014:2211-2218, *New England Journal of Medicine*.

5. VanderPluym JH. Adverse Pregnancy Outcomes and Migraine: What We Know and What We Can Do2022:8, *American Academy of Neurology*.

6. Aukes AM, Yurtsever FN, Boutin A, Visser MC, de Groot CJM. Associations Between Migraine and Adverse Pregnancy Outcomes: Systematic Review and Meta-analysis Vol 12: *Obstetrical & Gynecological Survey*; 2019.

7. Grossman TB, Robbins MS, Govindappagari S, Dayal AK. Delivery Outcomes of Patients with Acute Migraine in Pregnancy: A Retrospective Study. *Headache: The Journal of Head and Face Pain*. 2017;57:605-611.

8. Chen HM, Chen SF, Chen YH, Lin HC. Increased risk of adverse pregnancy outcomes for women with migraines: A nationwide population-based study *Cephalalgia*. 2009.

9. Purdue-Smithe AC, Stuart JJ, Farland LV, et al. Prepregnancy Migraine, Migraine Phenotype, and Risk of Adverse Pregnancy Outcomes. *Neurology*. 2023.

10. Tietjen GE, Khubchandani J, Herial N, et al. Migraine and vascular disease biomarkers: a population-based case-control study. *Cephalalgia* 2018;38(3):511-518.

11. Harmon AC, Cornelius DC, Amaral LM, et al. The role of inflammation in the pathology of preeclampsia. *Clinical science*. 2016;130(6):409-419.

12. Chambers JC, Fusi L, Malik IS, Haskard DO, De Swiet M, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. *JAMA*. 2001;285(12):1607-1612.

13. Tietjen GE, Herial NA, White L, Utley C, Kosmyna JM, Khuder SA. Migraine and biomarkers of endothelial activation in young women. *Stroke*. 2009;40(9):2977-2982.

14. Ishii R, Schwedt T, Kim S-K, Dumkrieger G, Chong C, Dodick D. Effect of Migraine on Pregnancy Planning: Insights From the American Registry for Migraine Research. Vol 95. *Mayo Clinic Proceedings*: Elsevier; 2020.

15. Society IH. IHS Classification ICHD-3. 2021. Accessed February 15, 2022.

16. Walter K. What is Migraine? *JAMA*. 2022;327(1):93-93.

17. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. *Cephalalgia* 1992;12(4):221-228.

18. Burch R. Epidemiology and Treatment of Menstrual Migraine and Migraine During Pregnancy and Lactation: A Narrative Review *Headache: The Journal of Head and Face Pain*. 2020;60(1):200-216.

19. Sances G, Granella F, Nappi RE, et al. Course of migraine during pregnancy and postpartum: a prospective study. *Cephalalgia*. 2003;23(3):197-205.

20. Melhado EM, Maciel JA, Guerreiro CA. Headache during gestation: evaluation of 1101 women. *Canadian journal of neurological sciences*. 2007;34(2):187-192.

21. Hutcheon J, Lisonkova S, Joseph K. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best practice & research Clinical obstetrics & gynaecology*. 2011;25(4):391-403.

22. Wilkerson RG, Ogunbodede AC. Hypertensive disorders of pregnancy. *Emergency Medicine Clinics*. 2019;37(2):301-316.

23. Negro A, Delaruelle Z, Ivanova TA, et al. Headache and Pregnancy: a systematic review. *The journal of headache and pain*. 2017;18:1-20.

24. Wabnitz A, Bushnell C. Migraine, cardiovascular disease, and stroke during pregnancy: systematic review of the literature. *Cephalalgia*. 2015;35(2):132-139.

25. Skajaa N, Szépligeti SK, Xue F, et al. Pregnancy, birth, neonatal, and postnatal neurological outcomes after pregnancy with migraine. *Headache: The Journal of Head and Face Pain*. 2019;59(6):869-879.

