Social and Demographic Disparities in the Adherence of Chronic Hypertension Medication During Pregnancy

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Abstract

Occurring in approximately 6-8% of all pregnancies, hypertensive disorders of pregnancy (HDP) are one of the major causes of pregnancy-related maternal and fetal morbidity and mortality worldwide. Although there are many low-cost medications that can adequately treat this condition, patient adherence to these medications can vary widely. The objective of this study was to assess adherence to anti-hypertensive medication by pregnant women and to identify the social and demographic factors associated with incomplete adherence. Using a cohort of 28,008 publicly-insured women who initiated anti-hypertensive treatment within the first 20 weeks of gestation, we assessed dosage within biweekly gestational intervals, created group-based trajectory models, and evaluated the association between the different trajectory groups and associated social and demographic characteristics. We found that age, race, geographic region, and adequacy of care were directly correlated with adherence, which can help focus interventions on the highest-risk patients to reduce the risk of bad outcomes from uncontrolled hypertension during pregnancy.

Summary

Hypertension commonly arises during pregnancy, and can be dangerous to the mother and baby if left untreated. Fortunately, many anti-hypertensive medications are inexpensive and proven safe and effective for pregnancy. Nonetheless, many patients start anti-hypertensive medications, but fail to continue them throughout the length of the pregnancy. This dangerous pattern leads to harmful and sometimes fatal outcomes. To help identify potential risk factors for non-adherence, we analyzed 28,008 women and their anti-hypertensive treatment usage throughout their pregnancy to understand social, demographic, and clinical factors that might be associated with non-adherence. We found that race, age, geographic region, and adequacy of prenatal care all are directly correlated with patterns of adherence.

1 Introduction

Movements toward equitable health systems and newfound emphases on intersectional research investigations have highlighted the well-known disparities in health care, most notably in terms of maternal and infant health. However, despite continued advancements in medical care, rates of maternal and fetal morbidity have consistently risen in the United States [1]. One of the most common examples of this trend is hypertensive disorders of pregnancy (HDP).

While HDPs have long been regarded one of the major causes of pregnancy-related and fetal deaths worldwide, recommendations for diagnosis and treatment have changed little in recent years [2]. As shown in Table 1, HDPs are classified into four distinct categories that vary in severity and impact [3]. The effects of HDP can range from minor to fatal.

Classification of Hypertension During Pregnancy

Clasification	**Criteria Met**
Chronic Hypertension	High blood pressure present prior to pregnancy or within the first 20 weeks of pregnancy.
Chronic hypertension with superimposed preeclampsia	The development of preeclampsia in a patient with chronic hypertension.
Gestational hypertension	High blood pressure developed after the first 20 weeks of pregnancy.
Preeclampsia	Development of hypertension and protein uria after first 20 weeks of pregnancy.

Table 1: The four major hypertensive disorders of pregnancy.

In the United States, HDPs occur in 1 in every 12 to 17 pregnancies at a rate that is rapidly increasing over time [4]. Between 2007 and 2019, the annual number of women diagnosed with HDP within the United States doubled, with studies identifying clear growing racial disparities in maternal morbidity and mortality associated with HDP [5]. For example, 58% of Black women in the United States have high blood pressure in comparison to 41% of White women [6]. Death rates from high blood pressure-related causes affect African-American women two times more than White women [6]. This indicates that research on HDP is especially critical in improving care for women of color.

Fortunately, a multitude of anti-hypertensive treatments (AHTs) are widely available, inexpensive, and approved as safe for use during pregnancy. The two most commonly used medications, labetalol (Normodyne, Trandate) and methyldopa (Aldomet), are most highly recommended by clinicians as they have been used for decades to treat HDP, and have been studied extensively with respect to HDPs and possible adverse pregnancy outcomes[1] (APOs) [7]. Although these AHTs have been proven effective in lowering blood pressure, non-adherence (patient discontinuation of chronic medication) is considered a critical barrier to effective treatment of the health condition [8].

Prevalence of non-adherence to AHT in pregnancy is estimated to lie between 3% and 65%, with the wide range of this projection due to the challenge of assessing adherence [9]. While non-adherence has been comprehensively studied and concluded to play an extensive role in increasing the dangerous and largely unknown risks of adverse pregnancy outcomes, major knowledge gaps among both the general public and healthcare professionals still remain [10]. In particular, there is insufficient research evaluating the social and demographic factors that impact adherence, especially as related to AHTs, and the possible outcomes of pregnancies. Studying hypertensive disorders of pregnancy and adherence to medication can enhance the prediction of health care outcomes, leading to more beneficial research and

[1]Pregnancy outcomes other than normal live birth (e.g. preterm birth, stillbirth, low birth weight, etc.).

solutions that can help promote adherence and reduce APOs.

2 Methods

Using a refined cohort of publicly insured women who received treatment for hypertensive disorders of pregnancy early in gestation, we assessed dosage within biweekly intervals during the second half of gestation, created group-based trajectory models, and evaluated the association between the different trajectory groups and social and demographic determinants.

