The association between narcolepsy during pregnancy and maternal-fetal risk factors/outcomes

ABSTRACT

Objective: We sought to determine whether narcolepsy in pregnancy is associated with adverse maternal-fetal outcomes. Material and Methods: A retrospective, cross-sectional analysis was performed using the nationwide inpatient sample (NIS) for the period 2008-2017. The primary exposure was narcolepsy with cataplexy, narcolepsy type 1 (NT1), and without cataplexy, narcolepsy type 2 (NT2), and the endpoints were a composite of maternal-fetal outcomes or risk factors. Results: A total of 7,742 hospitalizations among pregnant women with narcolepsy were identified (prevalence = 17.6 per 100,000), of which 6,769 (88%) were diagnosed with NT2. Statistically significant positive associations were found between narcolepsy and the following conditions: obesity (odds ratio (OR): 2.99, confidence interval (CI): 2.4-3.74), anemia (OR=1.41, CI: 1.13-1.77), pre-pregnancy hypertension (OR=1.93, CI: 1.37-2.7), pre-pregnancy diabetes (OR=1.7, CI: 1.08-2.84), and gestational hypertension (OR=1.58, CI: 1.13-2.20) in the ICD-9 group. Similar findings were noted in the ICD-10 group with the exception of gestational hypertension, gestational diabetes, and anemia. Conclusion: Given these important findings, we propose a global approach of screening for narcolepsy among women of reproductive age with pre-existing risk factors prior to conception to minimize pregnancy complications.

Keywords: Narcolepsy; Cataplexy; Pregnancy; Delivery, Obstetric; Morbidity; Hospitalization.
INTRODUCTION

Narcolepsy is a chronic hypersomnia that is separated into two types and formally named type 1 and type 2. Following the International Classification of Sleep Disorders, third edition (ICSD-3), type 1 narcolepsy can be characterized by cataplexy among other findings including a low CSF-hypocretin-1 concentration while type 2 narcolepsy is not associated with cataplexy. The prevalence of type 1 narcolepsy (NT1) is approximately 0.05% in the United States, with onset between 15 and 35 years of age. The true prevalence of type 2 narcolepsy (NT2) is not known as the presentation is more variable though it is estimated to be higher than that of type 1. It is estimated that only 25% of people who have narcolepsy have been diagnosed and are receiving treatment. There are no gender differences in the rates of narcolepsy.

Symptoms of narcolepsy include excessive daytime sleepiness (with sleep attacks), sleep paralysis, hypnagogic and hypnopompic hallucinations, and REM behavior disorder. Cataplexy is a sudden loss of muscle tone that is provoked by experiencing a typically strong positive emotion, such as laughter. This occurs due to the intrusion of REM atonia into the wake state. Comorbidities include type 2 diabetes mellitus and obstructive sleep apnea. Of note, weight gain is prevalent in individuals with narcolepsy, with an estimated 30% of patients fitting this description. It is hypothesized that the underlying cause for the weight gain may be a lack of orexin/hypocretin, which leads to decreased metabolism along with decreased appetite, though to a lesser degree.

Approximately 95% of individuals with NT1 have a deficiency of hypocretin (orexin)-producing neurons in the lateral hypothalamus. Orexin A and orexin B (also known as hypocretin 1 and hypocretin 2, respectively) are neuropeptides that regulate arousal, wakefulness, and appetite. In humans, the orexin A level is severely reduced or undetectable in the cerebrospinal fluid (CSF) of approximately 90% of patients with NT1. NT1 is characterized by a low orexin A level (<110 pg/ml) and cataplexy.

Multiple studies have suggested differences in prevalence among racial and ethnic groups. This difference is thought to arise from human leukocyte antigen (HLA) types as narcolepsy is tightly associated with HLA-DR2, HLA-DQA1, and HLA-DQB1*0602. HLA-DQB1*0602 has been found to be more prevalent in individuals with cataplexy. The HLA-DQB1*0602 allele is strongly associated with narcolepsy and is present in over 98% of individuals with narcolepsy type 1 and about 50% of individuals with narcolepsy type 2. Prior studies have suggested that African Americans are more likely to be HLA DQB1*0602 positive and hypocretin deficient when compared to Caucasians, Latinos, and Asians.