26. Adeney KL, Williams MA, Miller RS, Frederick IO, Sorensen TK, Luthy DA. Risk of preeclampsia in relation to maternal history of migraine headaches. *The Journal of Maternal-Fetal & Neonatal Medicine* 2005;18(3):167-172.

27. Sanchez SE, Qiu C, Williams MA, Lam N, Sorensen TK. Headaches and migraines are associated with an increased risk of preeclampsia in Peruvian women. *American journal of hypertension* 2008;21(3):360-364.

28. Gynecologists ACoOa. Task force on hypertension in pregnancy. *Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol*. 2013;122(5):1122-1131.

29. Suresh S, Amegashie C, Patel E, Nieman KM, Rana S. Racial Disparities in Diagnosis, Management, and Outcomes in Preeclampsia. *Current Hypertension Reports*. 2022;24(4):87-93.

30. Ananth CV, Brandt JS, Hill J, et al. Historical and recent changes in maternal mortality due to hypertensive disorders in the United States, 1979 to 2018. *Hypertension*. 2021;78(5):1414-1422.

31. Poon LCY, Kametas NA, Chelemen T, Leal A, Nicolaides KH. Maternal risk factors for hypertensive disorders in pregnancy: a multivariate approach. J*ournal of human hypertension*. 2010;24(2):104-110.

32. Øie LR, Kurth T, Gulati S, Dodick DW. Migraine and risk of stroke. *Journal of Neurology, Neurosurgery & Psychiatry*. 2020;91(6):593-604.

33. Facchinetti F, Allais G, Nappi RE, et al. Migraine is a risk factor for hypertensive disorders in pregnancy: a prospective cohort study. *Cephalalgia* 2009;29(3):286-292.

34. Bruce KH, Anderson M, Stark JD. Factors associated with postpartum readmission for hypertensive disorders of pregnancy. *American Journal of Obstetrics & Gynecology MFM*. 2021;3(5).

35. Bushnell CD, Jamison M, James AH. Migraines during pregnancy linked to stroke and vascular diseases: US population based case-control study. BMJ. 2009;338.

36. Kurth T, Kase CS, Schürks M, Tzourio C, Buring JE. Migraine and risk of haemorrhagic stroke in women: prospective cohort study. BMJ. 2010;341.

37. Amiri P, Kazeminasab S, Nejadghaderi SA, et al. Migraine: A Review on Its History, Global Epidemiology, Risk Factors, and Comorbidities. *Frontiers in Neurology*2022.

38. Stubberud A, Buse DC, Kristoffersen ES, Linde M, Tronvik E. Is there a causal relationship between stress and migraine? Current evidence and implications for management. *The journal of headache and pain*. 2021;22(1):1-11.

39. Kumar R, Asif S, Bali A, Dang AK, Gonzalez DA. The development and impact of anxiety with migraines: a narrative review. C*ureus*. 2022;14(6).

40. Rubertsson C, Hellström J, Cross M, Sydsjö G. Anxiety in early pregnancy: prevalence and contributing factors. *Archives of women's mental health*. 2014;17:221-228.

41. Woods SM, Melville JL, Guo Y, Fan MY, Gavin A. Psychosocial stress during pregnancy American journal of obstetrics and gynecology. *American journal of obstetrics and gynecology* 2010;202(1):61-e61.

