Role of Antihypertensive Treatment and Blood Pressure Control in the Occurrence of Adverse Pregnancy Outcomes: a Population-Based Study of Linked Electronic Health Records

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Abstract

Background: CH (CH) adversely impacts pregnancy. It remains unclear whether antihypertensive treatment alters these risks. We examined the role of antihypertensive treatment in the association between CH and adverse pregnancy outcomes.

Methods: Electronic health records from the UK Caliber and CPRD were used to define a cohort of women delivering between 1997-2016. Primary outcomes were pre-eclampsia, preterm birth (PTB), and FGR (FGR). We used multivariable logistic regression to compare outcomes in women with CH to women without CH, and propensity-score matching to compare antihypertensive agents.

Results: The study cohort consisted of 1,304,679 women and 1,894,184 births. 14,595 (0.77%) had CH, and 6,786 (0.36%) were prescribed antihypertensive medications in pregnancy. Overall, women with CH (vs no CH), had higher odds of: pre-eclampsia [adjusted odds ratio (aOR)=5.74 (95% CI: 5.44-6.07)]; PTB [aOR=2.53(2.39-2.67)]; and FGR [aOR=2.51(2.31-2.72)]. Women with CH prescribed treatment (vs untreated women) had higher odds of pre-eclampsia [aOR=1.17(1.05-1.30)], PTB [1.25(1.12-1.39)], and FGR [1.80(1.51-2.14)]. Women prescribed methyldopa (versus β-blockers) had higher odds of pre-eclampsia, [aOR=1.43(1.19-1.73)]; PTB [1.59(1.30-1.93)], but lower odds of FGR [aOR=0.66(0.48-0.90)]. Odds of adverse outcomes were similar in relation to calcium-channel-blockers (versus β-blockers) except for PTB [aOR=1.94(1.15-3.27)]. Among women prescribed treatment, lower average blood pressure (<135/85 mmHg) was associated with better pregnancy outcomes.

Conclusions: Treatment with antihypertensive agents and control of hypertension ameliorates some effects but higher risks of adverse outcomes persist. β-blockers versus methyldopa may be associated with better pregnancy outcomes except for FGR. Powered trials are needed to inform optimal treatment of CH during pregnancy.

Keywords: antihypertensive, chronic hypertension, perinatal outcome, pregnancy

Introduction

Chronic hypertension (CH) refers to high blood pressure (BP) (≥140/90 mm Hg) predating pregnancy or diagnosed before 20 weeks' gestation[1] and it is estimated to affect 0.6–1.3% of pregnant women in high-income countries.[2, 3] Previous reports from meta-analyses[4, 5] and cohort studies[3, 6-8] have demonstrated that women with CH have an increased risk of maternal and perinatal complications. Antihypertensive treatments are recommended for pregnant women with CH, or other forms of hypertension in pregnancy, to prevent severe hypertension with the aim of prolonging gestation to enable delivery of a healthy, normally grown infant at term.[9] However, there is a paucity of evidence to inform clinicians and women on the choice of antihypertensive medication and the degree to which overall control of hypertension affects outcome.[10-14]

International guidelines recommend labetalol, methyldopa or nifedipine as first-line agents for the treatment of hypertension in pregnancy.[1, 9, 15, 16] However, no consensus exists on whether certain antihypertensive agents reduce the risk of adverse pregnancy outcomes in addition to controlling maternal hypertension. A meta-analysis of randomized controlled trials (RCTs) examining the effect of antihypertensive treatment in pregnant women with CH showed a reduced risk of severe hypertension [5 trials, 446 women; risk ratio (RR)=0.33 (95% confidence interval (CI), 0.19–0.56)], compared to no treatment or placebo.[17] There was no significant effect of treatment on other clinically important outcomes, including pre-eclampsia and small-for-gestational-age infants, possibly due to insufficient power.[17, 18] Similarly, the most recent Cochrane review of treatment for mild-to-moderate hypertension (systolic blood pressure (sBP) 140–169 mmHg and/or diastolic blood pressure (dBP) 90–109 mmHg), reported that antihypertensive treatment reduced the risk of severe hypertension compared to no treatment or placebo [RR=0.49; (95% CI, 0.40–0.60); 20 trials, 2558 women], without evidence on the impact on other adverse perinatal outcomes.[19] The Cochrane review has also reported that β-blockers and calcium channel blockers are more effective than methyldopa in preventing severe hypertension.[19] However, two recent meta-analyses, including observational studies, raised concerns regarding the use of antihypertensive agents, particularly β-blockers, during pregnancy, as they were associated with higher risks of small-for-gestational-age infants in women with CH.[5, 20]

As the available literature examining the effect of different antihypertensive agents on pregnant women with CH is limited and does not investigate whether the observed effect is mediated by control of hypertension, and given that previous trials have lacked the power to detect effects on perinatal outcomes, we sought to investigate maternal and perinatal outcomes in pregnancies complicated with CH in a population-based cohort study using electronic health records data.

Objectives

The objectives of this study were to: 1) compare maternal and perinatal outcomes in pregnant women with CH (treated and untreated) to pregnant women without CH; 2) compare maternal and perinatal outcomes in women with treated CH against those untreated whilst assessing the modifying effect of BP level; 3) compare maternal and perinatal outcomes across different antihypertensive agents (methyldopa, β-blockers, and calcium channel blockers); and 4) investigate the relationship between BP level and pregnancy outcomes.

Methods

Because of the sensitive nature of the data collected for this study, access to use primary care data for research can be obtained by submitting an application to the Independent Scientific Advisory Committee at https://www.cprd.com/Data-access.

Study design and data sources

We created a longitudinal population-based cohort study using linked electronic health record from 1997 to 2016. Women were part of CALIBER (CArdiovascular research using LInked Bespoke studies and Electronic health Records). CALIBER linkage included anonymized primary care electronic patient records from the Clinical Practice Research Datalink (CPRD), data on hospital admissions from Hospital Episodes Statistics (HES), and data from Office for National Statistics (ONS) cause-specific mortality records.[21]

CPRD provides information about laboratory tests, clinical diagnoses, prescription details, and medical procedures (coded with the Read clinical coding scheme). The overall quality of the data recorded in a primary care practice is algorithmically marked by an "up-to-standard (UTS)" date by CPRD; the UTS indicates that data in the practice have continuous high-quality data fit for use in research.[22] HES provides information about diagnoses (coded with the tenth revision of the International Classification of Diseases (ICD-10)) and medical procedures

related to all hospital admissions across all hospitals in England. More details on the methods are available in the Supplementary. We followed the reporting of studies conducted using the RECORD-PE (REporting of studies Conducted using Observational Routinely-collected Data for PharmacoEpidemiology).

Study population

Women were eligible for inclusion if they registered with an UTS practice that consented to linkage with HES. All women were identified by a unique healthcare-specific identifier which enables linkage of participant data across electronic health record sources.

To assess the effect of antihypertensive agents on pregnancy outcomes, we included women with complete pregnancies with a minimum length of 20 weeks' gestation. Data on pregnancy were retrieved from the CPRD Pregnancy Register and the HES Maternity File. Firstly, records from the CPRD Pregnancy Register were used to identify 'complete pregnancy' that occurred between 1 January 1997 and 31 December 2016, and women aged between 11-49 years at delivery. Secondly, the same criteria were used to identify complete pregnancies from the HES Maternity File. Pregnancy records from the CPRD Pregnancy Register and the HES Maternity File were then merged, and overlapping records were removed (the study flow diagram and details of handling duplicate records are provided in the supplement Figure S1 & Figure S7).

Exposures

1. Chronic hypertension

CH was classified as an *inferred* or *diagnosed* record of hypertension taken from the validated CALIBER phenotype.[23] Pregnant women were classified as having *diagnosed hypertension* if they had a recorded diagnosis of hypertension during a consultation in primary care or during a hospitalization, or *inferred hypertension* if they received repeat prescriptions (at least two prescriptions within 6 months) of blood pressure lowering-medication or based on BP readings. Hypertension was considered if the diagnosis date or prescription date was before pregnancy or before 20 weeks' gestation.

2. Antihypertensive treatment

Data on antihypertensive medication were identified from the CPRD. Treated women were defined as women who were dispensed at least one prescription for an antihypertensive

treatment during pregnancy, including those on monotherapy or polytherapy. However, when we compared the effect of different antihypertensive agents (methyldopa, β-blockers, and calcium channel blockers), each agent was counted if a pregnant woman was exposed to merely one type of antihypertensive agent during pregnancy. Pregnant women who had prescriptions for multiple antihypertensive medications or switched to other agent(s) at any stage of pregnancy were excluded when comparing agent vs. agent (more details about women who switched to other medications during pregnancy can be found in the supplement Table S1).

Each pregnancy record was then classified into one of the following five categories:

1. Untreated normotensive
2. Untreated diagnosed hypertension
3. Treated diagnosed hypertension
4. Untreated inferred hypertension
5. Treated inferred hypertension

Following this, a treated group was identified, and this consisted of pregnant women who were prescribed antihypertensive agents for *diagnosed* or *inferred* hypertension during pregnancy. When we assessed the effect of being treated on adverse pregnancy outcomes in hypertensive women (treated vs. untreated), the untreated group included women with *untreated diagnosed hypertension* (15%) and not *untreated inferred hypertension* (85%). We chose to restrict the untreated group to those with *diagnosed hypertension* as we considered that these were more robust (data are shown in the supplement file separately for inferred and diagnosed hypertension Tables S2 & S3). In addition, treated women were subclassified according to the level of BP control to examine the effect of treatment according to the level of BP control.

3. Blood pressure level

BP readings that were measured during pregnancy were considered. The average readings of sBP and dBP during each pregnancy were calculated to be the BP if a pregnant woman had more than one BP measurement. BP was categorized into <115, 115–129, 130–139, 140–159, 160–179 and ≥180 mmHg categories for sBP, and <75, 75–84, 85–89, 90–94, 95–99 and ≥100 mmHg categories for dBP. In treated women with CH, we further categorized BP into two

categories: tight control (women assigned to this group if their sBP and dBP were both below 135/85 mmHg during the 1st and 2nd trimesters); or less-tight control group (if either sBP or dBP were ≥135/85 mmHg during the 1st and 2nd trimesters).

Potential confounders

For body mass index, the closest measurements to pregnancy start were considered, with records prior to two years before the start of pregnancy excluded. Other covariates include maternal age, smoking (non-smoker, former smoker, or current smoker), ethnicity (White, Black, South Asian, or other/mixed ethnic group), index of multiple deprivation (IMD), parity, and maternal comorbidities (pre-pregnancy diabetes and chronic kidney disease).

Outcomes

The primary outcomes included a diagnosis of pre-eclampsia, fetal growth restriction (FGR) based on Read or ICD-10 codes (codes are shown in the supplement, Table S14), preterm birth (<37 weeks' gestation), or very preterm birth (<32 weeks' gestation). Secondary outcomes included stillbirth, emergency Caesarean section, elective Caesarean section, and severe hypertension (≥160/110 mmHg).

The study was approved by the Independent Scientific Advisory Committee for the Medicines and Healthcare Products Regulatory Agency (protocol number 16_280_R).

Statistical analysis

We summarized the maternal and perinatal characteristics according to hypertension and treatment status using frequency and percentage for categorical variables and mean with standard deviation (SD) for continuous variables (Table S4). We performed logistic regression analysis to calculate the crude and adjusted odds ratios (OR) with 95% CIs. First, we assessed the association between CH and adverse pregnancy outcome compared to untreated normotensive pregnancies.

Among women with CH, we examined the effect of antihypertensive treatment on the risk of adverse pregnancy outcomes using propensity score matching. Propensity score matching is a method to reduce confounding of treatment effect estimates, in observational studies, by matching treatment and comparison groups so that they are as similar as possible on the observed background characteristics[24-27] (more details about the propensity score matching

method and results for diagnostic assessment can be found in the supplement, pages 2 & 46-49).

Modification of treatment effect by underlying BP level was examined using interaction terms between BP level (categorical variable as illustrated earlier) and treatment [(treated vs. untreated) or (methyldopa vs. β-blocker)] in analyses. The significance of the interaction was tested using the Wald test, and predictive marginal effects of the interaction terms were plotted to better visualize how much the predicted probability of pregnancy outcomes changed with changes in BP levels. In sensitivity analyses of the effect of treatment, we excluded women with severe hypertension (≥160/110 mmHg) to assess whether that influenced the observed associations. These analyses were also restricted to women aged at least 18 years at delivery (n=37 were excluded; 20 in the treated and 17 in the untreated group). Treated group was further subclassified based on BP levels to examine the associations between the treated (tight and less-tight control) and untreated women according to BP levels in the treated group (Table S5). We also repeated analyses to compare the effect of antihypertensive agents on each outcome using the whole cohort, without propensity score matching, using multivariable logistic regression (supplement Tables S6-S8). In addition, pregnancy outcomes of women who had been prescribed more than one antihypertensive agent were compared to those who prescribed one agent (Table S9).

The relationship between BP levels and pregnancy outcomes was examined using mean BP readings during pregnancy. The effect of higher BP was estimated separately in women with CH who were treated and in women with CH who were untreated, adjusting for maternal age, IMD, smoking status, body mass index, ethnicity, parity, and pre-pregnancy diabetes and kidney disease (Tables S10-S12). Finally, in a post-hoc analysis, we used cubic splines to allow for a non-linear relationship of the association between BP levels and FGR, using mean BP readings as a continuous variable. Spline coefficients cannot be interpreted directly; therefore, the model was displayed graphically, showing the predicted probability of FGR according to BP levels (Figure S6).[28] All statistical analyses were performed using Stata software (version 16), including the *postrcspline*[29] and *teffects psmach* packages.

Results

A total of 1,894,184 pregnancies in 1,304,679 women were identified between 1997 and 2016. Of these 14,595 (0.77%) had CH, and 6,786 (0.36%) were prescribed antihypertensive treatment. The summary characteristics of the women according to hypertension and treatment status are shown in Table S4. Women with CH were older on average, had a higher body mass index, and had a higher prevalence of pre-pregnancy diabetes (with higher percentages among the treated group) than the normotensive untreated group. Overall, of the total cohort of 1,894,184 pregnancies, there were 33609 (1.8%) pre-eclampsia cases, 76518 (4%) preterm birth, 21027 (1.1%) very preterm birth, 41495 (2.2%) FGR babies, 8626 (0.46%) stillbirths, 198061 (11%) emergency Caesarean births, and 152243 (8.9%) elective Caesarean birth. Similar patterns of baseline characteristics were found in women with *inferred* untreated hypertension (demographic characteristics are shown separately for *inferred* and *diagnosed* hypertension in Table S2).

Chronic hypertension

Overall, higher odds of all assessed outcomes were observed in both treated and untreated women with CH compared with women without CH (Table 1). After multivariate adjustment, there was a higher odds among untreated women with CH for pre-eclampsia, [adjusted OR (aOR)=5.75 (95% CI, 5.34–6.21)]; emergency Caesarean birth [aOR=1.24, (1.16–1.33)]; elective Caesarean birth [aOR=1.32, (1.23–1.41)]; and stillbirth [aOR=1.58, (1.24–2.01)] compared to women without CH. Similarly, treated women with CH, compared to women without CH, had higher odds of pre-eclampsia [aOR=5.73 (95% CI, 5.30–6.18)]; emergency Caesarean birth [aOR=1.26, (1.17–1.36)]; elective Caesarean birth [aOR=1.34, (1.24–1.44)]; and stillbirth [aOR=1.64, (1.28–2.10)]. The magnitude of the associations appeared higher in women requiring treatment for preterm birth [aOR=2.94, (95% CI, 2.73–3.16)]; very preterm birth [aOR=4.13, (3.67–4.65)]; and FGR [aOR=3.03, (2.72–3.37)] than in women not requiring treatment (preterm birth [aOR=2.13, (1.96–2.30)]; very preterm birth [aOR=2.38, (2.06–2.74)]; and FGR[aOR=1.99 (1.76–2.25)] compared to women without CH.

Antihypertensive agents

Among the women prescribed treatment, the majority were prescribed β-blockers only (2714, 40%) or methyldopa only (1957, 29%). The remainder of antihypertensive treatment was a

combination of more than one antihypertensive agent (1530, 23%), calcium channel blockers only (289, 4.3%), or a mixture of loop diuretics and thiazides (159, 2.3%), whereas (137, 2%) changed the treatment regimen (including those on monotherapy, from one agent to another) during pregnancy.

Treated compared to untreated pregnancies with CH

When we estimated the effect of antihypertensive treatment on pregnancy outcomes using the propensity matched sample, the adjusted analyses showed higher odds in the 'any treatment' women compared to untreated chronic hypertensive women for pre-eclampsia [aOR=1.17 (95% CI, 1.05–1.30)], preterm birth [aOR=1.25 (1.12–1.39)], very preterm birth [aOR=1.66 (1.38–2.00)], FGR [aOR=1.80 (1.51–2.14)], and severe hypertension [aOR=3.88 (3.39–4.45)]. However, the odds of stillbirth, emergency Caesarean birth, and elective Caesarean birth did not depend on treatment status (Table 2).

The additional analysis comparing pregnancy outcomes among the untreated and treated (tight and less-tight control separately) women, suggested that treated women who achieved tight control (BP<135/85 mmHg), versus untreated women, had a lower odds of pre-eclampsia [aOR=0.59 (95%CI, 0.46–0.76)]. Similar results were observed between the untreated and treated groups with tight control for other outcomes, except for a higher odds of FGR [aOR=1.55 (95%CI, 1.14–2.12)]. On the other hand, treated women with a less-tight control (BP≥135/85 mmHg) had higher odds of severe hypertension, pre-eclampsia, stillbirth, preterm birth, and FGR, compared to untreated women (Table S5).

The effect of specific antihypertensive agents

When we estimated the effect of specific antihypertensive agents among the treated group, methyldopa versus β-blockers was associated with a higher odds of severe hypertension in the second trimester [aOR=1.58 (95% CI, 1.20–2.10)], severe hypertension in the third trimester [aOR=1.71 (1.21–2.41)], pre-eclampsia [aOR=1.43 (1.19–1.73)], preterm birth [aOR=1.59 (1.30–1.93)] very preterm birth [aOR=1.44 (1.05–1.97)], and a lower odds of FGR [aOR=0.66 (0.48–0.90)]. No differences were found for stillbirth, emergency Caesarean birth, and elective Caesarean birth between the two agents (Tables 3 and 4).

When pregnancy outcomes were compared between women prescribed calcium channel blockers and β-blockers, we found similar effects on pregnancy outcomes except for preterm

birth, which was higher in those prescribed calcium channel blockers [aOR=1.94 (1.15–3.27)]. However, statistical power was limited due to the small number of women using calcium channel blockers (n=289), (Tables 3 and 4).

The probability of having adverse pregnancy outcomes was higher in pregnant women with higher BP levels, regardless of treatment (Figure 1, and Figures S3-S5). Additionally, the probability of pre-eclampsia, preterm birth, very preterm birth, and emergency Caesarean birth in the treated group with controlled dBP (95-99 mmHg) were lower than those in the untreated group (Figure S3).

Polytherapy compared to monotherapy

Among the treated women, 23% were exposed to polytherapy. Pregnant women who were prescribed more than one antihypertensive agent had a higher odds of severe hypertension [aOR=1.53 (1.31–1.78)], very preterm birth [aOR=1.33 (1.03–1.72)], and FGR [aOR=1.68 (1.33–2.13)], compared to those who were prescribed monotherapy. When we excluded women with severe hypertension from this analysis, an association between polytherapy and adverse outcomes was found only for FGR [aOR=1.66 (1.29–2.15)]. (Table S9)

Blood pressure levels

Data were available on pregnancy BP readings from 475,851 (36%) pregnancies (including untreated normotensive pregnancies or those with CH). After multivariate adjustment, there was higher odds of adverse maternal and perinatal outcomes among pregnancies with elevated BP (sBP≥140 mmHg and/or dBP≥90 mmHg), compared to normotensive pregnancies (sBP=115–129 mmHg and/or dBP=75–84 mmHg); (Table S10). The analyses of the effect of BP level in pregnancies with untreated CH (n=2,802) and treated hypertension (n=5,375) showed that the magnitude of the elevated risks was highest in women with sBP≥160 mmHg, meaning that women with highest uncontrolled hypertension had the highest risks compared to those with controlled hypertension (Tables S11 & S12).

When we assessed the effect of less-tight (BP≥135/85 mmHg; n=4295) versus tight (BP<135/85 mmHg; n=1080) control in treated women with CH, the adjusted effect estimates were higher for pre-eclampsia [aOR=2.38 (1.85–3.07)]; preterm birth [aOR=1.26 (1.02–1.56)]; very preterm birth [aOR=1.88 (1.29–2.73)]; emergency Caesarean birth [aOR=1.27 (1.02–

1.57); and severe hypertension [aOR=3.16 (1.99–5.03)]. No differences were found for FGR, stilbirth, and elective Caesarean birth (Table 5).

Discussions

This population-based cohort of 1,894,184 pregnancies confirms a high burden of adverse outcomes in pregnant women with CH. Women with CH had approximately a six-fold increase in the odds of pre-eclampsia; and in women requiring treatment there was almost a 3-fold increase in the odds of preterm births and FGR compared to women without CH. In women with CH, those requiring treatment (versus untreated) had higher odds of pre-eclampsia, preterm birth, and FGR, but no differences were found for stillbirth and Caesarean births. Different antihypertensive treatments have a different impact on adverse pregnancy outcomes; β-blockers (versus methyldopa) were associated with lower odds of severe hypertension, pre-eclampsia, and preterm birth, but a higher odds of FGR. The occurrence of adverse pregnancy outcomes varies according to BP levels, with better outcomes in women with lower BP levels during pregnancy, less-tight (versus tight) control was associated with a significant increase of adverse pregnancy outcomes.

This study clarifies key associations between CH and adverse pregnancy outcome. Our findings are consistent with the results from a recent meta-analysis of 94 observational studies which reported an association between CH and a higher risk of adverse pregnancy outcomes and suggested a higher risk of pregnancy complications in women requiring treatment compared to normotensive women.[5] A recent network meta-analysis (14 RCTs and 8 cohorts, comprising 4464 women with CH) comparing several agents versus placebo or no treatment reported that many agents, including nifedipine, methyldopa, ketanserin and pindolol, decreased the risk of severe hypertension.[20] However, the two meta-analyses highlighted the risk of small-for-gestational-age infants in women treated with β-blockers compared with the untreated hypertensive group.[5, 20]

Research based on 'real-world' evidence, using routinely-collected data from Electronic Health Records have been conducted to evaluate and compare the effectiveness and safety of medicine,[30] and a few prior observational studies used data from electronic health record to assess the patterns and effect of the use of antihypertensive treatment during pregnancy.[10, 31-33] Most of the previous cohort studies of women with CH compared

pregnancy outcomes without separating treated and untreated hypertensive groups. In studies that distinguished between treated and untreated groups, pregnancy outcomes were compared in treated women with either untreated normotensive[10-14] or untreated hypertensive pregnancies.[34-37] Our current results are consistent with those reporting a higher risk of pre-eclampsia[10, 11, 37], preterm birth[10-14, 34, 35] and small-for-gestational-age infants[10-12, 34-37] in treated women compared to untreated normotensive women[10-14] or untreated hypertensive women.[34-37] This is unsurprising as women with higher BP levels require antihypertensive treatment, predisposing them to higher odds of adverse pregnancy outcomes.

When we compared perinatal outcomes among the untreated and treated women with CH based on control level in the treated group. The results indicated a lower odds of pre-eclampsia among the treated women who achieved tight control (BP<135/85 mmHg) and no differences for other assessed outcomes, except for a higher odds of FGR. Whereas higher odds of almost all assessed outcomes were observed for treated women with less-tight control (BP≥135/85 mmHg), compared to untreated women, suggesting that increased odds of adverse perinatal outcomes in the treated group was mainly attributable to the level of BP control. It is possible that women who achieve tighter control of BP may also be those women who have less stiff blood vessels and therefore a less severe phenotype of CH. Thus, these women may also respond well to treatment. Further observational studies to try and stratify those more or less likely to respond to certain antihypertensive treatments by assessing arterial stiffness may help improve antihypertensive response to pharmacological treatment.

Evidence regarding control of hypertension in women with CH is very limited. The findings from a secondary analysis of CHIPS (Control of Hypertension In Pregnancy Study) study included just 961 women and highlighted the importance of tight control.[38] Our data on 475,851 pregnant women highlights that control of hypertension is critical in reducing the risk of adverse outcomes in women with CH. Furthermore, the findings from a multicenter trial suggested that less-tight control (target dBP 100 mmHg) was associated with a higher odds of severe maternal hypertension than tight control (target dBP 85 mmHg), but no differences were found in the perinatal outcomes.[39] However, this study included 987 women with either CH or gestational hypertension. In contrast, our study was powered to detect perinatal outcomes (including 5375 pregnant women with CH), suggesting that less-tight control

(versus tight control) was associated with higher odds of severe hypertension, pre-eclampsia, prematurity, and emergency Caesarean birth. To our knowledge, none of the previous observational studies compared pregnancy outcomes in treated women with CH to both normotensive (without CH) and untreated hypertensive women, in addition to an assessment of the role of BP level in these associations.

