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Hypertensive disorders of pregnancy and cardiometabolic outcomes in childhood: A systematic review

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Abstract

Background: Hypertensive disorders of pregnancy (HDPs) are among the leading causes of maternal and perinatal morbidity and mortality worldwide and have been suggested to increase long-term cardiovascular disease risk in the offspring.

Objective: The objective of this study was to investigate whether HDPs are associated with cardiometabolic markers in childhood.

Search strategy: PubMed, The Cochrane Library and reference lists of included studies up to January 2019.

Selection criteria: Studies comparing cardiometabolic markers in 2–18-year-old children of mothers with HDP in utero, to children of mothers without HDP.

Data collection and analysis: Sixteen studies reported in 25 publications were included in this systematic review, of which three were considered as having high risk of bias. Thus 13 studies were included in the evidence synthesis: respectively two and eight reported pregnancy induced hypertension and preeclampsia, and three studies reported on both HDPs.

Main results: Most studies ($n = 4/5$) found a higher blood pressure in children exposed to pregnancy induced hypertension. Most studies ($n = 7/10$) found no statistically significantly higher blood pressure in children exposed to preeclampsia. No association was found between exposure to HDP and levels of cholesterol, triglycerides or glucose ($n = 5/5$). No studies investigated an association with (carotid) intima-media thickness, glycated haemoglobin or diabetes mellitus type 2.

Conclusions: Most studies showed that exposure to pregnancy induced hypertension is associated with a higher offspring blood pressure. There is no convincing evidence for an association between exposure to preeclampsia and blood pressure in childhood. Based on current evidence, exposure to HDP is not associated with blood levels of cholesterol, triglycerides and glucose in childhood.

Keywords

Hypertension, pregnancy-induced, pre-eclampsia, eclampsia, HELLP Syndrome, child, cardiovascular diseases, blood pressure, blood glucose, cholesterol, triglycerides

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Introduction

Hypertensive disorders of pregnancy (HDPs) affect circa 10% of pregnancies.[1] Both in lower–middle and in high income countries, the incidence of HDPs has increased throughout the last decades.[2–6] HDPs are among the leading causes of maternal and perinatal morbidity and mortality worldwide.[7] Exposure to

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HDP has been suggested to increase long-term cardiovascular disease (CVD) risk in the offspring.

A previous systematic review by Davis et al. reported that children of mothers with preeclampsia had increased blood pressure (BP).[8] Pregnancy induced hypertension (PIH) was not addressed in the review, but there are indications that PIH is also associated with BP in childhood.[9–11] The consistency of evidence has not been assessed systematically so far. Depending on the HDP phenotype, different pathophysiological pathways are involved in the development and clinical course of the disease[12] and hence associations with cardiometabolic health in the offspring may be different as well.

We hypothesized that intra-uterine mechanisms underlie a possible association between HDP and cardiometabolic markers in childhood. HDP would affect the development of organs and vascular structures in the foetus, thereby programming the child towards adverse cardiometabolic health.[13] Besides intra-uterine mechanisms, certain factors which lead to HDP as well as to adverse cardiometabolic outcomes in the offspring may explain an association between HDP and cardiometabolic health in childhood. For instance, a woman's predisposition to develop high BP may be inherited by her child, and HDP is merely an early reflection of this predisposition.[14,15] Also, shared environment and lifestyle on the one hand may lead to the development of HDP and on the other hand may increase the risk of adverse cardiometabolic outcomes in the offspring.

We performed a systematic review to investigate whether in utero exposure to HDP – preeclampsia but also PIH, eclampsia and Haemolysis Elevated Liver enzymes and Low Platelets (HELLP) syndrome – is associated with adverse levels of cardiometabolic markers (BP, (carotid) intima-media thickness, cholesterol, triglycerides, fasting glucose, glycated haemoglobin (HbA1c), risk of diabetes mellitus type 2) in children up to 18 years of age.

Methods

Search strategy

This systematic review is reported in accordance with the recommendations as stated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Supplementary Material S.1 online).[16] On 13 March 2017 electronic searches were performed in PubMed using the search fields of title/abstract in combination with MEdical Subject Headings (MESH), and in The Cochrane Library. The search was updated on 15 January 2019. The search strategy was developed in collaboration with an information specialist at our department and is described in the Supplementary Material (S.2). Two authors (LPMP and MACJ) independently screened studies based on title, followed by independent screening of abstracts and full-text articles. An abstract and full-text screening form was used to ensure systematic screening (Supplementary S.3). Disagreements in the study selection process were discussed and in the case of no consensus being reached, a third author was consulted (LvR). References of included studies and previous systematic reviews were manually screened to identify studies that were not found in PubMed.

This review is aimed at reviewing the evidence for an association of HDP with cardiometabolic outcomes in childhood. Since this review is part of a project that also aims to systematically review the evidence for an association of gestational diabetes mellitus with cardiometabolic outcomes in childhood, the search strategy was designed to include both pregnancy conditions.

Inclusion and exclusion criteria

The inclusion and exclusion criteria are summarized in Supplementary Material S.4. Studies were included if they compared cardiometabolic outcomes in 2–18 year old children of a mother with diagnosed HDP with children of a mother without HDP. Diagnosed HDPs were (as defined by the International Society for the Study of Hypertension in Pregnancy at the start of this review[1]): PIH, preeclampsia, eclampsia and HELLP syndrome. PIH was defined as systolic BP (SBP) $\geq$ 140 mmHg or diastolic BP (DBP) $\geq$ 90 mmHg without proteinuria that occurs after 20 weeks of gestation in a woman with previously normal BP. Preeclampsia was defined as PIH with proteinuria ($\geq$0.3 g protein in a 24-h urine specimen). Eclampsia was defined as preeclampsia with grand mal seizures. HELLP syndrome was defined as severe preeclampsia with haemolysis, elevated liver enzymes and low platelet counts.[1] We excluded infants of mothers with pre-existing hypertension since we aimed to investigate the effects of pregnancy complications as such. We hypothesized that hypertensive disorders developed during pregnancy stimulate intra-uterine mechanisms that affect the development of organs and vascular structures in the foetus, thereby programming the child towards adverse cardiometabolic health. Cardiometabolic outcomes of interest were: SBP and DBP, (carotid) intima-media thickness, serum cholesterol, triglycerides, fasting glucose, HbA1c and diabetes mellitus type 2. We excluded studies with self-reported outcomes, outcome diabetes mellitus type 1, and non-original studies such as expert views, editorials or comments. All studies were published in peer-reviewed journals in the English language, and performed in human participants.

