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Incidence of postpartum hypertension within 2 years of a pregnancy complicated by preeclampsia: a systematic review and meta-analysis.

Running title: Postpartum hypertension after preeclampsia

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ABSTRACT

Background: Women with a history of hypertensive disorders of pregnancy (HDP) are at increased long-term risk of cardiovascular disease. However, there has been increasing evidence on the same risks in the months following birth.

Objectives: This review aims to estimate the incidence of hypertension in the first two years after HDP.

Search Strategy: MEDLINE, EMBASE and Cochrane databases were systematically searched in October 2019.

Selection Criteria: Observational studies comparing hypertension rate following HDP and normotensive pregnancies up to two years.

Data Collection and Analysis: A meta-analysis to calculate the odds ratio (OR) with a 95% confidence interval (CI) and a sub-group analysis excluding women with chronic hypertension were performed.

Main Results: Hypertension was diagnosed within the first two years following pregnancy in 468/1646 (28.4%) and 584/6395 (9.1%) of the HDP and control groups, respectively (OR=6.28; 95% CI 4.18-9.43; I^2=56%). The risk of hypertension in HDP group was significantly higher in the first six months following delivery (OR=18.33; 95% CI 1.35-249.48; I^2=84%) than at six to twelve months (OR=4.36; 95% CI 2.81-6.76; I^2=56%) or between one to two years postpartum (OR 7.24; 95% CI 4.44-11.80; I^2=9%). A sub-group analysis demonstrated a similar increase in the risk of developing postpartum hypertension after HDP (OR 5.75; 95% CI 3.92–8.44; I^2=49%) and preeclampsia (OR=6.83; 95% CI 4.25-10.96; I^2=53%).

Conclusions: The augmented risk of hypertension after HDP is highest in the early postpartum period suggesting that diagnosis and targeted interventions to improve maternal cardiovascular health may need to be commenced in the immediate postpartum period.

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Keywords: preeclampsia, pregnancy and postpartum, hypertension, cardiovascular disease prevention, meta-analysis

Tweetable abstract

The risk of hypertension within two years of birth is six-fold higher in women who experienced preeclampsia.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) that include preeclampsia, eclampsia, HELLP syndrome and gestational hypertension affect about 10% of pregnancies and have a deleterious effect on future maternal cardiovascular outcomes. Women with a history of HDP have an increased risk of coronary artery disease, cerebrovascular disease, peripheral arterial disease, and cardiovascular-related mortality to such an extent that preeclampsia and gestational hypertension were included by the American Heart Association among major risk factors for cardiovascular disease[1-3]. The augmented risk of cardiovascular disease is mainly due to the fact that women develop essential hypertension in the years following an HDP index pregnancy[4, 5]. In addition, the risk of developing hypertension and other cardiovascular disorders is higher in women with recurrent HDP than those with a single episode of HDP[6, 7]. Therefore, early diagnosis and targeted intervention of hypertension may play a key role in improving future cardiovascular health in women with a previous pregnancy affected by HDP.

The risk of developing cardiovascular disorders after HDP has been mostly assessed by large cohort studies examined several decades after delivery. In one meta-analysis which included about 3 million women between 1960 and 2006, the estimated relative risk (95% confidence intervals) of hypertension after preeclampsia was 3.70 (2.70-5.05) after 14 years mean follow-up[8]. However, more recent evidence on the timing of hypertension following HDP pregnancy, has suggested that women may develop hypertension within months or few years after giving birth. A register-based cohort study on 1.5 million primiparas demonstrated that the rate of antihypertensive medication use within one year of a HDP pregnancy was higher compared to normotensive pregnancy (11% versus 0.5%, respectively)[4]. In a smaller prospective cohort study of 200 women one year after severe preeclampsia, 41.5% of women had hypertension presenting as either sustained hypertension (14.5%), masked hypertension (17.5%), or hypertension only in a clinical setting (9.5%) [9]. These observations are corroborated by the findings that asymptomatic moderate-severe cardiac dysfunction/hypertrophy was observed more frequently in preterm preeclampsia (56%) compared to term preeclampsia (14%) or matched controls (8%)[10].