2.1 Study Cohort

We assembled a cohort of mother-infant linked pregnancies derived from the Medicaid Analytic eXtract (MAX) from the years 2000-2018. By including information on patient demographics, characteristics, and diagnostic claims, the MAX data was used to create a pregnancy cohort for studies of drug use and safety. After linking and cleaning the mother to infant data to eliminate duplicate data points and deliveries, the cohort was then restricted to pregnancies with maternal age at delivery 12-55 years for consistency, and further restricted to pregnancies with a binary malformation cohort flag. This restricted the scope of the studies to pregnancies in which in which the patient was on Medicaid at least 3 months prior to the birth and 1 month postpartum. After these restrictions, 2,723,514 pregnancies remained. The cohort was then restricted to women who initiated AHT during the first 20 weeks of gestation, with a focus on the medications methyldopa and labetalol, leaving 28,008 women remaining. Lastly, to guarantee a uniform time of observation, the cohort was restricted to full term births. The final cohort included 21,413 women.

2.2 Medication Exposure

As methyldopa and labetalol are both recommended first-line treatments of choice for HDP, a cohort was created with women on either of these two medications, and investigated alongside the cohort of women on any AHTs. The exposure to methyldopa and labetalol was derived by calculating all dispensings of the specific medication made between the last menstrual period (LMP) and the end of continuous enrollment. Days during pregnancy were referenced as LMP+0 to 269, in which LMP+0 indicates the last menstrual period and LMP+269 indicates the latest possible day before delivery. Days postpartum were referenced as Delivery+0 to 90 where Delivery+0 indicates the day of delivery, and Delivery+90 indicates 90 days postpartum. In addition, these variables accounted for stockpiling of overlapping dispensings. If a dispensing was made n days before the day's supply of previous dispensing ended, then both start and end date of this dispensing's day's supply would be shifted $n + 1$ days later (reference Appendix A.1 for stockpiling figure).

Using a specified set of indicators for everyday exposure, the total number of days exposed during the assessment period divided by the number of days included in the assessment period was calculated as the percent days covered (PDC). The MAX dataset included variables indicating the medication `_PDC_X` in which medication represents either methyldopa or labetalol, and `_X` represents the respective assessment period in months (e.g. `labetalol_PDC_preg_M5` or `methyldopa_PDC_M9`). Using the PDC, corresponding variables were created displaying: `_preg_X_X` or `_preg_X` where `x` indicates the month, or end months of the time interval (e.g. `_preg_M1_M5: 11days/141days = 0.08` or `_preg_M6: 28days/28days = 1)`. When calculating exposure for the entire cohort, the same approach was used, but instead considered all dispensings for any medication recorded.

2.3 Covariates

Several different patient characteristics were assessed as potential predictors of common adherence patterns. These included the maternal demographic characteristics (age, race/ethnicity, US census region, income), select chronic conditions, mental-health conditions, substance abuse/misuse, and census variables. County-level information on metropolitan area, unemployment rate, poverty rate, and education rate included in the MAX data were separated into quartile ranges of 1-4 for each variable. Instead of evenly distributing percentages into quartile, we distributed the rates of each variable among all pregnancies with respective to the year and assigned the quarterlies (reference Appendix A.2 for information on quartile creation).

We applied previously available indices containing detailed information on pregnancy and childbirth collected from the MAX data. The first was the Kotelchuck Index [11], also called the Adequacy of Prenatal Care Utilization (APNCU), which draws from the number of prenatal visits from when pregnancy care began (initiation) until delivery (received services). With the assumption that the earlier prenatal care begins the better, a 4 tier scale is devised from this information with every pregnancy being rated as: inadequate, intermediate, adequate, or adequate plus (as described below).

Inadequate: received fewer than 50% of expected visits

Intermediate: 50%-79%

Adequate: 80%-109%

Adequate Plus: 110% or more

Similarly, the obstetric comorbidity score (OCS) determines the risk of maternal morbidity [12]. The index integrates multiple compounding comorbidities and highlights the

cumulative risk that is associated with the patients' condition. 0 is denoted a 'perfect score' while larger numbers are associated with higher severity of risk. To appropriately depict different scores, we created four corresponding variables in which the scores were divided as following: $n = 0$, $n = 1$, $n = 2$, and $n \geq 3$. The obstetric comorbidity scoring system is displayed in Appendix B.

2.4 Trajectory Modeling

Group based trajectory modeling (GBTM) is a specialized application of finite mixture modeling that gathers individuals into meaningful subgroups to show statistically similar trajectories. It provides a statistical method to identify groups of distinctive trajectories that are summarized by a fixed set of different polynomial functions of age or time, as determined by maximum likelihood estimation. We used GBTMs (crneated with the add-on package "proc traj" in SAS, version 9.4.), to categorize women into groups of similar individual trajectories based on their medication usage within biweekly gestational intervals (see Appendix 3 for code and SAS package). This allowed for simultaneous estimation of group-assignment possibilities for each category of women.

Groups were divided into the following cohorts: women who were on any anti-hypertensive medication, and women who were on either methyldopa or labetalol. Trajectories were modeled using the censored normal distribution, and models were created separately for 2–8 groups. For each model, time was modeled with third-order (cubic) polynomials in each of the groups, the assumption being that with 19 time intervals, an order of 3 should be sufficiently flexible to capture meaningful changes in patterns of adherence over time. Evidence for polynomial over-fitting was assessed by comparing estimated and observed group trajectories, as there is no formal test for determining the optimal number of groups. Therefore, selection of the final number was based on combined assessment of 1) the Bayesian information criterion (with least negative values indicating better model fit), 2) the num-

ber of pregnancies included in the smallest group, and 3) the clinical meaningfulness of the trajectories [13].