Maternal-fetal outcomes have been studied extensively in obstructive sleep apnea, but studies on narcolepsy are lacking. Prior studies have included retrospective case-control and cohort designs. Research questions included whether caesarean sections in pregnant women with cataplexy was indicated as well as the appropriate management of narcolepsy during pregnancy and lactation. A European study found that less than 1% of pregnant women with cataplexy experienced cataplexy during delivery. The same cohort study found that weight gain during pregnancy was higher in women with narcolepsy as well as the rate of impaired glucose metabolism. The mean birth weight appeared to be within a normal range as was the gestational age. However, another study found higher rates of gestational diabetes. The aim of this paper is to provide updated information on the impact of narcolepsy on maternal-fetal outcomes using a nationally representative dataset covering the entire United States (US).

MATERIAL AND METHODS

We conducted a cross-sectional analysis of hospitalization records from January 1, 2008 through December 31, 2017 using the Nationwide Inpatient Sample (NIS). The NIS datasets constitute the largest all-payer, publicly available inpatient database in the US and are made available by the Healthcare Cost and Utilization Project (HCUP). The systematic sampling strategy ensures that hospitalizations in the NIS are representative of the population on important factors including month of admission, primary reason for hospitalization, and hospital size, location, ownership, and teaching status; and the result is an approximate 20% sample of hospital discharges from participating states, totaling seven million inpatient hospitalizations each year (35 million when weighted) from the 47 participating states.

Our study sample included pregnancy hospitalizations among women within the age range of 18 to 40 years. Diagnoses and procedures were coded using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes until the 3rd quarter of 2015, after which HCUP transitioned to ICD-10-CM format. To assess the study’s primary exposure, we first scanned the up to 30 diagnosis codes in each patient’s discharge record for an indication of narcolepsy with or without cataplexy. We next sub-divided these encounters into two mutually exclusive groups: 1) narcolepsy with cataplexy; and 2) narcolepsy without cataplexy. Neither the timing of the narcolepsy diagnosis nor the medication status during pregnancy was listed in the NIS dataset. The maternal outcomes/risk factors for the study included obesity, anemia, pre-pregnancy and gestational diabetes, pre-pregnancy, and gestational hypertension, preeclampsia and eclampsia. The delivery outcomes for the study were C-section, early delivery and stillbirth. Table 1 shows the list of ICD-9-CM and ICD-10-CM codes utilized for identifying the exposure and outcome variables for this study. We created a composite variable ‘any risk factor’, based on presence of any of the adverse maternal or delivery outcomes mentioned above.

For each inpatient hospitalization, the NIS database captures various sociodemographic, clinical, and hospital characteristics. Patient age in years was categorized as 18-24, 25-29, 30-34, and 35-40. Self-reported race/ethnicity, which is reported differently across states, was standardized by first grouping this as Hispanic or non-Hispanic (NH), and then further classifying the non-Hispanics by race (NH-White, NH-Black, or other).
Insurance status was based on the primary payer for the hospitalization, and was classified into Medicare, Medicaid, private, self-pay and other. Socioeconomic status was estimated from the median household income in the patient’s zip code of residence, and estimated values were classified into quartiles. Hospital characteristics captured included: US census region (Northeast, Midwest, South, and West), hospital size based on the number of short-term acute beds in a hospital (small, medium, and large), and location/teaching status (urban-teaching, urban-non-teaching, and rural).

We conducted joinpoint regression analyses to evaluate and describe the trends in rates of narcolepsy with/without cataplexy, narcolepsy with cataplexy, and narcolepsy without cataplexy over the study period 2008-2017. Joinpoint regression is a statistical modeling approach specifically designed to evaluate and describe the extent to which the rate of an outcome changes over time. The procedure first fits the annual prevalence data to a model with the minimum number of joinjoints (zero), suggesting that a straight line and single trend best fits the annual prevalence data\(^{19}\). Then, more joinpoints are added iteratively to test the statistical significance of the various models using Monte Carlo permutation method\(^{19}\). Once the final (best-fitting) model with the optimal number of joinpoints has been selected, the overall trend over the study period is characterized using average annual percent change (AAPC) measure and its 95% confidence interval (CI).

We conducted bivariate analyses to compare the socio-demographic and hospital characteristics across pregnant women grouped as having narcolepsy with/without cataplexy, narcolepsy with cataplexy and narcolepsy without cataplexy. Descriptive statistics were utilized to derive the prevalence of each of the maternal and delivery outcomes among the three exposure groups.