Elucidating the temporal pattern and magnitude of hypertension after a pregnancy affected by HDP would help to design and deliver cardiovascular disease preventive

strategies after HDP. The aim of this study is to review and analyse the available literature reporting the incidence of hypertension in the first two years after HDP compared to uncomplicated pregnancy.

MATERIALS AND METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to a priori designed protocol recommended for systematic review and meta-analysis[11]. MEDLINE, EMBASE and Cochrane Library databases were searched electronically in October 2019, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "preeclampsia", "hypertensive disorders of pregnancy", "essential hypertension", and "postpartum period" (Appendix S1). The search and selection criteria were restricted to human studies. No time and language restrictions were applied. Conference abstract, case reports, letters and editorials were excluded. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA and MOOSE guideline were followed[12-14]. The study was registered with the PROSPERO database (Registration number: CRD42019149123).

Study selection, data collection and data items

The primary outcome was to assess the incidence of hypertension after pregnancies complicated by HDP that include preeclampsia, eclampsia, HELLP syndrome and gestational hypertension within two years postpartum. We included case-control and cohort studies that presented data on how many patients suffer from hypertension from six weeks up to two years postpartum. The whole time period was divided into three groups: up to six months, six months to one year, one year to two years. Hypertension was defined when systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg occurs more than one occasion in a clinical setting[15]. The use of antihypertensive medication and lower approved cut-offs to define hypertension were also included as diagnostic criteria[16]. When data were available, only cases affected by preeclampsia were considered in the analysis. We excluded studies where chronic hypertension defined as pre-existing the index pregnancy or developing before 20 weeks were not clearly defined. If a study included patients with chronic hypertension,

we considered only articles that provided the number of patients affected by chronic hypertension. Moreover, we did not include articles with incidence rate and cumulative incidence of postpartum hypertension after HDP beyond two years postpartum.

All abstract screening was performed independently by two researchers (VG, AR). Then, the full text of those potentially eligible studies was retrieved and independently assessed for eligibility by the two researchers (VG, AR). Any inconsistency and disagreement were discussed with a third reviewer (EK) and a consensus was reached. Few articles in language other than English were translated to decide whether they would be suitable or not for inclusion. A reviewer (VG) extracted data regarding study characteristics and outcomes, in particular author, year, location, study type, population size, inclusion criteria, exclusion criteria, reported outcomes, blood pressure assessment method and setting, hypertension definition and time of measurement. If more than one study was published for the same cohort with equal endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology showed that this information would have been recorded initially, the authors were contacted.

Patients were not involved in the development of this study and a core outcome set was not used.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies. According to NOS, each study was judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of outcome of interest or exposure. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at the start of study. Assessment of the comparability of the study includes the evaluation of the comparability of groups based on the design or analysis. Finally, while the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up, the ascertainment of the exposure includes the evaluation of the type of the assessment of the exposure for cases and controls and the non-response rates. According to NOS a study can be awarded a maximum of one

star for each numbered item within the Selection and Outcome/Exposure categories. A maximum of two stars can be given for Comparability[17].

The overall quality of evidence for the outcome was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) system that rates fields, namely, risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect, plausible confounding and dose response gradient in order to obtain different categories for the quality of a body of evidence (high, moderate, low, very low). This reflects the degree of confidence of how near our estimate of the effect lies to the true effect and the level of confidence decreases with decreasing quality[18, 19].

Statistical analysis

The risk of hypertension after HDP and uncomplicated pregnancy was calculated pooling respectively events and cases of all studies. The tables including raw outcome data were used to calculate the overall combined odds ratio (OR) with its 95% confidence interval (CI). In order to obtain a more precise risk estimate of postpartum hypertension in women with HDP during their pregnancy a meta-analysis was performed using a random effects model because of the high level of heterogeneity among the selected studies. The significance of the combined OR calculated using the Mantel-Haenszel statistical method was determined by the Z test and the p-value. A continuity correction technique was used to handle zero count cells in the tables. The variance between the studies was tested using the I^2 statistics. The I^2 index expresses the percentage of the total variation across studies that are due to heterogeneity. I^2 values of 25, 50 and 75% correspond to low, moderate and high heterogeneity, respectively. Meta-regression was carried out using mixed-effects model. Sub-analyses were planned for factors significantly contributing to the statistical heterogeneity. Since the number of included studies was adequate, the publication bias was explored with funnel plots asymmetry tests. Statistical analyses were performed using R for statistical computing software.

