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Preventing cardiovascular disease after hypertensive disorders of pregnancy: Searching for the how and when

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Abstract

Background: Women with a history of a hypertensive disorder during pregnancy (HDP) have an increased risk of cardiovascular events. Guidelines recommend assessment of cardiovascular risk factors in these women later in life, but provide limited advice on how this follow-up should be organized.

Design: Systematic review and meta-regression analysis.

Methods: The aim of our study was to provide an overview of existing knowledge on the changes over time in three major modifiable components of cardiovascular risk assessment after HDP: blood pressure, glucose homeostasis and lipid levels. Data from 44 studies and up to 6904 women with a history of a HDP were compared with risk factor levels reported for women of corresponding age in the National Health And Nutrition Examination Survey, Estudio Epidemiólogico de la Insuficiencia Renal en España and Hong Kong cohorts ($N = 27{,}803$).

Results: Compared with the reference cohort, women with a HDP presented with higher mean blood pressure. Hypertension was present in a higher rate among women with a previous HDP from 15 years postpartum onwards. At 15 years postpartum (±age 45), one in five women with a history of a HDP suffer from hypertension. No differences in glucose homeostasis parameters or lipid levels were observed.

Conclusions: Based on our analysis, it is not possible to point out a time point to commence screening for cardiovascular risk factors in women after a HDP. We recommend redirection of future research towards the development of a stepwise approach identifying the women with the highest cardiovascular risk.

Keywords

Pregnancy, pre-eclampsia, hypertension, pregnancy-induced, hypertension, cardiovascular diseases, preventive medicine

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Introduction

Large cohort studies have consistently demonstrated an increased risk – up to seven-fold – of cardiovascular disease (CVD) later in life in women with a history of hypertensive disorders of pregnancy (HDPs) compared with women with uncomplicated pregnancies.[1,2] Manifestation of CVD occurs earlier in HDPs: approximately 6–8 years before controls.[1,2] Consensus on which mechanisms contribute to this increased risk has not been established. Current opinion is that HDP and CVD share common risk factors, including sympathetic driven hypertension, insulin resistance, inflammation and obesity.[1,3] Also pregnancy itself has been proven to enlarge future CVD risk: parity was

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independently associated in a J-shaped fashion, with two births representing the lowest risk.[4,5]

Pregnancy induces an extensive adaptation of the circulatory system, including major cardiac output and renal glomerular changes. Pregnancy may unmask limited cardiovascular reserves resulting in HDP and thus pregnancy complicated by HDP can be considered as a failed cardiovascular stress test.[6] Therefore, positive history of HDP may allow for early identification of women at risk of CVD and provide opportunities for prevention and intervention.[7]

The last three decades, there is an increasing imperative for primary CVD prevention in women.[8] Unfortunately, guidelines still fail to provide a uniform recommendation on risk stratification based on sex specific risk factors, such as HDP and subtypes.[4] The American Colleges of Obstetrics and Gynaecologists' Task Force on Hypertension in Pregnancy emphasizes the opportunity that early identification of a group of young women at risk offers for prevention, but appoints solely women with preterm pre-eclampsia or recurrent pre-eclampsia to be eligible for screening, whereas other guidelines do not discriminate between HDP phenotypes.[9–12] All guidelines suggest evaluation of blood pressure after HDP, although their recommendation regarding the commencement and the time interval of screening differs.[9–13] The recently published Dutch multidisciplinary guideline suggests optimization of modifiable cardiovascular risk factors to reduce risk of future CVD. The recommendation to screen at age 50 was obtained by consensus between the different participating disciplines rather than based on evidence.

Identification of deviating risk factor patterns is required to find a window of opportunity for screening and possibly allows for the creation of preventative programmes to reverse the increased risk of CVD. Established risk factors for CVD as adopted by the American Heart Association and the European Society of Cardiology risk assessment tools are age, sex, blood pressure, diabetes, lipid level, smoking, family history, impaired renal function, physical inactivity and body weight.[11,14] Existing evidence on the development of these risk factors in HDPs lacks longer follow-up. Only few studies reported on the fourth and fifth decade of life, the time frame in which the first clinical signs of cardiovascular disease is expected.[7]

We aim to provide an insight into the risk profile development of women who experienced HDP by performing a systematic review and meta-regression analysis on the course of blood pressure, fasting glucose and homeostasis model assessment of insulin resistance (HOMA-IR) as parameters for glucose metabolism and high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) in HDPs compared with a reference cohort.