After defining multiple models, we then determined the optimal number of groups and the appropriate degree of the polynomial (constant, linear, quadratic, or cubic). Because the group based modeling approach is a relatively new technique that continues to evolve, no consensus currently exists for the best model fit index. However, among several model selection criteria, the Bayesian Information Criterion (BIC) is widely recommended in this context [14].

BIC is defined as:

$$BIC = \log L - .05k \ \log N$$

where L is the value of the model's maximized likelihood, N is the sample size, and k is the number of parameters in the model. A larger BIC model is associated with a better fit of the data [15].

3 Results

Out of our initial cohort, 28,008 women were exposed to anti-hypertensive medication either prior to pregnancy, or within the first 20 gestational weeks. 21,543 women filled at least 1 additional anti-hypertensive prescription during pregnancy, and fulfilled the additional inclusion requirements implemented to ensure a uniform cohort, and lower the probability of inaccurate results (see Figure 1 for information on cohort creation).

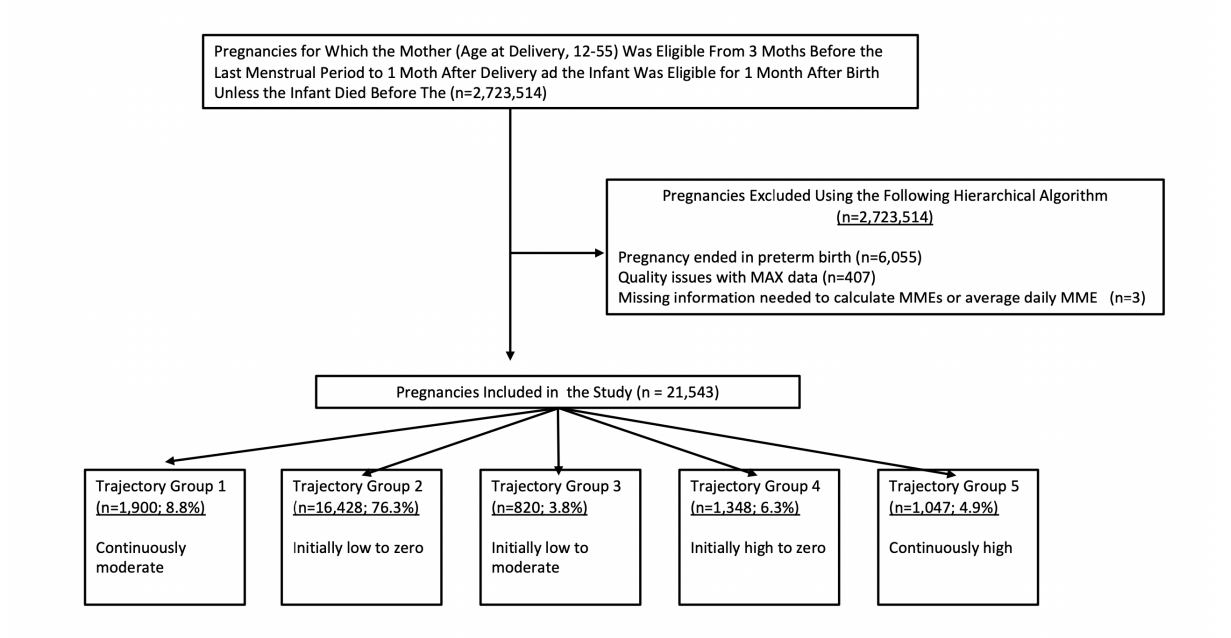

Figure 1: Cohort creation method of linked mother-child cohort using data nested within the Medicaid Analytic eXtract, 2000–2018.

3.1 Group-Based Trajectory Models

We created 8 separate models with 4 varying population cohorts by treatment: methyldopa only, labetalol only, methyldopa or labetalol, and any anti-hypertensive medication. Each population group had two corresponding models yielding either 4 or 5 trajectory groups. Upon analyzing the percentage of the population within each separate group, it was identified that while the model with 5 groups did not adhere to the BIC's distribution suggestion it displayed meaningful patterns of adherence [15]. The 5-group model was chosen as the final model chosen to represent the two cohorts chosen for analysis. The models were composed of the last 4 months of pregnancy, as the initial cohort was previously restricted to women who started AHT within the first 20 weeks of pregnancy and filled at least one prescription following. This constraint reduced the cohort to women with nearly identical patterns within

the first 5 months of pregnancy.

The trajectory code constructed group assignments and membership probabilities, parameter and covariance metric estimates, trajectory plot data, and parameter averages. Table 2 presents our interpretation of these outputs, displaying averages for every separate trajectory group per month, as well as predictions based on the trajectory groups behavior before and after that point in time.