RESULTS

General characteristics

15 studies were included in the systematic review after assessing 223 articles in full-text with respect to their eligibility for inclusion from the 8407 articles identified through the

search (Figure 1, Table S1, Table S2)[10, 20-33]. Among these studies, 14/15 were cohort studies and 1/15 was a case-control. The total population sample size ranged from 28 to 5105 patients and follow-up from 2 to 24 months postpartum. Four studies included women with chronic hypertension pre-existing the index pregnancy[22, 23, 26, 30], and 3 out of 4 provided the outcome data without these cases[22, 23, 30]. In 11 studies the authors reported the technique of blood pressure measurement. In 4 out of 11, hypertension was diagnosed using a standard sphygmomanometer[10, 20, 25, 33], and in 7 out of 11 an automatic device was employed[21, 22, 24, 27, 28, 31, 32]. In addition, in one study the incidence of hypertension was self-reported by patients by using a standardized questionnaire[23]. The cut-off of SBP/DBP to define hypertension in an office setting was defined in 12 studies and it was 140/90 mmHg in 10/12 studies[10, 20, 22, 24, 25, 27, 28, 30-33], 130/80 in one study[25] and 120/80 in another study[21]. Table S2 showed that women with a history of HDP were more likely to have a higher body mass index than controls in 7 studies[10, 21, 22, 26, 29, 30, 33] (46.7%) and to be older than controls in 5 studies[21, 23, 26, 29, 33] (33.3%). The number of early-onset preeclampsia was reported by four papers[23, 26, 32, 33], whereas those of HDP that required delivery before 37 weeks were described in other four studies[10, 20, 24, 27].

Synthesis of the results

Overall, 1646 women with a history of HDP were compared to 6395 women with a previous uneventful pregnancy (Figure 2). The total number of women who developed hypertension in the first two years was 468/1646 (28.4%) and 584/6395 (9.1%) in the HDP and control group, respectively (OR=6.28; 95% CI 4.18-9.43; I^2=56%). The OR of postpartum hypertension in HDP group was 18.33 (95% CI 1.35-249.48; I^2=84%) in the period up to six months, 4.36 (95% CI 2.81-6.76; I^2=56%) in the period from six to one year and 7.24 (95% CI 4.44-11.80; I^2=9%) between one year and two years. Data on preeclampsia were reported by 13 studies and Figure S1 shows the comparisons of the postpartum incidence of hypertension between women affected by preeclampsia and controls. In the pooled analysis an increased risk of hypertension was observed for preeclampsia (OR=7.49; 95% CI 4.58-12.26). Heterogeneity among the studies was moderate (I^2 = 60%). The same trend of HDP has been observed in the different time periods up to two years (up to six months OR=57.08; 95% CI 11.00-296.07; six months to

one year OR=4.83; 95% CI 2.78-8.37; one year to 2 years OR=7.44; 95% CI 4.19-13.21). The heterogeneity was 0%, 58% and 20% in up to six months, six months to one year and one year to two years, respectively. In both meta-analyses, heterogeneity was explained to some extent (45.3% and 36.9%, respectively) by the incidence of chronic hypertension as showed by meta-regression (p= 0.034 and 0.092, for HDP and PE model, respectively). Therefore, a sub-group analysis excluding this population was conducted.

Sub-group analysis

14 studies were eligible to perform the subgroup analysis because they excluded women with pre-existing hypertension in calculating the outcome. Among them, data on preeclampsia were reported by 12 studies. Pooled results of studies excluding hypertension before the index pregnancy reported an overall OR of 5.75 (95% CI 3.92–8.44; I^2=49%) for the risk of developing postpartum hypertension in women with a history of HDP compared to women without (Figure 3). The OR is reported at 13.39 (95% CI 1.27-141.04; I^2=72%), 4.13 (95% CI 2.82-6.07; I^2=54%), 8.73 (95% CI 4.66-16.35; I^2=23%) in the period up to six months, between six months and one year and between one and two years, respectively. Considering only data on preeclampsia, women with a pregnancy complicated by preeclampsia were at a significantly increased risk of postpartum hypertension than women with normotensive pregnancy (OR=6.83, 95% CI 4.25-10.96; I^2=53%) with the following discrepancies among the different periods: up to six months OR=43.95 (95% CI 5.72-338.04; I^2=0%), six months to one year OR=4.46 (95% CI 2.76-7.21; I^2= 56%), one year to two years OR=8.91 (95% CI 4.33-18.33; I^2= 33%) (Figure S2).