Few studies have directly compared the effectiveness of different antihypertensive agents in pregnant women with CH. A population-based Canadian study reported an increased risk of small-for-gestational-age infants in women with CH treated with β-blockers only compared to those treated with methyldopa only.[40] A UK cohort study of 974 births compared pregnancy outcomes between women on more than one antihypertensive agent and those on one agent reported a greater risk of pre-eclampsia (aOR=2.27) and preterm birth (aOR=3.05) among women on polytherapy with BP≥140/90 mmHg.[41] Similarly, we found more adverse pregnancy outcomes among women on polytherapy.

Evidence from RCTs comparing antihypertensive agents of CH in pregnancy is limited. Our study is in contrast with a limited meta-analysis of five trials (including <300 women for each assessed outcome) comparing methyldopa vs. other agents that showed no significant differences for severe hypertension or perinatal outcomes.[17] A more recent UK trial (including 112 women) comparing labetalol versus nifedipine for control of CH in pregnancy reported that both agents were effective in controlling mean BP, but it was not powered to assess other maternal and perinatal outcomes.[42] Our findings are consistent with an updated Cochrane meta-analysis of RCTs, including pregnant women with CH and gestational hypertension, which indicated that methyldopa (versus β-blockers) was less effective in preventing severe hypertension [nine trials, (592 women, RR=1.36, 95% CI, 1.08–1.71)].[19] Although the result for small-for-gestational-age infants suggested lower risk in those treated with methyldopa, this did not reach a significant level [six trials (577 babies, RR= 0.84; 95% CI 0.54 –1.31).[19] Nevertheless, most of the included trials were small and lacked statistical power to investigate perinatal outcomes.

Our study has several strengths. Using a large, nonselective cohort including 1,894,184 pregnancies with 14,595 pregnancies in women with CH, one of the largest described cohorts of pregnant women with CH, reduced the possibility of selection bias and provided sufficient statistical power to perform subgroup analyses by type of antihypertensive agents and BP

level, which could help rule out some sources of confounding by indication. For example, we were able to apply an active-comparator design, in which the antihypertensive agent was compared with another agent; as both groups had the same treatment indication (CH), this could reduce bias from confounding by indication.[43, 44] In addition, using an active-comparator can attenuate unmeasured differences between groups, and reduce unmeasured confounding.[40] Unlike most of the previous studies that compared the effects of antihypertensive treatment to either normotensive or untreated hypertensive pregnancies, we investigated the effect of treatment compared to both women without CH and women with CH not on treatment. We conducted extensive validation of our electronic health records of hypertension phenotype, with special consideration on whether CH was diagnosed or inferred, particularly for untreated pregnancies. We had data on hypertension severity, such as BP values, allowing us to investigate whether the observed associations were due to treatment or disease severity. Data were collected prospectively making it less vulnerable to bias. The quality and comprehensiveness of electronic health records data allowed us to control for several potential confounders. Finally, for some analyses we used propensity score matching which reduces variation in baseline characteristics across the study groups.

However, the findings from the current study should be considered in light of several limitations. These 'real-world' data did not allow us to know adherence with the use of prescribed antihypertensive treatment, although accurate data on adherence is often scarce even in trials. The data on antihypertensive treatment included prescriptions in the CPRD that represent those documented by general practitioners; thus, misclassification of exposure is possible if pregnant women received additional prescriptions from other secondary care settings or did not adhere to treatment regimens. The level of missingness in the electronic health records of smoking and body mass index limited the validity of using multiple imputation, so there may be residual confounding by these variables. However, an indicator category was created for missing values to adjust for this issue. Finally, the observational nature of this study introduces a potential issue of unmeasured confounding. However, we adjusted for important confounders, including maternal age and pre-pregnancy disease, and we also conducted subgroup analyses according to BP level and type of antihypertensive agent.

Perspectives

This large cohort study highlights that adverse maternal and perinatal outcomes associated with CH. These outcomes vary depending on the pharmacological agent used and critically, this study highlights the importance of adequate control of hypertension in pregnancy. Larger randomized studies may further inform pharmacological use during pregnancy complicated by CH.

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Table 1. Chronic hypertension and adverse perinatal outcomes according to treatment status

Outcome	No Chronic hypertension* (n=1,739,944)		Crude OR (95% CI)				Adjusted OR (95%CI)†	
			Chronic hypertension					
			Untreated (n=7,809)		Treated (n=6,786)		Untreated vs. No CH	Treated vs. NO CH
	Cases, n (%)	OR (95% CI)	Cases, n (%)	OR (95 %CI)	Cases, n (%)	OR (95 %CI)		
Pre-eclampsia	29,859 (1.6)	Reference	839 (11)	7.28 (6.77, 7.83)	861 (13)	8.79 (8.18, 9.45)	5.75 (5.34, 6.21)	5.73 (5.30, 6.18)
Emergency Caesarean section	172,748 (11)	Reference	1,074 (16)	1.57 (1.47, 1.68)	888 (15)	1.48 (1.38, 1.59)	1.24 (1.16, 1.33)	1.26 (1.17, 1.36)
Elective Caesarean section	138,260 (8.8)	Reference	1,083 (16)	1.98 (1.86, 2.11)	934 (16)	1.94 (1.81, 2.09)	1.32 (1.23, 1.41)	1.34 (1.24, 1.44)
Stillbirth	7,631 (0.44)	Reference	67 (0.86)	1.96 (1.54, 2.50)	66 (0.97)	2.23 (1.75, 2.84)	1.58 (1.24, 2.01)	1.64 (1.28, 2.10)
Preterm birth (<37 wks.)	63,460 (3.7)	Reference	677 (8.7)	2.51 (2.32, 2.71)	861 (13)	3.84 (3.57, 4.13)	2.13 (1.96, 2.30)	2.94 (2.73, 3.16)
Very preterm birth (<32 wks.)	17,507 (1)	Reference	203 (2.8)	2.73 (2.37, 3.14)	318 (5.1)	5.14 (4.59, 5.76)	2.38 (2.06, 2.74)	4.13 (3.67, 4.65)
FGR	34,584 (2)	Reference	270 (3.5)	1.77 (1.56, 1.99)	376 (5.5)	2.89 (2.61, 3.21)	1.99 (1.76, 2.25)	3.03 (2.72, 3.37)

CH indicates chronic hypertension; FGR indicates fetal growth restriction; IMD, index of multiple deprivation; and OR, odds ratio.

*The reference group refers to untreated women without chronic hypertension who were unexposed to antihypertensive treatment during pregnancy; 95 860 records with either unspecified hypertension, other hypertensive disorders during pregnancy or had antihypertensive prescription were excluded from analyses except for preeclampsia investigation.

†Adjusted for maternal age, deprivation index (practice IMD 2015), smoking, body mass index, ethnicity, parity, and prepregnancy disease (diabetes and kidney disease).

Table 2. Antihypertensive treatment during pregnancy and adverse perinatal outcomes in women with chronic hypertension (treated vs. untreated) using propensity score matched sample

Treatment / Outcome	Frequency n (%)		Treated vs. untreated (matched sample)*	
	Untreated (n=6,766)	Treated (n=6,766)	OR (95%CI)†	Adjusted OR (95%CI)†
Severe hypertension	299 (4.4)	994 (15)	3.72 (3.26, 4.26)	3.88 (3.39, 4.45)
Pre-eclampsia	741 (11)	860 (13)	1.18 (1.07, 1.31)	1.17 (1.05, 1.30)
Emergency Caesarean section	893/5,923 (15)	887/5,833 (15)	1.01 (0.91, 1.12)	1.00 (0.90, 1.12)
Elective Caesarean section	843/5,873 (14)	933 /5,879(16)	1.13 (1.02, 1.25)	1.11 (1.00, 1.23)
Stillbirth	46 (0.68)	66 (0.98)	1.44 (0.99, 2.10)	1.40 (0.96, 2.05)
Preterm birth (<37 wks.)	700 (10)	858 (13)	1.26 (1.13, 1.40)	1.25 (1.12, 1.39)
Very preterm birth (<32 wks.)	195/6,261 (3.1)	317/6,225 (5.1)	1.67 (1.39, 2.00)	1.66 (1.38, 2.00)
Fetal growth restriction	212 (3.1)	374 (5.5)	1.81 (1.52, 2.15)	1.80 (1.51, 2.14)

OR indicates odds ratio.

*Treated group refers to women who had at least one prescription of antihypertensive medication during pregnancy women are women with prescribed at least one prescription of antihypertensive medication during pregnancy;

† These models used propensity score matching, and a double adjustment (the adjusted model) was performed to remove residual confounding.

Table 3. Adverse perinatal outcomes in pregnancies complicated with chronic hypertension in the propensity score matched sample

Outcome \ Treatment	Frequency, n (%)		Frequency, n (%)		Frequency, n (%)	
	β-blockers (n=1,952)	**Methyldopa (n=1,952)**	**β-blockers (n=289)**	**CCB (n=289)**	**Methyldopa (n=289)**	**CCB (n=289)**
Severe hypertension (2nd trimester)	88 (4.5)	139 (7.2)	15 (5.2)	7 (2.4)	15 (5.2)	7 (2.4)
Severe hypertension (3rd trimester)	56 (2.9)	97 (5)	11 (3.8)	7 (2.4)	10 (3.5)	7 (2.4)
Pre-eclampsia	220 (11)	312 (16)	36 (12)	43 (15)	44 (15)	43 (15)
Emergency Caesarean section	248/1,665 (15)	273/1,705 (16)	43/258 (17)	44/237 (19)	41/248 (17)	44/237 (19)
Elective Caesarean section	287/1,704 (17)	247/1,679 (15)	31/246 (13)	52/245 (21)	41/248 (17)	52/245 (21)
Stillbirth	13 (0.67)	17 (0.87)	3 (1)	5 (1.7)	5 (1.7)	5 (1.7)
Preterm birth (<37 wks.)	199 (10)	292 (15)	29 (10)	50 (17)	51 (18)	50 (17)
Very preterm birth (<32 wks.)	74/1,827 (4.1)	100/1,760 (5.7)	19/279 (6.8)	17/256 (6.6)	17/255 (6.7)	17/256 (6.6)
Fetal growth restriction	106 (5.4)	71 (3.6)	22 (7.6)	18 (6.2)	12 (4.2)	18 (6.2)

CCB: Indicates calcium channel blockers.

Table 4. Adverse perinatal outcomes in pregnancies complicated with chronic hypertension in the propensity score matched sample

Outcome \ Treatment	Methyldopa vs. β-blockers (matched sample)*		Calcium channel blockers vs. β-blockers (matched sample)*		Calcium channel blockers vs. methyldopa (matched sample)†	
	OR (95%CI)‡	OR (95%CI)‡	OR (95%CI)‡	Adjusted OR (95%CI)‡	OR (95%CI)‡	Adjusted OR (95%CI CI)‡
Severe hypertension (2nd trimester)	1.63 (1.23, 2.14)	1.58 (1.20, 2.10)	0.46 (0.18, 1.14)	0.57 (0.20, 1.59)	0.45 (0.18, 1.13)	0.56 (0.21, 1.49)
Severe hypertension (3rd trimester)	1.77 (1.27, 2.48)	1.71 (1.21, 2.41)	0.63 (0.24, 1.65)	0.63 (0.22, 1.84)	0.69 (0.26, 1.85)	0.67 (0.22, 2.00)
Pre-eclampsia	1.50 (1.24, 1.80)	1.43 (1.19, 1.73)	1.23 (0.76, 1.98)	1.33 (0.78, 2.25)	0.97 (0.62, 1.54)	0.87 (0.53, 1.43)
Emergency Caesarean section	1.09 (0.90, 1.31)	1.03 (0.84, 1.25)	1.14 (0.72, 1.81)	1.23 (0.73, 2.08)	1.15 (0.72, 1.83)	1.04 (0.60, 1.79)
Elective Caesarean section	0.85 (0.71, 1.02)	0.83 (0.69, 1.01)	1.87 (1.15, 3.04)	2.14 (1.24, 3.70)	1.36 (0.86, 2.14)	1.63 (0.96, 2.76)
Stillbirth	1.31 (0.63, 2.71)	1.29 (0.62, 2.69)	-	-	-	-
Preterm birth (<37 wks.)	1.55 (1.28, 1.88)	1.59 (1.30, 1.93)	1.89 (1.15, 3.06)	1.94 (1.15, 3.27)	0.98 (0.64, 1.50)	1.07 (0.68, 1.69)
Very preterm birth (<32 wks.)	1.43 (1.05, 1.94)	1.44 (1.05, 1.97)	0.97 (0.49, 1.92)	1.01 (0.49, 2.11)	1.00 (0.50, 2.00)	1.15 (0.55, 2.40)
Fetal growth restriction	0.66 (0.48, 0.89)	0.66 (0.48, 0.90)	0.81 (0.42, 1.54)	0.75 (0.36, 1.56)	1.53 (0.72, 3.24)	1.45 (0.65, 3.23)

OR indicates odds ratio.

*The reference group refers to women who were prescribed β-blockers.

†The reference group refers to women who were prescribed methyldopa.

‡These models used propensity score matching, and a double adjustment (the adjusted model) was performed to remove residual confounding.

Table 5. Less-tight versus tight control of hypertension on pregnancy outcomes in treated women with chronic hypertension

Outcome \ Control	Tight control (N=1,080)*	Less-tight Control (N=4,295) †	Less tight vs. tight control	
	n (%)	n (%)	Crude OR (95%CI)	Adjusted OR (95%CI)‡
Severe hypertension in 3rd trimester	20 (1.8)	257 (6)	3.37 (2.13, 5.34)	3.16 (1.99, 5.03)
Pre-eclampsia	75 (6.9)	670 (16)	2.48 (1.93, 3.18)	2.38 (1.85, 3.07)
Emergency Cesarean section	131/939 (14)	622/3,662 (17)	1.26 (1.03, 1.55)	1.27 (1.02, 1.57)
Elective Cesarean section	141/949 (15)	633/3,673 (17)	1.19 (0.98, 1.45)	1.09 (0.89, 1.34)
Stillbirth	6 (0.6)	49 (1.1)	2.07 (0.88, 4.83)	1.83 (0.77, 4.31)
Preterm birth (<37 wks.)	122 (11)	600 (14)	1.28 (1.04, 1.57)	1.26 (1.02, 1.56)
Very preterm birth (<32 wks.)	33/991 (3.3)	248/3,943 (6.3)	1.95 (1.35, 2.82)	1.88 (1.29, 2.73)
Fetal growth restriction	54 (5)	255 (6)	1.20 (0.89, 1.62)	1.31 (0.96, 1.78)

OR indicates odds ratio.

*Tight control group refers to treated women with chronic hypertension whose average blood pressure in the first and second trimesters were both <135/85 mm Hg.

†Less-tight control group refers to treated women with chronic hypertension whose average blood pressure in the first and second trimesters were either ≥135/85 mm Hg.

‡Adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and prepregnancy disease (diabetes and kidney disease).

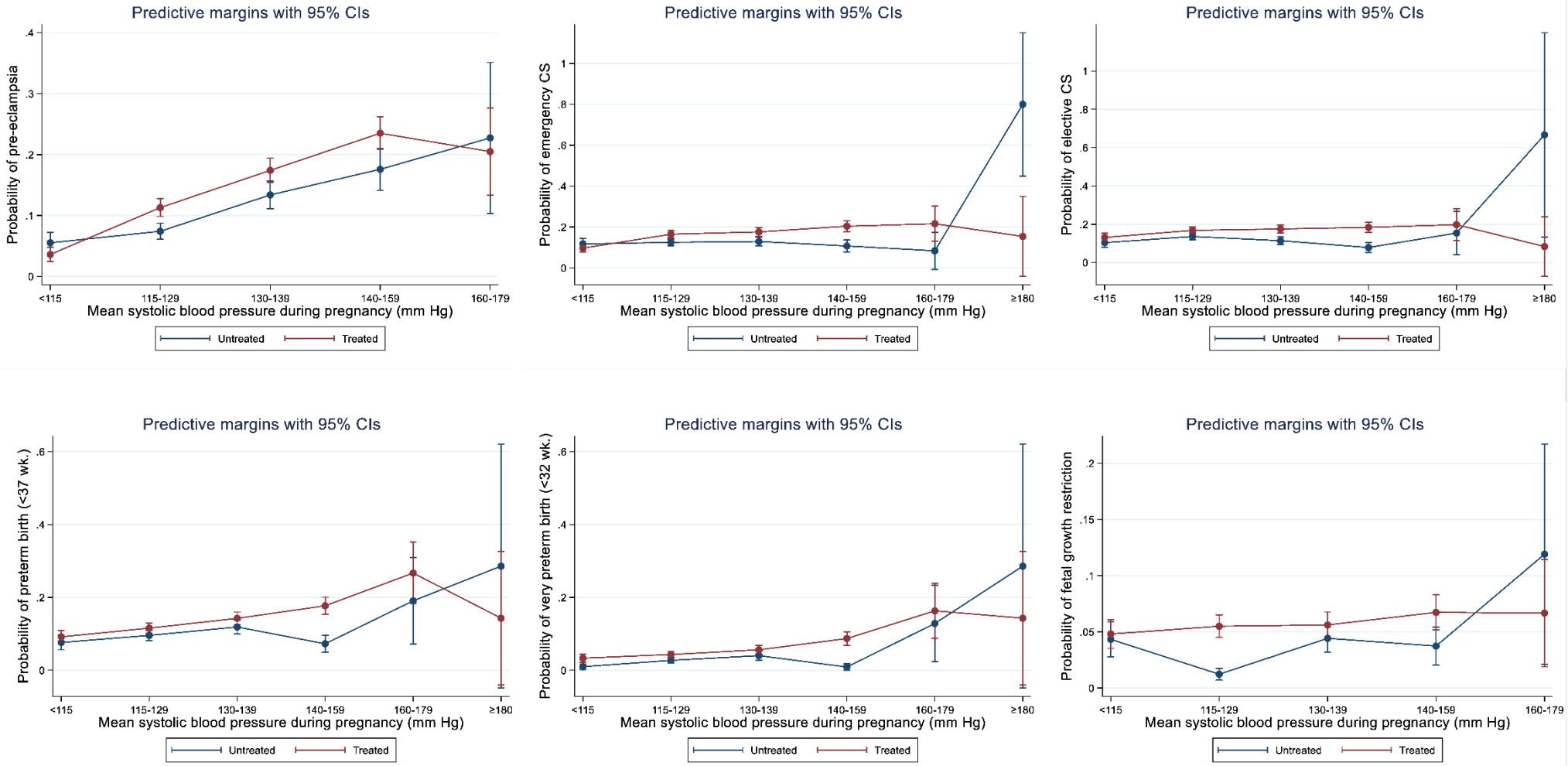

Figure 1. Predictive margins with 95% CIs of the probability of adverse perinatal outcomes by treatment across systolic blood pressure (SBP) levels.

These analyses were restricted to women with treated and untreated chronic hypertension matched using a propensity score and with available BP readings (N=8482). This model included an interaction term between antihypertensive agent and SBP levels. The large overlap in CIs suggests that the probabilities of adverse outcomes might be not different between both groups.

SUPPLEMENTARY MATERIALS

Role of Antihypertensive Treatment and Blood Pressure Control in the Occurrence of Adverse Pregnancy Outcomes: a Population-Based Study of Linked Electronic Health Records

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Supplementary methods

In propensity score matching, four separate comparisons were made. The first assessed adverse pregnancy outcomes in pregnancies that were prescribed antihypertensive treatment compared to untreated hypertensive pregnancies. In this model, the exposed group included pregnant women using any antihypertensive agent(s) (*inferred* or *diagnosed*), whereas the unexposed group included untreated pregnant women with *diagnosed* hypertension. The second comparison was of pregnancy outcomes in pregnant women with chronic hypertension using methyldopa versus β-blockers. Third, we compared pregnancy outcomes in those using calcium channel blockers versus β-blockers. Finally, we compared pregnancy outcomes in those using calcium channel blockers versus methyldopa. The propensity score algorithm was run separately for each comparison to match a record in the exposed group to the unexposed group. We used a logit model to create the propensity score for the probability of being treated, with the covariates of age (continuous), ethnicity, smoking, BMI, pre-pregnancy diabetes, parity, and index of multiple deprivation (IMD) (baseline characteristics before and after applying propensity score matching is shown in Table S13).

Propensity score matching analysis in this study was comprised of four steps. First, the propensity scores were estimated. Second, treatment and comparison units were matched by the closeness of their propensity scores, using 1:1 nearest-neighbour matching with a caliper width of 0.1 SDs of the logit of the propensity score.[1] Third, overlap and balance of propensity score distributions (balance plots) across treatment and comparison groups were assessed through visual inspection. Fourth step was to assess the balance of covariates (included in the propensity score estimation model) after matching using standardized differences to compare all covariates, with a value < 0.1 indicating good balance and a negligible difference between groups for the covariates.[2] Additionally, we used variance of ratios to assess the balance between the treatment and comparison groups, and kernel densities were plotted to examine balance of distributions of a continuous variable (maternal age) across matched treatment and comparison groups.[3]

Results of matching

The matching method achieved balance in measured covariates across the various treatment and comparison groups (standardized differences < 0.1 in nearly all covariates). Kernel density plots for the continuous variable (maternal age) between the two groups were reasonably similar. The distributions of the propensity scores are adequately overlapped with good balance.

Table S1. Treatment patterns during the first trimester of pregnancy across women with chronic hypertension

SWITCHERS from 1st TRIMESTER	**2nd TRIMESTER**				
	Diuretics	β-blockers	Methyldopa	Calcium channel blockers	Polytherapy*
Diuretics (n=142)	NA	4	9	0	2
β-blockers (n=2,027)	0	NA	27	5	43
Methyldopa (n=1,350)	0	29	NA	6	49
Calcium channel blockers (n=289)	0	6	17	NA	23
Polytherapy (n=1,146)	0	198	233	34	NA
SWITCHERS from 2nd TRIMESTER	**3rd TRIMESTER**				
Diuretics (n=45)	NA	1	1	0	2
β-blockers (n=1,616)	0	NA	10	1	31
Methyldopa (n=1,563)	0	18	NA	0	55
Calcium channel blockers (n=224)	0	2	6	NA	14
Polytherapy (n=606)	0	65	75	9	MA

*Polytherapy group includes women who were prescribed more than one agent during any stage of pregnancy.

Table S2. Baseline demographic characteristics for normotensive and hypertensive pregnancies

	Normotensive untreated pregnancies* n=1,739,944	Diagnosed untreated hypertension n=7,809	Diagnosed treated hypertension n=2,998	Inferred untreated hypertension n=43,785	Inferred treated hypertension n=3,788
Age (years), mean (SD)	28.9 (6)	32.7 (5.3)	34.5 (5.3)	31.4 (5.4)	31.2 (5.9)
Ethnicity, n (%)					
White	1,414,774 (81)	6,453 (83)	2,196 (73)	39,767 (91)	3,303 (87)
Black	69,944 (4)	623 (8)	422 (14)	1,010 (2.3)	152 (4)
South Asian	101,939 (5.9)	241 (3.1)	178 (5.9)	1,226 (2.8)	145 (3.8)
Other	81,695 (4.7)	207 (2.7)	118 (3.9)	872 (2)	97 (2.6)
Unknown	71,592 (4.1)	285 (3.7)	84 (2.8)	910 (2.1)	91 (2.4)
Smoking, n (%)					
Non-smoker	245,680 (14)	1,394 (18)	1,398 (47)	9,401 (22)	1,187 (31)
Ex-smoker	89,446 (5.1)	498 (6.4)	425 (14)	4,584 (11)	525 (14)
Current smoker	140,524 (8.1)	556 (7.1)	330 (11)	5,919 (14)	789 (21)
missing	1,264,294 (73)	5,361 (69)	845 (28)	23,881 (55)	1,287 (34)
Body mass index (kg/m2)					
Underweight (<18.5)	19,387 (1.1)	38 (0.5)	13 (0.4)	490 (1.1)	64 (1.7)
Normal (≥18.5 to <25)	275,769 (16)	1,033 (13)	502 (17)	8,386 (19)	949 (25)
Overweight (≥25 to <30)	146,769 (8.4)	938 (12)	652 (22)	6,429 (15)	723 (19)
Obese (≥30 to <40)	114,087 (6.6)	1,453 (19)	1,090 (36)	8,571 (20)	948 (25)
Severe obesity (≥40)	8,871 (0.5)	263 (3.4)	225 (7.5)	1,257 (2.9)	182 (4.8)

Missing	1,175,034 (68)	4,084 (52)	516 (17)	18,652 (43)	922 (24)
Pre-pregnancy diabetes, n (%)	5,704 (0.33)	334 (4.3)	193 (6.4)	824 (1.9)	189 (5)
Chronic kidney disease, n (%)	713 (0.04)	59 (0.76)	67 (2.2)	114 (0.26)	26 (0.69)
Parity, n (%)					
Nulliparous	325,890 (19)	1,312 (17)	497 (17)	9,728 (22)	752 (20)
Multiparous	1,106,208 (64)	4,596 (59)	2,033 (68)	25,962 (59)	2,454 (65)
Unknown	307,846 (18)	1,901 (24)	468 (16)	8,095 (18)	582 (15)
Maternal outcome					
Pre-eclampsia	29,859 (1.6)	839 (11)	490 (16)	2,050 (4.7)	371 (9.8)
Emergency Caesarean section	172,748 (11)	1,074 (16)	443 (18)	5,026 (13)	445 (13)
Elective Caesarean section	138,260 (8.8)	1,083 (16)	472 (18)	4,786 (12)	462 (14)
Stroke	137 (0.01)	3 (0.04)	-	4 (0.01)	4 (0.11)
Maternal Death	58	-	-	2	-
Fetal/neonatal outcome					
Stillbirth	7,631 (0.44)	67 (0.86)	29 (0.97)	269 (0.61)	37 (0.98)
Gestational age (wk.), mean (SD)	39.1 (2.6)	38.3 (3.1)	37.6 (3.7)	38.7 (2.8)	38.2 (3.2)
Preterm birth (<37 wk.)	63,460 (3.7)	677 (8.7)	436 (15)	2,794 (6.4)	425 (11)
Very preterm birth (<32 wks.)	17,507 (1)	203 (2.8)	178 (6.5)	753 (1.8)	140 (4)
Fetal growth restriction	34,584 (2)	270 (3.5)	160 (5.3)	1,304 (3)	216 (5.7)

* 95,860 records with either unspecified hypertension, other hypertensive disorders during pregnancy or exposed to antihypertensive agent were excluded from analyses except for pre-eclampsia investigation.