Data extraction and critical appraisal

Data of included studies were extracted by two authors (LPMP and MACJ) using a structured data collection form (Supplementary Material S.5), including the key characteristics of the studies' design and population, exposure, outcome measure(s), as well as measures of association between exposure and outcome. A third author (HAS) checked the data extraction for accuracy.

The methodological quality of each included study was assessed by one author (MACJ) and checked by another author (LPMP), using the Newcastle–Ottawa Quality Assessment Scale for cohort studies.[17] The scale consists of three categories for which a study can be awarded a maximum of two to four stars: selection (four stars), comparability (two stars) and outcome (three stars). More stars reflect better quality and thus lower risk of bias. Since the scale does not provide thresholds for the number of stars to identify studies with a high risk of bias, we defined our own criteria based on the results of the critical appraisal (Supplementary Material S.6). Studies were rated as having a high risk of bias when selection of exposed and non-exposed was not adequately reported or when loss to follow-up was high (>60%) and no reasons for this high loss were reported.

Evidence synthesis

Studies that were perceived as having a high risk of bias were excluded from evidence synthesis. Per HDP, the evidence was reviewed for each outcome separately. For continuous outcome measures, we compared mean levels between exposed and unexposed children, and if able to we compared regression coefficients with 95% confidence intervals (CIs) and/or *p*-values for the observed differences. Consideration was given to whether results varied between sexes and in the presence of confounding or mediating factors.

When multiple publications originated from the same study, we reported all those publications in the evidence synthesis section if these contained any novel result. In the case of duplicate results from one study, we reported only the publication with the most comprehensive data in the evidence synthesis section and reported the results of the overlapping publication(s) in the tables only.

Results

Study overview

A total of 8981 articles were identified, of which we assessed 127 full texts for eligibility (Figure 1). Twenty-four publications satisfied the eligibility criteria and were selected for data extraction and consecutively critical appraisal and synthesis. One publication was additionally identified after screening reference lists of included studies and previous systematic reviews. This study was not found with our search strategy because either the exposure or the outcome was not explicitly studied and hence no related MESH terms have been assigned to this publication.

With our search update in 2019, we identified 431 additional articles, of which three papers fulfilled full text assessment. However, none of these articles satisfied the eligibility criteria.

Thus in total, 25 publications were included in this systematic review.[9,10,18–40] These 25 publications originated from 16 population based studies. Eleven studies had one publication and five studies had multiple publications. The results of the included studies were reviewed per study instead of per publication.

Characteristics of the included studies

The characteristics of the 16 included studies are described in Table 1. Three studies included children of mothers with PIH, nine studies included children of mothers with preeclampsia and four studies reported on both HDPs separately. None of the studies investigated the association of eclampsia or HELLP syndrome with one of the outcomes of interest. Regarding the definition of PIH, there were no differences in BP threshold (BP $\geq$ 140 mmHg; DBP $\geq$ 90 mmHg, in absence of proteinuria), but in one study PIH could be defined at any time during pregnancy[9] while in other studies women had to be at least 20 weeks pregnant. Regarding preeclampsia, there were no differences in BP threshold (BP $\geq$ 140 mmHg; DBP $\geq$ 90 mmHg), nor in proteinuria threshold ($\geq$300 mg/24 h) between studies. One study in which preeclampsia was grouped into mild, moderate and severe preeclampsia defined hypertension by an increase in DBP only[30] (Supplementary Table S.7).

Fifteen studies were prospective cohort studies and one study was a cross-sectional study. Studies were performed in European countries, the USA, Australia, Argentina, Bolivia and Israel. The children of mothers with and without HDP were born between 1969 and 2004 and were mainly recruited from the general population or from hospitals. Cardiometabolic outcome measures were: SBP ($n = 15$ studies), DBP ($n = 12$ studies), serum cholesterol ($n = 6$ studies), triglycerides ($n = 5$ studies) and glucose ($n = 6$ studies). Measurement methods of the outcome measures were comparable (Supplementary Material S.8). None of the studies investigated the association of HDP with the other outcomes of interest in this review, that is, (carotid) intima-media thickness, HbA1c and diabetes mellitus type 2.