Methods

Data sources and searches

A systematic literature search in PubMed, Embase and The Cochrane Library was conducted. No filters were used, nor restrictions on publication year. Relevant synonyms for [*history of hypertensive disorders of pregnancy*] and [*risk factor*$^{\#}$] ($^{\#}$blood pressure OR glucose OR insulin OR HOMA-IR OR HDL-C OR LDL-C) were combined. After title and abstract screening by TKJG, remaining articles were screened on full text. Screening was performed based on the article's content meeting our inclusion criteria. The reference lists of selected articles, related reviews and meta-analyses were manually searched for additional eligible articles. Detailed search strategies are described in supplement 1 in the Supplementary Material online.

Eligibility criteria

We included prospective and retrospective cohort studies assessing women of any parity or age or with a history of a HDP. A cohort study was defined as a study that identified HDP as determinant and reported on selected risk factors as outcome. The relevance and validity of the studies was assessed using the Newcastle–Ottawa Scale[15] with some additions according to the evidence-based medicine guidelines as stated by Scholten et al.[16] (Supplementary Material supplement 2 – critical appraisal table and legend). Relevance of the study findings for applicability involved evaluation of the study population and reported outcomes (the prementioned risk factors). Studies in women with pre-existing cardiovascular comorbidities – such as pre-existent hypertension, renal failure and cardiac disease – prior to the index pregnancy were excluded from the analysis. Also studies conducted in women with previous early pre-eclampsia were excluded, for the pathophysiological mechanisms including vascular remodelling and risk factors associated with this type of HDP are thought to be different and thus the course to later CVD might be too.[17,18] Classification of the validity of the studies consisted of the evaluation of: selective inclusion, standardization of HDP and outcome and completeness of data, respectively loss to follow-up and missing data. Minimally, HDP status assessment was conducted through clinical and laboratory diagnostics. Assessment of HDP status based on recall through a questionnaire was considered of insufficient reliability. We also excluded articles that reported on only prevalence of the risk factor (e.g. hypertension, diabetes) rather that mean values for the derivative measurement (blood pressure, fasting glucose). Due to differences in the definition of the risk factors, these were considered

too heterogenic to incorporate into a reliable meta-analysis. Each relevance and validity criterion was classified with a two or three point scoring system. Only articles of sufficient methodological quality were included in the meta-analysis.

Statistical analysis

Studies were divided into groups based on years of follow-up from index pregnancy. Per category weighted mean values ($\chi w = \sum(\chi i * pi)$) and standard deviations (variance $\sigma^2 = \sum pi(\chi i - \chi w)^2$; standard deviation $\sigma = \sqrt{\text{variance}}$) were calculated. Given weighted means and standard deviations, number of participants with values above treatment thresholds could be calculated using Excel normal distribution formulas.[19]

Per risk factor, weighted mean values of women with a history of HDP were compared with reference cohorts. Blood pressure data were compared with the data of the Third National Health And Nutrition Examination Survey (NHANES III; 1988–1994), which consisted of 15.326 female US natives of 18–74 years old.[20] Officially, the definition of hypertension contains both a systolic (140 mmHg) and diastolic (90 mmHg) threshold. However, since we rely on reported cohort means, we were unable to extract individual data to see if patients would meet either of these criteria. As cardiovascular risk scores such as SCORE and SMART have their risk estimation based on systolic pressure we decided to define hypertension based on the systolic blood pressure only.[11,21]

The weighted mean fasting glucose values of all cases calculated as described above are compared with 11,148 women, citizens of Hong Kong.[22] Age category specific weighted mean fasting insulin and glucose were used to calculate homeostasis model assessment of insulin resistance (HOMA-IR), if not already reported by the selected articles. The ATP III (Third Adult Treatment Panel) age specific HOMA-IR values for non-diabetic women were used as reference, as these were reported most sensitive and specific in the EPIRCE study ($N = 1329$).[23] The data from the 1994–2002 NHANES cohort were used as control cohort for HDL-C and LDL-C levels data based on 4549 female adults of 20 years and older.[24]