Lastly, we conducted unadjusted and adjusted survey logistic regression model to assess the association between narcolepsy with/without cataplexy and each of the maternal and delivery outcomes. We conducted sensitivity analysis to evaluate the association between our exposure and outcome for the entire study period and for 2008-2015, 3rd quarter time period. This was done to study the impact of change from ICD-9-CM to ICD-10-CM format from the 4th quarter of 2015. All statistical analyses for the study were performed using R (version 3∙6∙1) and RStudio (version 1.2.5001) and the trends analyses were run using Joinpoint Regression Program, version 4.7.0.0 (National Cancer Institute). We assumed a 5% type I error rate for all hypothesis tests. This study was deemed exempt by the IRB of Baylor College of Medicine as the study was performed on publicly available, de-identified data.

## RESULTS

We analyzed a total of 43,797,082 pregnancy hospitalizations, of which 7,702 had a diagnosis of narcolepsy (prevalence = 17.6 per 100,000). The prevalence of NT1 and NT2 was 2.1 per 100,000 and 15.5 per 100,000, respectively; with NT2 accounting for most of the cases of narcolepsy (88%). Table 2 portrays the distribution of all narcolepsy, NT1 and NT2 by maternal sociodemographic features, discharge status, and hospital characteristics. Exclusive of mothers with missing information about age (about 2.8% of them), the prevalence of all narcolepsy, NT1 and NT2 increased progressively with maternal age reaching a zenith among oldest mothers (30-40 years). Of the available information provided, the overwhelming majority of cases of narcolepsy was accounted for by NH-Whites (71.1%) who also had the highest prevalence of narcolepsy regardless of the subtype. NH-Blacks followed with the second highest prevalence.

### Table 1. ICD-9 and ICD-10 codes utilized for the exposure and outcome variables.

| Condition                        | International Classification of Diseases, 9th Edition, Diagnosis Code* | International Classification of Diseases, 10th Edition, Diagnosis Code* |
|----------------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------|
| Exposure                         |                                                                        |                                                                       |
| Narcolepsy with or without cataplexy | 347.x                                                                | G47.4x                                                                 |
| Narcolepsy with cataplexy        | 347.01,347.11                                                         | G47.411,G47.421                                                       |
| Narcolepsy without cataplexy     | 347.00,347.10                                                         | G47.419,G47.429                                                       |
| Maternal outcomes                |                                                                        |                                                                       |
| Gestational diabetes             | 648.0x, 648.8x                                                        | O24.4x,O24.9x,O99.81x                                                 |
| Preeclampsia                     | 642.4x, 642.5x                                                        | O14.x                                                                 |
| Eclampsia                        | 642.0x                                                                | O15.x                                                                 |
| Gestational hypertension         | 642.3x                                                                | O13.x                                                                 |
| Obesity                          | 278.00, 278.01, 278.03, 649.1x, V85.3x, V85.4x, 793.91                | E66.0x,E66.1,E66.2,E66.8,E66.9,Z68.3x,Z68.4x,R93.9                   |
| Anemia                           | 280x, 281x, 282x, 283x, 284x, 285x, 648.2x                            | D5x,D60x,D61x,D62x,D63x,D64x,O99.0x                                   |
| Pre-pregnancy hypertension       | 401x, 402x, 403x, 404x, 405x, 642.0x, 642.1x, 642.2x, 642.7x           | I10x,I11x,I12x,I13x,I15x,I16x,O10x,O11x,O16x                          |
| Pre-pregnancy diabetes           | 249x, 250x, 648.0x                                                    | E08x,E09x,E10x,E11x,E13x,O24.0x,O24.1x,O24.3x,O24.8x                 |
| Delivery outcomes                |                                                                        |                                                                       |
| Cesarean section                 | 669.7x                                                                | O82                                                                   |
| Early-onset delivery             | 644.2x                                                                | O60.x                                                                 |
| Stillbirth                       | 656.4x, V27.1, V27.3, V27.4, V27.6, V27.7                           | O34.4x,Z37.1,Z37.3,Z37.4,Z37.6,Z37.7                                 |

Note: The code suffix "x" represents all possible codes that follow the stated code prefix.