Any Anti-hypertensive Models Averages and Predictions

	AVG1	AVG2	AVG3	AVG4	AVG5	PRED1	PRED2	PRED3	PRED4	PRED5
Month 6	54.24	0.51	0	62.21	93.98	52.42	0.40	0	60.63	92.79
Month 7	56.34	0	0	15.80	95.50	54.65	0	0	13.26	94.06
Month 8	53.29	0	13.91	0	94.80	51.78	0	11.74	0	93.47
Month 9	41.04	0	39.64	0	86.39	38.97	0	40.15	0	84.84

Table 2: SAS trajectory outputs where; AVGX is the average medication dosage, PREDX is the models automated prediction, and X = trajectory group number.

This output reveals that by month 6, 79.26% (n = 16428) of the cohort exhibit little to no adherence. During this interval, this low compliance trajectory group (2) had a starting average dosage of 0.51 (where full compliance is 100 per PDC calculation referenced in methods), with the three folllwing months all containing an average of 0 (table 2). The highest compliance group (5) accounted for 4.86% (n=1047) of the population, leaving the three intermediate groups representing 15.55% of the entire cohort. Group 1 had a continuously moderate trajectory, with an complete average dosage range of 15.3, and 3.05 between the months 6-8. Similarly, group 4 had an initially moderate trajectory but experienced a considerable reduction and eventual discontinuation at month 8. The two months preceding this discontinuation had average dosages of 62.12 (month 6) and 15.8 (month 7), and the month following (month 9) an average of 0. Conclusively, group 3 had a very low initial

trajectory, with months 6 and 7 both averaging at 0, but demonstrated an increase in the two succeeding months, with averages of 13.91 (month 8) and 39.64 (month 9).

Portrayed in figure 2, the cohort of women on any AHT (n = 12,543), were distributed into the 5 trajectory groups with the patterns: 1) continuously moderate, 2) continuously very low, 3) initially very low with considerable increase, 4) initially moderate with considerable reduction or discontinuation with zero, 5) continuously high.

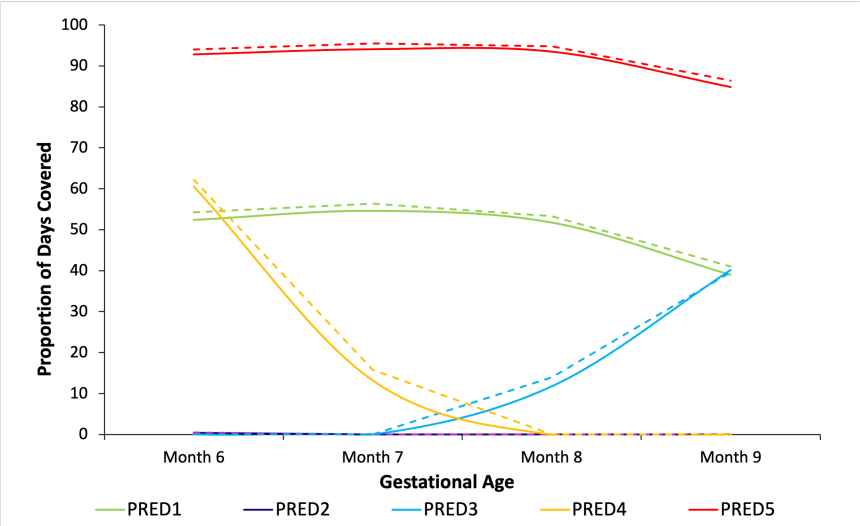

Figure 2: Trajectory models showing mean daily AHT dose in biweekly intervals where solid lines represent the predicted anti-hypertensive medication use in each pregnancy group, and dashed lines represent the observed average daily anti-hypertensive medication use.

3.2 Medication Use

Upon initial assessment of both cohorts, it was concluded that patients on methyldopa or labetalol (the two highest recommended anti-hypertensive medications), were 4.1 times more likely to be in the higher compliance group, while patients on any AHT were 2.9 times more likely to be in the low compliance group. Furthermore, there is evidence of a direct correlation between adequacy of prenatal care (APNCU), and the type of medication. About half (49.7%,

n=10710) of women used either methyldopa or labetalol, with 36% (n=3505) of women on these medications receiving inadequate care (where inadequate is defined as receiving less than 50% of expected prenatal visits). However, 44% (n=4767) of the women who were on any anti-hypertensive medication aside from methyldopa or labetalol received inadequate treatment. Subsequently, 36% (n=3768) of women on either methyldopa or labetalol received adequate plus treatment (receiving 110% or more of expected prenatal visits), whereas 30% (n=6738) on any medication aside from methyldopa or labetalol received the same (adequate plus) treatment.

3.3 Cohort Comparisons

A statistical analysis was run across the cohort of women on any AHT in reference to the highest adherence trajectory group. Out of the 101 binary variables (e.g., geographic region, race, preexisting medical conditions), an average of 48 variables from the non-reference groups had a statistical mean difference of less than 0.1 or greater than 0.1, indicating an imbalance of the treatment and control group (reference Appendix D for calculations). Our results found that women in the highest adherence group were generally older, white, resided in the Midwest census region, and more likely to deliver between the years 2009-2018, while in the lowest adherence group were generally black, younger, and resided in the southern census region.