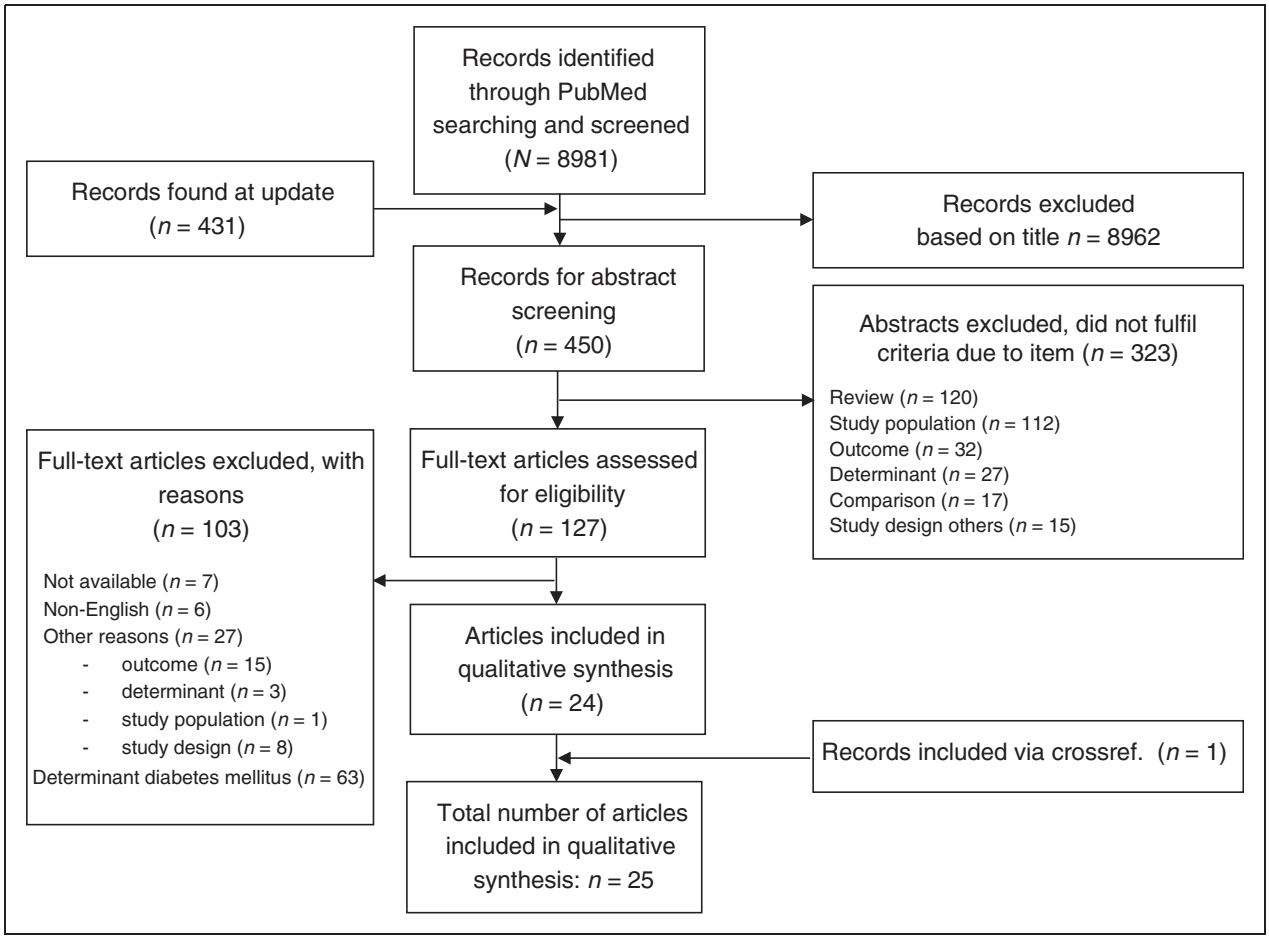

Figure 1. Flowchart of study selection.

Risk of bias assessment

Based on our predefined criteria, we identified three studies (one with preeclampsia and PIH, one with only PIH and one with only preeclampsia as the determinant) with a high risk of selection and information bias: the publications from the Hypertension in Pregnancy Offspring Study[9,21–23] and the studies by Lazdam et al.[27] and Hiller et al.[35] These studies were excluded from the evidence synthesis. Results of these studies are shown in Supplementary Material S.9 and S.10. Thus, evidence synthesis was performed for 13 studies (two with PIH, eight with preeclampsia and three studies reported on both hypertensive disorders separately) reported in 19 publications.

Evidence synthesis

Pregnancy induced hypertension

Associations with offspring blood pressure. BP was reported as an outcome in five studies (Table 2). Four of these five studies observed a higher BP in children of mothers with PIH than in children of mothers without PIH.[10,18,36–40] The study by Kotchen et al.[18] observed a 4.5 mmHg higher SBP and no different DBP at 3–6 years in PIH-exposed children. At 6–8 years, results were stratified for sex; PIH-exposed boys had a 4.8 mmHg higher SBP and no different DBP from unexposed boys, while PIH-exposed girls had no different BP from unexposed girls.[19] Belfort et al.[36] observed a 3.5 mmHg higher SBP at 6.5 years, and Miettola et al.[40] observed a 2.5% higher SBP and a 3.3% higher DBP at 16 years in PIH-exposed versus unexposed children. In the ALSPAC study, PIH-exposed children had a higher BP than unexposed children, with a mean difference in respectively SBP and DBP that remained similar during childhood: 1.98 and 0.97 mmHg at seven years,[37] 2.04 and 1.07 mmHg at nine years[38] 2.04 and 1.10 mmHg at 10–11 years,[10] and 2.06 and 1.11 mmHg at 17 years.[39] These associations were not mediated by birth weight, gestational age, method of delivery, or breastfeeding. One study[20] observed no association between exposure to PIH and SBP at 5–8 years of age. Thus, most studies observed a higher BP in children who were exposed to PIH.

Table 1. Characteristics of the 25 included publications originating from 16 population studies.