42. Bodnar LM, Catov JM, Klebanoff MA, Ness RB, Roberts JM. Prepregnancy body mass index and the occurrence of severe hypertensive disorders of pregnancy. *Epidemiology*. 2007:234-239.
43. Bartsch E, Medcalf KE, Park AL, Ray JG. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ* 2016;353.
44. Ros HS, Cnattingius S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. *American journal of epidemiology* 1998;147(11):1062-1070.
45. Bodnar LM, Ness RB, Markovic N, Roberts JM. The risk of preeclampsia rises with increasing prepregnancy body mass index. *Annals of epidemiology* 2005;15(7):475-482.
46. Ogunyemi D, Hullett S, Leeper J, Risk A. Prepregnancy body mass index, weight gain during pregnancy, and perinatal outcome in a rural black population. *The Journal of Maternal-Fetal Medicine* 1998;7(4):190-193.
47. Ogunwole SM, Mwinnyaa G, Wang X, Hong X, Henderson J, Bennett WL. Preeclampsia Across Pregnancies and Associated Risk Factors: Findings From a High-Risk US Birth Cohort. *Journal of the American Heart Association*. 2021;10(17).
48. VanderPluym JH. Adverse Pregnancy Outcomes and Migraine: What We Know and What We Can Do. *Neurology*. 2023.
49. Hastie R, Brownfoot FC, Cluver CA, et al. Predictive value of the signs and symptoms preceding eclampsia: a systematic review. O*bstetrics & Gynecology*. 2019;134(4):677-684.
50. Leonard SA, Kennedy CJ, Carmichael SL, Lyell DJ, Main EK. An expanded obstetric comorbidity scoring system for predicting severe maternal morbidity. *Obstetrics and gynecology*. 2020;136(3):440.
51. Shi J, Fassett MJ, Chiu VY, et al. Postpartum Migraine Headache Coding in Electronic Health Records of a Large Integrated Health Care System: Validation Study. 2022;6(11).
52. Gynecologists TACoOa. ACOG Practice Bulletin No. 203: chronic hypertension in pregnancy. *Obstetrics and gynecology*. 2019;133(1):e26-e50.
53. LeFevre ML, Force UPST. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: US Preventive Services Task Force recommendation statement. *Annals of internal medicine*. 2014;161(11):819-826.
54. Ford ND, Cox S, Ko JY, et al. Hypertensive Disorders in Pregnancy and Mortality at Delivery Hospitalization — United States, 2017–2019. *MMWR Morb Mortal Wkly Rep 2022* 71:585-591.
55. Butwick AJ, Druzin ML, Shaw GM, Guo N. Evaluation of US state–level variation in hypertensive disorders of pregnancy. *JAMA Network Open*. 2020;3(10):e2018741-e2018741.
56. Qiu C, Williams MA, Calderon-Margalit R, Cripe SM, Sorensen TK. Preeclampsia risk in relation to maternal mood and anxiety disorders diagnosed before or during early pregnancy. American journal of hypertension, 22(4), 397-402. *American journal of hypertension* 2009;22(4):397-402.
57. Bijl RC, Cornette JM, Brewer AN, et al. Patient-reported preconceptional characteristics in the prediction of recurrent preeclampsia. *Pregnancy Hypertension*. 2022;28:44-50.
58. Labgold K, Stanhope KK, Joseph NT, Platner M, Jamieson DJ, Boulet SL. Validation of hypertensive disorders during pregnancy: ICD-10 codes in a high-burden southeastern United States Hospital. *Epidemiology*. 2021;32(4):591-597.

Table 1 – Distribution of demographic and clinical characteristics according to migraine status among 10181 deliveries at Grady Memorial Hospital