As presented in table 3, black women were the only racial group in which a higher percentage of the population belonged to the low compliance adherence group as opposed to the high compliance. Notably, black women were found to be 1.8 times more likely to be in the low adherence group (with a 22% difference between the high adherence group), whereas white and Hispanic women are 1.3 and 1.5 percent more likely to be in the high adherence group. Additionally, women under 25 were 1.8 times more likely to be in the low adherence group, while women older than 34 were 1.9 times more likely to be in the high

adherence group. Moreover, women who delivered between the years 2000-2005 were 1.5 times more likely to be in the lowest adherence group, but by the years 2015-2018, women were 1.4 times more likely to the in the highest adherence group as opposed to the lowest. Our results showed that over the time interval 2000-2018, the percentage of women in the highest adherence group more than doubled.

Upon evaluation of the obstetric comorbidity score, our results concluded that women with an OCS of 0 (indicating no risk of maternal mortality) were 6 times more likely to discontinue their medication by the 6th month of pregnancy. Alternatively, women with an OCS of 3 or greater were 2.6 times more likely to continue AHT throughout the second half of pregnancy. The two other OCS variables (scores of 1 or 2) are consistent with this correlation. Women with an OCS of 1 and 2 were 1.15 and 1.5 times more likely to take their anti-hypertensive medication when compared to women with an OCS of 0. Upon evaluation of the second prenatal index investigated in this study (adequacy of prenatal care), women with an inadequate APNCU score (having received fewer than 50% of expected prenatal visits) were 1.2 times more likely to be in the lowest adherence group. Women in the adequate plus APNCU category (having received 110% or more expected prenatal visits) were 1.4 times more likely to be in the high adherence group.

Lastly, while the variables indicating prior mental health conditions (anxiety, depression, bipolar disorder, schizophrenia) and substance abuse (alcohol, smoking, or other substance abuse) were analyzed, we were unable to find any find information implicating any type of correlation. The statistical mean difference between the low compliance and high compliance groups showed no indication of imbalance, deeming these results statistically non-significant.

Maternal Covariate	Full Cohort (n=21,543)		Trajectory Group									
			Group 1 (n=1,900)		Group 3 (n=16,428)		Group 3 (n=820)		Group 4 (n=1,348)		Group 5 (n=1,047)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Maternal Race/Ethinicity												
White	8536	39.62	6356	0.39	332	0.40	584	0.43	501	0.48	858	0.39
Black/African-American	8033	37.29	6140	0.37	315	0.38	469	0.35	347	0.33	618	0.28
Hispanic/Latino	3477	16.14	2800	0.17	118	0.14	192	0.14	123	0.12	501	0.23
Asian	416	1.93	311	0.02	16	0.02	36	0.03	19	0.02	66	0.03
Other/Unknown	1081	5.02	821	0.05	39	0.05	67	.05	57	0.05	138	0.06
US Census region												
Northeast	2965	13.76	240	0.13	2350	0.14	63	0.08	177	0.13	135	0.13
Midwest	6725	31.22	663	0.35	5004	0.30	261	0.32	432	0.32	365	0.35
South	6690	31.05	647	0.34	5004	0.30	285	0.35	420	0.31	334	0.32
West	5163	23.97	350	0.18	4070	0.25	211	0.26	319	0.24	213	0.20
Age												
<24	5904	27.41	505	0.27	4451	0.27	222	0.27	505	0.37	221	0.21
25-29	6756	31.36	584	0.31	5071	0.31	246	0.30	584	0.43	271	0.26
30-34	5422	25.17	466	0.25	4006	0.24	201	0.25	466	0.35	283	0.27
>35	3943	18.30	337	0.18	2848	0.17	150	0.18	337	0.25	271	0.26
Obstetric comorbidity score												
0	2813	13.06	305	0.16	1966	0.12	97	0.12	305	0.23	140	0.13
1	5179	24.04	403	0.21	4018	0.24	156	0.19	403	0.30	199	0.19
2	4949	22.97	386	0.20	3759	0.23	182	0.22	386	0.29	236	0.23
3	9154	42.49	806	0.42	6685	0.41	385	0.47	806	0.60	472	0.45
Delivery Year												
2000-2005	4020	18.66	318	0.17	3099	0.19	137	0.17	318	0.24	148	0.14
2006-2010	5963	27.68	457	0.24	4591	0.28	217	0.26	457	0.34	241	0.23
2011-2014	6654	30.89	621	0.33	4847	0.30	255	0.31	621	0.46	310	0.30
2015-2018	5458	25.34	504	0.27	3891	0.24	211	0.26	504	0.37	348	0.33
Mental-health conditions												
Anxiety	2376	11.03	176	0.09	1830	0.11	70	0.09	192	0.14	108	0.10
Depression	5472	25.40	520	0.27	4141	0.25	185	0.23	378	0.28	248	0.24
Bipolar	618	2.87	0.03	472	0.03	24	0.03	36	0.03	27	0.03	0.03
Schizophrenia	73	0.34	10	0.01	45	0.00	3	5472	25.40	0.01	2	0.00
Substance abuse/dependence												
Alcohol	150	0.70	14	0.01	117	0.01	5	0.01	4	0.00	10	0.01
Smoking	2854	13.25	321	0.17	2404	0.15	103	0.13	13	0.01	13	0.01
Other substance use	74	0.34	13	0.01	48	0.00	2	0.00	11	0.01	0	0.00

Table 3: Characteristics of 21,543 Women on Who Had at Least 1 Dispensed AHT Prescription During Pregnancy and a Full Term Pregnancy, Medicaid Analytic eXtract, 2000–2018.