Publication bias, study quality and quality of evidence

No evidence of publication bias has been detected in studies including women with pregnancies affected by HDP (p=0.890) or preeclampsia (p=0.666), as illustrated by funnel plots (Figures S3 and S4). The NOS quality scores were high among 5 of the 15 studies with a NOS score of 8 (Table S1). The mean±SD overall score for all 15 studies was 6.9±1.0. The quality of evidence, according to GRADE, was calculated for the incidence of hypertension after HDP and after preeclampsia. In the former analysis, it

was low for the results obtained up to six months and from six month to one year and it was moderate for the incidence of hypertension assessed between one to two years (Table S3). In the latter analysis, the quality of evidence was moderate in the first and in the last period and low between six months and one year (Table S4). The low/moderate quality of evidence was mainly because any study design other than randomized controlled trials carries a high risk of bias. The difference in the quality of evidence among different periods was due to the magnitude of association and the impact of the 'risk of bias' and/or 'inconsistency' parameters (Tables S3 and S4).

DISCUSSION

Main findings

The risk of developing hypertension within two years in women with a history of HDP is six-fold higher compared to women after normotensive pregnancy. A subgroup analysis of studies where pre-existing hypertension was excluded, revealed that there is a similar overall OR and trend for developing hypertension in the three postpartum periods analysed, with the risk being more than 10-fold in the first six months, 4-fold at six months to one year and 8-fold at one to two years.

Strengths and limitations

This systematic review enlightens the magnitude of the risk of developing hypertension within the first two years after delivery in women who experienced HDP in the index pregnancy by a comprehensive review and analysis of the current literature. We included study where HDP were precisely defined and where women with chronic hypertension were excluded or defined clearly. However, the current study has some limitations to be considered. First, the quality assessment of the studies showed that only five studies reached a score equal or more than 8. Furthermore, the quality of evidence is low or moderate according to GRADE, therefore, caution is needed when interpreting the results. For instance, only around one third of the studies reported a significantly higher maternal age in women with a history of HDP than in controls. This could be due to a selection bias of the control group, in particular in the smaller studies, and it might explain why the control group had a relative high risk of hypertension (9.1%).

Second, the risk of hypertension was highest in the immediate postpartum period (< six months), however, it might be due to an overestimation of the risk because of the paucity of studies in this time period or to a delayed resolution of pregnancy hypertension. However, Behrens et al.[4] also described the highest risk of developing hypertension in the year after delivery compared to the following years after excluding prescription of any antihypertensive drug that could be related to a treatment for HDP (i.e. use of antihypertensive from 20 weeks of gestation up to three months postpartum). Another aspect to be addressed regarding the immediate postpartum is when the follow-up should be started after delivery. We included studies reporting outcomes past six weeks postpartum, but we acknowledge that literature regarding the time when preeclampsia resolves is unclear. Guidelines reported 6 weeks or three months as the point where normalization of blood pressure after preeclampsia would be expected[34, 35]. Thus, current evidence from published literature is not enough to define the best screening period in the postpartum to detect hypertension. Third, heterogeneity in population and in hypertension definition in addition to the failure of obtaining sufficient details could make results of the meta-analysis misleading and impossible to be adjusted by using statistical tests.