	Overall (n=10181)	Migraine (n=210) (2.06%)	No Migraine N=9971 (97.9%)	P-value
Maternal Characteristics				
Age at admission (years), mean (SD)	27.6 (6.4)	28.0 (5.4)	27.6 (6.4)	0.26
Race/Ethnicity, n (%)				<0.0001
Hispanic	2182 (21.4)	17 (8.1)	2165 (21.7)	
Black or African American	7178(70.50)	174 (82.9)	7004 (70.2)	
White or Caucasian	304 (3.0)	11 (5.2)	293 (2.9)	
Asian	243 (2.4)	4 (1.90)	239 (2.4)	
Alaskan Indian/Alaskan Native	28 (0.28)	0 (0)	28 (0.30)	
Hawaiian/Pacific Islander	15 (0.15)	0 (0)	15 (0.15)	
Multi Race	80 (0.8)	3 (1.4)	77 (0.8)	
Other	151 (1.5)	1 (0.5)	150 (1.5)	
Gestational age at first prenatal visit (weeks), mean (SD)	17.13 (8.6)	14.9 (7.92)	17.18 (8.6)	<0.0001
Missing	1584	11	1573	
Gestational age (weeks), mean (SD)	37.77 (3.11)	37.4 (2.5)	37.8 (3.12)	<0.0001
Missing	22	0	22	
Parity, n (%)				0.12
Nulliparous	3291 (32.3)	57 (27.0)	3234 (32.4)	
Multiparous	6890 (67.7)	154 (73.0)	6737 (67.6)	
Diagnoses, n (%)				
Anxiety Disorder	335 (3.3)	24 (11.4)	311 (3.1)	<0.0001
Reaction to Stress Disorder	115 (1.1)	6 (2.9)	109 (1.1)	0.03
Obesity	1922 (18.9)	68 (32.4)	1854 (18.6)	<0.0001
Anemia	2202 (21.6)	40 (19.05)	2162 (21.7)	0.36
Pre-pregnancy diabetes	327 (3.2)	12 (5.7)	315 (3.2)	0.04
Gestational Diabetes	674 (6.6)	12 (5.7)	662 (6.6)	0.59
Chronic Hypertension	1190 (11.7)	52 (24.8)	138 (11.4)	<0.0001
Tobacco Use during pregnancy, n (%)	752 (7.4)	20 (9.52)	732 (7.34)	0.24
Insurance Status, n (%)				0.008
Medicaid/Medicare	8774 (86.1)	186 (88.6)	8588 (86.1)	
Commercial	906 (8.90)	23 (11.0)	883 (8.9)	
Self-Pay	501 (4.9)	1 (0.5)	500 (5.0)	

Table 1 – Distribution of demographic and clinical characteristics according to migraine status among 10181 deliveries at Grady Memorial Hospital (cont.)

	Overall (n=10181)	Migraine (n=210) (2.06%)	No Migraine n=9971 (97.94%)	P-value
Pregnancy and Delivery Characteristics				
Prenatal Visits, mean (SD)	5.91 (4.1)	7.8 (4.0)	5.9 (4.1)	<0.0001
Multiple Gestation, n (%)	210 (2.1)	6 (2.9)	204 (2.05)	0.41
Mode of Delivery, n (%)				0.0008
Cesarean	3021 (29.7)	87 (41.2)	2934 (29.4)	
Operative	492 (4.8)	9 (4.3)	483 (4.8)	
Vaginal	6668 (65.5)	114 (54.3)	6554 (65.7)	
Length of hospital stay (days), mean (SD)	3.6 (3.2)	4.4 (3.64)	3.5 (3.2)	<0.0001
Postpartum Readmission				
Inpatient Admissions ≥ 1, n (%)	215 (2.1)	9 (4.3)	206 (2.1)	
Emergency Department Visits ≥ 1, n (%)	246 (2.4)	4 (1.9)	242 (2.4)	