Table S3. Chronic hypertension and adverse perinatal outcomes compared to normotensive untreated group (based on definition/treatment of hypertension)

	Chronic hypertension (diagnosed**) vs. normotensive**[†]			**Chronic hypertension (**inferred**) vs. normotensive**[†]		
Exposure / **Outcome**	**Crude OR (95%CI)**			**Crude OR (95%CI)**		
	Diagnosed (treated + untreated) N=10,807	Untreated n=7,809	Treated n=2,998	Inferred (treated + untreated) N=53,784	Untreated n= 43,785	Treated n=3,788
Pre-eclampsia	8.58 (8.09, 9.09)	7.28 (6.77, 7.82)	11.8 (10.7, 13.2)	3.28 (3.14, 3.42)	2.97 (2.84, 3.11)	6.57 (5.90, 7.31)
Emergency Caesarean section[‡]	1.62 (1.54, 1.71)	1.57 (1.47, 1.68)	1.76 (1.59, 1.95)	1.23 (1.19, 1.26)	1.22 (1.19, 1.26)	1.28 (1.16, 1.41)
Elective Caesarean section[§]	2.08 (1.97, 2.19)	1.98 (1.86, 2.11)	2.34 (2.12, 2.69)	1.47 (1.42, 1.52)	1.46 (1.41, 1.50)	1.66 (1.50, 1.83)
Stillbirth	2.03 (1.66, 2.49)	1.96 (1.54, 2.50)	2.22 (1.54, 3.20)	1.47 (1.31, 1.64)	1.40 (1.24, 1.59)	2.24 (1.62, 3.10)
Preterm birth (<37 wk.)	3.03 (2.85, 3.23)	2.51 (2.32, 2.71)	4.50 (4.06, 4.98)	1.92 (1.84, 1.99)	1.80 (1.73, 1.87)	3.33 (3.02, 3.69)
Very preterm birth (<32 wk.)[‖]	3.76 (3.39, 4.17)	2.73 (2.37, 3.14)	6.65 (5.71, 7.75)	1.93 (1.80, 2.06)	1.76 (1.63, 1.89)	3.99 (3.36, 4.72)
Fetal growth restriction	2.04 (1.85, 2.25)	1.77 (1.56, 1.99)	2.78 (2.37, 3.26)	1.62 (1.54, 1.71)	1.51 (1.43, 1.60)	2.98 (2.60, 3.42)
Exposure / **Outcome**	**Adjusted OR (95%CI)***			**Adjusted OR (95%CI)***		
	Diagnosed (treated + untreated)	**Untreated**	**Treated**	**Diagnosed (treated + untreated)**	**Untreated**	**Treated**
Pre-eclampsia	6.24 (5.87, 6.64)	5.85 (5.43, 6.30)	7.19 (6.49, 7.97)	2.55 (2.44, 2.66)	2.37 (2.26, 2.48)	4.73 (4.23, 5.28)
Emergency Caesarean section[b]	1.27 (1.20, 1.35)	1.24 (1.16, 1.33)	1.36 (1.22, 1.51)	1.09 (1.06, 1.12)	1.08 (1.05, 1.12)	1.18 (1.07, 1.31)
Elective Caesarean section[c]	1.33 (1.26, 1.41)	1.32 (1.23, 1.41)	1.36 (1.23, 1.51)	1.18 (1.15, 1.22)	1.17 (1.13, 1.21)	1.32 (1.20, 1.47)
Stillbirth	1.56 (1.27, 1.92)	1.58 (1.24, 2.01)	1.53 (1.06, 2.22)	1.26 (1.12, 1.42)	1.22 (1.08, 1.38)	1.73 (1.25, 1.40)
Preterm birth (<37 wk.)	2.48 (2.33, 2.65)	2.13 (2.96, 2.31)	3.43 (3.08, 3.81)	1.65 (1.59, 1.72)	1.75 (1.51, 1.64)	2.57 (2.31, 2.85)
Very preterm birth (<32wk)[d]	3.17 (2.85, 3.53)	2.38 (2.07, 2.75)	5.27 (4.50, 6.17)	1.76 (1.64, 1.88)	1.63 (1.51, 1.76)	3.26 (2.74, 3.87)
Fetal growth restriction	2.34 (2.12, 2.58)	1.99 (1.76, 2.25)	3.35 (2.85, 3.94)	1.65 (1.56, 1.74)	1.55 (1.46, 1.64)	2.82 (2.46, 3.25)

[†]The reference group refers to normotensive women who were unexposed to antihypertensive treatment during pregnancy; [‡] in the analysis of emergency caesarean section, elective caesarean section was excluded; [§] in the analysis of elective caesarean section, emergency caesarean section was excluded; [‖] in the analysis of very preterm birth, deliveries between 33-<37 were excluded.
*Adjusted for maternal age, deprivation index (practice IMD 2015), smoking, body mass index, ethnicity, parity, and pre-pregnancy disease (diabetes, kidney disease).

Table S4. Baseline demographic characteristics for women with and without CH during pregnancy

	No chronic hypertension* n=1,739,944	Untreated chronic hypertension n=7,809	Treated chronic hypertension n=6,786
Age (years), mean (SD)	28.9 (6)	32.7 (5.3)	32.7 (5.9)
Ethnicity, n (%)			
White	1,414,774 (81)	6,453 (83)	5,499 (81)
Black	69,944 (4)	623 (8)	574 (8.5)
South Asian	101,939 (5.9)	241 (3.1)	323 (4.8)
Other	81,695 (4.7)	207 (2.7)	215 (3.2)
Unknown	71,592 (4.1)	285 (3.7)	175 (2.6)
Smoking, n (%)			
Non-smoker	245,680 (14)	1,394 (18)	2,585 (38)
former smoker	89,446 (5.1)	498 (6.4)	950 (14)
Current smoker	140,524 (8.1)	556 (7.1)	1,119 (16)
missing	1,264,294 (73)	5,361 (69)	2,132 (31)
Body mass index (kg/m2), n (%)			
Underweight (kg/m2)	19,387 (1.1)	38 (0.5)	77 (1.1)
Normal (18.5–24.9)	275,769 (16)	1,033 (13)	1,451 (21)
Overweight (18.5–24.9)	146,769 (8.4)	938 (12)	1,375 (20)
Obese (18.5–24.9)	114,087 (6.6)	1,453 (19)	2,038 (30)
Severe obesity (18.5–24.9)	8,871 (0.5)	263 (3.4)	407 (6)
Missing (%)	1,175,034 (68)	4,084 (52)	1,438 (21)
Pre-pregnancy diabetes, n (%)	5,704 (0.33)	334 (4.3)	382 (5.6)
Pre-pregnancy chronic kidney disease, n (%)	713 (0.04)	59 (0.76)	93 (1.4)
Parity, n (%)			
Nulliparous	325,890 (19)	1,312 (17)	1,249 (18)
Multiparous	1,106,208 (64)	4,596 (59)	4,487 (66)
Unknown	307,846 (18)	1,901 (24)	1,050 (15)
Stroke†	137 (0.01)	3 (0.04)	4 (0.06)
Maternal death†	58	-	-
Gestational age at delivery (weeks), mean (SD)	39.1 (2.6)	38.3 (3.1)	38.2 (3.2)

***This group included untreated women without chronic hypertension; 95,860 records with either unspecified hypertension, other hypertensive disorders during pregnancy or exposed to antihypertensive agents were excluded from analyses except for pre-eclampsia investigation. Women with inferred untreated hypertension were also excluded (n=43,785).** † **This is related to stroke or death during pregnancy (between the pregnancy start date and delivery date)**

Table S5. Antihypertensive treatment and adverse perinatal outcomes in women with chronic hypertension (treated vs. untreated) according to control level in the treated group, using propensity score-matched sample

Outcome	n (%)	Crude OR (95%CI)	Adjusted OR (95%CI)*
Severe hypertension in 3rd trimester			
Untreated chronic hypertension (n=6,766)	132 (1.95)	Reference	Reference
Tight control[†] (n=1,076)	20 (1.86)	0.95 (0.59, 1.53)	0.96 (0.59, 1.54)
Less-tight control[‡] (n=4,287)	257 (5.99)	3.21 (2.59, 3.97)	3.11 (2.50, 3.86)
Pre-eclampsia			
Untreated chronic hypertension (n=6,766)	741 (10.9)	Reference	Reference
Tight control[†] (n=1,076)	74 (6.88)	0.60 (0.47, 0.77)	0.59 (0.46, 0.76)
Less-tight control[‡] (n=4,287)	670 (15.6)	1.51 (1.35, 1.69)	1.47 (1.31, 1.65)
Emergency Cesarean section[§]			
Untreated chronic hypertension (n=5,923)	893 (15.1)	Reference	Reference
Tight control[†] (935)	130 (13.9)	0.91 (0.75, 1.11)	0.92 (0.75, 1.13)
Less-tight control[‡] (3,654)	622 (17.0)	1.16 (1.03, 1.29)	1.12 (0.99, 1.26)
Elective Cesarean section[‖]			
Untreated chronic hypertension (n=5,873)	843 (14.3)	Reference	Reference
Tight control[†] (n=946)	141 (14.9)	1.05 (0.86, 1.27)	1.12 (0.92, 1.37)
Less-tight control[‡] (n=3,665)	633 (17.3)	1.25 (1.11, 1.39)	1.25 (1.06, 1.33)
Stillbirth			
Untreated chronic hypertension (n=6,766)	46 (0.68)	Reference	Reference
Tight control[†] (n=1,076)	6 (0.56)	0.82 (0.35, 1.29)	0.93 (0.39, 2.20)
Less-tight control[‡] (n=4,287)	49 (1.14)	1.69 (1.13, 2.53)	1.69 (1.11, 2.51)
Preterm birth (<37 wks.)			
Untreated chronic hypertension (n=6,766)	700 (10.4)	Reference	Reference
Tight control[†] (n=1,076)	121 (11.3)	1.10 (0.89, 1.35)	1.04 (0.85, 1.29)
Less-tight control[‡] (n=4,287)	600 (14.0)	1.41 (1.26, 1.58)	1.39 (1.23, 1.56)
Very preterm birth (<32 wks.)[#]			
Untreated chronic hypertension (n=6,261)	195 (3.11)	Reference	Reference
Tight control[†] (n=988)	33 (3.34)	1.07 (0.74, 1.56)	1.01 (0.69, 1.48)
Less-tight control[‡] (n=3,935)	248 (6.30)	2.09 (1.73, 2.54)	2.06 (1.69, 2.50)
Fetal growth restriction			
Untreated chronic hypertension (n=6,766)	212 (3.13)	Reference	Reference
Tight control[†] (n=1,076)	54 (5.02)	1.63 (1.20, 2.21)	1.55 (1.14, 2.12)
Less-tight control[‡] (n=4,287)	253 (5.90)	1.94 (1.61, 2.34)	1.96 (1.62, 2.37)

* Adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy disease (diabetes, kidney disease). [†]Tight control group refers to treated women with chronic hypertension whose average blood pressure in the 1st & 2nd trimesters was both <135/85 mmHg. [‡]Less-tight control group refers to treated women with chronic hypertension whose average blood pressure in the 1st & 2nd trimesters was ≥135/85 mmHg. Treated women without available data on blood pressure readings were excluded (n=1430). [§]In the analysis of emergency Cesarean section, elective Cesarean section were excluded. [‖] In the analysis of elective Cesarean section, emergency Cesarean section were excluded. [#] In the analysis of very preterm birth, deliveries between 33-37 were excluded

Table S6. Antihypertensive treatment during pregnancy and adverse perinatal outcomes in women with chronic hypertension (treated vs untreated) using original cohort

Treatment / Outcome	Frequency n (%)		Treated vs. untreated [†]	
	Untreated (n=7,792)	Treated (n=6,766)	Crude OR (95% CI)	Adjusted OR (95% CI)[*]
Severe hypertension	235 (3)	994 (15)	**5.54 (4.78, 6.41)**	**4.13 (3.53, 4.82)**
Pre-eclampsia	836 (11)	860 (13)	**1.21 (1.09, 1.34)**	**1.17 (1.04, 1.31)**
Emergency Caesarean section[‡]	1,071 (16)	887/5,833 (15)	0.94 (0.86, 1.04)	0.95 (0.85, 1.07)
Elective Caesarean section[§]	1,081 (16)	933 /5,879(16)	0.98 (0.89, 1.08)	1.05 (0.94, 1.17)
Stillbirth	67 (0.86)	66 (0.98)	1.14 (0.81, 1.60)	1.31 (0.89, 1.91)
Preterm birth (<37 wk.)	674 (8.7)	858 (13)	**1.54 (1.38, 1.71)**	**1.38 (1.23, 1.55)**
Very preterm birth (<32 wks.)[‖]	201/7,319 (2.7)	317/6,225 (5.1)	**1.90 (1.59, 2.27)**	**1.66 (1.38, 2.00)**
Fetal growth restriction	269 (3.5)	374 (5.5)	**1.64 (1.39, 1.92)**	**1.45 (1.21, 1.73)**

[†] Treated woman with chronic hypertension vs untreated with chronic hypertension using original cohort (N=14,558); [*] adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy diabetes; [‡] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; [§] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [‖] in the analysis of very preterm birth, deliveries between 33-<37 were excluded.

Table S7. The effect of antihypertensive agents on adverse perinatal outcomes in women with chronic hypertension using original cohort

Outcome \ Treatment	Methyldopa vs. β-blockers (unmatched sample)[†]		calcium channel blockers vs. β-blockers (unmatched sample)[‡]		calcium channel blockers vs. methyldopa (unmatched sample)[§]	
	Crude OR (95% CI)	**Adjusted OR (95% CI)[*]**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)[*]**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)[*]**
Severe hypertension (2nd trimester)	**1.54 (1.20, 1.97)**	**1.46 (1.13, 1.88)**	0.50 (0.23, 1.08)	0.50 (0.22, 1.11)	**0.32 (0.15, 0.70)**	**0.34 (0.15, 0.73)**
Severe hypertension (3rd trimester)	**1.65 (1.22, 2.23)**	**1.60 (1.17, 2.17)**	0.78 (0.36, 1.71)	0.80 (0.36, 1.80)	0.47 (0.22, 1.03)	0.51 (0.23, 1.13)
Pre-eclampsia	**1.77 (1.49, 2.12)**	**1.59 (1.32, 1.91)**	1.63 (1.15, 2.31)	1.43 (0.98, 2.07)	0.92 (0.65, 1.30)	0.93 (0.65, 1.33)
Emergency Caesarean section[‖]	**1.20 (1.01, 1.43)**	1.10 (0.91, 1.33)	**1.44 (1.01, 2.03)**	1.33 (0.91, 1.96)	1.20 (0.84, 1.70)	1.19 (0.81, 1.74)
Elective Caesarean section[#]	0.99 (0.83, 1.18)	0.86 (0.71, 1.03)	**1.55 (1.11, 2.14)**	1.38 (0.97, 1.97)	**1.56 (1.12, 2.18)**	**1.56 (1.09, 2.23)**
Stillbirth	0.90 (0.49, 1.67)	0.78 (0.41, 1.48)	1.81 (0.69, 4.76)	1.54 (0.56, 4.27)	2.00 (0.73, 5.47)	2.02 (0.72, 5.67)
Preterm birth (<37 wk.)	**1.65 (1.38, 1.97)**	**1.55 (1.29, 1.86)**	**1.96 (1.41, 2.73)**	**1.88 (1.32, 2.66)**	1.19 (0.86, 1.65)	1.14 (0.81, 1.59)
Very preterm birth (<32 wks.)[**]	**1.56 (1.17, 2.09)**	**1.43 (1.06, 1.92)**	**1.85 (1.08, 3.15)**	1.54 (0.87, 2.72)	1.18 (0.69, 2.01)	1.08 (0.63, 1.87)
Fetal growth restriction	**0.60 (0.45, 0.80)**	**0.65 (0.49, 0.88)**	1.06 (0.64, 1.76)	0.99 (0.59, 1.69)	**1.76 (1.03, 3.00)**	**1.76 (1.02, 3.04)**

[†] Methyldopa vs. β-blockers using unmatched sample (N=4,654); [‡] calcium channel blockers vs. β-blockers using unmatched sample (N=2,991); [§] calcium channel blockers vs methyldopa using unmatched sample (N=2,241); *adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy diabetes; [‖] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; [#] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [**] in the analysis of very preterm birth, deliveries between 33-<37 were excluded.

Table S8. Associations between antihypertensive agents and adverse perinatal outcomes in women with chronic hypertension based on subgroup analyses

Outcome \ Treatment	**Methyldopa vs. β-blockers** (matched sample)[†]				**calcium channel blockers vs. β-blockers** (matched sample)[‡]			
	Cases in each group		OR (95% CI)	Interaction *p*-value	Cases in each group		OR (95% CI)	Interaction *p*-value
	β-blockers	**Methyldopa**			**β-blockers**	**CCB**		
Nulliparity women (exposed vs. unexposed)	n=333	n=354			n=46	n=53		
Severe hypertension (2nd trimester)	13	23	1.71 (0.85, 3.43)	0.13	1	2	-	-
Severe hypertension (3rd trimester)	13	20	1.4 7(0.72, 3.01)	0.29	1	5	-	-
Pre-eclampsia	50	65	1.27 (0.85, 1.91)	0.24	8	12	1.39 (0.51, 3.77)	0.52
Emergency Caesarean section[‖]	75/273	98/310	1.22 (0.85, 1.75)	0.28	12/41	21/40	2.67 (1.07, 6.67)	0.04
Elective Caesarean section[#]	60/258	44/256	0.68 (0.44, 1.06)	0.09	5/34	13/32	3.97 (1.22, 12.9)	0.02
Stillbirth	1	3	-	-	0	0	-	-
Preterm birth (<37 wk.)	41	46	1.06 (0.68, 1.67)	0.79	9	11	1.08 (0.40, 2.88)	0.88
Very preterm birth (<32 wks.)[*]	20/312	13/321	0.62 (0.30, 1.26)	0.19	6/43	5/47	0.73 (0.21, 2.60)	0.63
Fetal growth restriction	24	15	0.57 (0.29, 1.11)	0.10	5	5	0.85 (0.23, 3.16)	0.81
Child's sex, male (exposed vs. unexposed)*	n=675	n=593			n=104	n=83		
Severe hypertension (2nd trimester)	35	39	1.29 (0.80, 2.06)	0.30	5	2	-	-
Severe hypertension (3rd trimester)	19	29	1.77 (0.98, 3.20)	0.06	5	3	-	-
Pre-eclampsia	93	98	1.24 (0.91, 1.69)	0.17	18	11	0.73 (0.32, 1.65)	0.45
Emergency Caesarean section[‖]	134/513	143/474	1.22 (0.93, 1.61)	0.16	29/82	19/56	0.94 (0.46, 1.92)	0.86
Elective Caesarean section[#]	162/541	119/450	0.84 (0.64, 1.11)	0.22	22/75	27/64	1.76 (0.87, 3.55)	0.12
Stillbirth	6	5	0.95 (0.29, 3.12)	0.93	2	1	-	-
Preterm birth (<37 wk.)	94	94	1.16 (0.85, 1.59)	0.34	14	14	1.30 (0.58, 2.92)	0.52
Very preterm birth (<32 wks.)[*]	28/609	31/530	1.29 (0.76, 2.18)	0.16	8/98	5/74	0.82 (0.26, 2.60)	0.73
Fetal growth restriction	27	25	1.05 (0.61, 1.84)	0.88	5	7	1.82 (0.56, 5.97)	0.32
Child's sex, female (exposed vs. unexposed)*	N=568	N=599			n=66	n=95		
Severe hypertension (2nd trimester)	26	34	1.25 (0.74, 2.12)	0.40	1	3	-	-
Severe hypertension (3rd trimester)	15	27	1.74 (0.92, 3.31)	0.09	0	2	-	-

Pre-eclampsia	46	101	2.30 (1.59, 3.33)	0.00	9	14	1.09 (0.44, 2.70)	0.84
Emergency Caesarean section‖	104/449	123/480	1.14 (0.85, 1.54)	0.38	12/57	23/72	1.76 (0.79, 3.94)	0.17
Elective Caesarean section#	119/464	119/476	0.97 (0.72, 1.30)	0.82	9/54	23/72	2.35 (0.98, 5.60)	0.06
Stillbirth	1	3	-	-	1	0	-	-
Preterm birth (<37 wk.)	44	95	2.24 (1.15, 3.28)	0.00	6	21	2.84 (1.08, 7.48)	0.04
Very preterm birth (<32 wks.)*	17/541	35/539	2.14 (1.18, 3.87)	0.01	5/65	9/83	1.46 (0.46, 4.59)	0.52
Fetal growth restriction	40	25	0.58 (0.35, 0.97)	0.04	8	5	0.40 (0.13, 1.29)	0.13
Over five-year period/ 1998-2002	n=294	n=482			n=43	n=48		
Severe hypertension (2nd trimester)	15	41	-	-	3	1	-	-
Severe hypertension (3rd trimester)	2	19	-	-	0	1	-	-
Pre-eclampsia	17	60	2.32 (1.33, 4.06)	0.00	2	4	-	-
Emergency Caesarean section‖	31/252	52/424	1.00 (0.62, 1.60)	0.99	4/38	3/42	-	-
Elective Caesarean section#	42/263	57/429	0.81 (0.52, 1.24)	0.33	5/39	6/45	1.05 (0.29, 3.74)	0.95
Stillbirth	0	7	-	-	1	1	-	-
Preterm birth (<37 wk.)	21	44/282	2.10 (1.26, 3.52)	0.01	3	11	-	-
Very preterm birth (<32 wks.)*	7/280	26/440	2.45 (1.05, 5.72)	0.04	1/41	2/39	-	-
Fetal growth restriction	7	18	1.59 (0.66, 3.86)	0.30	0	2	-	-
2003-2007 (exposed vs. unexposed)	**N=443**	**N=681**			n=67	n=71		
Severe hypertension (2nd trimester)	18	46	1.73 (0.98, 3.01)	0.06	9	2	-	-
Severe hypertension (3rd trimester)	22	48	0.80 (0.43, 1.51)	0.50	6	0	-	-
Pre-eclampsia	75	117	1.02 (0.74, 1.40)	0.91	12	16	1.33 (0.58, 3.08)	0.50
Emergency Caesarean section‖	32/389	74/615	1.53 (0.99, 2.36)	0.06	7/61	11/57	1.84 (0.66, 5.15)	0.24
Elective Caesarean section#	54/411	66/607	0.81 (0.55, 1.18)	0.27	6/60	14/60	1.38 (0.42, 4.62)	0.60
Stillbirth	5	7	0.91 (0.29, 2.88)	0.87	0	1	-	-
Preterm birth (<37 wk.)	35	107	2.17 (1.45, 3.25)	0.00	7	12	1.74 (0.64, 4.73)	0.28
Very preterm birth (<32 wks.)*	11/419	29/603	1.87 (0.93, 3.79)	0.08	4/64	6/65	-	-
Fetal growth restriction	28	25	0.56 (0.32, 0.98)	0.04	10	4	-	-
2008-2012 (exposed vs. unexposed)	n=552	n=508			n=78	n=93		
Severe hypertension (2nd trimester)	22	36	1.83 (1.06, 3.16)	0.03	1	4	-	-

Severe hypertension (3rd trimester)	17	23	1.48 (0.78, 2.82)	0.22	4	4	-	-
Pre-eclampsia	61	95	1.85 (1.31, 2.62)	0.00	14	16	0.95 (0.43, 2.09)	0.90
Emergency Caesarean section‖	111/475	96/422	0.97 (0.71, 1.32)	0.83	14/69	16/77	1.03 (0.46, 2.30)	0.94
Elective Caesarean section#	77/441	86/412	1.25 (0.89, 1.77)	0.21	9/64	16/77	1.60 (0.66, 3.92)	0.30
Stillbirth	4	1	-	-	0	1	-	-
Preterm birth (<37 wk.)	77	74	1.05 (0.75, 1.48)	0.77	11	15	1.17 (0.50, 2.73)	0.71
Very preterm birth (<32 wks.)*	32/507	31/465	1.06 (0.64, 1.77)	0.82	9/76	9/87	0.86 (0.32, 2.29)	0.76
Fetal growth restriction	27	19	0.76 (0.41, 1.38)	0.36	5	5	0.83 (0.23, 2.98)	0.77
2013-2016 (exposed vs. unexposed)	n=663	n=282			n=101	n=77		
Severe hypertension (2nd trimester)	33	16	1.13 (0.62, 2.11)	0.68	2	0	-	-
Severe hypertension (3rd trimester)	15	7	1.09 (0.44, 2.71)	0.85	1	2	-	-
Pre-eclampsia	67	40	1.47 (0.97, 2.24)	0.07	8	7	1.16 (0.40, 3.36)	0.78
Emergency Caesarean section‖	74/549	51/244	1.70 (1.14, 2.52)	0.01	18/90	14/61	1.19 (0.54, 2.62)	0.66
Elective Caesarean section#	114/589	38/231	0.82 (0.55, 1.23)	0.34	11/83	16/63	2.23 (0.95, 5.22)	0.07
Stillbirth	4	2	-	-	2	2	-	-
Preterm birth (<37 wk.)	66	44	1.67 (1.11, 2.52)	0.01	8	12	2.15 (0.83, 5.54)	0.12
Very preterm birth (<32 wks.)*	24/621	14/252	1.46 (0.74, 2.88)	0.27	5/98	0	-	-
Fetal growth restriction	44	9	0.46 (0.22, 0.96)	0.04	7	7	1.34 (0.85, 4.00)	0.60

Abbreviation: CCB= calcium channel blockers. † Methyldopa vs. β-blockers using matched sample (N=3,904); the reference group refers to women who were on β-blockers; ‡ calcium channel blockers vs. -blockers using matched sample (N=578); the reference group refers to women who were on β-blockers; § calcium channel blockers vs. methyldopa using matched sample (N=578); the reference group refers to women who were on methyldopa; ‖ in the analysis of emergency Caesarean section, elective Caesarean section were excluded; # in the analysis of elective Caesarean section, emergency Caesarean section were excluded; * in the analysis of very preterm birth, deliveries between 33-<37 were excluded. **Data on child's sex was available from hospital records only.