Study number	Reference number	First author	Year of publication	Study design	Location (name of study)	Recruitment period: year of birth	Source population Children from pregnant women recruited from…	Eligible population Children from mothers with and without HDP who were supposed to participate *n* (no. exposed/ unexposed)	Population for analysis: *N* (no. exposed/ unexposed)	Outcome	Age at outcome measurement	Child confounders	Maternal confounders
Hypertensive disorders: pregnancy induced hypertension													
1	18	Kotchen[a]	1979	PC	Lexington, Kentucky, USA	1971–1974	Hospital ($N = 409$; n exposed=74/ n unexposed=335) (46% White and 54% Black)	129 (74/random sample of 55 out of 335)	100 (53/47)	SBP and DBP	3–6 years	–	–
	19	Kotchen[a]	1982	Idem	Idem	Idem	Idem	Idem	112 (62/50) 107 (59/48)	Idem	3–6 and 6–9 years	–	–
2	20	Bergel	2000	PC	Rosario, Argentina	1987–1990	Prenatal clinics ($n = 614$)	614 (not reported)	518 (not reported)	SBP	5–9 years	Sex, age, height, BMI at outcome measurement, treatment status (calcium *vs.* placebo)	–
3	21	Svensson[a,b]	1986	PC	Göteborg, Sweden (Hypertension in Pregnancy Offspring Study)	1969–1973	General population ($n = 17{,}000$ pregnancies)	521 (261/260)[e]	54 (39/15)[f]	SBP and DBP	10–15 years[g]	–	–
	22	Himmelmann[a,b]	1993	Idem	Idem	Idem	Idem	Idem	59 (42/17)[f]	Idem	10.6–16.4 years	Sex, birth weight, age, weight, height, heart rate at outcome measurement	–
	9	Himmelmann[a,b]	1994	Idem	Idem	Idem	Idem	Idem	Idem	Idem	10.6–16.4 years and 18.2 years	Idem	–
	23	Himmelmann[a,b]	1997	Idem	Idem	Idem	Idem	Idem	Idem	Idem and glucose at follow-up	10.6–16.4 years and 18.2 years	Idem	–
Hypertensive disorders: preeclampsia													
4	24	Kvehaugen[a]	2010	PC	Ullevål, Oslo, Norway (CHASE Study)	2001–2004	Hospital ($n = 149$)	149 (not reported)	40 (23/17)	SBP and DBP	5–8 years	–	–

(continued)

Table 1. Continued

Study number	Reference number	First author	Year of publication	Study design	Location (name of study)	Recruitment period: year of birth	Source population Children from pregnant women recruited from…	Eligible population Children from mothers with and without HDP who were supposed to participate *n* (no. exposed/ unexposed)	Population for analysis: *N* (no. exposed/ unexposed)	Outcome	Age at outcome measurement	Child confounders	Maternal confounders
	25	Kvehaugen[a]	2011	Idem	Idem	Idem	Idem	149 (not reported)	34 (20/14)	SBP, DBP, triglycerides, cholesterol (total, HDL, LDL)	Idem	–	–
5	26	Palti	1989	PC	Rehovot, Israel	1980	Hospital	Not reported	188 (94/94 matched on sex, birth date, birth order, maternal age, marital status, ethnicity)	SBP and DBP	6 years	–	–
6	27	Lazdam[b]	2012	PC	Oxford, United Kingdom	1998–2003	Hospital ($N = 964$; n exposed $=428$/n unexposed $=536$)	618 (309/309)	47 (33/14; their mothers were matched on age, parity and year of delivery)	SBP, cholesterol (LDL, total, HDL), triglycerides and glucose	6–13 years	–	–
7	28	Langford	1980	PC	Hinds County, Mississippi, USA	1965–1967	Schools (Black females)	586 (186/400)	413 (115/298)	SBP and DBP	7–11 years	–	–
8	29	Alsnes	2014	PC	Stavanger, Norway	1993–1995	Hospital ($N = 12{,}804$; n exposed $=307$/n unexposed $= 12{,}497$)	926 (307/619)	601 (218/383)	Cholesterol (total, HDL, non-HDL) and glucose	10–11 years	–	–
9	30	Øglaend	2009	PC	Stavanger, Norway	1993–1995	General population ($N = 239{,}000$)	890 (276/614)	537 (181/356)	SBP and DBP	11–12 years	BMI at outcome measurement	BMI, BP
10	31	Tenhola[a]	2003	PC	Kuopio, Finland	1984–1986	Hospital	Not reported (84/not reported)	120 (60/ 60) For BP: 119 (59/60) (unexposed children were matched on sex, gestational age and birth size)	SBP, DBP, cholesterol (total, HDL, LDL), triglycerides and glucose	12 years	Weight and height at outcome measurement	–

(continued)

Table 1. Continued

Study number	Reference number	First author	Year of publication	Study design	Location (name of study)	Recruitment period: year of birth	Source population Children from pregnant women recruited from…	Eligible population Children from mothers with and without HDP who were supposed to participate *n* (no. exposed/ unexposed)	Population for analysis: *N* (no. exposed/ unexposed)	Outcome	Age at outcome measurement	Child confounders	Maternal confounders
	32	Tenhola[a]	2006	Idem	Idem	Idem	Idem	Idem	114 (57/57 matched on sex, gestational age and birth size)	SBP and DBP	Idem	–	–
11	33	Jayet	2010	PC	La Paz, Bolivia	1990–1996[c]	La Paz	146 (56/90)	138 (48/90)	SBP and DBP	13–14 years	–	–
12	34	Vatten	2003	CS	Nord Trøndelag, Norway (The Young-HUNT Study)	1979–1984[d]	General population ($N = 4980$)	4980 (not reported)	4096 (243/3853)	SBP and DBP	13–19 years	Birth weight, gestational age, age and BMI at outcome measurement. Birthweight adjusted for length of gestation as effect modifier	–
Hypertensive disorders: pregnancy induced hypertension and preeclampsia													
13	35	Hiller[b]	2007	PC	South Australia (Australian Calcium Trial)	1992–1998	General population (not reported)	414 (65*/28#/321§) *Gestational hypertension #Preeclampsia §Normotensive pregnancy	179 (31*/136§) (12#/136§) *Gestational hypertension #Preeclampsia §Normotensive pregnancy	SBP and DBP	4–7 years	–	–
14	36	Belfort	2012	PC	Seven medical centres, USA (Infant Health and Developme-nt Program (IHDP))	1984	Hospital ($N = 1080$)	931 (not reported)	694 (112*/582§) (22#/672§) *Preeclampsia #Other hypertensive disorders §Normotensive pregnancy	SBP	6.5 years	Sex, age, height, behavioural state at outcome measurement, and blood pressure measurement method (gestational age as effect modifier)	Age, education, ethnicity, annual household income