Figure 1: Inclusion/Exclusion tree for final analytic sample

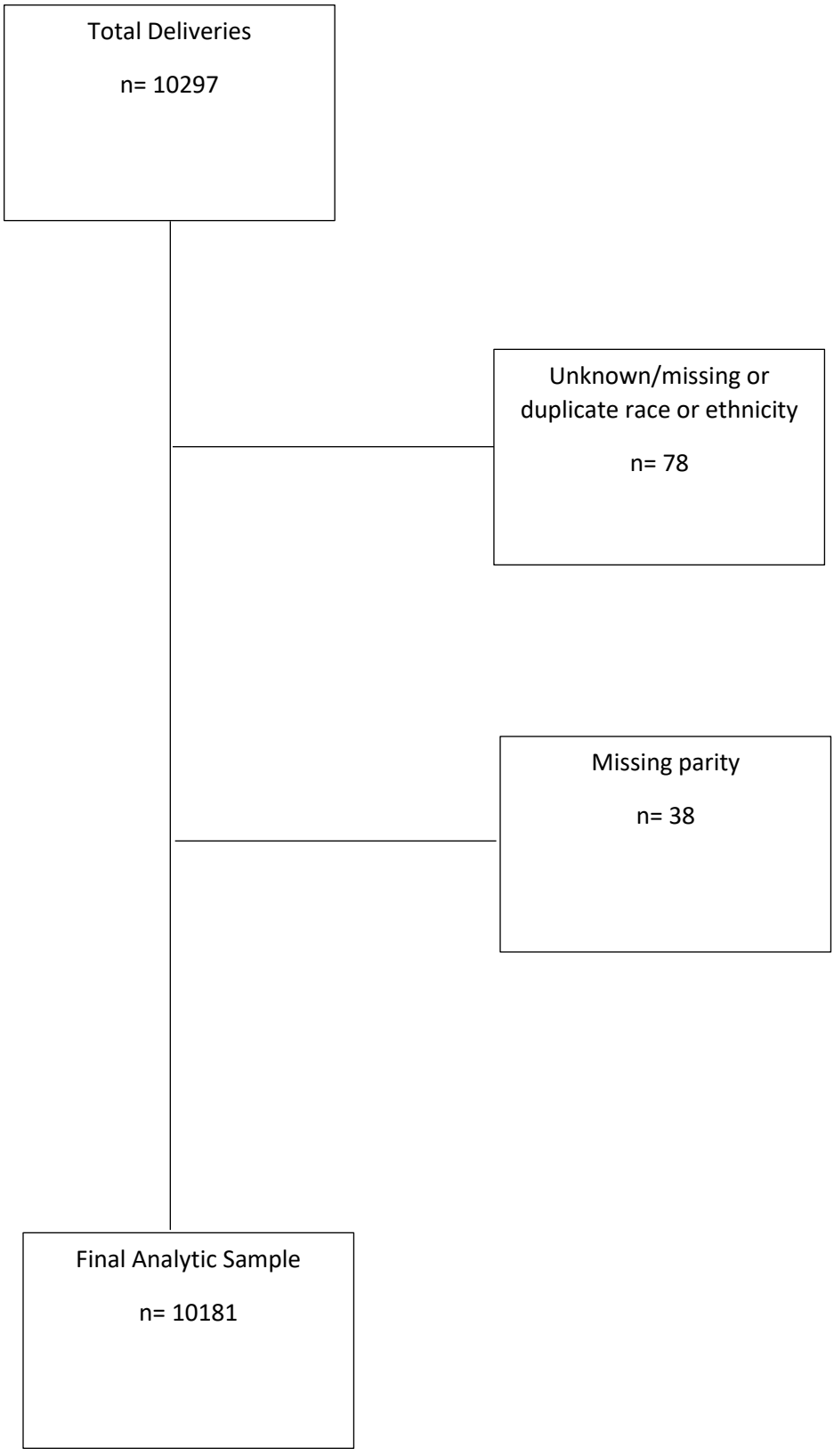

Table 2: Prevalence of Migraine diagnosis subtype based on ICD-10-CM among 10181 deliveries

Subtype	N, %
No Migraine	9971 (97.9)
Migraine without Aura	15 (0.15)
Migraine with Aura	25 (0.25)
Chronic Migraine	1 (0.01)
Other Migraine	7 (0.07)
Unspecified Migraine	192 (1.90)
Ophthalmoplegic Migraine	1 (0.01)
Any Migraine	210 (2.06)

Table 3: Prevalence of Hypertensive disorders of pregnancy diagnosis subtype based on ICD-10-CM among 10181 deliveries

Subtype	N, %
No HDP	6754 (66.3)
Pre-eclampsia without Severe Features/ Gestational Hypertension	2738 (26.9)
Pre-eclampsia with Severe Features/ Eclampsia	689 (6.8)
Any HDP	3427 (33.7)

Table 4. Crude and Adjusted Odd Ratios for the association between migraine status and HDP among 10181 deliveries at Grady Memorial Hospital