4 Discussion

4.1 Key Findings

The current study confirmed a multitude of social and demographic factors that were directly correlated with patterns of non-adherence. Our results showed evidence of a correlation between the type of anti-hypertensive medication and adherence. Women who were on anti-hypertensive medication other than methyldopa or labetalol had much lower patterns of adherence and lower APNCU scores. As methyldopa and labetalol are the preferred methods of treatment for HDP, we can make the conclusion that a poor prenatal physician-patient relationship (i.e., those receiving fewer than 50% of prenatal clinical visits) was associated with the use of medications that are not as effective in treating HDP. Some of the alternatives to methyldopa and labetalol (e.g., angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers and renin inhibitors) are proven to be effective in treating high blood pressure alone but have been associated with birth defects such as: fetal hypocalvaria, renal defects, anuria, and fetal or neonatal death [16]. AHTs have been proven an important part in preventing APOs after and during delivery, but prescriptions of AHTs that are not well studied and researched with respect to pregnancy can not only build physician-patient distrust but can lead to non-adherence in the usage of any anti-hypertensive medication.

Consistent with findings from prior studies on other drugs and conditions, further analysis demonstrated that race impacts adherence. Our results identified that black women have lower adherence to all types of AHT medication, further supporting prior research indicating that black women are more likely to have certain birth risk factors, ultimately contributing to higher rates of infant mortality as well as long-term physical and cognitive infant risks [17, 18]. The data also demonstrates a correlation between age and adherence, as low adherence was found to be associated with younger age and higher adherence with older age. Similarly, time (in the form of delivery year) was also found to correspond to adherence. With the percentage

of women in the highest adherence group more than doubling over the years 2000-2018, we can conclude that that time positively influenced patterns of adherence. These data can help more efficiently target social programs intended to improve maternal and fetal outcomes.

Obstetric Comorbidity Score (OCS) also displayed a negative relationship with patterns of adherence. The higher comorbidity score a woman retained indicated a higher adherence to AHT. With this information, it is reasonable to conclude that pregnancies perceived as more high risk, and mothers who have preexisting conditions are more likely to continue taking their medication throughout the entirety of the pregnancy. Additionally, the two lower tiers of the APNCU index (inadequate and intermediate) showed a strong correlation with patterns of adherence. With this data, we can draw the conclusion that the number of prenatal doctor visits directly impacts adherence of medication for HDP.

4.2 Limitations and Strengths

This study's large cohort size and availability of detailed patient-level information on clinical and demographic variables was a significant strength of the project. While interest in using trajectory models to summarize medication use during pregnancy is increasing, only a few studies have used these methods so far, with none analyzing the social and demographic variables in any medication adherence. The use of GBTMs provided a more intuitive representation of AHT adherence and utilization patterns during pregnancy. Instead of using single exposure measures or arbitrary cutpoints, the trajectory models naturally incorporated both quantity and timing of medication availability and allows for a visual representation of complex exposure patterns. As such, trajectory models can be useful for gaining insight into common exposure patterns and can inform the exposure definition to be considered in causal association studies, regardless of whether the definition will ultimately be based on the trajectory groups.

A significant limitation of this study included the possibility of false exposure to medication. Since filling a prescription does not necessarily imply that the medication was actually taken as prescribed, there is a high chance of data misclassification throughout the cohort. Although this is a smaller concern for our study, due to our work with chronic disorders, we work under the assumption that if women go through the effort to fill a prescription multiple times, they are more likely to actually be taking the medication. This can led to an overestimate of exposure among women with only 1 or a few dispensing(s) throughout pregnancy, as well as to misspecification of timing of exposure, particularly among those with high-dose use at the beginning but low-dose/no use at the end of pregnancy.

Lastly, the findings in this study only reflected the Medicaid population. This over represents socioeconomically disadvantaged women and their infants. While the findings can generalizable to other populations, if there is a significant difference in the types of antihypertensive medications used, our findings may not be fully generalizable to the broader population of obstetrical patients.

4.3 Implications and Future Work

The significance of this research lies within its capability to create and promote equitable health systems that benefit everyone. By working to understand what type of racial and social systems operate on micro scales, we can work to implement change through policy, education, and outreach to healthcare providers themselves. Ultimately, research alike this study can help support vulnerable populations by targeting and addressing the underlying drivers of racial and ethnic disparities in maternal health, and developing potential levers to reduce these disparities. Instead of dismissing non-adherence on the basis of biased presumptions, evaluating the types and implications of certain patterns can help us understand how to better solve them. In addition to showing how prescription AHT is used during pregnancy among women, our findings reveal how specific social and demographic factors

can impact adherence. These results can help clinicians understand changes in AHT adherence patterns during pregnancy, and consequently can reduce of APOs with an emphasis on already underrepresented and undeserved communities.