Results

Study selection

The systematic search (supplement 1, Supplementary Material) yielded 8709 unique studies. Figure 1 shows the articles retrieved from the searches, reviewed and included in the analysis. After selection based on title

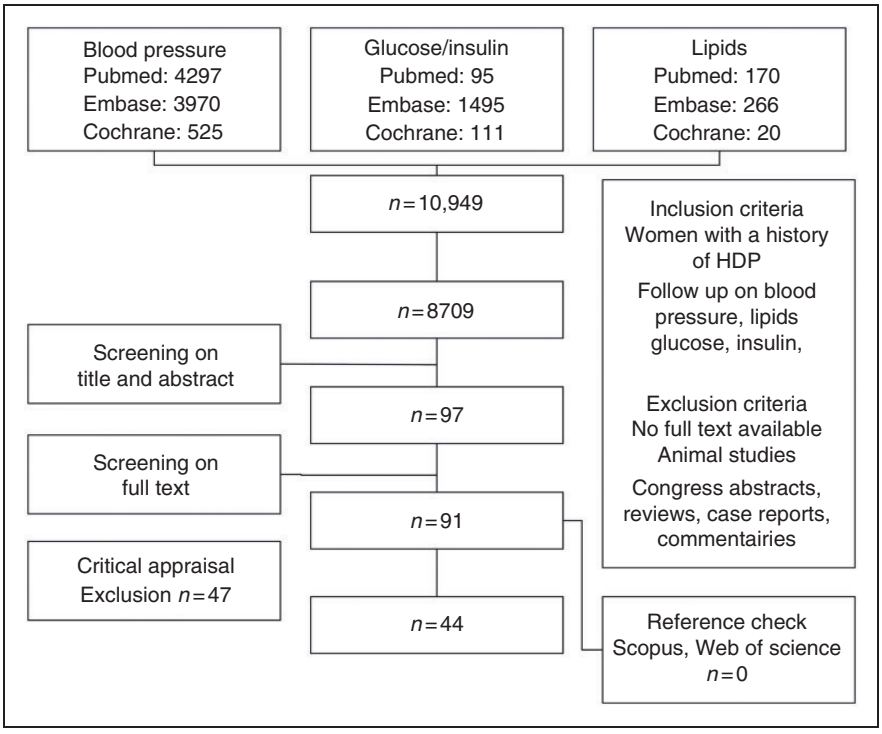

Figure 1. Flowchart (last search 20 October 2015).
HDP: hypertensive disorder during pregnancy

and abstract and subsequent full-text screening, 91 articles were considered potentially eligible for answering our question. Thirteen articles were excluded based on determinant discrepancies[25–37] (supplement 2 – critical appraisal Table 1). Four studies were at risk for selection bias.[38–41] The eligible outcomes were missing or reported with incompatible stratification in seven studies.[42–49] Three studies used a questionnaire to establish previous HDP, which was thought to be of insufficient reliability.[37,50,51] Fifteen articles were excluded from analysis for they reported only prevalences of hypertension, diabetes or dyslipidaemia and not mean values.[52–67] Last, two studies reported too large proportion of loss to follow-up.[68,69] When two manuscripts were published on the same cohort, the oldest was excluded.[70–72]

Study characteristics

Table 2a in supplement 3 lists the characteristics of the 36 studies reporting on blood pressure. The majority of the studies report on women with a history of pre-eclampsia.[35,72–96] Sample sizes differ from 26[79] to 3225[88] participants. In total the analysis was performed with 36 studies, consisting of 6904 HDPs.[35,65,72–95,97–107] Only two studies reported on women over the age of 55 years.[80,96] All studies report on non-recurrent complications of pregnancy. If reported, phenotype of HDP is specified: pre-eclampsia, pregnancy induced hypertension (PIH) or both (HDP).