(continued)

Table 1. Continued

Study number	Reference number	First author	Year of publication	Study design	Location (name of study)	Recruitment period: year of birth	Source population Children from pregnant women recruited from. . .	Eligible population Children from mothers with and without HDP who were supposed to participate *n* (no. exposed/ unexposed)	Population for analysis: *N* (no. exposed/ unexposed)	Outcome	Age at outcome measurement	Child confounders	Maternal confounders
15	37	Staley[a]	2015	Idem	Avon, UK (ALSPAC)	1991–1992	General population ($N = 14{,}273$)	Not reported	6619 (253[*]/5295[¶]) (954[#]/5295[¶]) (117[§]/5295[¶]) [*]Existing hypertension [#]Gestational hypertension [§]Preeclampsia [¶]Normotensive pregnancy	SBP and DBP	7–18 years	Sex, height, BMI at outcome measurement (gestational age, birth weight, breastfeeding as mediators)	Parity, age, parental BMI, education, smoking during pregnancy, occupational social class (mode of delivery as mediator)
	38	Geelhoed[a]	2010	PC	Idem	Idem	Idem	13,678 (not reported)	6668 (1118[*]/5345[§]) (205[#]/5345[§]) [*]Gestational hypertension [#]Preeclampsia [§]Normotensive pregnancy	SBP and DBP	9 years	Sex, age, weight, height at outcome measurement (gestational age, birth weight as mediators)	Parity, age, parental BMI, education, smoking during pregnancy, occupational social class (mode of delivery as mediator)
	10	Lawlor[a]	2012	Idem	Idem	Idem	Idem	11,443 (not reported) for outcome BP 11,719 (not reported) for outcomes cholesterol and triglycerides	BP: 4654 (771[*]/3781[§]) (102[#]/3781[§]) Cholesterol and triglycerides: 3537 (598[*]/2869) (70[#]/2869) [*]Gestational hypertension [#]Preeclampsia [§]Normotensive pregnancy	SBP, DBP, cholesterol (HDL, non-HDL) and triglycerides	9–12 years	Sex, age, weight, height at outcome measurement, dietary sodium intake (gestational age, birth weight as mediators)	Idem

(continued)

Table 1. Continued

Study number	Reference number	First author	Year of publication	Study design	Location (name of study)	Recruitment period: year of birth	Source population Children from pregnant women recruited from…	Eligible population Children from mothers with and without HDP who were supposed to participate *n* (no. exposed/ unexposed)	Population for analysis: *N* (no. exposed/ unexposed)	Outcome	Age at outcome measurement	Child confounders	Maternal confounders
	39	Fraser	2013	Idem	Idem	Idem	Idem	13,617 (not reported)	2888 (431[*]/2404[§]) (53[#]/2404[§]) [*]Gestational hypertension [#]Preeclampsia [§]Normotensive pregnancy	SBP, DBP, cholesterol (total, HDL, LDL) triglycerides and glucose	17 years	Sex, age (gestational age, birth weight, BMI at outcome measurement as mediators)	Parity, age, maternal pre-pregnancy BMI, household social class, smoking during pregnancy (mode of delivery as mediator)
16	40	Miettola	2013	PC	Oulu and Lapland, Finland (Northern Finland Birth Cohort 1986 (NFB1986))	1985–1986	General population (not reported)	9432 (not reported)	BP: 5573 (331[*]/5045[§]) (197[#]/5045[§]) Cholesterol and triglycerides: 3.7–8.2% missing Glucose: 3.7–14.1% missing [*]Gestational hypertension [#]Preeclampsia [§]Normotensive pregnancy	SBP, DBP, cholesterol (total, HDL, LDL), triglycerides and glucose	16 years	Sex, birth weight, gestational age, BMI at outcome measurement	Parity, socioeconomic status, prepregnancy BMI

[a]These publications have used the same population study: Kotchen et al. (1979, 1982); Svensson et al., Himmelmann et al. (1993, 1994, 1997); Tenhola et al. (2003, 2006); Kvehaugen et al. (2010 and 2011); Geelhoed et al., Lawlor et al., Fraser et al., Staley et al. (2010, 2012, 2013, 2015).
[b]Defined as a high risk of bias study in the risk of bias assessment.
[c]Year of birth was estimated by earliest year of recruitment (2004) minus oldest age (14 years) at participation and latest year of recruitment (2009) minus youngest age (13 years) at participation.
[d]Year of birth was estimated by earliest year of recruitment (1995) minus oldest age (16 years) at participation and latest year of recruitment (1997) minus youngest age (13 years) at participation.
[e]Reported in Svensson A, Andersch B and Hansson L. Prediction in later hypertension following a hypertensive pregnancy. *J Hypertens* 1983; 03: 391–398.
[f]Hypertensive pregnancies consists of two groups: children of mothers who had sustained hypertension after hypertensive pregnancy, and children of mothers who were normotensive after hypertensive pregnancy.
[g]This age is reported in the paper, but study population is the same as the study population in papers by Himmelman et al. (1993, 1994, 1997).
HDP: hypertensive disorders of pregnancy; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; BMI: body mass index; PC: prospective cohort study; CS: cross-sectional study.

Table 2. Studies on the association between pregnancy induced hypertension and systolic blood pressure or diastolic blood pressure (mmHg) in childhood.