5 Practical Takeaways

Improving the well-being of mothers and children is an important public health goal for the United States, but often neglects portions of the population by failing to address the social and demographic disparities in maternal illnesses and morbidity. In this study, we show how to approach research questions intersectionally, and understand the nature of connected social categorizations. With the guiding question, "What can we learn from patterns of adherence in pregnancy induced hypertension?", we placed an emphasis on identifying race, gender and class identities as mutually constituted, rather than separate systems of inequality. By structuring our study this way, we were able to identify known healthcare disparities through a broad range of dimensions, and spark conformation on how to address such inequalities. In this context, research is more than an attempt to investigate a topic or area of interest, but instead analysis of a fundamental social problem, studied to equip policy makers with pragmatic, action-oriented recommendations for alleviating the problem.

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References

[1] J. Cottrell, K. Cummings, D. Jude, and D. Chaffin. The effect of impedance cardiography directed antihypertensive therapy on fetal growth restriction rates and perinatal mortality in women with chronic hypertension. *Pregnancy Hypertension*, 28:123–127, 2022.

[2] E. Abalos, L. Duley, and D. W. Steyn. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database of Systematic Reviews*, 2014.

[3] M. A. Brown, M. D. Lindheimer, M. de Swiet, A. V. Assche, and J.-M. Moutquin. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the international society for the study of hypertension in pregnancy (isshp). *Hypertension in Pregnancy*, 20(1):ix–xiv, 2001.

[4] K. Tihtonen, T. Kööbi, H. Huhtala, and J. Uotila. Hemodynamic adaptation during pregnancy in chronic hypertension. *Hypertension in Pregnancy*, 26(3):315–328, 2007.

[5] A. R. Kern-Goldberger, A. Friedman, L. Moroz, and C. Gyamfi-Bannerman. Racial disparities in maternal critical care: Are there racial differences in level of care? *Journal of Racial and Ethnic Health Disparities*, 9(2):679–683, 2021.

[6] Advancing maternal health legislation to eliminate racial disparities. *PsycEXTRA Dataset*, 2021.

[7] K. L. Ales and M. E. Charlson. The prediction of adverse outcomes in antepartum hypertension. *Clinical and Experimental Hypertension. Part B: Hypertension in Pregnancy*, 8(1):95–112, 1989.

[8] T. Podymow and P. August. Update on the use of antihypertensive drugs in pregnancy. *Hypertension*, 51(4):960–969, 2008.

[9] R. Lennestål, P. Otterblad Olausson, and B. Källén. Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants. *European Journal of Clinical Pharmacology*, 65(6):615–625, 2009.

[10] L. Malha and P. August. Safety of antihypertensive medications in pregnancy: Living with uncertainty. *Journal of the American Heart Association*, 8(15), 2019.

[11] M. Kotelchuck. An evaluation of the kessner adequacy of prenatal care index and a proposed adequacy of prenatal care utilization index. *American Journal of Public Health*, 84(9):1414–1420, 1994.

[12] S.-G. Beland. Development of a comorbidity score based on institutionalization:comparative performance with a comorbidity score modeled on mortality. *Journal of Gerontology amp; Geriatric Research*, 02(01), 2012.

[13] G. Sweeten. Group-based trajectory models. *Encyclopedia of Criminology and Criminal Justice*, page 1991–2003, 2014.

[14] D. S. Nagin. Group-based trajectory modeling: An overview. *Handbook of Quantitative Criminology*, page 53–67, 2009.

[15] Bayesian information criterion. *Encyclopedia of Measurement and Statistics*, 2007.

[16] National high blood pressure education program working group report on hypertension in the elderly. national high blood pressure education program working group. *Hypertension*, 23(3):275–285, 1994.

[17] Medications for high blood pressure during pregnancy, Dec 2021.

[18] R. Luoto, E. Kharazmi, E. Whitley, J. Raitanen, M. Gissler, and E. Hemminki. Systolic hypertension in pregnancy and cardiovascular mortality: A 44-year follow-up study. *Hypertension in Pregnancy*, 27(1):87–94, 2008.