Baseline characteristics of the studies on fasting glucose, fasting insulin, HOMA-IR, HDL-C and LDL-C are displayed in Tables 2b and 2c (supplement 3).

Blood pressure

HDPs had an overall higher mean blood pressure (Figure 2(a)) compared with controls.[35,65,72–95,97–107] The large standard deviation in follow-up categories 15–20 years and 40–45 years post-partum can be explained by the small sample sizes, for both categories consist of only two studies.[65]

From 15 years after the index pregnancy onwards, HDPs show hypertension at a higher rate compared with reference populations. At 15 year follow-up, which is approximately at age 45, one in five (+/− 20%) of HDPs suffer from hypertension versus 17.6% in the NHANES cohort ($p < 0.0001$; estimated

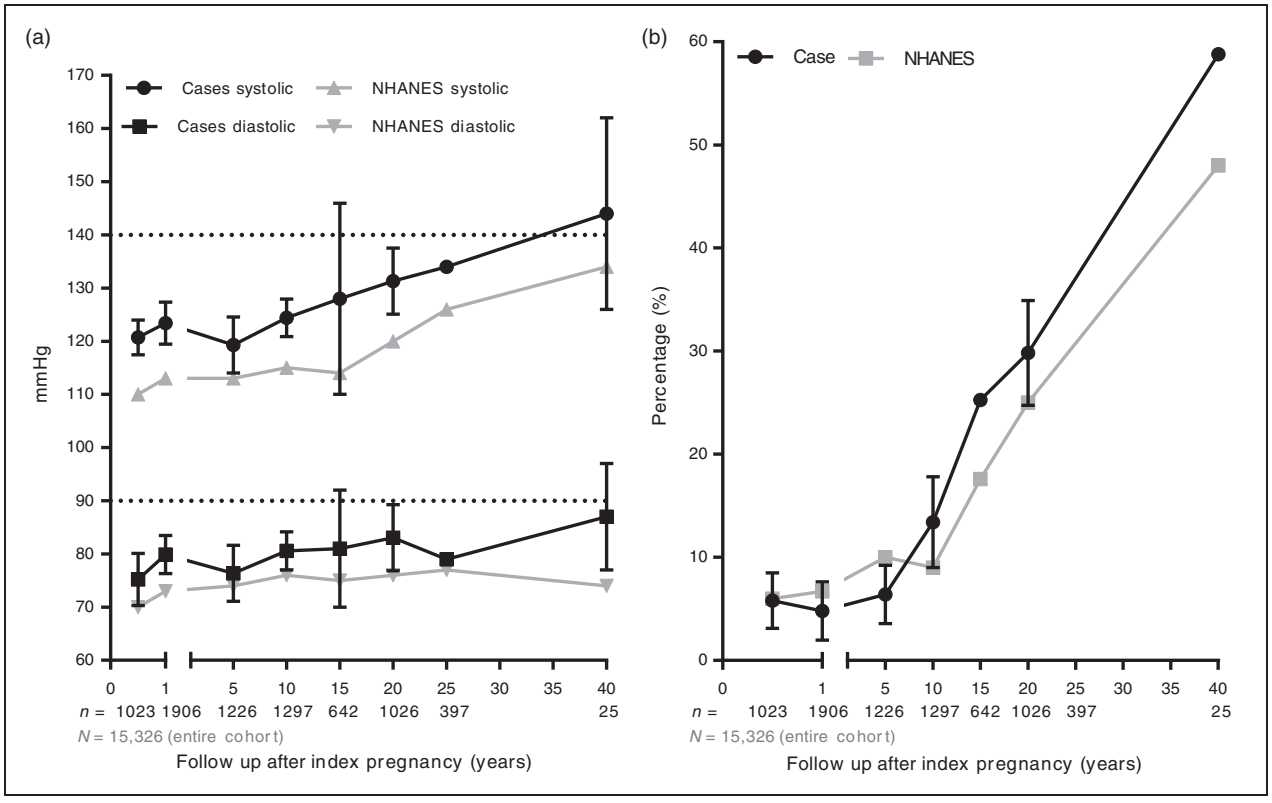

Figure 2. (a) Weighted mean blood pressure. (b) Prevalence of hypertension. Sample sizes are shown below the x-axis. Ranges or standard deviations are missing in the plots, since these are not reported in the NHANES manuscript.
NHANES: National Health And Nutrition Examination Survey

with the standard deviation of our analysis applied to NHANES for NHANES did not report on standard deviations). This is illustrated in Figure 2(b), which displays the calculated percentages of hypertension, derived from the raw data on mean values and deviations per follow-up category. The NHANES III cohort is used as reference, displaying values from the age corresponding to the mean age per follow-up category.[20]