					PIH		Normotensive pregnancy			
Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	(Sub)group	Mean (SD)	*N*	Mean (SD)	*N*	Mean difference	95% CI or *p*-value[a]
Systolic blood pressure										
1	18	Kotchen (1979)	3–6	All children	97.6 (1.3)	53	93.1 (1.5)	47	4.5[b]	$p < 0.03$
	19	Kotchen (1982)	3–6	Boys	99.2 (1.8 SE)	29	98.5 (1.9 SE)	26	0.7[b]	p=n.s.
				Girls	101.5 (1.4 SE)	33	98.7 (1.5 SE)	24	2.88[b]	p=n.s.
			6–9	Boys	104.3 (1.8 SE)	28	99.5 (1.3 SE)	26	4.8[b]	$p < 0.05$
				Girls	99.3 (1.3 SE)	31	100.5 (2.1 SE)	22	–1.2[b]	p=n.s.
2	20	Bergel (2000)	5–9	All children	Not reported	Not reported	Not reported	Not reported	Crude: 0.0	–0.9, 0.9
									Adjusted[c]: 0.2	–0.6, 1.1
14	36	Belfort (2012)	6.5	All children	Not reported	22	Not reported	672	Crude: not reported	Not reported
									Adjusted[d]: 3.5	0.0, 7.0
15	37	Staley (2015)	7	All children	Not reported	954	Not reported	5.295	Crude: 2.51	1.82, 3.20
									Adjusted[e]: 1.98	1.32, 2.65
	38	Geelhoed (2010)	9	All children	105.2 (10.1)	1.118	102.2 (9.1)	5.345	Crude: 3.06	2.46, 3.66
									Adjusted[f]: 2.04	1.42, 2.67
	10	Lawlor (2012)	10–11	All children	106 (9)	1.039	104 (9)	5.367	Crude: 2[b]	$p < 0.001$
									Adjusted[g]: geometric mean: 2.04	1.33, 2.76
	39	Fraser (2013)	17	All children	120.5 (11.3)	431	117.6 (10.4)	2.404	Crude: not reported	Not reported
									Adjusted[h]: 2.06	1.28, 2.84
16	40	Miettola (2013)	16	All children	Geometric mean (IQR): 117 (107, 128)	331	Geometric mean (IQR): 114 (106, 123)	5.045	Crude: 3[b]	$p < 0.001$
									Adjusted[i]: % difference: 2.5	1.4, 3.6

(continued)

Table 2. Continued

Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	(Sub)group	PIH		Normotensive pregnancy		Mean difference	95% CI or *p*-value[a]
					Mean (SD)	*N*	Mean (SD)	*N*		
				Boys	Geometric mean (IQR): 124 (117, 133)	Not reported	Geometric mean (IQR): 120 (113, 128)	Not reported	Crude: 4.0[b]	$p < 0.001$
				Girls	Geometric mean (IQR): 110 (104, 117)	Not reported	Geometric mean (IQR): 109 (103, 117)	Not reported	Crude: 1.0[b]	$p = 0.138$
Diastolic blood pressure										
1	18	Kotchen (1979)	3–6	All children	40.9 (1.9)	53	40.8 (3.3)	47	0.1[b]	p=n.s.
	19	Kotchen (1982)	3–6	Boys	57.0 (1.7 SE)	29	60.3 (2.5 SE)	26	–3.3[b]	p=n.s.
				Girls	60.3 (1.6 SE)	33	59.8 (2.5 SE)	24	0.5[b]	p=n.s.
			6–9	Boys	59.4 (2.0 SE)	28	56.9 (2.1 SE)	26	2.5[b]	p=n.s.
				Girls	54.4 (1.9 SE)	31	56.5 (3.0 SE)	22	–2.1[b]	p=n.s.
15	37	Staley (2015)	7	All children	Not reported	954	Not reported	5.295	Crude: 1.07	0.57, 1.57
									Adjusted[e]: 0.97	0.46, 1.48
	38	Geelhoed (2010)	9	All children	58.2 (6.0)	1.118	57.2 (6.4)	5.345	Crude: 1.44	1.03, 1.86
									Adjusted[c]: 1.07	0.60, 1.54
	10	Lawlor (2012)	10–11	All children	61 (8)	1.039	60 (8)	5.367	Crude: not reported	Not reported
									Adjusted[g]: geometric mean: 1.10	0.47, 1.73
	39	Fraser (2013)	17	All children	66 (7.2)	431	64.5 (6.8)	2.404	Crude: 1.5[b]	$p < 0.001$
									Adjusted[h]: 1.11	0.54, 1.69
16	40	Miettola (2013)	16	All children	Geometric mean (IQR): 69 (65, 74)	331	Geometric mean (IQR): 67 (62, 72)	5.045	Crude: 2[b]	$p < 0.001$
									Adjusted[i]: % difference: 3.3	2.0, 4.6

(continued)

Table 2. Continued

Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	(Sub)group	PIH		Normotensive pregnancy		Mean difference	95% CI or *p*-value[a]
					Mean (SD)	*N*	Mean (SD)	*N*		
				Boys	Geometric mean (IQR): 70 (65, 75)	Not reported	Geometric mean (IQR): 68 (63, 73)	Not reported	Crude: 2.0[b]	$p = 0.006$
				Girls	Geometric mean (IQR): 69 (64, 74)	Not reported	Geometric mean (IQR): 66 (62, 71)	Not reported	Crude: 3.0[b]	$p < 0.001$

[a]*p*=n.s., not statistically significant.
[b]We calculated the mean difference if this was not reported by the authors.
[c]Adjusted for offspring sex, body mass index, height, age at outcome measurement, and calcium supplement status during pregnancy.
[d]Adjusted for offspring sex, height z-score, age, blood pressure measurement method, child behavioural state at outcome measurement; maternal age, maternal education, annual household income and ethnicity.
[e]Adjusted for offspring sex, body mass index, height at outcome measurement; maternal age, prepregnancy body mass index (BMI), parity, smoking during pregnancy, education and head of household social class.
[f]Adjusted for offspring weight, height, and height squared at outcome measurement; maternal age, parental prepregnancy BMI, parity, maternal smoking during pregnancy, and social class.
[g]Adjusted for offspring sex, body mass index, height, height-squared, age and dietary sodium at outcome measurement; maternal age, pre-pregnancy BMI, nulliparity, smoking during pregnancy, education and head of household social class.
[h]Adjusted for offspring sex and age; maternal age, prepregnancy BMI, parity, maternal smoking during pregnancy, and household social class.
[i]Adjusted for offspring sex; nulliparity, maternal prepregnancy BMI and socioeconomic position.
PIH: pregnancy induced hypertension; CI: confidence interval; SE: standard error; IQR: interquartile range