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**Table 1. ICD-9 and ICD-10 codes utilized for the exposure and outcome variables.**

**Condition** | **International Classification of Diseases, 9th Edition, Diagnosis Code** | **International Classification of Diseases, 10th Edition, Diagnosis Code**
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Exposure | Narcolepsy with or without cataplexy | 347.x | G47.4x
| Narcolepsy with cataplexy | 347.01,347.11 | G47.411,G47.421
| Narcolepsy without cataplexy | 347.00,347.10 | G47.419,G47.429

Maternal outcomes

| Condition | International Classification of Diseases, 9th Edition, Diagnosis Code | International Classification of Diseases, 10th Edition, Diagnosis Code |
--- | --- | ---
Gestational diabetes | 648.0x, 648.8x | O24.4x,O24.9x,O99.81x
Preeclampsia | 642.4x, 642.5x | O14.x
Eclampsia | 642.0x | O15.x
Gestational hypertension | 642.3x | O13.x
Obesity | 278.00, 278.01, 278.03, 649.1x, V85.3x, V85.4x, 793.91 | E66.0x,E66.1,E66.2,E66.8,E66.9,Z68.3x,Z68.4x,R93.9
Anemia | 280x, 281x, 282x, 283x, 284x, 285x, 648.2x | D5x,D60x,D61x,D62x,D63x,D64x,O99.0x
Pre-pregnancy hypertension | 401x, 402x, 403x, 404x, 405x, 642.0x, 642.1x, 642.2x, 642.7x | I10x,I11x,I12x,I13x,I15x,I16x,O10x,O11x,O16x
Pre-pregnancy diabetes | 249x, 250x, 648.0x | E08x,E09x,E10x,E11x,E13x,O24.0x,O24.1x,O24.3x,O24.8x

Delivery outcomes

| Condition | International Classification of Diseases, 9th Edition, Diagnosis Code | International Classification of Diseases, 10th Edition, Diagnosis Code |
--- | --- | ---
Cesarean section | 669.7x | O82
Early-onset delivery | 644.2x | O60.x
Stillbirth | 656.4x, V27.1, V27.3, V27.4, V27.6, V27.7 | O34.4x,Z37.1,Z37.3,Z37.4,Z37.6,Z37.7

Note: The code suffix "x" represents all possible codes that follow the stated code prefix.
Table 2. Sociodemographics of pregnant women with narcolepsy with or without cataplexy.