Table S8. Continue from the previous page; Associations between antihypertensive agents and adverse perinatal outcomes in women with chronic hypertension based on subgroup analyses

Outcome \ Treatment	calcium channel blockers vs. methyldopa (matched sample)[§]			
	Cases in each group		OR (95% CI)	Interaction *p*-value
	Methyldopa	CCB		
Nulliparity women (exposed vs. unexposed)	n=38	n=53		
Severe hypertension (2nd trimester)	0	2	-	-
Severe hypertension (3rd trimester)	1	5	-	-
Pre-eclampsia	8	12	1.10 (0.40, 3.02)	0.86
Emergency Caesarean section[‖]	15/34	21/40	1.40 (0.56, 3.51)	0.47
Elective Caesarean section[#]	4/23	13/32	-	-
Stillbirth	0	0	-	-
Preterm birth (<37 wk.)	5	11	1.73 (0.55, 5.47)	0.35
Very preterm birth (<32 wks.)[*]	2/35	5/47	-	-
Fetal growth restriction	3	5	-	-
Child's sex, male (exposed vs. unexposed)**	n=83	n=83		
Severe hypertension (2nd trimester)	4	2	-	-
Severe hypertension (3rd trimester)	2	3	-	-
Pre-eclampsia	16	11	0.64 (0.28, 1.48)	0.30
Emergency Caesarean section[‖]	17/63	19/56	1.39 (0.63, 3.04)	0.41
Elective Caesarean section[#]	20/66	27/64	1.68 (0.82, 3.46)	0.16
Stillbirth	1	1	-	-
Preterm birth (<37 wk.)	13	14	1.09 (0.48, 2.49)	0.83
Very preterm birth (<32 wks.)[*]	4/74	5/74	1.27 (0.33, 4.92)	0.73
Fetal growth restriction	2	7	-	-
Child's sex, female (exposed vs. unexposed)**	n=79	n=95		
Severe hypertension (2nd trimester)	1	3	-	-
Severe hypertension (3rd trimester)	2	2	-	-
Pre-eclampsia	13	14	0.88 (0.36, 2.00)	0.76
Emergency Caesarean section[‖]	24/61	23/72	0.72 (0.35, 1.48)	0.37
Elective Caesarean section[#]	18/55	23/72	0.96 (0.46, 2.04)	0.93
Stillbirth	0	0	-	-
Preterm birth (<37 wk.)	17	21	1.03 (0.50, 2.13)	0.93
Very preterm birth (<32 wks.)[*]	6/86	9/83	1.27 (0.43, 3.73)	0.68
Fetal growth restriction	7	5	0.57 (0.17, 1.88)	0.37
Over five-year period/ 1998-2002	n=68	n=48		
Severe hypertension (2nd trimester)	7	1	-	-
Severe hypertension (3rd trimester)	3	1	-	-
Pre-eclampsia	5	4	-	-
Emergency Caesarean section[‖]	7/54	3/42	-	-

Elective Caesarean section[#]	14/61	6/45	0.52 (0.18, 1.47)	0.216
Stillbirth	3	1	-	-
Preterm birth (<37 wk.)	11	11	1.54 (0.61, 3.91)	0.36
Very preterm birth (<32 wks.)[*]	2/59	2/39	-	-
Fetal growth restriction	4	2	-	-
2003-2007 (exposed vs. unexposed)	n=97	n=71		
Severe hypertension (2nd trimester)	3	1	-	-
Severe hypertension (3rd trimester)	5	0	-	-
Pre-eclampsia	17	16	1.37 (0.64, 2.94)	0.42
Emergency Caesarean section[‖]	9/87	11/57	2.07 (0.80, 5.38)	0.13
Elective Caesarean section[#]	10/88	14/60	2.37 (0.98, 5.78)	0.06
Stillbirth	2	1	-	-
Preterm birth (<37 wk.)	19	12	0.83 (0.38, 1.85)	0.66
Very preterm birth (<32 wks.)[*]	7/85	6/65	1.13 (0.36, 3.55)	0.83
Fetal growth restriction	3	4	-	-
2008-2012 (exposed vs. unexposed)	n=77	n=93		
Severe hypertension (2nd trimester)	3	4	-	-
Severe hypertension (3rd trimester)	1	4	-	-
Pre-eclampsia	16	16	0.79 (0.37, 1.71)	0.55
Emergency Caesarean section[‖]	12/67	16/77	1.20 (0.52, 2.76)	0.67
Elective Caesarean section[#]	10/65	16/77	1.44 (0.60, 3.44)	0.41
Stillbirth	0	1	-	-
Preterm birth (<37 wk.)	13	15	0.95 (0.42, 2.13)	0.90
Very preterm birth (<32 wks.)[*]	8/72	9/87	0.92 (0.34, 2.53)	0.88
Fetal growth restriction	4	5	-	-
2013-2016 (exposed vs. unexposed)	n=47	n=77		
Severe hypertension (2nd trimester)	2	0	-	-
Severe hypertension (3rd trimester)	1	2	-	-
Pre-eclampsia	6	7	0.68 (0.21, 2.17)	0.52
Emergency Caesarean section[‖]	13/40	14/61	0.62 (0.25, 1.51)	0.29
Elective Caesarean section[#]	7/34	16/63	1.31 (0.48, 3.59)	0.60
Stillbirth	0	2	-	-
Preterm birth (<37 wk.)	8	12	0.90 (0.34, 2.39)	0.83
Very preterm birth (<32 wks.)[*]	0	0	-	-
Fetal growth restriction	1	7	-	-

Abbreviation: CCB= calcium channel blockers. [†] Methyldopa vs. β-blockers using matched sample (N=3,904); the reference group refers to women who were on β-blockers; [‡] calcium channel blockers vs. -blockers using matched sample (N=578); the reference group refers to women who were on β-blockers; [§] calcium channel blockers vs. methyldopa using matched sample (N=578); the reference group refers to women who were on methyldopa; [‖] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; [#] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [*] in the analysis of very preterm birth, deliveries between 33-<37 were excluded. **Data on child's sex was available from hospital records only.

Table S9. Antihypertensive treatment during pregnancy and adverse perinatal outcomes in women with chronic hypertension (multiple agents vs. single agent)

Outcome \ Treatment	**Monotherapy (N=5,239)**	**Polytherapy (N=1,527)**	**Treated** (polytherapy vs. monotherapy)[†]		Excluding severe hypertension[‡] (N=5,772)
	n (%)	n (%)	Crude OR (95%CI)	Adjusted OR (95%CI)*	Adjusted OR (95%CI)*
Severe hypertension	674 (13)	320 (21)	1.80 (1.55, 2.08)	1.53 (1.31, 1.78)	-
Pre-eclampsia	645 (12)	215 (14)	1.17 (0.99, 1.38)	1.03 (0.87, 1.23)	0.97 (0.79, 1.19)
Emergency Caesarean section[§]	667/4,555 (15)	220/1,278 (17)	1.21 (1.03, 1.43)	1.15 (0.96, 1.38)	1.13 (0.92, 1.39)
Elective Caesarean section[‖]	684/4,572 (15)	249 (19)	1.34 (1.14, 1.57)	1.21 (1.02, 1.44)	1.24 (1.03, 1.49)
Stillbirth	49 (0.94)	17 (1.1)	1.19 (0.68, 2.08)	1.16 (0.65, 2.05)	1.32 (0.68, 2.54)
Preterm birth (<37 wk.)	639 (12)	219 (14)	1.21 (1.02, 1.42)	1.13 (0.95, 1.34)	1.07 (0.87, 1.30)
Very preterm birth (<32 wks.)[#]	223/4,823 (4.6)	94/1,402 (6.7)	1.48 (1.16, 1.90)	1.33 (1.03, 1.72)	1.34 (0.99, 1.81)
Fetal growth restriction	258 (4.92)	116 (7.6)	1.59 (1.26, 1.99)	1.68 (1.33, 2.13)	1.66 (1.29, 2.15)

[†] The reference group in these models refers women on monotherapy of antihypertensive treatment (N=6,766); [‡] in this model we excluded women who had at least one event of severe hypertension ≥160/110; [§] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; [‖] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [#] in the analysis of very preterm birth, deliveries between 33-<37 were excluded

Table S10. Relationship between blood pressure levels and adverse perinatal outcomes, including pregnancy records with available blood pressure readings

SBP / Outcome	<115 mm Hg	115–129 mm Hg	130–139 mm Hg	140–159 mm Hg	160–179 mm Hg	≥180 mm Hg
Pre-eclampsia[†]						
Population (N=439,186)	251,115	150,313	29,101	8,180	423	54
Cases, (%)	3,720 (1.5)	4,717 (3.1)	1,639 (5.6)	808 (9.9)	52 (13)	10 (19)
Crude OR (95% CI)	0.46 (0.44, 0.48)	Reference	1.84 (1.74, 1.95)	3.38 (3.13, 3.66)	4.33 (3.23, 5.79)	7.02 (3.53, 13.9)
Adjusted OR (95% CI)*	0.45 (0.49, 0.53)	Reference	1.73 (1.63, 1.84)	3.11 (2.87, 3.36)	3.83 (2.85, 5.14)	6.80 (3.38, 13.7)
Emergency CS[‡,]**						
Population (N=444,391)	353,384	158,294	25,757	6,585	326	46
Cases, (%)	21,024 (8.3)	15,461 (9.8)	2,857 (11)	783 (12)	43 (13)	7 (15)
Crude OR (95% CI)	0.84 (0.82, 0.85)	Reference	1.15 (1.10, 1.20)	1.25 (1.15, 1.35)	1.40 (1.02, 1.94)	-
Adjusted OR (95% CI)*	0.93 (0.91, 0.95)	Reference	1.09 (1.04, 1.14)	1.13 (1.05, 1.23)	1.27 (0.91, 1.78)	-
Elective CS [§,]**						
Population (N=435,676)	248,992	154,742	25,107	6,470	319	46
Cases, (%)	16,632 (6.7)	11,910 (7.7)	2,207 (8.8)	668 (10)	36 (11)	7 (15)
Crude OR (95% CI)	0.86 (0.84, 0.88)	Reference	1.16 (1.10, 1.21)	1.38 (1.27, 1.52)	1.53 (1.08, 2.16)	-
Adjusted OR (95% CI)*	0.98 (0.96, 1.01)	Reference	1.02 (0.97, 1.07)	1.10 (1.01, 1.19)	1.00 (0.70, 1.44)	-
Preterm birth (<37 wk.)[**]						
Population (N=475,851)	270,016	170,203	27,964	7,253	362	53
Cases, (%)	11,092 (4.1)	7,246 (4.3)	1,474 (5.3)	551 (7.6)	45 (12)	6 (11)
Crude OR (95% CI)	0.96 (0.93, 0.99)	Reference	1.25 (1.18, 1.33)	1.85 (1.69, 2.02)	3.19 (2.33, 4.37)	-
Adjusted OR (95% CI)*	0.95 (0.92, 0.98)	Reference	1.23 (1.17, 1.31)	1.80 (1.64, 1.97)	3.02 (2.20, 4.15)	-
Very preterm birth (<32 wk.)[‖,]**						
Population (N=460,728)	261,728	164,755	26,952	6,903	339	51
Cases, (%)	2,804 (1.1)	1,798 (1.1)	462 (1.7)	201 (2.9)	22 (6.5)	4 (7.8)

Crude OR (95% CI)	0.98 (0.92, 1.04)	Reference	1.59 (1.43, 1.75)	2.72 (2.34, 3.15)	6.29 (4.07, 9.71)	-
Adjusted OR (95% CI)*	0.95 (0.89, 1.01)	Reference	1.56 (1.41, 1.74)	2.63 (2.26, 3.05)	5.72 (3.69, 8.87)	-
Stillbirth**						
Population (N=475,851)	270,016	170,203	27,964	7,253	362	53
Cases, (%)	1,389 (0.51)	957 (0.56)	195 (0.70)	70 (0.97)	6 (1.7)	1 (1.9)
Crude OR (95% CI)	0.91 (0.84, 0.99)	Reference	1.24 (1.06, 1.45)	1.72 (1.35, 2.20)	-	-
Adjusted OR (95% CI)*	0.93 (0.86, 1.01)	Reference	1.18 (1.01, 1.38)	1.58 (1.23, 2.01)	-	-
Fetal growth restriction**						
Population (N=475,851)	270,016	170,203	27,964	7,253	362	53
Cases, (%)	6,386 (2.4)	3,276 (1.9)	620 (2.2)	199 (2.7)	15 (4.1)	2 (3.8.9)
Crude OR (95% CI)	1.23 (1.18, 1.29)	Reference	1.16 (1.06, 1.26)	1.44 (1.24, 1.66)	2.20 (1.31, 3.70)	-
Adjusted OR (95% CI)*	1.07 (1.02, 1.12)	Reference	1.24 (1.14, 1.35)	1.62 (1.40, 1.87)	2.74 (1.62, 4.61)	-
DBP / Outcome	**<75 mm Hg**	**75–84 mm Hg**	**85–89 mm Hg**	**90–94 mm Hg**	**95–99 mm Hg**	**≥100 mm Hg**
Pre-eclampsia[†]						
Population (N=439,186)	346,673	79,615	8,612	3,079	777	430
Cases, (%)	6,052 (1.8)	3,602 (4.5)	717 (8.3)	368 (12)	115 (15)	92 (21)
Crude OR (95% CI)	0.37 (0.35, 0.39)	Reference	1.92 (1.75, 2.08)	2.86 (2.56, 3.21)	3.67 (3.00, 4.48)	5.74 (4.55, 7.25)
Adjusted OR (95% CI)*	0.42 (0.40, 0.44)	Reference	1.84 (1.69, 2.00)	2.73 (2.43, 3.06)	3.45 (2.82, 4.23)	5.59 (4.41, 7.08)
Emergency CS[‡,]**						
Population (N=444,391)	355,701	77,582	7,451	2,626	667	364
Cases, (%)	30,609 (8.6)	8,158 (11)	915 (12)	339 (13)	96 (14)	58 (16)
Crude OR (95% CI)	0.80 (0.78, 0.82)	Reference	1.19 (1.11, 1.28)	1.26 (1.12, 1.42)	1.43 (1.15, 1.78)	1.61 (1.22, 2.14)
Adjusted OR (95% CI)*	0.92 (0.90, 0.95)	Reference	1.12 (1.03, 1.20)	1.18 (1.04, 1.33)	1.23 (0.98, 1.53)	1.56 (1.16, 2.10)
Elective CS [§,]**						
Population (N=435,676)	349,092	75,730	7,293	2,565	646	350
Cases, (%)	24,000 (6.9)	6,306 (8.3)	757 (10)	278 (11)	75 (12)	44 (13)
Crude OR (95% CI)	0.81 (0.79, 0.84)	Reference	1.28 (1.18, 1.38)	1.33 (1.18, 1.52)	1.45 (1.14, 1.84)	1.58 (1.15, 2.17)

Adjusted OR (95% CI)*	0.99 (0.96, 1.02)	Reference	1.12 (1.03, 1.21)	1.10 (0.97, 1.25)	1.09 (0.85, 1.39)	1.20 (0.87, 1.67)
Preterm birth (<37 wk.)**						
Population (N=475,851)	379,701	83,888	8,208	2,904	742	408
Cases, (%)	15,544 (4.1)	3,894 (4.6)	548 (6.7)	277 (9.5)	95 (13)	56 (14)
Crude OR (95% CI)	0.88 (0.85, 0.91)	Reference	1.47 (1.34, 1.61)	2.17 (1.91, 2.46)	3.02 (2.43, 3.75)	3.27 (2.46, 4.34)
Adjusted OR (95% CI)*	0.87 (0.83, 0.90)	Reference	1.46 (1.33, 1.60)	2.17 (1.91, 2.47)	2.95 (2.37, 3.68)	3.02 (2.26, 4.03)
Very preterm birth (<32 wk.)‖,**						
Population (N=460,728)	368,039	81,061	7,830	2,729	691	378
Cases, (%)	3,882 (1.1)	1,067 (1.32)	170 (2.2)	102 (3.7)	44 (6.4)	26 (6.9)
Crude OR (95% CI)	0.80 (0.75, 0.86)	Reference	1.66 (1.41, 1.96)	2.91 (2.37, 3.58)	5.10 (3.73, 6.96)	5.54 (3.71, 8.28)
Adjusted OR (95% CI)*	0.78 (0.72, 0.83)	Reference	1.66 (1.41, 1.95)	2.92 (2.37, 3.59)	4.87 (3.55, 6.67)	4.92 (3.27, 7.39)
Stillbirth**						
Population (N=475,851)	379,701	83,888	8,208	2,904	742	408
Cases, (%)	1,982 (0.52)	535 (0.64)	58 (0.71)	30 (1)	9 (1.2)	4 (0.98)
Crude OR (95% CI)	0.82 (0.74, 0.90)	Reference	1.11 (0.84, 1.46)	1.63 (1.12, 2.35)	-	-
Adjusted OR (95% CI)*	0.85 (0.77, 0.94)	Reference	1.07 (0.82, 1.41)	1.52 (1.05, 2.20)	-	
Fetal growth restriction**						
Population (N=475,851)	397,701	83,888	8,208	2,904	742	408
Cases, (%)	8,397 (2.2)	1,713 (2)	225 (2.7)	96 (3.3)	43 (5.8)	24 (5.9)
Crude OR (95% CI)	1.08 (1.03, 1.10)	Reference	1.35 (1.17, 1.59)	1.64 (1.33, 2.12)	2.95 (2.16, 4.17)	3.00 (1.98, 4.21)
Adjusted OR (95% CI)*	0.92 (0.87, 0.97)	Reference	1.46 (1.27, 1.69)	1.86 (1.51, 2.30)	3.42 (2.49, 4.68)	3.25 (2.13, 4.49)

Abbreviations: DBP=diastolic blood pressure; CS=Caesarean section; SBP=systolic blood pressure. † Data on blood pressure readings in pre-eclampsia analyses were restricted to readings from 1st and 2nd trimesters. *Adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy diabetes and chronic kidney disease. ‡ in the analysis of emergency Caesarean section, elective Caesarean section were excluded; **This model was restricted to records with available data on blood pressure readings, records with other hypertensive disorders of pregnancy or unspecified hypertension were excluded; § in the analysis of elective Caesarean section, emergency Caesarean section were excluded; ‖ in the analysis of very preterm birth, deliveries between 33-<37 were excluded.

Table S11. Relationship between blood pressure levels and adverse perinatal outcomes, including pregnancy records with untreated chronic hypertension

SBP / Outcome	<115 mm Hg	115–129 mm Hg	130–139 mm Hg	140–159 mm Hg	160–179 mm Hg	≥180 mm Hg
Pre-eclampsia[†]						
Population (N=2,508)	482	1,024	599	365	43	4
Cases, (%)	28 (5.8)	83 (8.1)	75 (13)	48 (13)	9 (21)	0
Crude OR (95% CI)	0.70 (0.45, 1.09)	Reference	1.62 (1.17, 2.26)	1.76 (1.21, 2.58)	3.00 (1.39, 6.48)	-
Adjusted OR (95% CI)*	0.73 (0.46, 1.15)	Reference	1.62 (1.16, 2.27)	1.83 (1.24, 2.69)	3.22 (1.45, 7.13)	-
Emergency CS[‡,]**						
Population (N=2,512)	432	1,075	616	346	39	4
Cases, (%)	49 (11)	124 (12)	88 (14)	48 (14)	4 (10)	1 (25)
Crude OR (95% CI)	0.98 (0.69, 1.39)	Reference	1.28 (0.95, 1.71)	1.24 (0.86, 1.77)	-	-
Adjusted OR (95% CI)*	1.20 (0.83, 1.75)	Reference	1.28 (0.94, 1.74)	1.22 (0.84, 1.78)	-	-
Elective CS [§,]**						
Population (N=2,488)	429	1,075	603	337	40	4
Cases, (%)	46 (11)	124 (12)	75 (12)	39 (12)	5 (13)	1 (25)
Crude OR (95% CI)	0.92 (0.64, 1.32)	Reference	1.09 (0.80, 1.48)	1.00 (0.68, 1.47)	-	-
Adjusted OR (95% CI)*	1.13 (0.78, 1.64)	Reference	1.90 (0.74, 1.39)	0.93 (0.63, 1.38)	-	-
Preterm birth (<37 wk.)[**]						
Population (N=2,802)	478	1,199	691	385	44	5
Cases, (%)	24 (5)	86 (7)	64 (9.3)	35 (9.1)	6 (14)	1 (20)
Crude OR (95% CI)	0.68 (0.43, 1.09)	Reference	1.32 (0.94, 1.85)	1.29 (0.86, 1.95)	2.04 (0.84, 4.97)	-
Adjusted OR (95% CI)*	0.66 (0.40, 1.07)	Reference	1.46 (1.03, 2.09)	1.46 (0.95, 2.24)	2.58 (1.01, 6.62)	-
Very preterm birth (<32 wk.)[‖,]**						
Population (N=2,641)	458	1,132	649	357	40	5
Cases, (%)	4 (0.87)	19 (1.7)	22 (3.4)	7 (2)	2 (5)	1 (20)

Crude OR (95% CI)	0.52 (0.17, 1.53)	Reference	2.06 (1.10, 3.83)	1.17 (0.49, 2.81)	-	-
Adjusted OR (95% CI)*	0.47 (0.15, 1.42)	Reference	2.59 (1.35, 4.97)	1.42 (0.57, 3.52)	-	-
Stillbirth**						
Population (N=2,802)	478	1,199	691	385	44	5
Cases, (%)	1 (0.421)	9 (0.75)	2 (0.29)	4 (1)	0	0
Crude OR (95% CI)	-	-	-	-	-	-
Adjusted OR (95% CI)*	-	-	-	-	-	-
Fetal growth restriction**						
Population (N=2,802)	478	1,199	691	385	44	5
Cases, (%)	22 (4.6)	27 (2.3)	20 (2.9)	14 (3.6)	1 (2.3)	1 (20)
Crude OR (95% CI)	2.09 (1.18, 3.72)	Reference	1.29 (0.72, 2.32)	1.63 (0.85, 3.15)	-	-
Adjusted OR (95% CI)*	2.12 (1.17, 3.87)	Reference	1.40 (0.77, 2.55)	1.91 (0.98, 3.75)	-	-
DBP / Outcome	**<75 mm Hg**	**75–84 mm Hg**	**85–89 mm Hg**	**90–94 mm Hg**	**95–99 mm Hg**	**≥100 mm Hg**
Pre-eclampsia†						
Population (N=2,508)	899	1,065	297	161	48	38
Cases, (%)	54 (6)	102 (9.6)	43 (16)	26 (16)	10 (21)	8 (21)
Crude OR (95% CI)	0.60 (0.43, 0.85)	Reference	1.60 (1.09, 2.34)	1.82 (1.14, 2.90)	2.48 (1.20, 5.13)	2.52 (1.12, 5.64)
Adjusted OR (95% CI)*	0.61 (0.43, 0.87)	Reference	1.47 (0.99, 2.18)	1.87 (1.16, 3.03)	2.62 (1.23, 5.54)	2.76 (1.21, 6.32)
Emergency CS‡,**						
Population (N=2,512)	890	1,074	295	167	51	35
Cases, (%)	84 (9)	149 (14)	46 (16)	21 (13)	11 (21)	3 (9)
Crude OR (95% CI)	0.65 (0.49, 0.86)	Reference	1.15 (0.80, 1.64)	0.89 (0.55, 1.46)	1.71 (0.86, 3.41)	-
Adjusted OR (95% CI)*	0.70 (0.52, 0.95)	Reference	0.97 (0.67, 1.42)	0.85 (0.51, 1.43)	1.40 (0.67, 2.90)	-
Elective CS §,**						
Population (N=2,488)	909	1,049	282	165	45	38
Cases, (%)	103 (11)	124 (12)	33 (12)	19 (12)	5 (11)	6 (16)
Crude OR (95% CI)	0.95 (0.72, 1.25)	Reference	0.99 (0.66, 1.49)	0.97 (0.58, 1.62)	-	-
Adjusted OR (95% CI)*	1.08 (0.81, 1.44)	Reference	0.90 (0.59, 1.37)	0.93 (0.55, 1.58)	-	-

Preterm birth (<37 wk.)[**]						
Population (N=2,802)	993	1,198	328	186	56	41
Cases, (%)	49 (4.9)	96 (8)	33 (10)	22 (12)	9 (14)	8 (14)
Crude OR (95% CI)	0.60 (0.42, 0.85)	Reference	1.28 (0.85, 1.95)	1.53 (0.94, 2.52)	-	-
Adjusted OR (95% CI)*	0.52 (0.36, 0.76)	Reference	1.23 (0.80, 1.90)	1.68 (1.01, 2.79)	-	-
Very preterm birth (<32 wk.)[‖,**]						
Population (N=2,641)	951	1,125	304	174	50	37
Cases, (%)	7 (0.7)	23 (2)	9 (3)	10 (5.8)	2 (4)	4 (11)
Crude OR (95% CI)	0.36 (0.15, 0.83)	Reference	1.46 (0.67, 3.19)	2.92 (1.37, 6.24)	-	-
Adjusted OR (95% CI)*	0.30 (0.13, 0.73)	Reference	1.46 (0.65, 3.30)	3.54 (1.58, 7.93)	-	-
Stillbirth**						
Population (N=2,802)	993	1,198	328	186	56	41
Cases, (%)	3 (0.3)	9 (0.75)	2 (0.61)	1 (0.54)	1 (1.8)	0
Crude OR (95% CI)	-	-	-	-	-	-
Adjusted OR (95% CI)*	-	-	-	-	-	-
Fetal growth restriction**						
Population (N=2,802)	993	1,198	328	186	56	41
Cases, (%)	25 (2.5)	32 (2.7)	14 (4.3)	8 (4.3)	2 (3.6)	4 (9.8)
Crude OR (95% CI)	0.94 (0.55, 1.60)	Reference	1.62 (0.86, 3.08)	-	-	-
Adjusted OR (95% CI)*	0.86 (0.48, 1.50)	Reference	1.52 (0.79, 2.92)	-	-	-

Abbreviations: DBP=diastolic blood pressure; CS=Caesarean section; SBP=systolic blood pressure. [†] Data on blood pressure readings in pre-eclampsia analyses were restricted to readings from 1st and 2nd trimesters. *Adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy diabetes and chronic kidney disease. [‡] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; **This model was restricted to records with available data on blood pressure readings, records with other hypertensive disorders of pregnancy or unspecified hypertension were excluded; [§] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [‖] in the analysis of very preterm birth, deliveries between 33-<37 were excluded.