Interpretation

This review quantifies the risk of hypertension in the immediate postpartum period after a pregnancy complicated by HDP, highlighting the importance of early diagnosis and intervention for hypertension in this period. These results are consistent with growing evidence on the association between HDP and cardiovascular diseases, but prior research and meta-analysis were focused on the long-term consequences rather than those soon after delivery[8, 36]. The results of studies with more immediate cardiovascular follow-up after delivery (and the current meta-analysis) provide more reliable data on the development of cardiovascular diseases after delivery. The Nurses' Health Study II demonstrated that women who reported a first pregnancy affected by HDP presented higher rates of hypertension (HR 2.8; 95% CI 2.6-3.0), type 2 diabetes mellitus (HR 1.7; 95% CI 1.4-1.9), and hypercholesterolemia (HR 1.4; 95% CI 1.3-1.5) within five years postpartum[37]. A recent prospective observational cohort that followed 4484 women for mean 3.2 years after their first pregnancy showed that women with any hypertensive

disorder of pregnancy had higher adjusted risk of hypertension at follow-up compared with controls (RR 2.7; 95% CI 2.0-3.6)[38]. Moreover, a register-based study showed that women with HDP had twice the risk of cardiovascular readmissions (acute myocardial infarction, stroke or heart failure) within three years compared to normal pregnancies[39]. One case-control study (n=142) demonstrated an elevated risk of hypertension at two years following delivery for women with preeclampsia[10]. Lastly, a large Danish register-based cohort study with a ten-year follow-up revealed that rates of persistent hypertension were 12-fold to 25-fold higher in the first year after delivery and 4-fold to 10-fold higher between one and five years in women with a hypertensive disorder of pregnancy than in women with a normotensive pregnancy[4].

The temporal shift from decades to early postpartum years in maternal cardiovascular care highlights the need to bridge the gap between obstetric care and adult preventive medicine[40]. First of all, an awareness campaign about the significance of a history of pregnancy complications should be focused on family practitioners and cardiovascular specialists. Secondly, given the earlier risk of developing hypertension in women after HDP, serial blood pressure monitoring should be scheduled in the first months to years following birth. It would appear useful to evaluate blood pressure measurements at 8-12 weeks postpartum and again within two years of the index HDP pregnancy. If hypertension is diagnosed, lifestyle changes, medical therapy and standard follow-up should be highly encouraged (Figure 4). To support such proposals, a prospective blood pressure screening trial should be conducted to understand the optimal regimen for monitoring blood pressure after previous HDP.

This systematic review shows that there is a paucity of research in the first months after delivery compared to the following years. This research should be focused on developing effective screening, follow-up and targeted intervention strategies for women after preeclampsia despite presenting a unique opportunity for early intervention. In particular, no research has investigated how to identify subjects at increased risk of cardiovascular diseases among women with HDP or preeclampsia in the peripartum period. Some cardiac functional abnormalities, such as diastolic dysfunction, left ventricular remodeling and reduced left ventricular contractility in the peripartum period might be unique markers in order to identify women at higher risk of future cardiovascular diseases.

Conclusion

This systematic review defines the risk of developing hypertension in the first two years after a hypertensive pregnancy and highlights the window of opportunity for cardiovascular prevention in women with a diagnosis of hypertension after delivery.

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DISCLOSURE OF INTERESTS

None. Completed disclosure of interest forms are available to view online as supporting information.

CONTRIBUTION TO AUTHORSHIP

VG screened abstracts, selected eligible papers, extracted data and wrote the first draft of the paper; AR screened abstracts and selected eligible papers; EK performed the statistical analysis and helped in the final selection of papers in case of disagreement; AK reviewed the manuscript critically; BT designed the study and performed revisions to the manuscript.

DETAILS OF ETHICS APPROVAL

Not applicable.