Associations with cholesterol and triglycerides. Two studies included blood cholesterol and triglycerides as outcome (Table 3). In one study,[40] a 2.1 mmol/L higher total cholesterol level was observed at 16 years of age in children exposed to PIH. No association was found between exposure to PIH and high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides. In the other study, also no association was found between exposure to PIH and HDL cholesterol, non-HDL cholesterol and triglycerides at 9–10 years,[10] nor with total, HDL- and LDL-cholesterol and triglycerides at 17 years.[39]

Associations with glucose. Two studies included blood glucose as outcome and observed no association between exposure to PIH and glucose at 16[40] and 17 years[39] (Table 3).

Preeclampsia

Associations with offspring blood pressure. BP was reported as an outcome in ten studies (Table 4). Three studies observed a higher BP in children of mothers with preeclampsia, with increases in SBP ranging from 2.9 mmHg to 3.2 mmHg and increases in DBP ranging from 1.7 mmHg to 3.6 mmHg.[26,31,34] Five studies observed no different BP between children of mothers with and without preeclampsia.[24–26,30,33,36,40] In the ALSPAC study, the association of exposure to preeclampsia with BP was not consistently observed throughout childhood; children of mothers with preeclampsia had no statistically significantly higher BP at 7[37] and 10–11 years,[10] but they had a 2.05 mmHg higher SBP at nine years[38] and a 1.71 mmHg higher DBP at 17 years.[39] This association was mediated by birth weight, gestational age, mode of delivery and body mass index (BMI) at outcome assessment. Langford and Watson[28] stratified results for sex; preeclampsia-exposed boys and girls had no different SBP at 7–11 years, but preeclampsia-exposed girls had a 5.8 mmHg higher DBP than unexposed girls. Thus, most studies observed no consistent association between exposure to preeclampsia and BP in childhood.

Associations with cholesterol and triglycerides. Five studies included blood cholesterol as outcome, of which four studies also included triglycerides (Table 5). In the study by Kvehaugen et al.[25] a 0.58 mmol/L higher median level of total cholesterol was observed at 5–8 years in children of mothers with preeclampsia. Four studies observed no association between exposure to preeclampsia and total cholesterol in childhood.[29,31,39,40] All five studies observed no association between exposure to preeclampsia and the level of HDL, non-HDL and LDL cholesterol in childhood.[25,29,31,39,40] Similarly, no association was found between preeclampsia and the level of triglycerides in childhood. Thus, most studies observed no association between exposure to preeclampsia and cholesterol or triglycerides in childhood.

Associations with glucose. Four studies included blood glucose as outcome and observed no association between exposure to preeclampsia and the level of glucose in childhood[29,31,39,40] (Table 5).

Discussion

Summary of findings

This systematic review of 16 studies scopes the association between HDP and cardiometabolic markers in childhood. Most studies showed that exposure to PIH was associated with a higher BP in childhood. There was no convincing evidence that preeclampsia is also associated with higher BP in childhood. No association was observed between exposure to PIH or preeclampsia and cholesterol, triglycerides and glucose. There were no studies that investigated the association between HDP and (carotid) intima-media thickness, HbA1c and diabetes mellitus type 2. None of the studies investigated the association of eclampsia or HELLP syndrome with one of the outcomes of interest.

Comparison of findings with existing evidence

This is the first systematic review of the association between PIH and cardiovascular risk factors in childhood. In 2012, Davis et al.[8] systematically reviewed the association between preeclampsia and cardiovascular risk factors in childhood and early adulthood. In their meta-analysis, exposure to preeclampsia was associated with a 2.39 mmHg (95% CI 1.74, 3.05) higher SBP and a 1.35 mm Hg (95% CI 0.90, 1.80) higher DBP. In contrast, most studies in our review observed no higher SBP or DBP in children exposed to preeclampsia compared with those unexposed. The discrepancy between our findings and those by Davis et al. can be explained by more recently published studies in which no association was found between exposure to preeclampsia and SBP or DBP.[36,40] In addition, the study by Lazdam et al.,[41] in which a strong association between preeclampsia and BP in adulthood was observed, was not included in our evidence synthesis since we investigated an association only in childhood.

In line with the results of Davis et al., we observed no association between in utero exposure to preeclampsia and levels of cholesterol and glucose in childhood.

We did not perform a quantitative meta-analysis because the ages at which cardiometabolic outcomes

Table 3. Studies on the associations between pregnancy induced hypertension and cholesterol, triglycerides and glucose (mmol/L).