Table S12. Relationship between blood pressure levels and adverse perinatal outcomes, including pregnancy records with treated chronic hypertension

SBP / Outcome	<115 mm Hg	115–129 mm Hg	130–139 mm Hg	140–159 mm Hg	160–179 mm Hg	≥180 mm Hg
Pre-eclampsia[†]						
Population (N=5,375)	1,029	1,835	1,403	971	122	15
Cases, (%)	38 (3.7)	207 (11)	244 (17)	228 (23)	25 (21)	3 (20)
Crude OR (95% CI)	0.30 (0.21, 0.43)	Reference	1.66 (1.36, 2.02)	2.41 (1.96, 2.97)	2.03 (1.28, 3.22)	-
Adjusted OR (95% CI)*	0.31 (0.22, 0.45)	Reference	1.66 (1.36, 2.03)	2.40 (1.94, 2.96)	2.02 (1.26, 3.24)	-
Emergency CS[‡,]**						
Population (N=4,892)	940	1,702	1,304	845	88	13
Cases, (%)	91 (9.7)	279 (16)	229 (18)	172 (20)	19 (22)	2 (15)
Crude OR (95% CI)	0.55 (0.43, 0.70)	Reference	1.09 (0.90, 1.32)	1.30 (1.06, 1.61)	1.40 (0.83, 2.37)	-
Adjusted OR (95% CI)*	0.63 (0.48, 0.82)	Reference	1.07 (0.87, 1.31)	1.36 (1.08, 1.71)	1.37 (0.78, 2.41)	-
Elective CS [§,]**						
Population (N=4,910)	976	1,709	1,303	824	86	12
Cases, (%)	127 (13)	286 (17)	228 (18)	151 (18)	17 (20)	1 (8.3)
Crude OR (95% CI)	0.74 (0.59, 0.93)	Reference	1.06 (0.87, 1.28)	1.12 (0.90, 1.38)	1.23 (0.71, 2.12)	-
Adjusted OR (95% CI)*	0.91 (0.72, 1.16)	Reference	0.99 (0.81, 1.21)	1.07 (0.85, 1.34)	1.06 (0.60, 1.86)	-
Preterm birth (<37 wk.)[**]						
Population (N=5,702)	1,067	1,988	1,532	996	105	14
Cases, (%)	127 (13)	286 (17)	228 (18)	151 (18)	17 (20)	1 (8.3)
Crude OR (95% CI)	0.78 (0.61, 1.00)	Reference	1.27 (1.04, 1.55)	1.65 (1.33, 2.04)	2.79 (1.77, 4.40)	-
Adjusted OR (95% CI)*	0.77 (0.59, 0.99)	Reference	1.31 (1.07, 1.60)	1.69 (1.36, 2.11)	2.95 (1.85, 4.70)	-
Very preterm birth (<32 wk.)[‖,]**						
Population (N=5,236)	1,002	1,838	1,392	898	92	14
Cases, (%)	33 (3.3)	79 (4.3)	78 (5.6)	78 (8.7)	15 (16)	2 (14)

Crude OR (95% CI)	0.76 (0.50, 1.15)	Reference	1.32 (0.96, 1.82)	2.12 (1.53, 2.93)	4.34 (2.39, 7.88)	-
Adjusted OR (95% CI)*	0.76 (0.49, 1.16)	Reference	1.34 (0.97, 1.86)	2.12 (1.52, 2.95)	4.22 (2.28, 7.81)	-
Stillbirth**						
Population (N=5,702)	1,067	1,988	1,532	996	105	14
Cases, (%)	5 (0.47)	16 (0.8)	15 (0.78)	18 (1.8)	3 (2.9)	-
Crude OR (95% CI)	-	Reference	1.22 (0.60, 2.47)	2.27 (1.15, 4.47)	-	-
Adjusted OR (95% CI)*	-	Reference	1.20 (0.58, 2.44)	2.16 (1.08, 4.31)	-	-
Fetal growth restriction**						
Population (N=5,702)	1,067	1,988	1,532	996	105	14
Cases, (%)	51 (4.8)	111 (5.6)	86 (5.6)	67 (6.7)	7 (6.7)	-
Crude OR (95% CI)	0.85 (0.60, 1.19)	Reference	1.01 (0.75, 1.34)	1.22 (0.89, 1.67)	-	-
Adjusted OR (95% CI)*	0.70 (0.49, 1.00)	Reference	1.14 (0.84, 1.53)	1.42 (1.03, 1.95)	-	-
DBP / Outcome	**<75 mm Hg**	**75–84 mm Hg**	**85–89 mm Hg**	**90–94 mm Hg**	**95–99 mm Hg**	**≥100 mm Hg**
Pre-eclampsia†						
Population (N=5,375)	1,682	1,933	823	533	233	151
Cases, (%)	71 (4.2)	269 (14)	172 (21)	137 (25)	54 (23)	42 (28)
Crude OR (95% CI)	0.27 (0.21, 0.36)	Reference	1.63 (1.32, 2.02)	2.04 (1.62, 2.57)	1.87 (1.34, 2.60)	2.38 (1.63, 3.48)
Adjusted OR (95% CI)*	0.27 (0.21, 0.36)	Reference	1.62 (1.31, 2.01)	2.05 (1.62, 2.60)	1.88 (1.34, 2.64)	2.29 (1.55, 3.38)
Emergency CS‡,**						
Population (N=4,892)	1,556	1,768	770	488	192	118
Cases, (%)	169 (11)	311 (18)	149 (19)	106 (22)	30 (16)	27 (23)
Crude OR (95% CI)	0.57 (0.47, 0.70)	Reference	1.12 (1.91, 1.40)	1.30 (1.01, 1.67)	0.87 (0.58, 1.31)	1.39 (0.89, 2.17)
Adjusted OR (95% CI)*	0.62 (0.50, 0.77)	Reference	1.13 (0.89, 1.42)	1.37 (1.05, 1.79)	0.84 (0.51, 1.31)	1.38 (0.85, 2.22)
Elective CS §,**						
Population (N=4,910)	1,622	1,768	752	459	200	109
Cases, (%)	235 (15)	311 (18)	131 (17)	77 (17)	38 (19)	18 (17)
Crude OR (95% CI)	0.79 (0.66, 0.95)	Reference	0.99 (0.79, 1.24)	0.94 (0.72, 1.24)	1.10 (0.75, 1.60)	0.93 (0.55, 1.56)
Adjusted OR (95% CI)*	0.96 (0.79, 1.17)	Reference	0.98 (0.77, 1.23)	0.97 (0.73, 1.29)	1.10 (0.74, 1.60)	0.88 (0.52, 1.51)

Preterm birth (<37 wk.)[**]						
Population (N=5,702)	1,791	2,079	901	565	230	136
Cases, (%)	161 (9)	259 (12)	133 (15)	112 (20)	57 (25)	29 (21)
Crude OR (95% CI)	0.69 (0.56, 0.85)	Reference	1.22 (0.97, 1.52)	1.74 (1.36, 2.22)	2.32 (1.67, 3.21)	1.90 (1.24, 2.93)
Adjusted OR (95% CI)*	0.67 (0.54, 0.83)	Reference	1.27 (1.01, 1.59)	1.86 (1.45, 2.38)	2.51 (1.80, 3.50)	1.88 (1.21, 2.91)
Very preterm birth (<32 wk.)[‖,**]						
Population (N=5,236)	1,676	1,911	821	504	200	124
Cases, (%)	46 (2.7)	91 (4.8)	53 (6.5)	51 (10)	27 (14)	17 (14)
Crude OR (95% CI)	0.56 (0.39, 0.81)	Reference	1.38 (0.97, 1.96)	2.25 (1.57, 3.22)	3.12 (1.98, 4.93)	3.18 (1.82, 5.53)
Adjusted OR (95% CI)*	0.56 (0.38, 0.81)	Reference	1.44 (1.01, 2.06)	2.35 (1.64, 3.39)	3.25 (2.04, 5.19)	3.19 (1.81, 5.61)
Stillbirth**						
Population (N=5,702)	1,791	2,079	901	565	230	136
Cases, (%)	11 (0.61)	20 (0.96)	10 (1.1)	8 (1.4)	6 (2.6)	2 (1.5)
Crude OR (95% CI)	0.64 (0.30, 1.33)	Reference	1.16 (0.54, 2.48)	-	-	-
Adjusted OR (95% CI)*	0.64 (0.30, 1.38)	Reference	1.20 (0.56, 2.60)	-	-	-
Fetal growth restriction**						
Population (N=5,702)	1,791	2,079	901	565	230	136
Cases, (%)	87 (4.9)	98 (4.7)	57 (6.3)	42 (7.4)	27 (12)	11 (8.1)
Crude OR (95% CI)	1.03 (0.77, 1.39)	Reference	1.37 (0.98, 1.91)	1.63 (1.12, 2.36)	2.69 (1.71, 4.22)	1.78 (0.93, 3.40)
Adjusted OR (95% CI)*	0.83 (0.61, 1.13)	Reference	1.49 (1.06, 2.10)	1.76 (1.21, 2.58)	2.97 (1.87, 4.72)	1.90 (0.98, 3.68)

Abbreviations: DBP=diastolic blood pressure; CS=Caesarean section; SBP=systolic blood pressure. [†] Data on blood pressure readings in pre-eclampsia analyses were restricted to readings from 1st and 2nd trimesters. *Adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy diabetes and chronic kidney disease. [‡] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; **This model was restricted to records with available data on blood pressure readings, records with other hypertensive disorders of pregnancy or unspecified hypertension were excluded; [§] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [‖] in the analysis of very preterm birth, deliveries between 33-<37 were excluded.

Table S13. Baseline demographic characteristics in the cohort and matched sample

Covariates \ Study group	Treated vs untreated				Methyldopa vs. β-blockers			
	Pre-Propensity Score Matching (raw data)		Post-Propensity Score Matching		Pre-Propensity Score Matching (raw data)		Post-Propensity Score Matching	
	Treated n=6,766	Untreated n=7,792	Treated n=6,766	Untreated n=6,766	Methyldopa n=1,952	β-blockers n=2,702	Methyldopa n=1,952	β-blockers n=1,952
Age (years), mean (SD)	33 (5.8)	33 (5.2)	33 (5.8)	33 (5.4)	33 (5.7)	32 (5.8)	33 (5.7)	33 (5.4)
Ethnicity, n (%)								
White	5,479 (81)	6,439 (83)	5,479 (81)	5,641 (83)	1,554 (80)	2,379 (88)	1,554 (80)	1,596 (82)
Black	574 (8.5)	622 (8)	574 (8.5)	550 (8.1)	174 (8.9)	114 (4.2)	174 (8.9)	130 (6.7)
South Asian	323 (4.8)	241 (3.1)	323 (4.8)	229 (3.8)	96 (4.9)	99 (3.7)	96 (4.9)	97 (5)
Other	215 (3.2)	207 (3.1)	215 (3.2)	183 (2.7)	70 (3.6)	64 (2.4)	70 (3.6)	70 (3.6)
Unknown	175 (2.6)	283 (3.6)	175 (2.6)	163 (2.4)	58 (3)	46 (1.7)	58 (3)	59 (3.0)
Smoking, n (%)								
Non-smoker	2,578 (38)	1,392 (18)	2,578 (38)	2,787 (41)	743 (38)	962 (36)	743 (38)	748 (38)
Ex-smoker	949 (14)	495 (6.4)	949 (14)	832 (12)	262 (13)	400 (15)	262 (13)	220 (11)
Current smoker	1,112 (16)	552 (7.1)	1,112 (16)	983 (15)	282 (14)	529 (20)	282 (14)	319 (16)
missing	2,127 (31)	5,353 (68)	2,127 (31)	2,164 (32)	665 (34)	811 (30)	665 (34)	665 (34)
Body mass index (kg/m2)								
Underweight (<18.5)	77 (1.1)	37 (0.5)	77 (1.1)	59 (0.9)	18 (0.9)	35 (1.3)	18 (0.9)	12 (0.6)
Normal (≥18.5 to <25)	1,445 (21)	1,032 (13)	1,445 (21)	1,482 (22)	378 (19)	679 (25)	378 (19)	515 (26)
Overweight (≥25 to <30)	1,374 (20)	936 (12)	1,374 (20)	1,469 (22)	400 (20)	562 (21)	400 (20)	391 (20)
Obese (≥30 to <40)	2,035 (30)	1,451 (19)	2,035 (30)	2,020 (30)	614 (31)	690 (26)	614 (31)	550 (28)
Severe obesity (≥40)	407 (6)	263 (3.4)	407 (6)	345 (5.1)	123 (6.3)	127 (4.7)	123 (6.3)	89 (4.6)
Missing	1,428 (21)	4,073 (52)	1,428 (21)	1,391 (21)	419 (21)	609 (22)	419 (21)	395 (20)
Diabetes, n (%)	381 (5.6)	332 (4.3)	381 (5.6)	312 (4.6)	175 (9)	62 (2.3)	175 (9)	171 (8.8)
Parity, n (%)								
Nulliparous	1,240 (18)	1,303 (17)	1,240 (18)	1,281 (19)	354 (18)	559 (21)	354 (18)	333 (17)
Multiparous	4,477 (66)	4,590 (59)	4,477 (66)	4,462 (66)	1,282 (66)	1,726 (64)	1,282 (66)	1,295 (66)
Unknown	1,049 (16)	1,899 (24)	1,049 (16)	1,023 (15)	316 (16)	417 (15)	316 (16)	324 (17)

Table S14. CPRD and HES codes used to identify variables

Variable	CPRD – Read code diagnoses	HES – ICD10 Hospital diagnoses
Pre-eclampsia	L124.00: Mild or unspecified pre-eclampsia L124.11; Mild pre-eclampsia L124.12: Toxaemia NOS L124000: Mild or unspecified pre-eclampsia unspecified L124100: Mild or unspecified pre-eclampsia - delivered L124200: Mild or unspecified pre-eclampsia - delivered with p/n comp L124300: Mild or unspecified pre-eclampsia - not delivered L124400: Mild or unspecified pre-eclampsia with p/n complication L124500: Mild pre-eclampsia L124600: Pre-eclampsia, unspecified L124z00: Mild or unspecified pre-eclampsia NOS L125.00: Severe pre-eclampsia L125000: Severe pre-eclampsia unspecified L125100: Severe pre-eclampsia - delivered L125200: Severe pre-eclampsia - delivered with postnatal complication L125300: Severe pre-eclampsia - not delivered L125400: Severe pre-eclampsia with postnatal complication L125z00: Severe pre-eclampsia NOS L126.00: Eclampsia L126000: Eclampsia unspecified L126100: Eclampsia - delivered L126200: Eclampsia - delivered with postnatal complication L126300: Eclampsia - not delivered L126400: Eclampsia with postnatal complication L126500: Eclampsia in pregnancy L126600: Eclampsia in labour L126z00: Eclampsia NOS L127.00: Pre-eclampsia or eclampsia with pre-existing hypertension L127000: Pre-eclampsia or eclampsia with hypertension unspecified L127100: Pre-eclampsia or eclampsia with hypertension - delivered L127200: Pre-eclampsia or eclampsia with hypertension - del+p/n comp L127300: Pre-eclampsia or eclampsia with hypertension - not delivered L127400: Pre-eclampsia or eclampsia with hypertension + p/n comp L127z00: Pre-eclampsia or eclampsia + pre-existing hypertension NOS L129.00: Moderate pre-eclampsia L12A.00: HELLP - Syndrome haemolysis, elev liver enzyme low platelets L12B.00: Proteinuric hypertension of pregnancy Lyu1.00: [X]Oedema,proteinuria+hypertens in pregnancy,childbrth,puerp Q000.11: Fetus affected by maternal toxaemia	O14: Pre-eclampsia O14.0: Mild to moderate pre-eclampsia O14.1: Severe pre-eclampsia O14.2: HELLP syndrome O14.9: Pre-eclampsia, unspecified O15: Eclampsia O15.0: Eclampsia in pregnancy O15.1: Eclampsia in labour O15.2: Eclampsia in the puerperium O15.9: Eclampsia, unspecified as to time period
Preterm birth	Q110.00: Very premature - less than 1000g or less than 28 weeks Q111.00: Premature - weight 1000g-2499g or gestation of 28-37weeks 6351: Baby premature 36-38 weeks 6352: Baby v. premature 32-36 weeks 6353: Baby extremely prem.28-32 week 6356: Baby premature 26-28 weeks 6357: Baby premature 24-26 weeks 635..13: Premature baby 635A.00: Baby premature 37 weeks 635B.00: Baby premature 36 weeks 635C.00: Preterm infant status 635C.11: Preterm L14..11: Premature labour L142.11: Premature delivery L143.00: Premature labour and delivery	O60: Preterm labour and delivery O60.1: Preterm spontaneous labour with preterm delivery O60.3: Preterm delivery without spontaneous labour

	L143100: Premature labour with premature delivery Q11..11: Baby born premature Q112.11: Extreme prematurity - less than 28 weeks Q116.00 : Premature infant 28-37 weeks Q11z.00: Born premature NOS Qyu1100: [X]Other preterm infants Q317100: Prematurity with interstitial pulmonary fibrosis	
Fetal growth restriction	Q10z.00: Fetal growth retardation NOS Q10z.11: Intrauterine growth retardation	O36.5: Maternal care for poor fetal growth
Diabetes	6761: Diabetic pre-pregnancy counselling 7276: Pan retinal photocoagulation for diabetes 9360: Patient held diabetic record issued 13AB.00: Diabetic lipid lowering diet 13AC.00: Diabetic weight reducing diet 13B1.00: Diabetic diet 2BBF.00: Retinal abnormality - diabetes related 2BBk.00: O/E - right eye stable treated prolif diabetic retinopathy 2BBL.00: O/E - diabetic maculopathy present both eyes 2BBl.00: O/E - left eye stable treated prolif diabetic retinopathy 2BBM.00: O/E - diabetic maculopathy absent both eyes 2BBo.00: O/E - sight threatening diabetic retinopathy 2BBP.00: O/E - right eye background diabetic retinopathy 2BBQ.00: O/E - left eye background diabetic retinopathy 2BBR.00: O/E - right eye preproliferative diabetic retinopathy 2BBS.00: O/E - left eye preproliferative diabetic retinopathy 2BBT.00: O/E - right eye proliferative diabetic retinopathy 2BBV.00: O/E - left eye proliferative diabetic retinopathy 2BBW.00: O/E - right eye diabetic maculopathy 2BBX.00: O/E - left eye diabetic maculopathy 2G51000: Foot abnormality - diabetes related 2G5A.00: O/E - Right diabetic foot at risk 2G5B.00: O/E - Left diabetic foot at risk 2G5C.00: Foot abnormality - diabetes related 2G5E.00: O/E - Right diabetic foot at low risk 2G5F.00: O/E - Right diabetic foot at moderate risk 2G5G.00: O/E - Right diabetic foot at high risk 2G5H.00: O/E - Right diabetic foot - ulcerated 2G5I.00: O/E - Left diabetic foot at low risk 2G5J.00: O/E - Left diabetic foot at moderate risk 2G5K.00: O/E - Left diabetic foot at high risk 2G5L.00: O/E - Left diabetic foot - ulcerated 2G5V.00: O/E - right chronic diabetic foot ulcer 2G5W.00: O/E - left chronic diabetic foot ulcer 66A3.00: Diabetic on diet only 66A4.00: Diabetic on oral treatment 66A5.00: Diabetic on insulin 66A8.00: Has seen dietician - diabetes 66A9.00: Understands diet - diabetes 66Aa.00: Diabetic diet - poor compliance 66AA.11: Injection sites - diabetic 66Ab.00: Diabetic foot examination 66Ac.00: Diabetic peripheral neuropathy screening 66AD.00: Fundoscopy - diabetic check 66AG.00: Diabetic drug side effects 66Ag.00: Insulin needles changed daily 66AH.00: Diabetic treatment changed 66Ah.00: Insulin needles changed for each injection	E10: Insulin-dependent diabetes mellitus E11: Non-insulin-dependent diabetes mellitus E13: Other specified diabetes mellitus E14: Unspecified diabetes mellitus G590: Diabetic mononeuropathy G632: Diabetic polyneuropathy H280: Diabetic cataract H360: Diabetic retinopathy M142: Diabetic arthropathy N083: Glomerular disorders in diabetes mellitus O240: Diabetes mellitus in pregnancy: Pre-existing diabetes mellitus, insulin-dependent O241: Diabetes mellitus in pregnancy: Pre-existing diabetes mellitus, non-insulin-dependent O243: Diabetes mellitus in pregnancy: Pre-existing diabetes mellitus, unspecified

66AI.00: Diabetic - good control
66Ai.00: Diabetic 6 month review
66AJ.00: Diabetic - poor control
66Aj.00: Insulin needles changed less than once a day
66AJ.11: Unstable diabetes
66AJ100: Brittle diabetes
66AJz00: Diabetic - poor control NOS
66AK.00: Diabetic - cooperative patient
66AL.00: Diabetic-uncooperative patient
66Am.00: Insulin dose changed
66An.00: Diabetes type 1 review
66AN.00: Date diabetic treatment start
66Ao.00: Diabetes type 2 review
66AO.00: Date diabetic treatment stopp.
66AP.00: Diabetes: practice programme
66Ap.00: Insulin treatment initiated
66AQ.00: Diabetes: shared care programme
66Aq.00: Diabetic foot screen
66AR.00: Diabetes management plan given
66AS.00: Diabetic annual review
66AT.00: Annual diabetic blood test
66AU.00: Diabetes care by hospital only
66AV.00: Diabetic on insulin and oral treatment
66AW.00: Diabetic foot risk assessment
66AX.00: Diabetes: shared care in pregnancy - diabetol and obstet
66AY.00: Diabetic diet - good compliance
68A7.00: Diabetic retinopathy screening
68A9.00: Diabetic retinopathy screening offered
68AB.00: Diabetic digital retinopathy screening offered
7L10000: Continuous subcutaneous infusion of insulin
7L19800: Subcutaneous injection of insulin
889A.00: Diab mellit insulin-glucose infus acute myocardial infarct
8A13.00: Diabetic stabilization
8B3l.00: Diabetes medication review
8BL2.00: Patient on maximal tolerated therapy for diabetes
8CA4100: Pt advised re diabetic diet
8CAQ.00: Advice about blood glucose control
8CP2.00: Transition of diabetes care options discussed
8H2J.00: Admit diabetic emergency
8H3O.00: Non-urgent diabetic admission
8H7r.00: Refer to diabetic foot screener
8HBG.00: Diabetic retinopathy 12 month review
8HBH.00: Diabetic retinopathy 6 month review
8Hl1.00: Referral for diabetic retinopathy screening
8HLE.00: Diabetology D.V. done
8I3k.00: Insulin therapy declined
8I3W.00: Diabetic foot examination declined
8I3X.00: Diabetic retinopathy screening refused
8I57.00: Patient held diabetic record declined
9OLD.00: Diabetic patient unsuitable for digital retinal photography
C10..00: Diabetes mellitus
C100.00: Diabetes mellitus with no mention of complication
C100000: Diabetes mellitus, juvenile type, no mention of complication
C100011: Insulin dependent diabetes mellitus
C100100: Diabetes mellitus, adult onset, no mention of complication
C100111: Maturity onset diabetes
C100112: Non-insulin dependent diabetes mellitus
C100z00: Diabetes mellitus NOS with no mention of complication
C101.00: Diabetes mellitus with ketoacidosis