Glucose metabolism and lipids

A total of 22 studies in 3032 post-HDP women reporting on glucose homeostasis metabolites were included in the analysis. Sixteen studies reported on post-pre-eclampsia women, four on multiple phenotypes of HDP and two combined all phenotypes into the category HDP. Sample sizes varied from 13[108] to 698[109] women with previous HDP. Only Haukkamaa et al.[80] and Collén et al.[96] reported on fasting glucose and insulin after the age of 50.

Figure 3(a) and (b) displays mean fasting glucose and HOMA-IR over follow-up time after index pregnancy.[35,73,80,81,83,84,89,94–96,98,99,102,103,107–115] In the analysis of the course of fasting glucose development over time, no difference between HDPs and controls can be detected. The control cohort for the fasting glucose is formed by 11,148 Chinese women from the Hong Kong cohort of Ko et al.[22] The age specific thresholds according to ATP III as calculated in the EPIRCE trial were used to compare with HOMA-IR data in the HDPs.[116]

In all 24 studies combined, 5304 former HDP women contributed to the analysis on lipid spectrum. Weighted mean values for HDL-C and LDL-C are displayed in Figure 3(c) and (d).[35,71,72,74,80,81,84,89,91,95,99–103,106–111,113,114,117–119] The large standard deviation for mean HDL-C in the