| Total pregnancy hospitalizations | Narcolepsy with or without cataplexy n=7702 %=100 | Narcolepsy with cataplexy (NT1) n=938 %=100 | Narcolepsy without cataplexy (NT2) n=6769 %=100 |
|----------------------------------|-----------------------------------------------|------------------------------------------|-----------------------------------------------|
| Age                              |                                               |                                          |                                               |
| 18-24 years                      | 12697220 1201 15.6% 9.5 224 23.9% 1.8 976 14.4% 7.7 |                                          |                                               |
| 25-29 years                      | 12664112 1870 24.3% 14.8 263 28.0% 2.1 1608 23.8% 12.7 |                                          |                                               |
| 30-34 years                      | 11559164 2447 31.8% 21.2 237 25.3% 2.1 2210 32.6% 19.1 |                                          |                                               |
| 35-40 years                      | 6258439 1928 25.0% 30.8 199 21.2% 3.2 1734 25.6% 27.7 |                                          |                                               |
| Missing                           | 618147 256 3.3% 41.4 15 1.6% 2.4 241 3.6% 39.0 |                                          |                                               |
| Race/Ethnicity                   |                                               |                                          |                                               |
| NH-White                          | 21129103 5474 71.1% 25.9 662 70.6% 3.1 4812 71.1% 22.8 |                                          |                                               |
| NH-Black                          | 6305449 1077 14.0% 17.1 94 10.0% 1.5 988 14.6% 15.7 |                                          |                                               |
| Hispanic                          | 8248856 282 3.7% 3.4 49 5.2% 0.6 233 3.4% 2.8 |                                          |                                               |
| Other                             | 4235134 242 3.1% 5.7 25 2.7% 0.6 217 3.2% 5.1 |                                          |                                               |
| Missing                           | 3878539 628 8.2% 16.2 109 11.6% 2.8 519 7.7% 13.4 |                                          |                                               |
| Disposition                       |                                               |                                          |                                               |
| Routine                           | 42170008 7010 91.0% 16.6 839 89.4% 2.0 6176 91.2% 14.6 |                                          |                                               |
| Transfer                          | 434653 314 4.1% 72.2 50 5.3% 11.5 264 3.9% 60.7 |                                          |                                               |
| Discharged AMA                    | 245118 70 0.9% 28.6 - - - 65 1.0% 26.5 |                                          |                                               |
| Other                             | 904762 298 3.9% 32.9 44 4.7% 4.9 254 3.8% 28.1 |                                          |                                               |
| Missing                           | 15725 - - - - - - - - - - - - - - - - |                                          |                                               |
| Household Income                  |                                               |                                          |                                               |
| Lowest quartile                   | 12348446 1881 24.4% 15.2 179 19.1% 1.4 1707 25.2% 13.8 |                                          |                                               |
| Second quartile                   | 10926465 2035 26.4% 18.6 247 26.3% 2.3 1787 26.4% 16.4 |                                          |                                               |
| Third quartile                    | 10576457 2037 26.4% 19.3 283 30.2% 2.7 1754 25.9% 16.6 |                                          |                                               |
| Highest quartile                  | 9243429 1695 22.0% 18.3 219 23.3% 2.4 1476 21.8% 16.0 |                                          |                                               |
| Missing                           | 702285 54 0.7% 7.7 - - - 44 0.7% 6.3 |                                          |                                               |
| Primary Payer                     |                                               |                                          |                                               |
| Medicare                          | 2785764 1071 13.9% 38.4 168 17.9% 6.0 903 13.3% 32.4 |                                          |                                               |
| Medicaid                          | 13613792 783 10.2% 5.8 93 9.9% 0.7 690 10.2% 5.1 |                                          |                                               |
| Private                           | 15466812 1887 24.5% 12.2 232 24.7% 1.5 1655 24.4% 10.7 |                                          |                                               |
| Other                             | 1923034 186 2.4% 9.7 - - - 176 2.6% 9.2 |                                          |                                               |
| Missing                           | 10007679 3775 49.0% 37.7 435 46.4% 4.3 3345 49.4% 33.4 |                                          |                                               |
| Hospital Region                   |                                               |                                          |                                               |
| Northwest                         | 7150793 1116 14.5% 15.6 158 16.8% 2.2 959 14.2% 13.4 |                                          |                                               |
| Midwest                           | 9350291 2586 33.6% 27.7 339 36.1% 3.6 2247 33.2% 24.0 |                                          |                                               |
| South                             | 16855552 2931 38.1% 17.4 313 33.4% 1.9 2623 38.8% 15.6 |                                          |                                               |
| West                              | 10440444 1069 13.9% 10.2 129 13.8% 1.2 940 13.9% 9.0 |                                          |                                               |
| Hospital Bed Size                 |                                               |                                          |                                               |
| Small                             | 5995364 1086 14.1% 18.1 110 11.7% 1.8 981 14.5% 16.4 |                                          |                                               |
| Medium                            | 12431079 2007 26.1% 16.1 257 27.4% 2.1 1750 25.9% 14.1 |                                          |                                               |
| Large                             | 25156287 4589 59.6% 18.2 571 60.9% 2.3 4018 59.4% 16.0 |                                          |                                               |
| Missing                           | 214350 20 0.3% 9.3 - - - 20 0.3% 9.3 |                                          |                                               |
| Hospital Location and Teaching Status |                                               |                                          |                                               |
| Rural                             | 4412453 631 8.2% 14.3 73 7.8% 1.7 558 8.2% 12.6 |                                          |                                               |
| Urban non-teaching                | 14439394 2019 26.2% 14.0 178 19.0% 1.2 1841 27.2% 12.7 |                                          |                                               |
| Urban teaching                    | 24730883 5032 65.3% 20.3 687 73.2% 2.8 4350 64.3% 17.6 |                                          |                                               |
| Missing                           | 214350 20 0.3% 9.3 - - - 20 0.3% 9.3 |                                          |                                               |

Note: Prevalence represents the rate of outcomes (narcolepsy with or without cataplexy, narcolepsy with cataplexy, narcolepsy without cataplexy) in each of the patient characteristic groups. As per HCUP guidelines, values less than or equal to 10 are suppressed to prevent patient identification.
More than 90% of hospitalized mothers diagnosed with narcolepsy were routinely discharged although the prevalence of narcolepsy was highest among those transferred to other facilities. Among those with available information on income, mothers in the lowest household income bracket appeared to have the least prevalence of narcolepsy; however, there was only minimal variation across the remaining income groups. While patients covered by Medicare had the highest prevalence of narcolepsy, those on Medicaid had the lowest. Narcolepsy prevalence was also greatest in the Midwest but lowest in the West. Most of the diagnosed cases of narcolepsy among pregnant women were documented in medium and large hospitals (accounting for >85% of cases), and in urban non-teaching and teaching hospitals.