C101000: Diabetes mellitus, juvenile type, with ketoacidosis
C101100: Diabetes mellitus, adult onset, with ketoacidosis
C101y00: Other specified diabetes mellitus with ketoacidosis
C101z00: Diabetes mellitus NOS with ketoacidosis
C102.00: Diabetes mellitus with hyperosmolar coma
C102000: Diabetes mellitus, juvenile type, with hyperosmolar coma
C102100: Diabetes mellitus, adult onset, with hyperosmolar coma
C102z00: Diabetes mellitus NOS with hyperosmolar coma
C103.00: Diabetes mellitus with ketoacidotic coma
C103000: Diabetes mellitus, juvenile type, with ketoacidotic coma
C103100: Diabetes mellitus, adult onset, with ketoacidotic coma
C103y00: Other specified diabetes mellitus with coma
C103z00: Diabetes mellitus NOS with ketoacidotic coma
C104.00: Diabetes mellitus with renal manifestation
C104.11: Diabetic nephropathy
C104000: Diabetes mellitus, juvenile type, with renal manifestation
C104100: Diabetes mellitus, adult onset, with renal manifestation
C104y00: Other specified diabetes mellitus with renal complications
C104z00: Diabetes mellitis with nephropathy NOS
C105.00: Diabetes mellitus with ophthalmic manifestation
C105000: Diabetes mellitus, juvenile type, + ophthalmic manifestation
C105100: Diabetes mellitus, adult onset, + ophthalmic manifestation
C105y00: Other specified diabetes mellitus with ophthalmic complicatn
C105z00: Diabetes mellitus NOS with ophthalmic manifestation
C106.00: Diabetes mellitus with neurological manifestation
C106.11: Diabetic amyotrophy
C106.12: Diabetes mellitus with neuropathy
C106.13: Diabetes mellitus with polyneuropathy
C106000: Diabetes mellitus, juvenile, + neurological manifestation
C106100: Diabetes mellitus, adult onset, + neurological manifestation
C106y00: Other specified diabetes mellitus with neurological comps
C106z00: Diabetes mellitus NOS with neurological manifestation
C107.00: Diabetes mellitus with peripheral circulatory disorder
C107.11: Diabetes mellitus with gangrene
C107.12: Diabetes with gangrene
C107000: Diabetes mellitus, juvenile +peripheral circulatory disorder
C107100: Diabetes mellitus, adult, + peripheral circulatory disorder
C107200: Diabetes mellitus, adult with gangrene
C107300: IDDM with peripheral circulatory disorder
C107400: NIDDM with peripheral circulatory disorder
C107z00: Diabetes mellitus NOS with peripheral circulatory disorder
C108.00: Insulin dependent diabetes mellitus
C108.11: IDDM-Insulin dependent diabetes mellitus
C108.12: Type 1 diabetes mellitus
C108.13: Type I diabetes mellitus
C108000: Insulin-dependent diabetes mellitus with renal complications
C108011: Type I diabetes mellitus with renal complications
C108012: Type 1 diabetes mellitus with renal complications
C108100: Insulin-dependent diabetes mellitus with ophthalmic comps
C108200: Insulin-dependent diabetes mellitus with neurological comps
C108211: Type I diabetes mellitus with neurological complications
C108212: Type 1 diabetes mellitus with neurological complications
C108300: Insulin dependent diabetes mellitus with multiple complicatn
C108400: Unstable insulin dependant diabetes mellitus
C108411: Unstable type I diabetes mellitus
C108412: Unstable type 1 diabetes mellitus
C108500: Insulin dependent diabetes mellitus with ulcer
C108511: Type I diabetes mellitus with ulcer
C108512: Type 1 diabetes mellitus with ulcer

C108600: Insulin dependent diabetes mellitus with gangrene
C108700: Insulin dependent diabetes mellitus with retinopathy
C108711: Type I diabetes mellitus with retinopathy
C108712: Type 1 diabetes mellitus with retinopathy
C108800: Insulin dependant diabetes mellitus - poor control
C108811: Type I diabetes mellitus - poor control
C108812: Type 1 diabetes mellitus - poor control
C108900: Insulin dependant diabetes maturity onset
C108911: Type I diabetes mellitus maturity onset
C108912: Type 1 diabetes mellitus maturity onset
C108A00: Insulin-dependent diabetes without complication
C108A11: Type I diabetes mellitus without complication
C108B00: Insulin dependent diabetes mellitus with mononeuropathy
C108C00: Insulin dependent diabetes mellitus with polyneuropathy
C108D00: Insulin dependent diabetes mellitus with nephropathy
C108D11: Type I diabetes mellitus with nephropathy
C108E00: Insulin dependent diabetes mellitus with hypoglycaemic coma
C108E11: Type I diabetes mellitus with hypoglycaemic coma
C108E12: Type 1 diabetes mellitus with hypoglycaemic coma
C108F00: Insulin dependent diabetes mellitus with diabetic cataract
C108F11: Type I diabetes mellitus with diabetic cataract
C108G00: Insulin dependent diab mell with peripheral angiopathy
C108H00: Insulin dependent diabetes mellitus with arthropathy
C108H11: Type I diabetes mellitus with arthropathy
C108J00: Insulin dependent diab mell with neuropathic arthropathy
C108J11: Type I diabetes mellitus with neuropathic arthropathy
C108J12: Type 1 diabetes mellitus with neuropathic arthropathy
C108y00: Other specified diabetes mellitus with multiple comps
C108z00: Unspecified diabetes mellitus with multiple complications
C109.00: Non-insulin dependent diabetes mellitus
C109.11: NIDDM - Non-insulin dependent diabetes mellitus
C109.12: Type 2 diabetes mellitus
C109.13: Type II diabetes mellitus
C109000: Non-insulin-dependent diabetes mellitus with renal comps
C109011: Type II diabetes mellitus with renal complications
C109012: Type 2 diabetes mellitus with renal complications
C109100: Non-insulin-dependent diabetes mellitus with ophthalm comps
C109111: Type II diabetes mellitus with ophthalmic complications
C109112: Type 2 diabetes mellitus with ophthalmic complications
C109200: Non-insulin-dependent diabetes mellitus with neuro comps
C109211: Type II diabetes mellitus with neurological complications
C109212: Type 2 diabetes mellitus with neurological complications
C109300: Non-insulin-dependent diabetes mellitus with multiple comps
C109400: Non-insulin dependent diabetes mellitus with ulcer
C109411: Type II diabetes mellitus with ulcer
C109412: Type 2 diabetes mellitus with ulcer
C109500: Non-insulin dependent diabetes mellitus with gangrene
C109511: Type II diabetes mellitus with gangrene
C109512: Type 2 diabetes mellitus with gangrene
C109600: Non-insulin-dependent diabetes mellitus with retinopathy
C109611: Type II diabetes mellitus with retinopathy
C109612: Type 2 diabetes mellitus with retinopathy
C109700: Non-insulin dependant diabetes mellitus - poor control
C109711: Type II diabetes mellitus - poor control
C109712: Type 2 diabetes mellitus - poor control
C109900: Non-insulin-dependent diabetes mellitus without complication
C109A00: Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11: Type II diabetes mellitus with mononeuropathy
C109B00: Non-insulin dependent diabetes mellitus with polyneuropathy

C109B11: Type II diabetes mellitus with polyneuropathy
C109C00: Non-insulin dependent diabetes mellitus with nephropathy
C109C11: Type II diabetes mellitus with nephropathy
C109C12: Type 2 diabetes mellitus with nephropathy
C109D00: Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D11: Type II diabetes mellitus with hypoglycaemic coma
C109D12: Type 2 diabetes mellitus with hypoglycaemic coma
C109E00: Non-insulin depend diabetes mellitus with diabetic cataract
C109E11: Type II diabetes mellitus with diabetic cataract
C109E12: Type 2 diabetes mellitus with diabetic cataract
C109F00: Non-insulin-dependent d m with peripheral angiopath
C109F11: Type II diabetes mellitus with peripheral angiopathy
C109F12: Type 2 diabetes mellitus with peripheral angiopathy
C109G00: Non-insulin dependent diabetes mellitus with arthropathy
C109G11: Type II diabetes mellitus with arthropathy
C109G12: Type 2 diabetes mellitus with arthropathy
C109H00: Non-insulin dependent d m with neuropathic arthropathy
C109H11: Type II diabetes mellitus with neuropathic arthropathy
C109H12: Type 2 diabetes mellitus with neuropathic arthropathy
C109J00: Insulin treated Type 2 diabetes mellitus
C109J11: Insulin treated non-insulin dependent diabetes mellitus
C109J12: Insulin treated Type II diabetes mellitus
C109K00: Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10A.00: Malnutrition-related diabetes mellitus
C10A000: Malnutrition-related diabetes mellitus with coma
C10A100: Malnutrition-related diabetes mellitus with ketoacidosis
C10B.00: Diabetes mellitus induced by steroids
C10B000: Steroid induced diabetes mellitus without complication
C10C.00: Diabetes mellitus autosomal dominant
C10C.11: Maturity onset diabetes in youth
C10C.12: Maturity onset diabetes in youth type 1
C10D.00: Diabetes mellitus autosomal dominant type 2
C10D.11: Maturity onset diabetes in youth type 2
C10E.00: Type 1 diabetes mellitus
C10E.11: Type I diabetes mellitus
C10E.12: Insulin dependent diabetes mellitus
C10E000: Type 1 diabetes mellitus with renal complications
C10E100: Type 1 diabetes mellitus with ophthalmic complications
C10E112: Insulin-dependent diabetes mellitus with ophthalmic comps
C10E200: Type 1 diabetes mellitus with neurological complications
C10E300: Type 1 diabetes mellitus with multiple complications
C10E311: Type I diabetes mellitus with multiple complications
C10E312: Insulin dependent diabetes mellitus with multiple complicat
C10E400: Unstable type 1 diabetes mellitus
C10E411: Unstable type I diabetes mellitus
C10E412: Unstable insulin dependent diabetes mellitus
C10E500: Type 1 diabetes mellitus with ulcer
C10E511: Type I diabetes mellitus with ulcer
C10E512: Insulin dependent diabetes mellitus with ulcer
C10E600: Type 1 diabetes mellitus with gangrene
C10E700: Type 1 diabetes mellitus with retinopathy
C10E711: Type I diabetes mellitus with retinopathy
C10E712: Insulin dependent diabetes mellitus with retinopathy
C10E800: Type 1 diabetes mellitus - poor control
C10E812: Insulin dependent diabetes mellitus - poor control
C10E900: Type 1 diabetes mellitus maturity onset
C10E911: Type I diabetes mellitus maturity onset
C10E912: Insulin dependent diabetes maturity onset
C10EA00: Type 1 diabetes mellitus without complication

C10EA11: Type I diabetes mellitus without complication
C10EB00: Type 1 diabetes mellitus with mononeuropathy
C10EC00: Type 1 diabetes mellitus with polyneuropathy
C10EC11: Type I diabetes mellitus with polyneuropathy
C10ED00: Type 1 diabetes mellitus with nephropathy
C10EE00: Type 1 diabetes mellitus with hypoglycaemic coma
C10EF00: Type 1 diabetes mellitus with diabetic cataract
C10EG00: Type 1 diabetes mellitus with peripheral angiopathy
C10EH00: Type 1 diabetes mellitus with arthropathy
C10EJ00: Type 1 diabetes mellitus with neuropathic arthropathy
C10EK00: Type 1 diabetes mellitus with persistent proteinuria
C10EL00: Type 1 diabetes mellitus with persistent microalbuminuria
C10EM00: Type 1 diabetes mellitus with ketoacidosis
C10EM11: Type I diabetes mellitus with ketoacidosis
C10EN00: Type 1 diabetes mellitus with ketoacidotic coma
C10EN11: Type I diabetes mellitus with ketoacidotic coma
C10EP00: Type 1 diabetes mellitus with exudative maculopathy
C10EP11: Type I diabetes mellitus with exudative maculopathy
C10EQ00: Type 1 diabetes mellitus with gastroparesis
C10ER00: Latent autoimmune diabetes mellitus in adult
C10F.00: Type 2 diabetes mellitus
C10F.11: Type II diabetes mellitus
C10F000: Type 2 diabetes mellitus with renal complications
C10F011: Type II diabetes mellitus with renal complications
C10F100: Type 2 diabetes mellitus with ophthalmic complications
C10F200: Type 2 diabetes mellitus with neurological complications
C10F211: Type II diabetes mellitus with neurological complications
C10F300: Type 2 diabetes mellitus with multiple complications
C10F311: Type II diabetes mellitus with multiple complications
C10F400: Type 2 diabetes mellitus with ulcer
C10F411: Type II diabetes mellitus with ulcer
C10F500: Type 2 diabetes mellitus with gangrene
C10F600: Type 2 diabetes mellitus with retinopathy
C10F611: Type II diabetes mellitus with retinopathy
C10F700: Type 2 diabetes mellitus - poor control
C10F711: Type II diabetes mellitus - poor control
C10F900: Type 2 diabetes mellitus without complication
C10F911: Type II diabetes mellitus without complication
C10FA00: Type 2 diabetes mellitus with mononeuropathy
C10FA11: Type II diabetes mellitus with mononeuropathy
C10FB00: Type 2 diabetes mellitus with polyneuropathy
C10FB11: Type II diabetes mellitus with polyneuropathy
C10FC00: Type 2 diabetes mellitus with nephropathy
C10FD00: Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11: Type II diabetes mellitus with hypoglycaemic coma
C10FE00: Type 2 diabetes mellitus with diabetic cataract
C10FE11: Type II diabetes mellitus with diabetic cataract
C10FF00: Type 2 diabetes mellitus with peripheral angiopathy
C10FG00: Type 2 diabetes mellitus with arthropathy
C10FH00: Type 2 diabetes mellitus with neuropathic arthropathy
C10FJ00: Insulin treated Type 2 diabetes mellitus
C10FJ11: Insulin treated Type II diabetes mellitus
C10FK00: Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FL00: Type 2 diabetes mellitus with persistent proteinuria
C10FL11: Type II diabetes mellitus with persistent proteinuria
C10FM00: Type 2 diabetes mellitus with persistent microalbuminuria
C10FM11: Type II diabetes mellitus with persistent microalbuminuria
C10FN00: Type 2 diabetes mellitus with ketoacidosis
C10FP00: Type 2 diabetes mellitus with ketoacidotic coma

C10FQ00: Type 2 diabetes mellitus with exudative maculopathy
C10FR00: Type 2 diabetes mellitus with gastroparesis
C10M.00: Lipoatrophic diabetes mellitus
C10y.00: Diabetes mellitus with other specified manifestation
C10y100: Diabetes mellitus, adult, + other specified manifestation
C10yy00: Other specified diabetes mellitus with other spec comps
C10yz00: Diabetes mellitus NOS with other specified manifestation
C10z.00: Diabetes mellitus with unspecified complication
C10z000: Diabetes mellitus, juvenile type, + unspecified complication
C10z100: Diabetes mellitus, adult onset, + unspecified complication
C10zy00: Other specified diabetes mellitus with unspecified comps
C10zz00: Diabetes mellitus NOS with unspecified complication
C314.11: Renal diabetes
C350011: Bronzed diabetes
Cyu2.00: [X]Diabetes mellitus
Cyu2000: [X]Other specified diabetes mellitus
F171100: Autonomic neuropathy due to diabetes
F345000: Diabetic mononeuritis multiplex
F35z000: Diabetic mononeuritis NOS
F372.00: Polyneuropathy in diabetes
F372.11: Diabetic polyneuropathy
F372.12: Diabetic neuropathy
F372000: Acute painful diabetic neuropathy
F372100: Chronic painful diabetic neuropathy
F372200: Asymptomatic diabetic neuropathy
F381300: Myasthenic syndrome due to diabetic amyotrophy
F381311: Diabetic amyotrophy
F3y0.00: Diabetic mononeuropathy
F420.00: Diabetic retinopathy
F420000: Background diabetic retinopathy
F420100: Proliferative diabetic retinopathy
F420200: Preproliferative diabetic retinopathy
F420300: Advanced diabetic maculopathy
F420400: Diabetic maculopathy
F420500: Advanced diabetic retinal disease
F420600: Non proliferative diabetic retinopathy
F420700: High risk proliferative diabetic retinopathy
F420800: High risk non proliferative diabetic retinopathy
F420z00: Diabetic retinopathy NOS
F440700: Diabetic iritis
F464000: Diabetic cataract
G73y000: Diabetic peripheral angiopathy
K01x100: Nephrotic syndrome in diabetes mellitus
K01x111: Kimmelstiel - Wilson disease
L180500: Pre-existing diabetes mellitus, insulin-dependent
L180600: Pre-existing diabetes mellitus, non-insulin-dependent
L180X00: Pre-existing diabetes mellitus, unspecified
M037200: Cellulitis in diabetic foot
M21yC00: Insulin lipohypertrophy
M21yC11: Insulin site lipohypertrophy
M271000: Ischaemic ulcer diabetic foot
M271100: Neuropathic diabetic ulcer - foot
M271200: Mixed diabetic ulcer - foot
N030000: Diabetic cheiroarthropathy
N030011: Diabetic cheiropathy
N030100: Diabetic Charcot arthropathy
Q441.00: Neonatal diabetes mellitus
R054200: [D]Gangrene of toe in diabetic
R054300: [D]Widespread diabetic foot gangrene

	TJ23.00: Adverse reaction to insulins and antidiabetic agents TJ23z00: Adverse reaction to insulins and antidiabetic agents NOS U602311: [X] Adverse reaction to insulins and antidiabetic agents ZC2C800: Dietary advice for diabetes mellitus ZC2C900: Dietary advice for type I diabetes ZC2CA00: Dietary advice for type II diabetes ZRbH.00: Perceived control of insulin-dependent diabetes ZV65312: [V]Dietary counselling in diabetes mellitus	
Chronic kidney disease	1Z10.00: Chronic kidney disease stage 1 1Z17.00: Chronic kidney disease stage 1 with proteinuria 1Z17.11: CKD stage 1 with proteinuria 1Z18.00: Chronic kidney disease stage 1 without proteinuria 1Z11.00: Chronic kidney disease stage 2 1Z19.00: Chronic kidney disease stage 2 with proteinuria 1Z19.11: CKD stage 2 with proteinuria 1Z1A.00: Chronic kidney disease stage 2 without proteinuria 1Z1A.11: CKD stage 2 without proteinuria 1Z12.00: Chronic kidney disease stage 3 1Z15.00: Chronic kidney disease stage 3A 1Z16.00: Chronic kidney disease stage 3B 1Z1B.00: Chronic kidney disease stage 3 with proteinuria 1Z1B.11: CKD stage 3 with proteinuria 1Z1C.00: Chronic kidney disease stage 3 without proteinuria 1Z1C.11: CKD stage 3 without proteinuria 1Z1D.00: Chronic kidney disease stage 3A with proteinuria 1Z1D.11: CKD stage 3A with proteinuria 1Z1E.00: Chronic kidney disease stage 3A without proteinuria 1Z1E.11: CKD stage 3A without proteinuria 1Z1F.00: Chronic kidney disease stage 3B with proteinuria 1Z1F.11: CKD stage 3B with proteinuria 1Z1G.00: Chronic kidney disease stage 3B without proteinuria 1Z13.00: Chronic kidney disease stage 4 1Z1H.00: Chronic kidney disease stage 4 with proteinuria 1Z1J.00: Chronic kidney disease stage 4 without proteinuria 1Z1J.11: CKD stage 4 without proteinuria 1Z14.00: Chronic kidney disease stage 5 1Z1K.00: Chronic kidney disease stage 5 with proteinuria 1Z1L.00: Chronic kidney disease stage 5 without proteinuria 1Z1L.11: CKD stage 5 without proteinuria	
HDP	L123.00: Transient hypertension of pregnancy L123000: Transient hypertension of pregnancy unspecified L123100: Transient hypertension of pregnancy - delivered L123300: Transient hypertension of pregnancy - not delivered L123400: Transient hypertension of pregnancy + postnatal complication L123500: Gestational hypertension L123600: Transient hypertension of pregnancy L123z00: Transient hypertension of pregnancy NOS L12.00 Hypertension complicating pregnancy/childbirth/puerperium L12z.00 Unspecified hypertension in pregnancy/childbirth/puerperium L12z000 Unspecified hypertension in preg/childb/puerp unspecified L12z100 Unspecified hypertension in preg/childb/puerp - delivered L12z200 Unspecified hypertension in preg/childb/puerp -del +p/n comp L12z300 Unspecified hypertension in preg/childb/puerp - not deliv L12zz00 Unspecified hypertension in preg/childb/puerp NOS Q000.00 Fetus or neonate affected by maternal hypertensive disease	O13; Gestational (pregnancy induced) hypertension O10.9: Unspecified pre-existing hypertension complicating pregnancy, childbirth and the puerperium O16: Unspecified maternal hypertension

Women with these codes (HDP: hypertensive disorders of pregnancy) were excluded from analyses except for pre-eclampsia analysis when comparing hypertensive with normotensive pregnancies