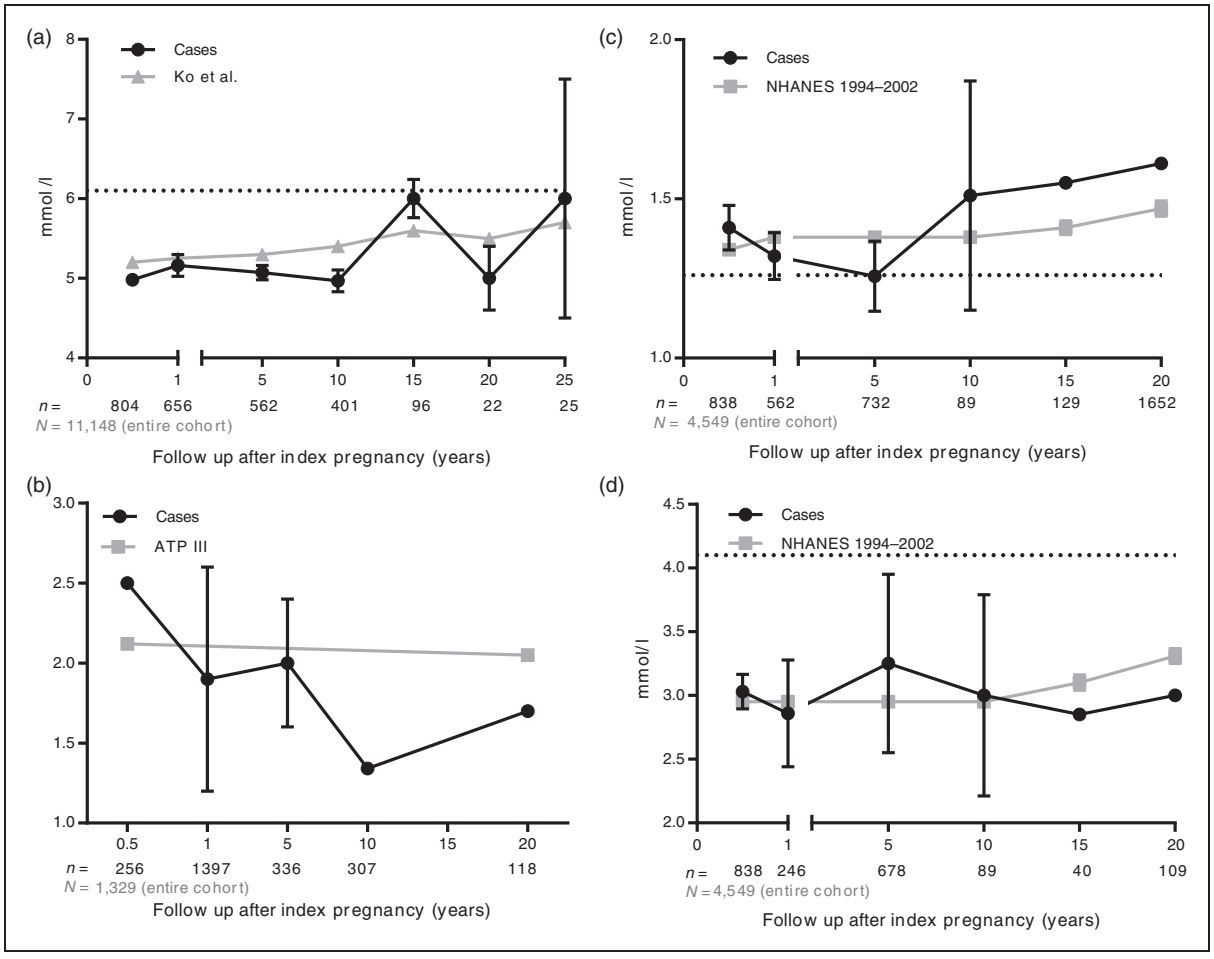

Figure 3. (a) Weighted mean fasting glucose. (b) Homeostasis model assessment of insulin resistance. (c) Weighted mean high-density lipoprotein cholesterol. (d) Weighted mean low-density lipoprotein cholesterol. Sample sizes are shown below the x-axis. NHANES: National Health And Nutrition Examination Survey; ATP III: Third Adult Treatment Panel

10-year post-partum group is because this category yields only one study.[89]

Discussion

This meta-regression analysis shows that HDPs have an overall higher blood pressure during post-partum follow-up. Furthermore, HDPs develop hypertension at a faster pace compared with the reference cohort, reporting on 20% hypertension in HDPs at 15 years post-partum (approximately age 45).[20] In current practice, women with a history of HDP are discharged from the obstetrics department without a strategy for cardiovascular follow-up although the increased risk of future CVD is evident.[120] Current guidelines are not uniform in their advice on screening and treatment in women with a history of HDP.[9-13] These data do not show a specific time-frame for screening. A stepwise approach in screening starting at a young age seems to be the most appropriate strategy. Possibly also other risk factors then the classical cardiovascular factors could be of value in this high risk female population.

First we show an overall higher blood pressure without increase in difference over time after HDP. Second, our analysis on blood pressure and subsequently calculated hypertension rates shows hypertension prevalence from 5% up to 59% at 40 year follow-up after index pregnancy. Interestingly, when looking at hypertension rates until 10 years post-partum the NHANES cohort shows higher rates.[20] This could be due to a variable number of factors: medication use, pooling of data, non-pregnant subjects (including infertile women). Growing evidence suggests that female infertility is associated with increased cardiovascular risk.[121]