Table 3 summarizes the frequencies of the maternal-fetal outcomes in pregnant women with narcolepsy. There is a noticeable increase in the rates of obesity as well as pre-pregnancy hypertension in both NT1 and NT2 narcolepsy groups (17.4% and 18.7% of our respective population of interest displaying obesity compared to 7.2% in the general population; and 8% and 13.9% of the same population displaying hypertension compared to 4.1% in the general population).

### Table 3. Frequencies of various pregnancy and delivery outcomes/risk factors among women with all narcolepsy (regardless of subtype).

| Outcomes                        | Narcolepsy with or without cataplexy | Narcolepsy with cataplexy | Narcolepsy without cataplexy |
|---------------------------------|--------------------------------------|---------------------------|------------------------------|
|                                 | n=43785396                           | n=43792160                | n=43786329                   |
| Maternal characteristics        |                                      |                           |                              |
| Obesity                         |                                      |                           |                              |
| No                              | 40640526                             | 40640303                  | 40641301                     |
| Yes                             | 3144870                               | 3146130                   | 3145028                      |
| Anemia                          |                                      |                           |                              |
| No                              | 37772346                             | 37777994                  | 37773146                     |
| Yes                             | 6013050                               | 6014166                   | 6013183                      |
| Pre-pregnancy hypertension      |                                      |                           |                              |
| No                              | 41992008                             | 41997835                  | 41992972                     |
| Yes                             | 1793388                               | 1794325                   | 1793458                      |
| Pre-pregnancy diabetes          |                                      |                           |                              |
| No                              | 42781446                             | 42787796                  | 42782355                     |
| Yes                             | 1003950                               | 1004364                   | 1003975                      |
| Gestational hypertension        |                                      |                           |                              |
| No                              | 42261182                             | 42267708                  | 42262066                     |
| Yes                             | 1524214                               | 1524452                   | 1524264                      |
| Gestational diabetes            |                                      |                           |                              |
| No                              | 40833992                             | 40840419                  | 40834870                     |
| Yes                             | 2051404                               | 2051741                   | 2051459                      |
| Preeclampsia                    |                                      |                           |                              |
| No                              | 42223849                             | 42230412                  | 42224738                     |
| Yes                             | 1561547                               | 1561748                   | 1561592                      |
| Eclampsia                       |                                      |                           |                              |
| No                              | 43746495                             | 43753249                  | 43747428                     |
| Yes                             | 38901                                 | 38911                     | 38901                        |
| Delivery characteristics        |                                      |                           |                              |
| C-section                       |                                      |                           |                              |
| No                              | 43703256                             | 4370010                   | 43704179                     |
| Yes                             | 82140                                | 82150                     | 82150                        |
| Early delivery                  |                                      |                           |                              |
| No                              | 41419196                             | 41425735                  | 41420880                     |
| Yes                             | 2366200                              | 2366425                   | 2366250                      |
| Stillbirth                      |                                      |                           |                              |
| No                              | 43528596                             | 43535345                  | 43529292                     |
| Yes                             | 256800                               | 256815                    | 256800                       |
| Composite outcome               |                                      |                           |                              |
| Any risk factor                 |                                      |                           |                              |
| No                              | 28415179                             | 28418727                  | 28415715                     |
| Yes                             | 15370217                             | 15373433                  | 15370615                     |

Note: As per HCUP guidelines, values less than or equal to 10 are suppressed to prevent patient identification.
The percentages of anemia and pre-pregnancy diabetes also increased in the narcolepsy without cataplexy group (for anemia this percentage jumps to 16.5% compared to 13.7% in the general population and for pre-pregnancy diabetes the percentage is 6.1% compared to 2.3% in the general population. Gestational hypertension and pre-eclampsia were more common in the narcolepsy with cataplexy group (for gestational hypertension the percentage increases to 5.3% compared to 3.5% in the general population and for pre-eclampsia the percentage increases to 4.8% compared to 3.6% in the general population). Cesarean sections were also more common in the narcolepsy with cataplexy group (1.1% compared to 0.2% in the general population). Unlike the previous condition, the rates of gestational diabetes, eclampsia, and preterm delivery were not increased in pregnant women with narcolepsy.