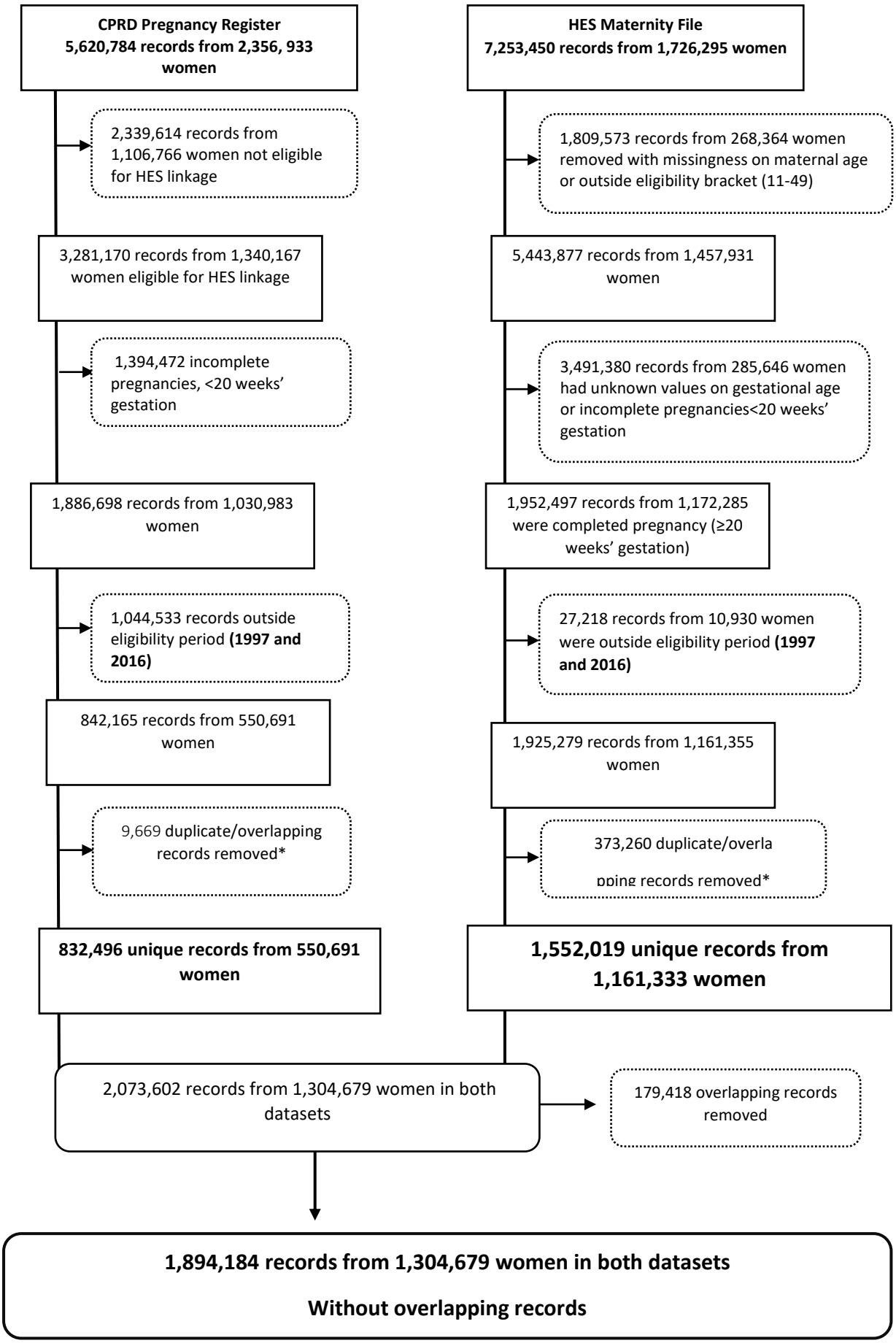


Figure S1. Flow diagram of pregnancy cohort from CPRD and HES datasets

*dealing with overlapping records illustrated in **Figure.S7**

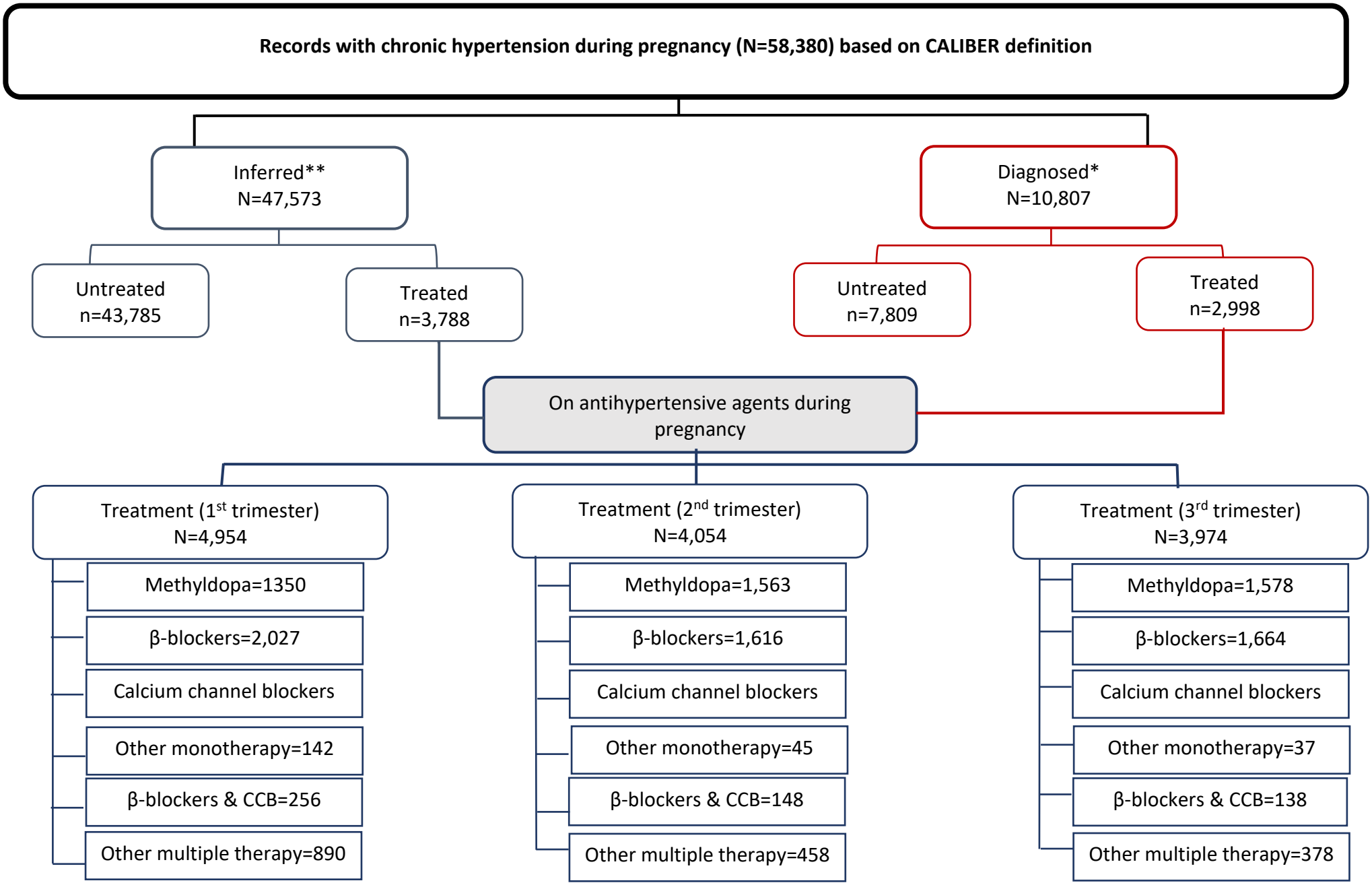


Figure S2. Flow diagram for women with chronic hypertension during pregnancy

*Diagnosed: Diagnosis of hypertension during a consultation in primary or secondary care; **Inferred: Based on continuous blood pressure readings or blood pressure lowering medication

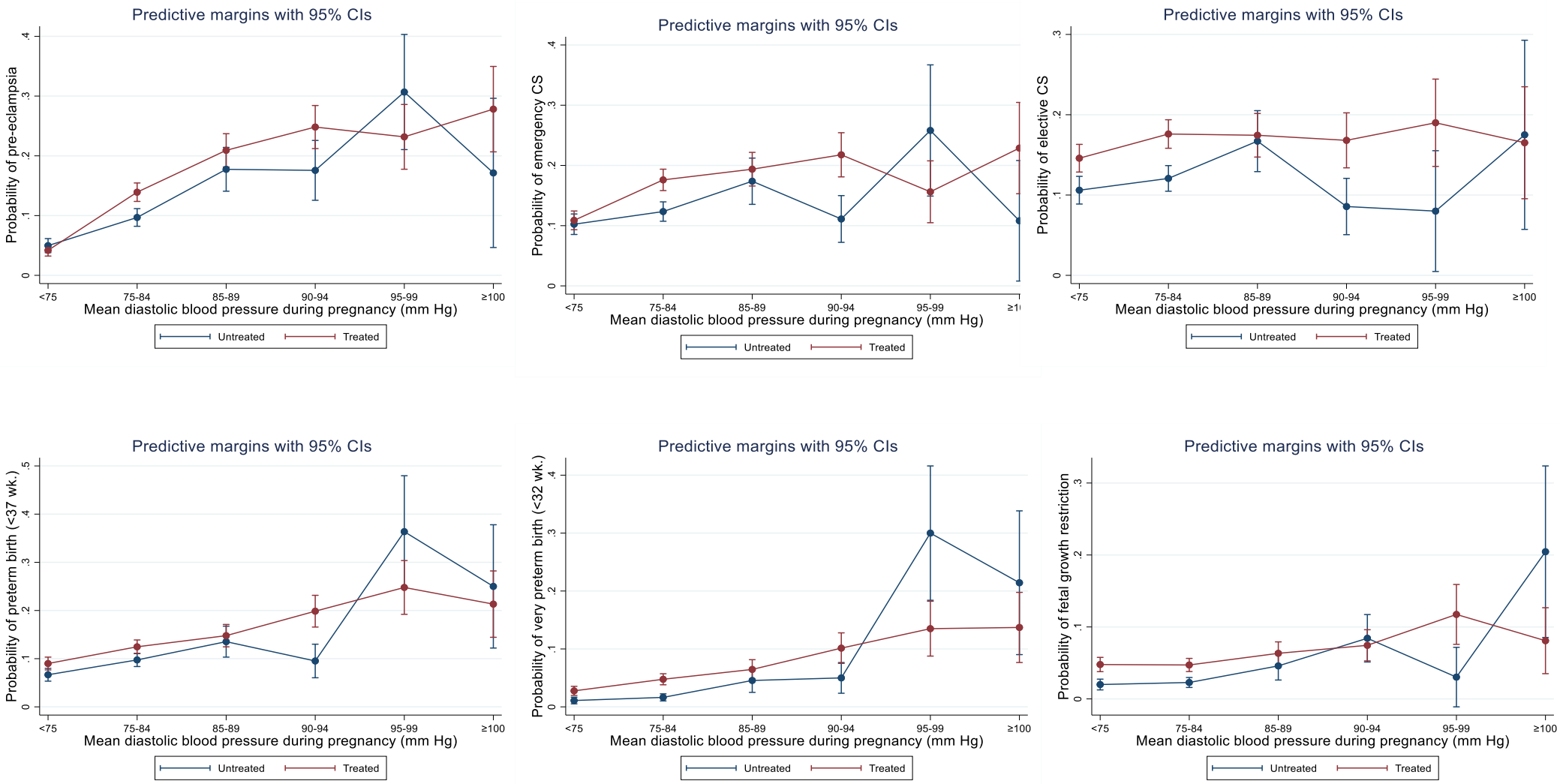


Figure S3. Predictive margins with 95% CIs of the probability of adverse perinatal outcomes by treatment across dBP levels.

These analyses were restricted to women with treated and untreated chronic hypertension matched using a propensity score (N=9,654) and with available BP readings. This model included an interaction term between antihypertensive agent and dBP levels. The large overlap in confidence intervals suggests that the probabilities of adverse outcomes might be not different between both groups.

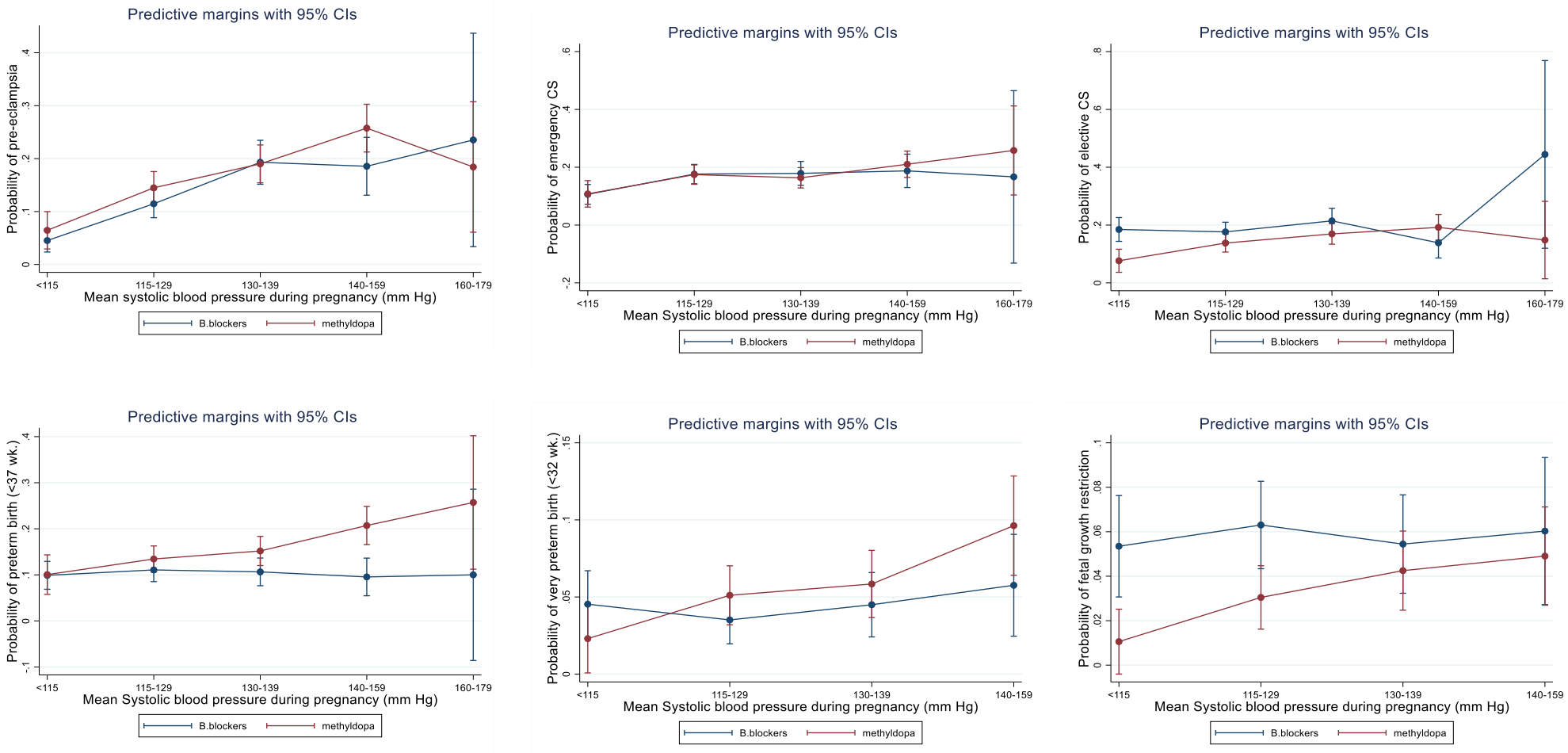


Figure S4. Predictive margins with 95% CIs of the probability of adverse perinatal outcomes by type of antihypertensive agent across sBP levels.

These analyses were restricted to patients with available BP readings from the propensity score matching sample (N=3,222). This model included an interaction term between antihypertensive agent and sBP levels. The large overlap in confidence intervals suggests that the probabilities of adverse outcomes is not different between both groups.

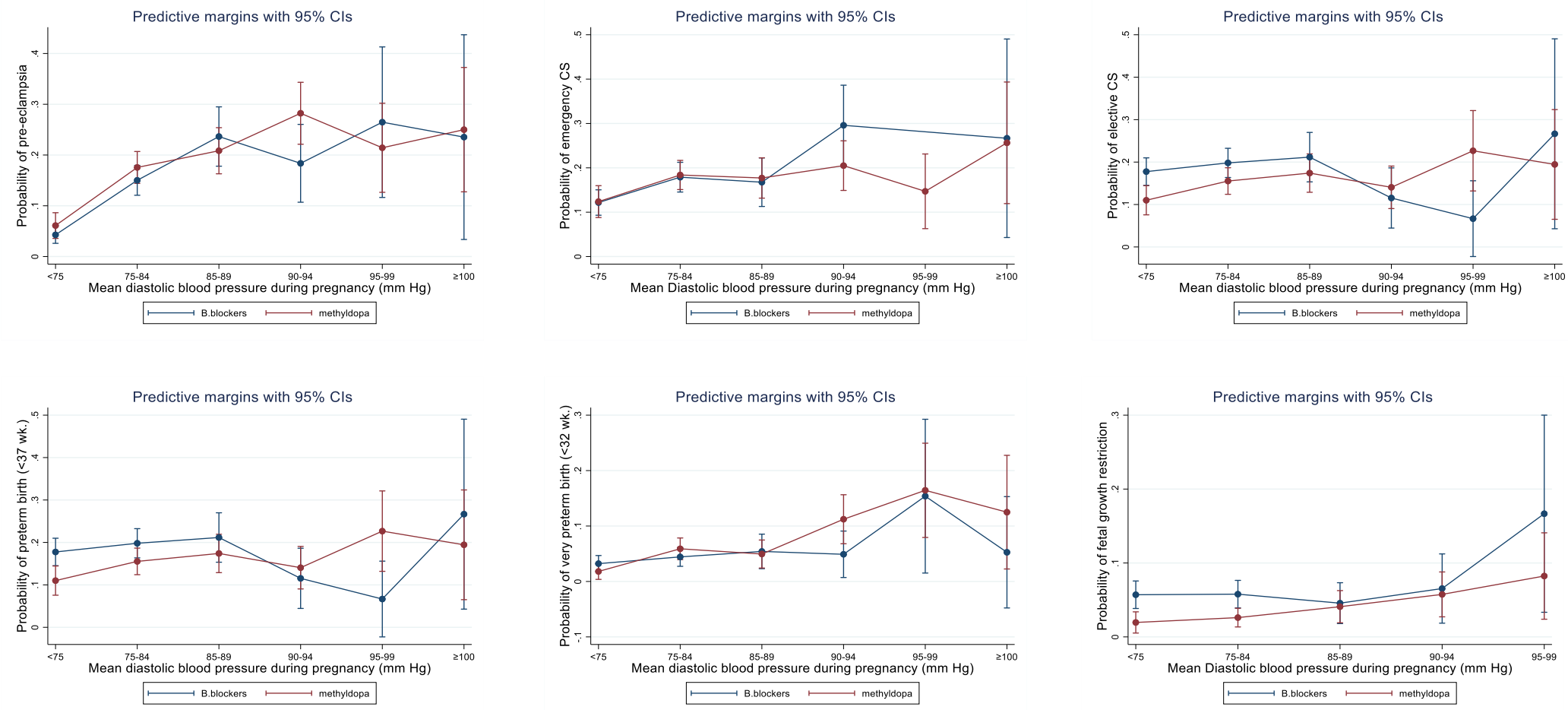
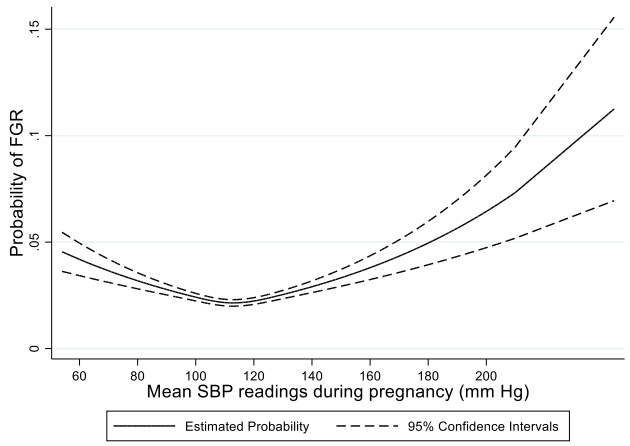


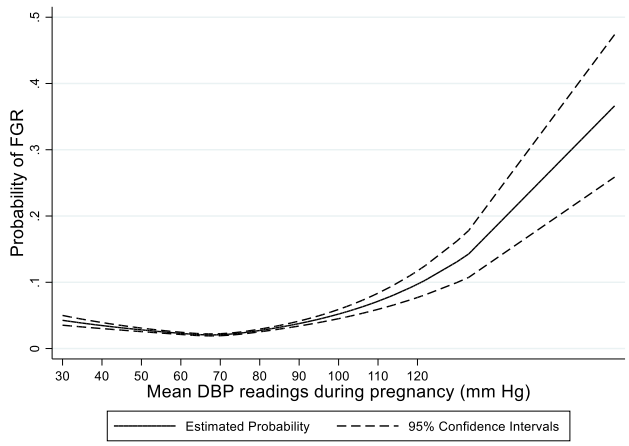
Figure S5. Predictive margins with 95% CIs of the probability of adverse perinatal outcomes by type of antihypertensive agent across dBP levels.

These analyses were restricted to patients with available BP readings from the propensity score matching sample (3,222). This model included an interaction term between antihypertensive agent and dBP levels. The large overlap in confidence intervals suggests that the probabilities of adverse outcomes is not different between both groups.

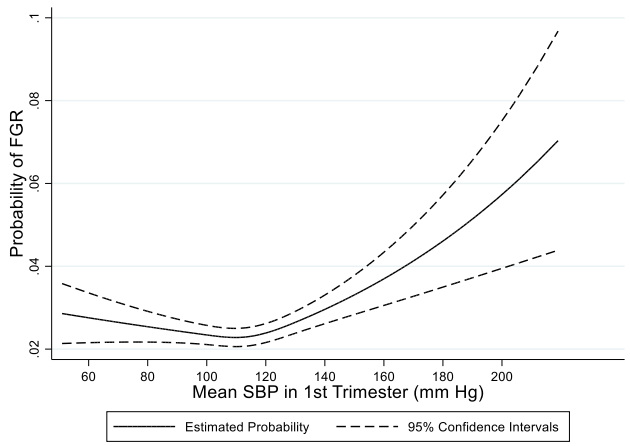
Figure S6. Spline plots of the relationship between BP levels fetal growth restriction (FGR)

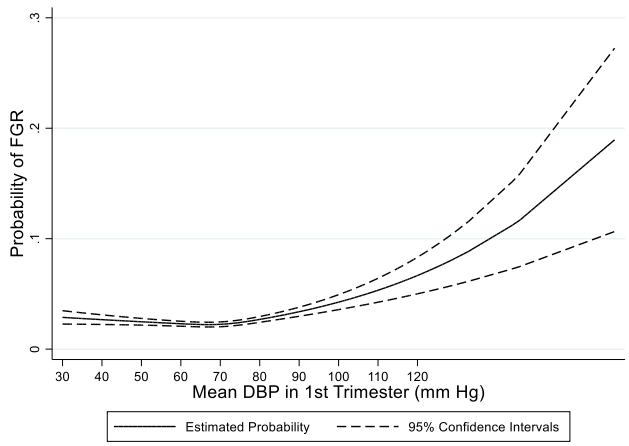
1. Relationship between BP level and fetal growth restriction including all records with available BP readings, results from adjusted models (N=475,851)*



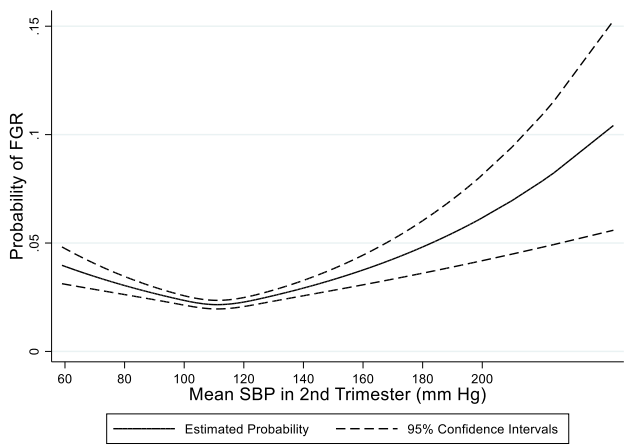


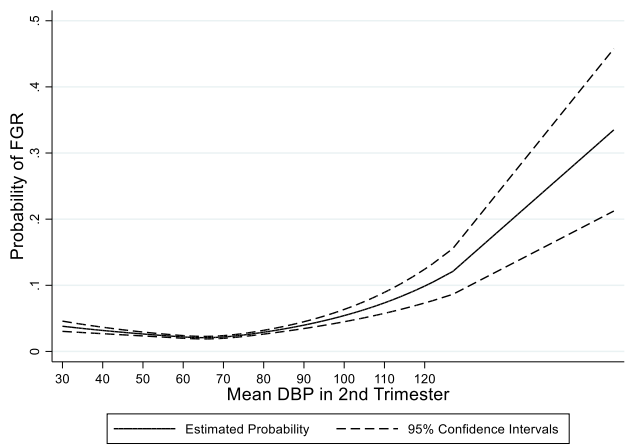
1.1. First trimester (relationship between BP level and fetal growth restriction, (N= 264,080))



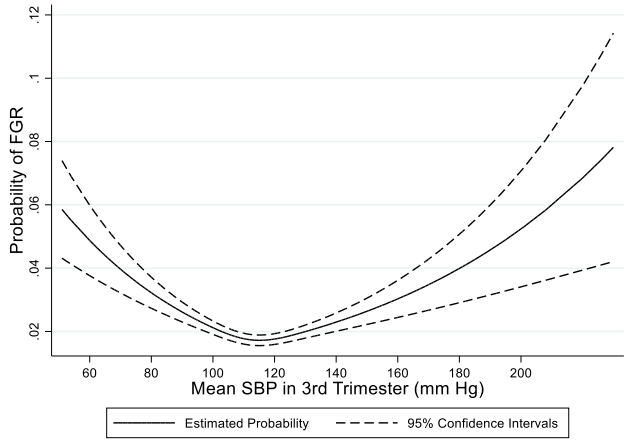


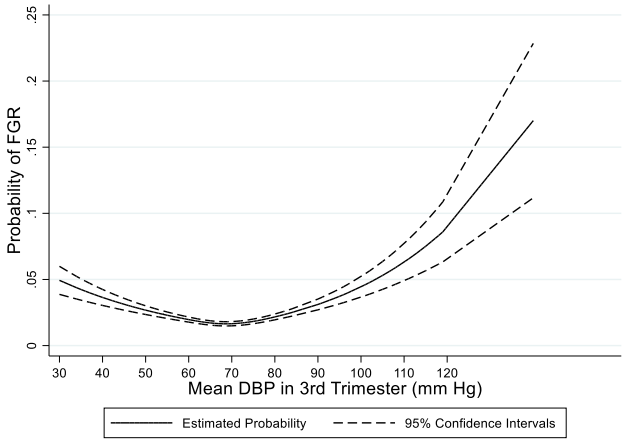
1.2. Second trimester (relationship between BP level and fetal growth restriction, N=302,122))



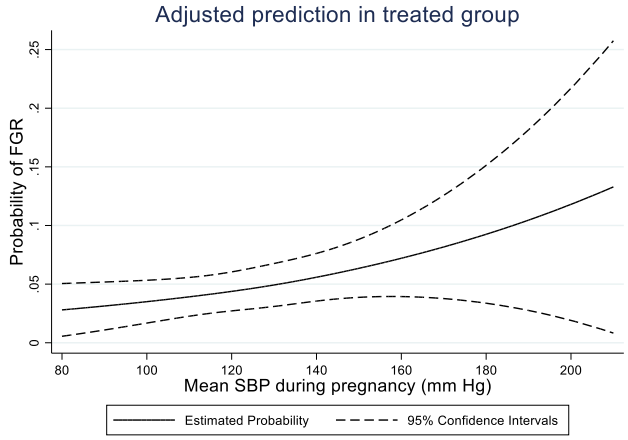


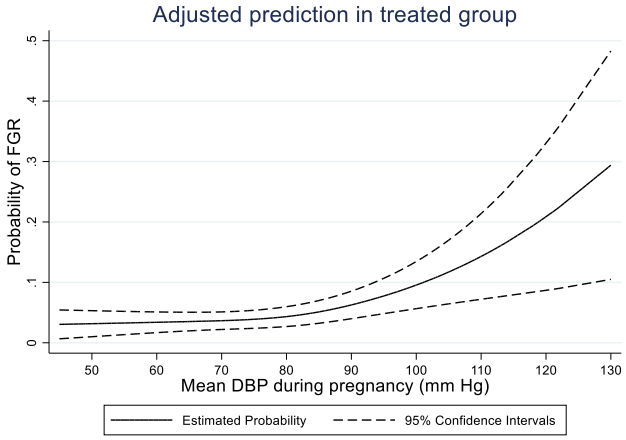
1.3. Third trimester (relationship between BP level and fetal growth restriction, N=323,736)