As explained, we excluded studies that reported on hypertension only, because of differences in definition. These excluded studies report hypertension rates of 10–65%.[35,65,72,73,77–81,84,88,89,93,96,98,99,112,114,122,123] The difference between reported prevalence of hypertension is striking; it could imply that our result underestimates the number of women with hypertension after a HDP. Also, prevalence in the excluded studies might have been subject to publication bias. The results presented on glucose homeostasis parameters did not show any difference in course of development when comparing post-HDP women with the general population. Feig et al. did find a two-fold increased risk of developing diabetes when followed up to 16.5 years after pregnancy complicated by HDP.[56] Our analysis is possibly restricted by sample size in higher age categories, reporting on measurements in only 22–26 participants. Furthermore, the discrepancy might be explained by confounding variables, in particular, obesity, which in itself is associated with insulin resistance, and is a well-known risk factor of HDP and hypertension.[124] HOMA-IR development shows a decline in the first year post-partum, possibly indicating a remission period after physiological insulin resistance during pregnancy.[125] The World Health Organization global report on diabetes shows prevalence of diabetes in Asia to be 8.7% versus 7.3% in Europe.[126] Our meta-regression analysis involves 26 studies from Europe, two from Asia, 10 from the Americas and three from the Western Pacific. The risk of glucose homeostasis disturbances in the pooled population of our analysis possibly is more towards the European average. Comparing this with the Hong Kong cohort might thus have underestimated the difference between HDPs and the 'general' population.

Regarding lipid levels, small studies conducted pre-pregnancy and shortly post-partum reported unfavourable alterations in lipid spectrum in HDPs compared with controls.[31,81,84,127] However, in larger cohort studies with longer follow-up, this difference resolves.[64] Finally, in our analysis, with a mean follow-up of eight years (range 0.1–23 years) the course of HDL-C and LDL-C over time did not deviate in HDPs compared with reference cohorts. Dyslipidaemia rates among all female residents are 52% in Europe and 48% in the Americas, resulting in an overestimation of our analysis. But of the 23 studies on lipids in our analysis, eight were of Dutch origin, with an average prevalence 22.4% of dyslipidaemia in the female population.[128]

The interpretation of our findings is hindered by a few limitations. The studies included in our analysis mostly report on pre-eclampsia. Hypertension in pregnancy is present in approximately 10% of pregnancy; pre-eclampsia in 2–8% of pregnancy.[129] It is thought that the severity of the event resembles the amount of cardiovascular distress and consecutive risk of CVD later in life.[130] By pooling all studies, containing different phenotypes of HDP assessed at different moments in time, we might have overestimated the real effect of HDP. Separate analysis of the HDP phenotypes (early onset pre-eclampsia, late onset pre-eclampsia, pregnancy induced hypertension) resulted in insufficient sample size for meta-analysis. Therefore, we chose to merge the results into one group of post-HDP women. Meta-regression does not allow correction for confounding (including difference in body mass index, age, race, smoking, family history). Methodological limitations, embedded in the nature of a meta-regression analysis, including publication bias, have to be taken into consideration.

The consensus for screening in the HDP population is inconsistent. The evidence presented in this paper and other meta-analyses is consistent in terms of blood pressure, showing increased hypertension risk from

the age of 45 years onwards. The absolute risk for a cardiovascular event remains low because these are age driven and our population of interest is young. It is understandable that screening strategies are so diverse since this absolute risk is leading in screening implementation.[131] Second, treatment strategy is not well investigated. Furthermore, it is unclear who is the highest risk (PIH versus pre-eclampsia, early versus late onset, with and without premature birth and foetal growth restriction). We question whether future research should not be redirected towards the development of a stepwise screening programme taking all different mechanisms (classical risk factors, HDP phenotype, genetics, etc.) into account. Combined with lifestyle behaviour and family history of CVD, risk stratification and consecutive treatment (non-pharmacological and pharmacological) targets and follow-up can be established. Since the absolute risk is so low, the first appropriate step would be lifestyle intervention.[132–134]

Perspectives

In conclusion, this systematic review and meta-regression analysis confirmed an altered onset and development of hypertension in women with a history of HDP as compared with women without these pregnancy complications. We could not identify an optimal time frame for screening. Interestingly, guidelines published in the last six years have made different recommendations. We could not perform sub analysis on HDP phenotype. Phenotyping and other (non-)classical and/or stepwise CVD risk factor screening and, possibly, incorporating more mechanistic research could be the future direction to improve CVD health in this high risk female population.

Author contribution

TKJG, BBR, JERL, MLB and ATL contributed to the conception or design of the work. TKJG performed searches and article selections. TKJG, BBR, AF, JERL, MLB and ATL contributed to the analysis and/or interpretation of data for the work. TKJG drafted the manuscript. BBR, AF, JERL, MLB and ATL critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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