A Methods of Creation

A.1 Stockpiling Method

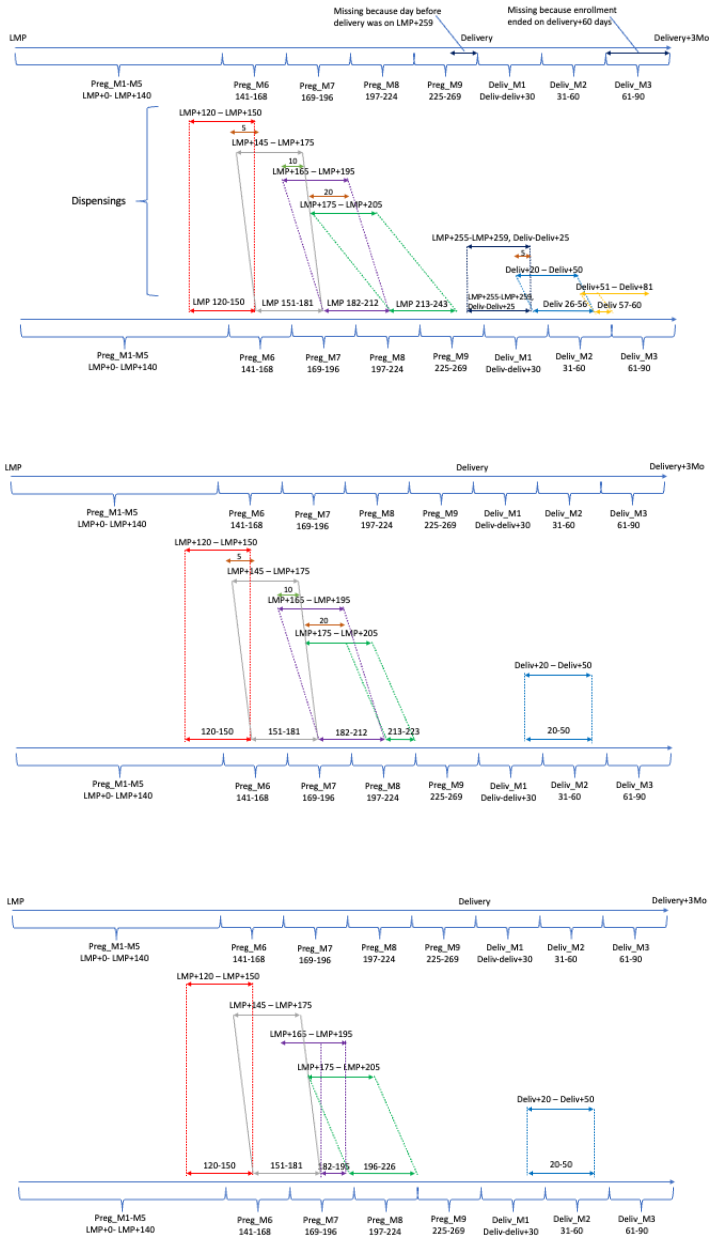

Figure 3: Example for a Methyldopa exposure of stockpiling.

A.2 Quartile Creation

Unemployment

- Create continuous variable "Unemployment" for each pregnancy, using information provided in sheet "Unemployment":
  - For DELIVERY in years 2000-2007, assign value from column "Unemploymentrate2007"
  - For DELIVERY in year X (where X=2008, 2009,..., 2018), assign value from column "UnemploymentrateX" (where X=2008, 2009,..., 2018)
  - Variable "Unemployment¡year¿Q": SEPARATELY for each DELIVERY year, create quartiles of unemployment (do this only for women who had DELIVERY in that specific year).
  - Variable "UnemploymentNEWQ": combine Unemployment¡year¿Q variables into one.
- Create categorical variable "metropolitanarea" where:
  - E.g., if woman A had Q1 in 2000, and woman B had Q3 in 2003, UnemploymentNEWQ would now be =1 for woman A and =3 for woman B.
- Please report N pregnancies in the respective UnemploymentNEWQ categories 1-4.

Pregnancy	FIPS Code	Unemployment Rate
1	A	5%
2	B	10%
3	A	5%
4	C	30%
5	D	40%
6	E	7%
7	F	50%
8	E	7%

Table 4: Example of a constellation for a cohort of 8 pregnancies with x delivery year where FIPS code is a published series of standardized codes used for interchange between government agencies and other communities.

Using the figure above as a model, the quartiles would range as follows:

Q1 $\leq 5\%$ (will therefore include all from FIPS A)

Q2 > 5 & $\leq 7\%$ (will include all from FIPS E)

Q3 > 7 & $\leq 30\%$ (will include all from FIPS B & C)

Q4 $> 30\%$ (will include all from FIPS D F)

B Indices

Risks scores for obstetric comorbidities

Factor	SSM	Non-transfusion SSM
Gestational diabetes mellitus	1	1
Maternal age 35 years	2	1
Previous cesarean birth	4	0
Delivery BMI 40	5	4
Major mental health disorder	7	4
Neuromuscular disease	9	8
Chronic hypertension.	10	7
Substance use disordder	10	5
Asthma, acute or moderate/severe	11	9
Gastrointestinal disease	12	8
Preterm birth (<37 weeks)	18	12
Anemia, preixisting	20	7
HIV/AIDS	30	13
Cardiac disease, prexisting	31	23
Pulmonary hypertension	50	32
Placenta accreta spectrum	59	36

Table 5: The obstetric comoridity scoring system.

C Trajectory Modeling

Link to code : `https://github.com/elizabethnyam/adherence-sas-trajectory`

Link to SAS package : `https://www.andrew.cmu.edu/user/bjones/download.htm`

D Statistical Analysis

For continuous variables, standardized difference mean difference (d) is calculated:

$$d = \frac{\overline{x}_{\text{treatment}} - \overline{x}_{\text{control}}}{\sqrt{\frac{s^2_{\text{treatment}} + s^2_{\text{control}}}{2}}}$$

Where X(treatment) and X(control) denote the sample mean of the covariate in treated (exposed) and untreated (unexposed) subjects, respectively. And s refers to the standard deviation.

For binary/categorical variables, (d) is calculated:

$$d = \frac{\hat{p}_{\text{treatment}} - \hat{p}_{\text{control}}}{\sqrt{\frac{\hat{p}_{\text{treatment}}(1 - \hat{p}_{\text{treatment}}) + \hat{p}_{\text{control}}(1 - \hat{p}_{\text{control}})}{2}}}$$

Where p(treatment) and p(control) denote the prevalence of the binary variable in treated and untreated subjects, respectively.