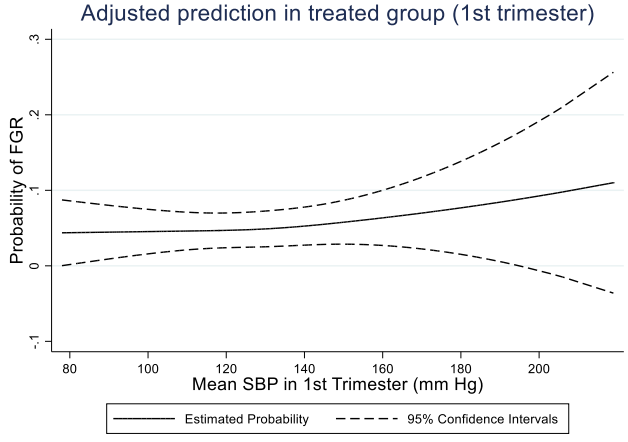


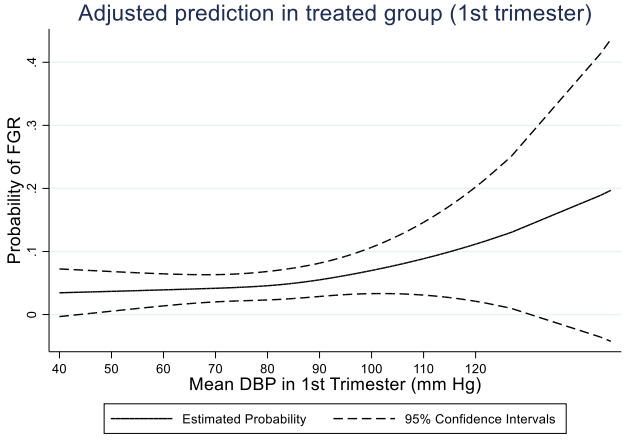
2. Relationship between BP level and fetal growth restriction restricted to pregnancies with chronic hypertension and on antihypertensive agent(s) during pregnancy, N=5,702)



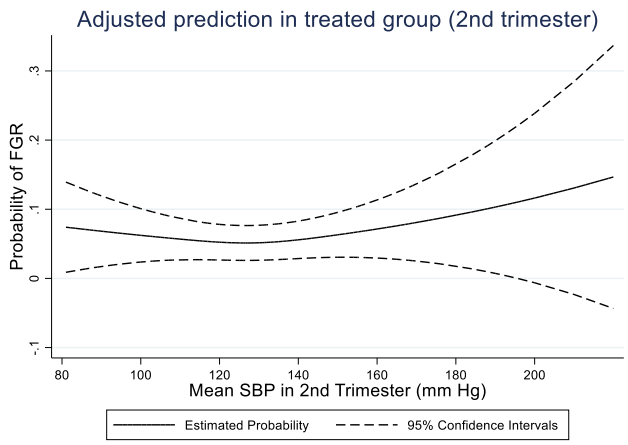


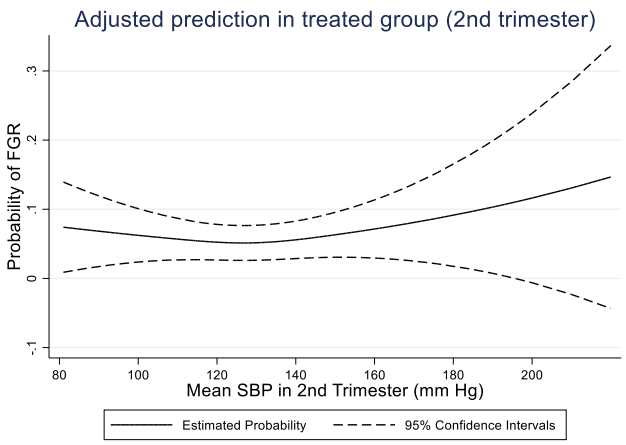
2.1. First trimester (relationship between BP level and fetal growth restriction in treated hypertensive group, N=3,270)



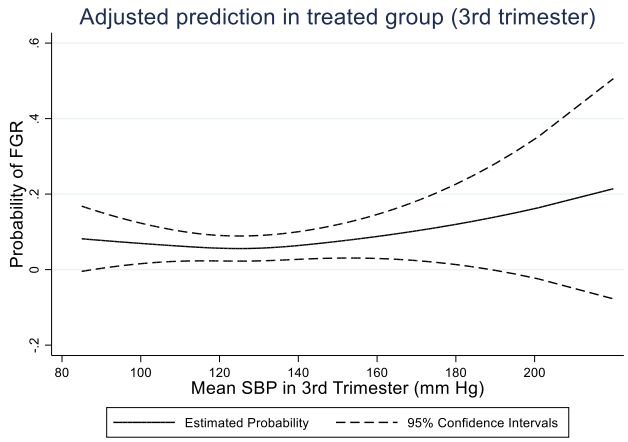


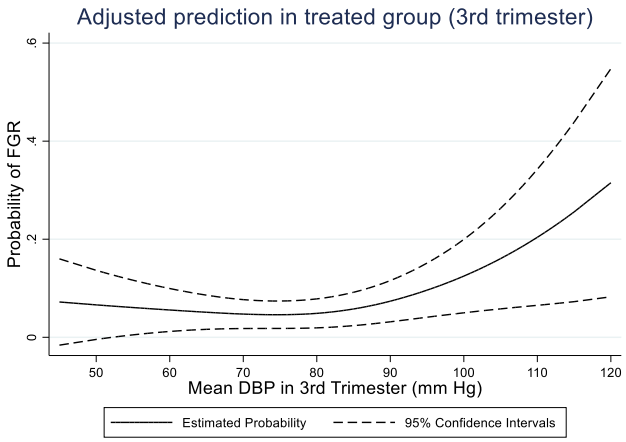
2.2. Second trimester (relationship between BP level and fetal growth restriction in treated hypertensive group, N=2,819)





2.3. Third trimester (relationship between BP level and fetal growth restriction in treated hypertensive group, N=2,491)





*Records with either unspecified hypertension, other hypertensive disorders during pregnancy or exposed to antihypertensive agent were excluded from these analyses. All models were generated using BP as spline variable (cubic spline with three knots) and were adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy diabetes and chronic kidney disease.

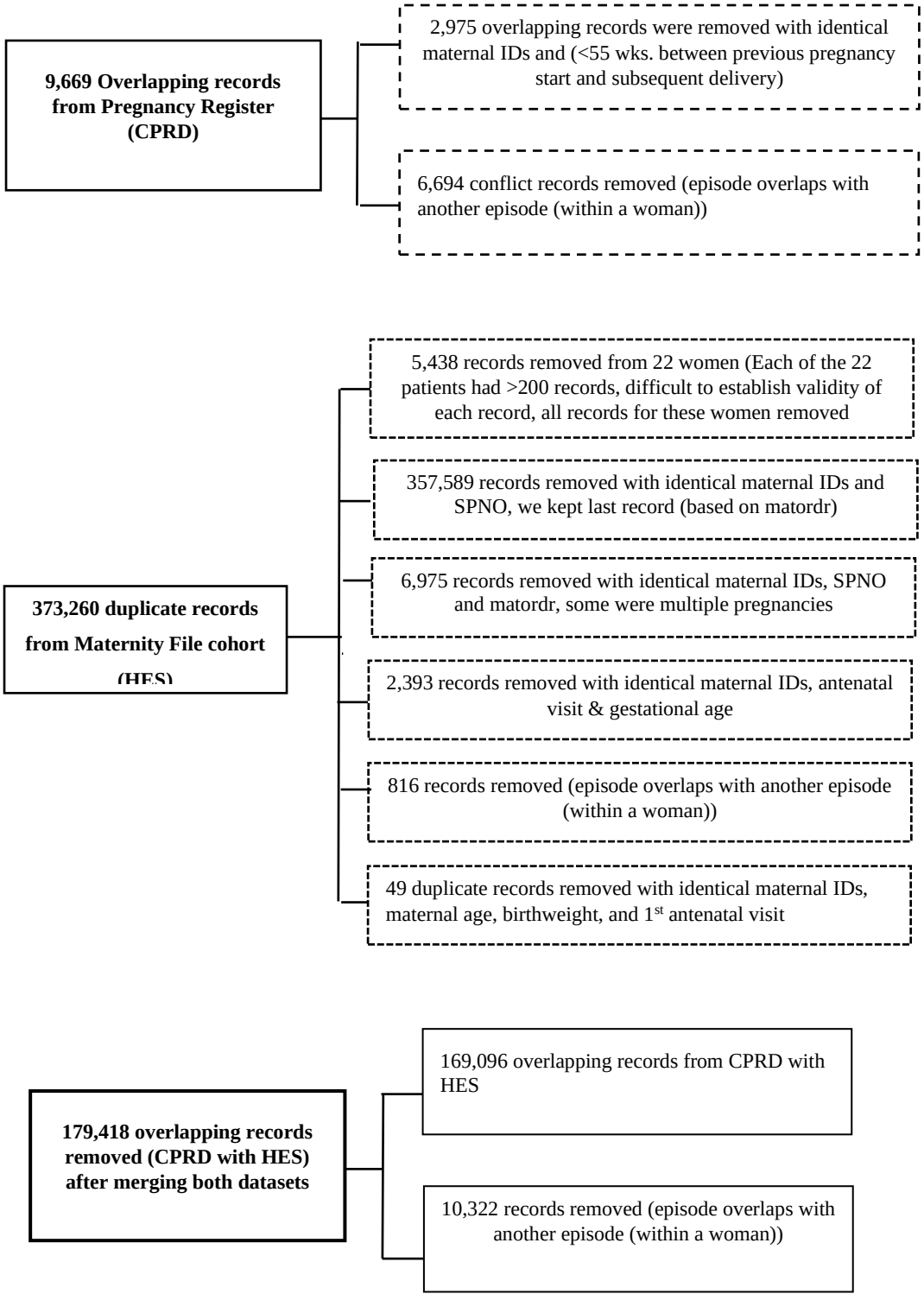
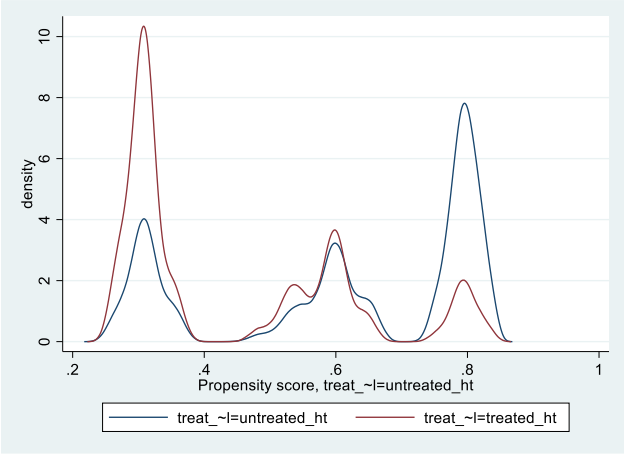


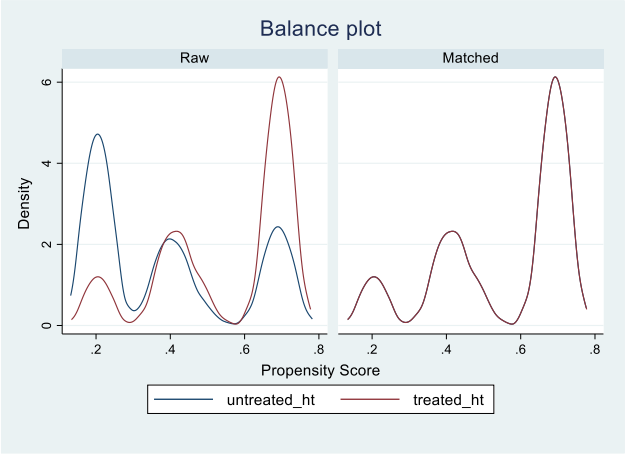
Figure S7. Dealing with duplicate/overlapping records

Diagnostic assessment for propensity score matching (treated vs. untreated)

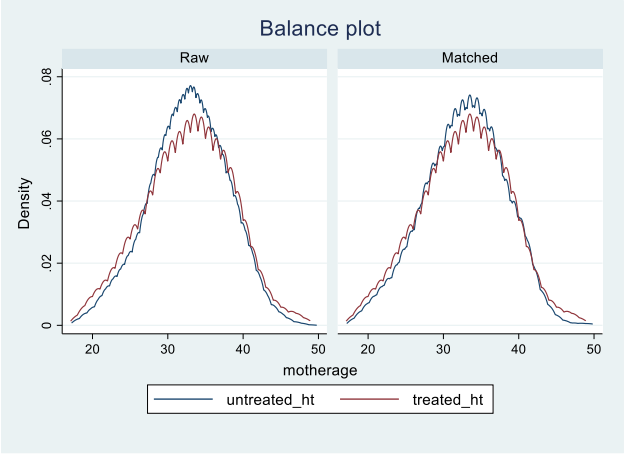
Number of obs =	14,558	13,532
Treated obs =	6,766	6,766
Control obs =	7,792	6,766

	Standardized differences		Variance ratio	
	Raw	Matched	Raw	Matched
smoking	-.8029749	-.0116006	1.002282	.990602
e2015_imd_10	.0049165	-.0044307	.9244505	.9499361
ethnic_hes	.0134123	.0593653	.9354637	1.125767
motherage	.0001151	-.0057676	1.24921	1.182
parity	-.1718425	.0170241	.8332076	.9953997
bmi	-.6833243	.0135876	.6674505	1.019405
diabetes	.0632263	.0462734	1.302721	1.208098





Mother age, continuous variable

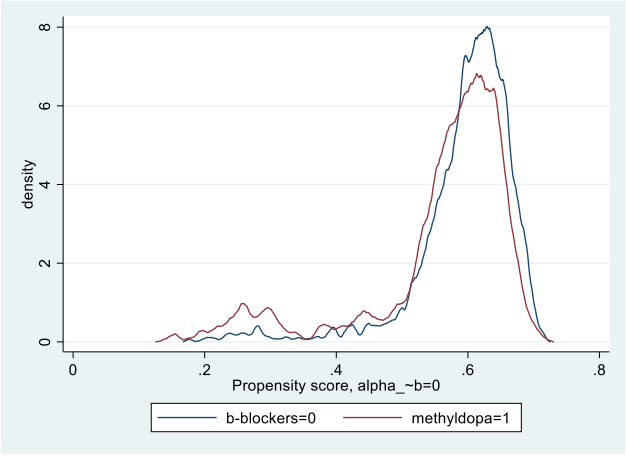


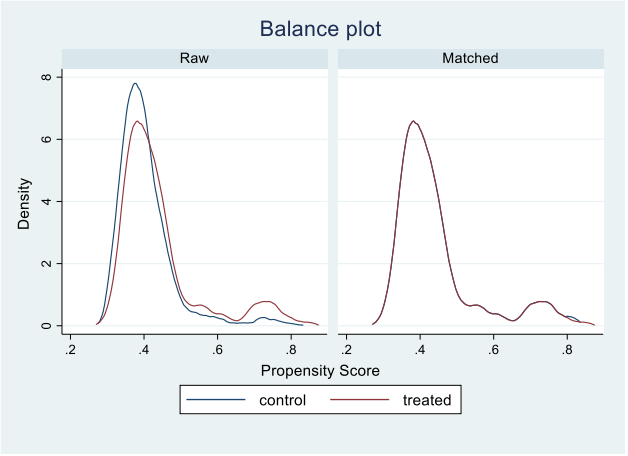
Diagnostic assessment for propensity score matching (methyldopa vs. β-blockers)

Covariate balance summary

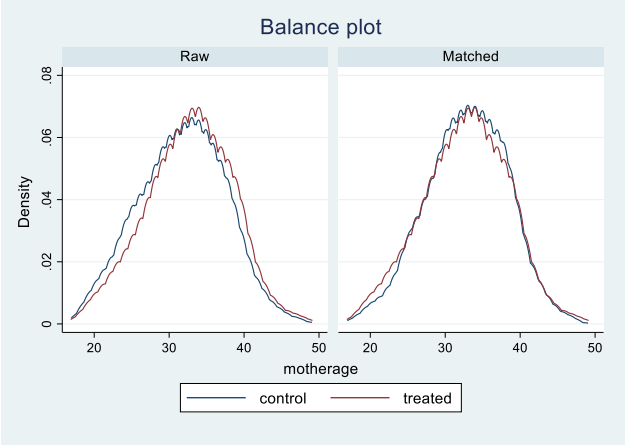
	Raw	Matched
Number of obs =	4,654	3,904
Treated obs =	1,952	1,952
Control obs =	2,702	1,952

	Standardized differences		Variance ratio	
	Raw	Matched	Raw	Matched
smoking	.0866368	-.0000748	1.069856	1.000107
e2015_imd_10	.0163308	.0132794	.9789923	.9807839
ethnic_hes	.1825681	.0203529	1.497676	.9962426
motherage	.166595	-.0371963	.980408	1.128888
parity	.0558617	-.0254832	.9566343	1.018725
bmi	-.0251983	.0308687	.964967	1.043757
diabetes	.2924059	.0072084	3.640849	1.021093





Mother age, continuous variable

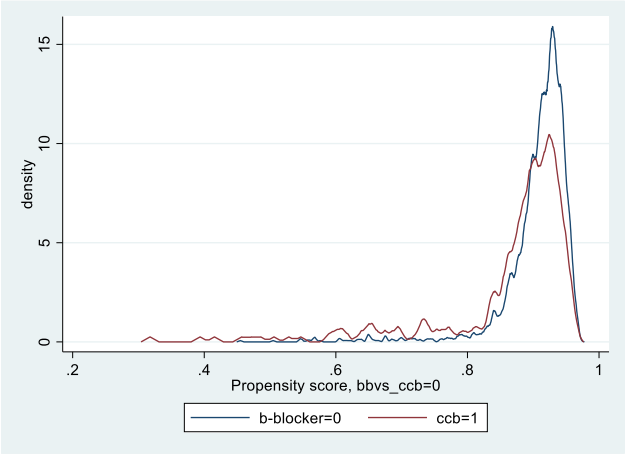


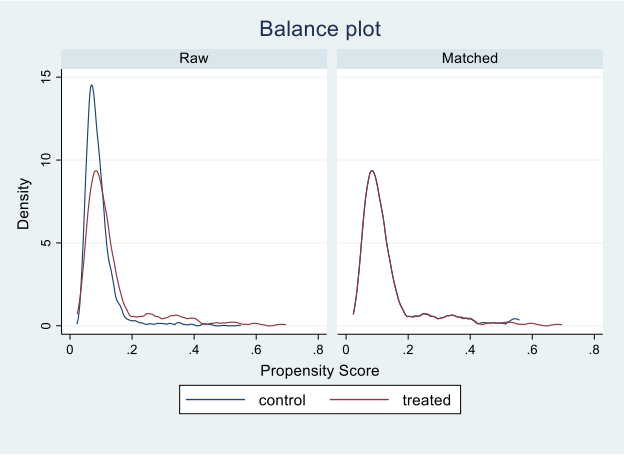
Diagnostic assessment for propensity score matching (calcium channel blockers vs. β-blockers)

Covariate balance summary

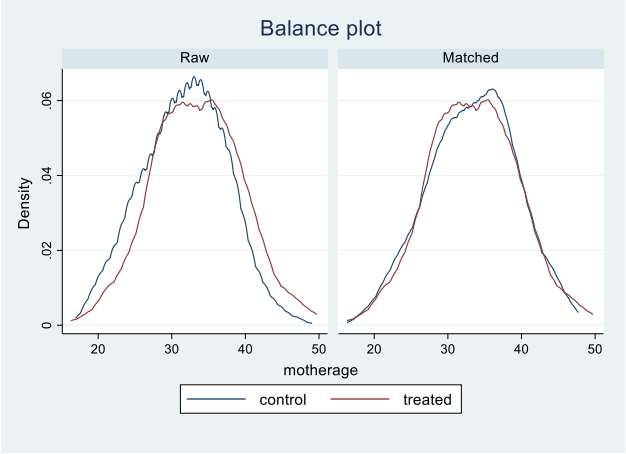
	Raw	Matched
Number of obs =	2,991	578
Treated obs =	289	289
Control obs =	2,702	289

	Standardized differences		Variance ratio	
	Raw	Matched	Raw	Matched
smoking	.1051499	.0809293	1.085994	1.060063
e2015_imd_10	.2037168	.0615079	.9326104	.9697613
ethnic_hes	.251726	.0286034	1.492381	.9446205
motherage	.2947889	.0158528	1.060711	1.02577
parity	.0363377	-.0719775	.9365495	1.018436
bmi	-.0951402	.0357488	.8728326	1.062151
diabetes	.3764114	-.0520101	4.644544	.8892308





Mother age, continuous variable

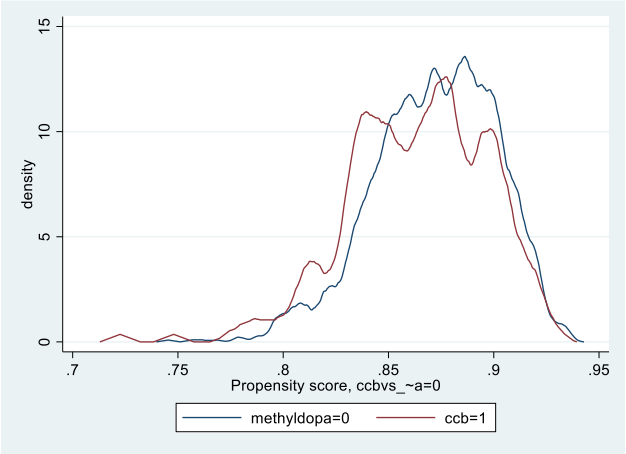


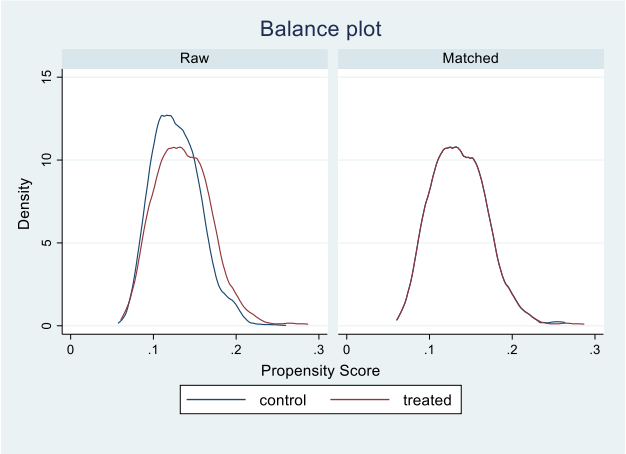
Diagnostic assessment for propensity score matching (calcium channel blockers vs. methyldopa)

Covariate balance summary

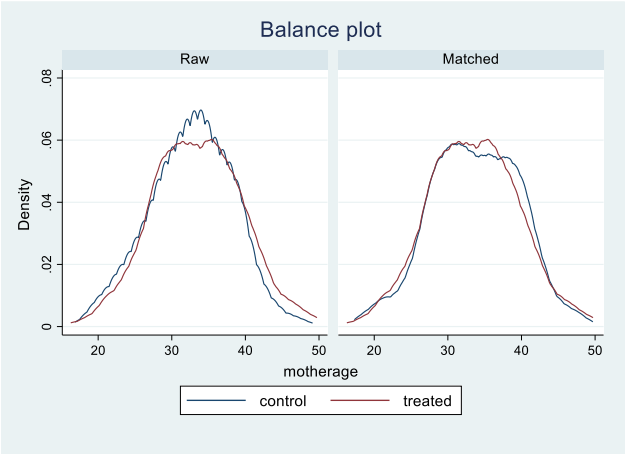
	Raw	Matched
Number of obs =	2,241	578
Treated obs =	289	289
Control obs =	1,952	289

	Standardized differences		Variance ratio	
	Raw	Matched	Raw	Matched
smoking	.018541	.014333	1.015084	1.009742
e2015_imd_10	.188217	.0418164	.9526228	1.006839
ethnic_hes	.0629638	.18925	.9964649	1.443102
motherage	.1321016	-.0387607	1.081907	1.026788
parity	-.0200386	-.0751836	.9790047	1.224783
bmi	-.0699873	.1309886	.9045207	1.274467
diabetes	.0918444	-.0520101	1.275676	.8892308





Mother age, continuous variable



Supplementary references:

1. Lunt M. Selecting an appropriate caliper can be essential for achieving good balance with propensity score matching. *American journal of epidemiology*. 2014;179:226-235.

2. Austin PC, Grootendorst P and Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Statistics in medicine*. 2007;26:734-753.

3. Garrido MM, Kelley AS, Paris J, Roza K, Meier DE, Morrison RS and Aldridge M. Methods for constructing and assessing propensity scores. *Health Serv Res*. 2014;49:1701-1720.