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FIGURE LEGENDS

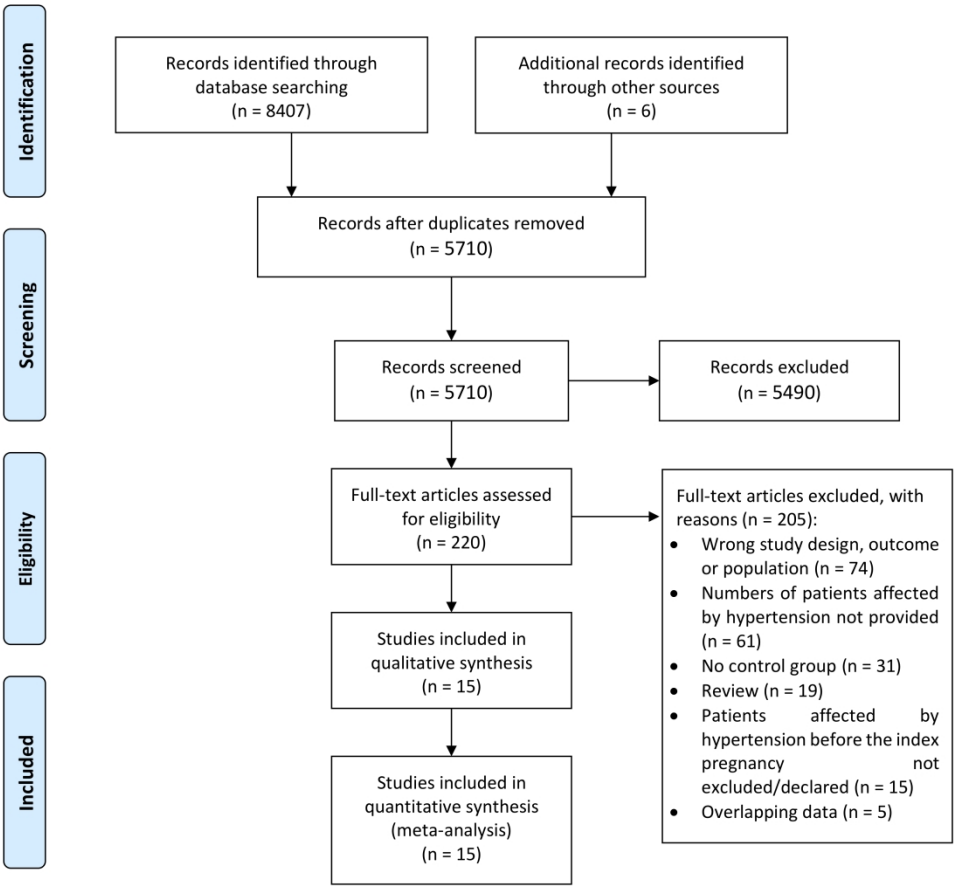
Figure 1. PRISMA Flow Diagram

Figure 2. The incidence of hypertension after hypertensive disorders of pregnancy (HDP) up to two years postpartum

Figure 3. The incidence of hypertension after hypertensive disorders of pregnancy (HDP) up to two years postpartum (excluding cases with chronic hypertension).

Figure 4. Flow-chart for cardiovascular system evaluation after hypertensive disorders of pregnancy.

HDP hypertensive disorders of pregnancy, BP blood pressure, CVS cardiovascular system, HT hypertension, ACC/AHA American College of Cardiology/American Heart Association



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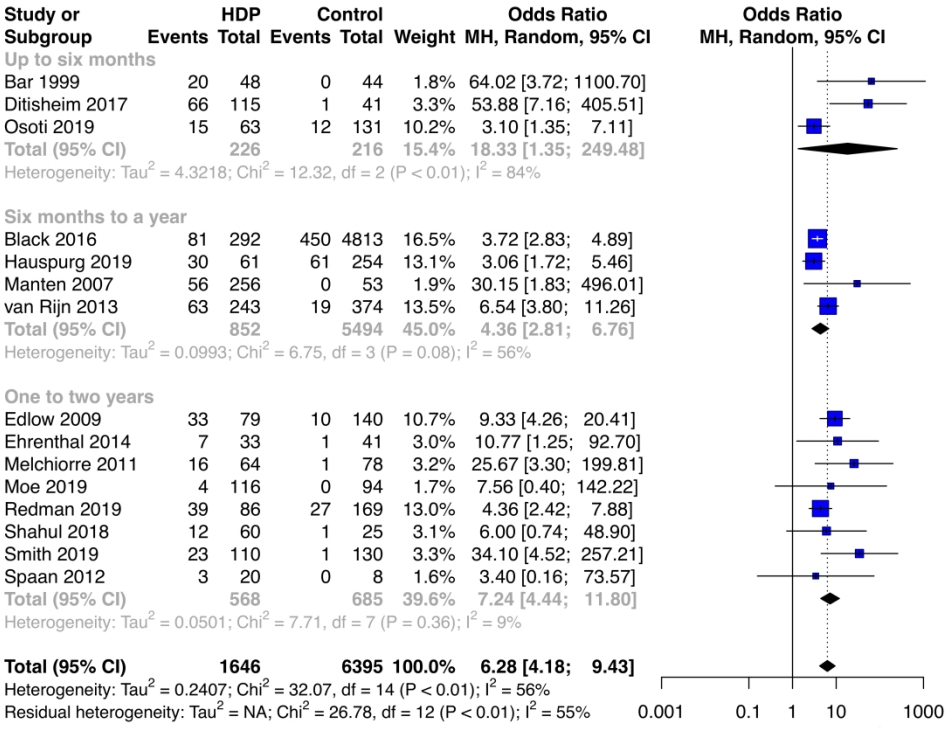