Due to coding differences related to the transition from ICD-9 to ICD-10 (shown in Figure 1) in 2015, the results have been split to distinguish these periods. Overall there was a 27.8% average annual increase in the rates of narcolepsy hospitalizations over the study period (AAPC: 27.8, 95%CI: 20.1, 36.1). Table 4 lists the unadjusted and adjusted odds ratios for the association between all narcolepsy (NT1 and NT2) and various outcomes or risk factors. Statistically significant findings among pregnant women with narcolepsy (regardless of subtype) on the aforementioned maternal-fetal outcomes/risk factors include obesity (AOR=2.99, 95%CI: 2.40-3.74), anemia (AOR=1.41, 95%CI: 1.13-1.77), pre-pregnancy hypertension (AOR=1.93, 95%CI: 1.37-2.7), pre-pregnancy diabetes (AOR=1.7, 95%CI: 1.08-2.84), and gestational hypertension (AOR=1.58, 95%CI: 1.13-2.20) in the ICD-9 era. In the overall study period, gestational hypertension,

Table 4. Unadjusted and adjusted survey logistic regression models to assess the association between narcolepsy with/without cataplexy and various outcomes.

| Outcomes               | Narcolepsy/cataplexy (all years) | Narcolepsy/cataplexy (2008-2015 3rd quarter) |
|------------------------|-----------------------------------|-----------------------------------------------|
|                        | Unadjusted OR | Adjusted OR | Unadjusted OR | Adjusted OR |
| **Maternal characteristics** |                      |                      |                      |                      |
| Obesity                | 2.93(2.57-3.34)* | 2.06(1.80-2.36)* | 3.14(2.52-3.91)* | 2.99(2.40-3.74)* |
| Anemia                 | 1.22(1.06-1.40)* | 1.11(0.97-1.28) | 1.35(1.09-1.69)* | 1.41(1.13-1.77)* |
| Pre-pregnancy hypertension | 3.54(3.06-4.11)* | 1.90(1.62-2.23)* | 2.51(1.80-3.50)* | 1.93(1.37-2.70)* |
| Pre-pregnancy diabetes  | 2.58(2.06-3.22)* | 1.41(1.11-1.79)* | 1.93(1.15-3.22)* | 1.70(1.08-2.84)* |
| Gestational hypertension | 1.08(0.82-1.41) | 1.01(0.77-1.32) | 1.75(1.25-2.45)* | 1.58(1.13-2.20)* |
| Gestational diabetes    | 0.74(0.59-0.93)* | 0.80(0.64-1.01) | 1.24(0.95-1.63) | 1.19(0.91-1.56) |
| Preeclampsia           | 0.89(0.66-1.21) | 0.92(0.68-1.24) | 1.41(0.96-2.07) | 1.37(0.93-2.02) |
| Eclampsia              | 1.39(0.39-5.60) | 1.35(0.34-5.43) | 3.45(0.86-4.89) | 3.50(0.87-5.06) |
| **Delivery outcomes**  |                      |                      |                      |                      |
| C-section              | 1.34(0.50-3.60) | 1.51(0.57-4.04) | 1.49(0.37-6.02) | 1.51(0.37-6.08) |
| Early delivery         | 0.65(0.50-0.85)* | 0.77(0.59-1.01) | 1.18(0.87-1.59) | 1.18(0.87-1.59) |
| Stillbirth             | 0.33(0.11-1.03) | 0.35(0.11-1.07) | 0.58(0.13-2.08) | 0.51(0.13-2.06) |
| **Composite outcome**  |                      |                      |                      |                      |
| Any risk factor        | 1.64(1.48-1.81)* | 1.38(1.25-1.53)* | 1.68(1.44-1.97)* | 1.65(1.41-1.93)* |

Notes: OR = Odds ratio; *Statistically significant; Models are adjusted for age, race, disposition, primary payer, household income, hospital region, hospital bed-size and hospital location, and teaching status.
gestational diabetes and anemia were not found to have a statistical association with narcolepsy. Similarly, caesarean section, pre-term delivery or stillbirth were not associated with narcolepsy in pregnant women.