	No Migraine *n*=9971	Migraine *n*=210	Crude OR (95% CI)	Adjusted OR* (95% CI)
No HDP (n, %)	6621 (66.40%)	133 (63.33%)	Ref	Ref
Preeclampsia without Severe Features/Gestational Hypertension (n, %)	2674 (26.8%)	64 (30.5%)	1.19 (0.88,1.60)	1.33 (0.97, 1.81)
Preeclampsia with Severe Features/Eclampsia (n,%)	676 (6.8%)	13 (6.2%)	0.96 (0.54, 1.7)	1.14 (0.64, 2.06)
Any HDP (n,%)	3350 (33.6%)	77 (36.7%)	1.14 (0.87, 1.51)	1.29 (0.96. 1.73)

* Adjusted for age at admission, anxiety disorder, obesity disorder, chronic hypertension, race/ethnicity, parity, insurance, and number of prenatal visits

Table 5: Cumulative incidence for postpartum readmission by migraine status among 10181 deliveries at Grady Memorial Hospital

Status at discharge	Number of deliveries *n*=10181	Postpartum Readmission *n*=419	Cumulative incidence (%)
No Migraine	9971 (97.9%)	406 (96.9%)	4.07
Any Migraine	210 (2.1%)	13 (3.10%)	6.19

Table 6: Evaluation of the joint association between migraine status and maternal and sociodemographic characteristics in relation to the odds of HDP among exposure groups at Grady Memorial Hospital

		No HDP *n*=6754	Any HDP *n*=3427	Adjusted OR* (95% CI)
Exposure Groups				
Migraine Status	Chronic Hypertension	--	--	--
No	No	5582	3251	ref
Yes	No	85	73	1.36 (1.0, 1.86)
No	Yes	1039	99	0.60 (0.20, 1.81)
Yes	Yes	48	4	0.82 (0.28, 2.36)
Migraine Status	Obesity	--	--	--
No	No	5561	2556	ref
Yes	No	91	51	1.40 (0.98, 1,98)
No	Yes	1060	794	0.77 (0.42, 1.44)
Yes	Yes	42	26	1.08 (0.65, 1.8)
Migraine Status	Anemia	--	--	--
No	No	5242	2567	ref
Yes	No	110	60	1.29 (0.96, 1.74)
No	Yes	1379	783	1.13 (0.56, 2.30)
Yes	Yes	23	17	1.47 (0.32, 6.73)
Migraine Status	Reaction to Stress	--	--	--
No	No	6556	3306	ref
Yes	No	129	75	1.29 (0.96, 1.74)
No	Yes	65	44	1.14 (0.24, 5.40)
Yes	Yes	4	2	1.47 (0.22, 10.0)
Migraine Status	Parity	--	--	--
No	Nulliparous	1742	1492	ref
Yes	Nulliparous	29	28	1.36 (0.78, 2.33)
No	Multiparous	4879	1858	0.94 (0.48, 1.81)
Yes	Multiparous	104	49	1.27 (0.89, 1.82)
Migraine Status	Age	--	--	--
No	≤ 27	3254	1933	ref
Yes	≤ 27	65	35	1.0 (0.65, 1.52)
No	> 27	3367	1417	1.70 (0.93, 2.97)
Yes	> 27	68	42	1.65 (1.1, 2.45)
Migraine Status	Race/Ethnicity Category	--	--	--
No	non-Hispanic Black	4351	2653	ref
Yes	non- Hispanic Black	107	67	1.34 (0.98, 1.83)
No	non-Hispanic White	203	90	0.89 (0.57, 1.4)
Yes	non-Hispanic White	6	5	1.19 (0.76, 1.86)
No	Hispanic	1652	513	0.79 (0.32, 1.93)
Yes	Hispanic	14	3	1.06 (0.45, 2.44)
No	Other	415	94	0.70 (0.18, 2.69)
Yes	Other	6	2	0.94 (0.26, 3.33)

* Adjusted for age at admission, anxiety disorder, obesity disorder, chronic hypertension, race/ethnicity, parity, insurance, and number of prenatal visits. **chronic hypertension, obesity, anemia, reaction to stress, parity, age at admission, and race/ethnicity as interaction terms