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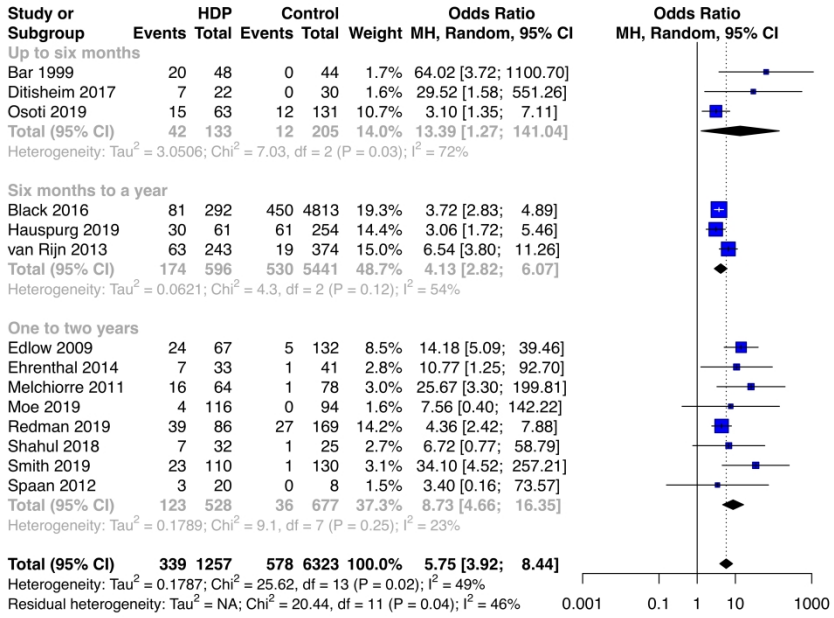

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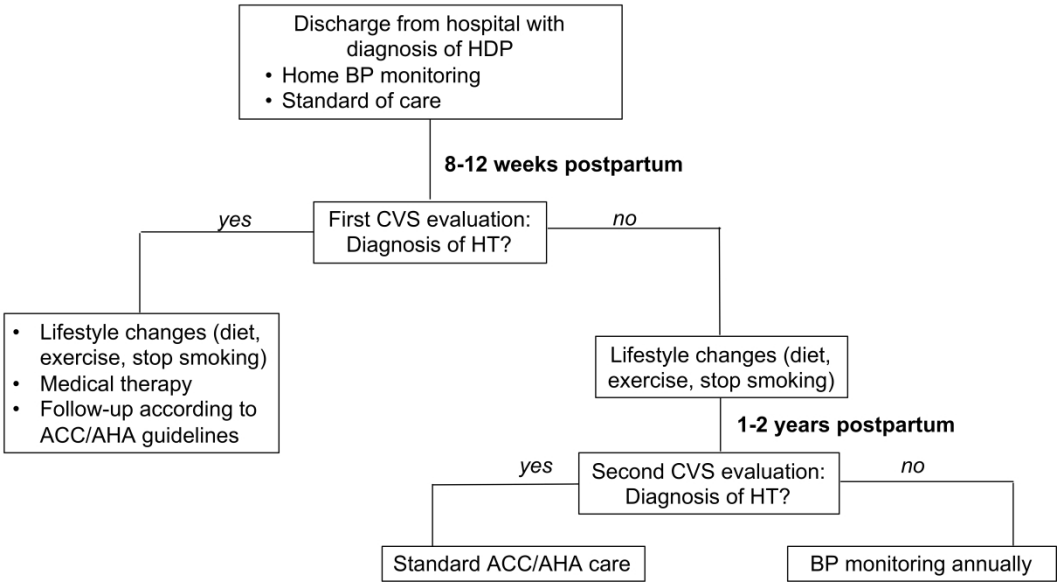

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