**DISCUSSION**

In this study, we observed significant positive associations between narcolepsy and the following risk factors and pregnancy-related conditions: maternal obesity, anemia, pre-pregnancy hypertension and diabetes, and gestational hypertension. These associations persisted after adjusting for potential confounders such as age, race, disposition, and income. The prevalence of narcolepsy with and without cataplexy in this study matches that of previously published data. Similar to Calbo-Ferrandiz’s study, there was not an increased rate of preterm labor or caesarean sections in the narcolepsy group. In addition, obesity was more prevalent in the narcolepsy group as was anemia and pre-pregnancy diabetes, findings that are consistent with those of other investigators.

Our study also revealed that pregnant women with narcolepsy were older than those without narcolepsy. This may explain why there was a higher prevalence of obesity, as BMI tends to increase with age, though narcolepsy alone is associated with obesity.

Given the fact that non-Hispanic blacks are more likely to be HLA-DQB1*0602 gene positive, we expected a higher prevalence of narcolepsy but the rates were unchanged. This could be explained by under-diagnosis of narcolepsy in pregnant women or the attribution of clinical features of narcolepsy to other clinical conditions that tend to present with similar features (e.g., obstructive sleep apnea).

The possible overdiagnosis of sleep apnea may be explained by confounding factors such as the fact that African Americans are more likely to have a higher BMI than are their White counterparts. Surprisingly, our results show the regional patterns in narcolepsy prevalence coincide with that of the regions with the highest BMI such as the South and the Midwest. Studies have shown an association between socioeconomic status and sleep quality. We found that the narcolepsy diagnosis was lowest in those at the lowest income quartile and highest in those at the third income quartile.

To our knowledge, this is the largest study in the United States evaluating maternal-fetal risk factors/outcomes in pregnant women with narcolepsy. When coupled with the association that narcolepsy can occur simultaneously with obstructive sleep apnea in approximately 24% of cases, appropriate screening prior to conception is essential in order to minimize adverse maternal-fetal outcomes. From the research, pregnant women typically are not often screened for narcolepsy due to the similarities that present in pregnancy, obstructive sleep apnea and narcolepsy. However, narcolepsy presents unique challenges that prevent treatment while pregnant as many of the available options are deemed to be potentially teratogenic, but overall there is inadequate data which leads to varied management by clinicians.

Many women with narcolepsy will discontinue pharmacotherapy during pregnancy and resort to alternative management strategies, though others will continue medications during pregnancy with stimulants and antidepressants most commonly used. Pascoe et al. (2019) found that when comparing the various pharmacotherapy groups used to treat narcolepsy, pregnancy and fetal outcomes were comparable.

One major limitation of the study is that the data incorporates both ICD-9 and ICD-10 data which are not comparable. Based on Figure 1, it appears that the prevalence of narcolepsy increased dramatically after 2015. However, this could be attributed in large part to the International Classification of Disease being updated from ICD-9 to ICD-10 in 2015. During this transition, ailments had to be diagnosed and recorded in more detail which may have led to errors in coding. Implementing this new system caused an increase in codes from 14,000 ICD-9 codes to over 70,000 ICD-10. One could consider the increase of narcolepsy diagnosis due in part to increased clinician awareness stemming doctors having to spend more time writing the increased documentation needed for ICD-10. We hypothesize that the change in coding from ICD-9 to ICD-10 had a side effect of increasing the number of diagnosed cases for narcolepsy without there being a true increase in incidence. More research needs to be done on this topic to ascertain the exact cause for this change in prevalence. In addition, there may be a sample bias, missing data, and testing differences among hospitals in the National Information System. It is possible that some of these findings may be explained by medications taken during pregnancy, but this data was not included in the NIS. Pregnant women are more likely to suffer for sleep disturbances such as insomnia and obstructive sleep apnea. Future studies should examine if the association between lifestyle factors and socio-economic status on narcolepsy in pregnant women, is similar to the one that has already been established in the general population.

In conclusion, the findings of this study reveal significant differences in maternal-fetal outcomes/risk factors in pregnant women with narcolepsy. Given these important findings, we propose a global approach of screening for narcolepsy among women of reproductive age with pre-existing risk factors prior to conception to minimize adverse maternal-fetal outcomes.

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