					PIH			Normotensive pregnancy			
Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	Outcome	(Sub)group	Mean (SD)	*N*	Mean (SD)	*N*	Mean difference	95% CI or *p*-value
Cholesterol											
15	10	Lawlor (2012)	9–10	HDL cholesterol	All children	1.38 (0.29)	598	1.40 (0.31)	2.869	Crude: not reported	Not reported
										Adjusted[a]: –0.01	–0.03, 0.02
				Non-HDL cholesterol	All children	2.88 (0.64)	598	2.87 (0.65)	2.869	Crude: not reported	Not reported
										Adjusted[a]: 0.01	–0.05, 0.07
	39	Fraser (2013)	17	Total cholesterol	All children	3.8 (0.6)	431	3.8 (0.7)	2.404	Crude: not reported	$p = 0.76$
										Adjusted[b]: 0.01	–0.06, 0.08
				HDL cholesterol	All children	1.3 (0.3)	431	1.3 (0.3)	2.404	Crude: not reported	$p = 0.18$
										Adjusted[b]: –0.01	−0.05, 0.02
				LDL cholesterol	All children	2.1 (0.6)	431	2.1 (0.6)	2.404	Crude: not reported	$p = 0.25$
										Adjusted[b]: 0.03	−0.03, 0.09
16	40	Miettola (2013)	16	Total cholesterol	All children	Geometric mean (IQR): 4.27 (3.80, 4.70)	316	Geometric mean (IQR): 4.18 (3.70, 4.70)	4.518	Crude: 0.09[a]	$p = 0.088$
										Adjusted[c]: % difference: 2.1	0.05, 4.2
					Boys	Geometric mean (IQR): 4.13 (3.70, 4.85)	Not reported	Geometric mean (IQR): 4.02 (3.60, 4.50)	Not reported	Crude: 0.11[a]	$p = 0.113$
					Girls	Geometric mean (IQR): 4.43 (4.00, 4.90)	Not reported	Geometric mean (IQR): 4.35 (3.90, 4.80)	Not reported	Crude: 0.08[a]	$p = 0.393$
				HDL cholesterol	All children	Geometric mean (IQR): 1.40 (1.24, 1.61)	316	Geometric mean (IQR): 1.38 (1.20, 1.59)	4.518	Crude: 0.02[a]	$p = 0.349$
										Adjusted[c]: % difference: 2.4	−0.03, 4.8

(continued)

Table 3. Continued

Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	Outcome	PIH (Sub)group	PIH Mean (SD)	PIH *N*	Normotensive pregnancy Mean (SD)	Normotensive pregnancy *N*	Mean difference	95% CI or *p*-value
					Boys	Geometric mean (IQR): 1.31 (1.17, 1.50)	Not reported	Geometric mean (IQR): 1.29 (1.14, 1.48)	Not reported	Crude: 0.02[a]	$p = 0.575$
					Girls	Geometric mean (IQR): 1.49 (1.30, 1.72)	Not reported	Geometric mean (IQR): 1.46 (1.29, 1.66)	Not reported	Crude: 0.03[a]	$p = 0.344$
				LDL cholesterol	All children	Geometric mean (IQR):	316	Geometric mean (IQR):	4.518	Crude: 0.05[a]	$p = 0.288$
						2.22 (1.90, 2.60)		2.17 (1.90, 2.60)		Adjusted[c]: % difference: 1.8	−1.2, 4.8
					Boys	Geometric mean (IQR): 2.19 (1.80, 2.60)	Not reported	Geometric mean (IQR): 2.12 (1.80, 2.50)	Not reported	Crude: 0.07[a]	$p = 0.166$
					Girls	Geometric mean (IQR): 2.25 (1.90, 2.60)	Not reported	Geometric mean (IQR): 2.23 (1.90, 2.60)	Not reported	Crude: 0.02[a]	$p = 0.907$
Triglycerides											
15	10	Lawlor (2012)	9–10	Triglycerides	All children	Geometric mean (95% CI): 1.03 (1.00, 1.06)	598	Geometric mean (95% CI): 1.03 (1.01, 1.04)	2.869	Crude: not reported	Not reported
										Adjusted[a]: ratio of geometric mean: 0.98	0.94, 1.04
	39	Fraser (2013)	17	Triglycerides	All children	Median (IQR): 0.8 (0.6, 1.0)	431	Median (IQR): 0.8 (0.6, 1.0)	2.404	Crude: not reported	$p = 0.985$
										Adjusted[b]: per cent difference in means: −1.1	−4.9, 2.9

(continued)

Table 3. Continued

Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	Outcome	PIH (Sub)group	PIH Mean (SD)	PIH *N*	Normotensive pregnancy Mean (SD)	Normotensive pregnancy *N*	Mean difference	95% CI or *p*-value
16	40	Miettola (2013)	16	Triglycerides	All children	Geometric mean (IQR): 0.72 (0.55, 0.95)	316	Geometric mean (IQR): 0.75 (0.57, 0.97)	4.518	Crude: −0.03[a]	$p = 0.219$
										Adjusted[c]: % difference: -4.0	−8.6, 0.8
					Boys	Geometric mean (IQR): 0.69 (0.50, 0.93)	Not reported	Geometric mean (IQR): 0.74 (0.55, 0.95)	Not reported	Crude: −0.05[a]	$p = 0.109$
					Girls	Geometric mean (IQR): 0.76 (0.58, 0.99)	Not reported	Geometric mean (IQR): 0.77 (0.59, 0.98)	Not reported	Crude: −0.01[a]	$p = 0.985$
Glucose											
15	39	Fraser (2013)	17	Glucose	All children	5.0 (0.4)	431	5.1 (0.6)	2.404	Crude: −0.1[a]	$p = 0.25$
										Adjusted[b]: −0.04	−0.10, 0.02
16	40	Miettola (2013)	16	Glucose	All children	Geometric mean (IQR): 5.14 (4.90, 5.40)	316	Geometric mean (IQR): 5.14 (4.90, 5.40)	4.518	Crude: 0[a]	$p = 0.946$
										Adjusted[c]: % difference: −0.1	−1.2, 1.0
					Boys	Geometric mean (IQR): 5.28 (5.05, 5.50)	Not reported	Geometric mean (IQR): 5.28 (5.00, 5.50)	Not reported	Crude: 0.00[a]	$p = 0.998$
					Girls	Geometric mean (IQR): 4.99 (4.80, 5.20)	Not reported	Geometric mean (IQR): 5.02 (4.80, 5.30)	Not reported	Crude: −0.03[a]	$p = 0.813$

[a]Adjusted for offspring sex and age, body mass index (BMI), height and height-squared at outcome measurement; maternal age, nulliparity, smoking during pregnancy, prepregnancy BMI, education and head of household social class.
[b]Adjusted for offspring sex and age; maternal age, parity, smoking during pregnancy, prepregnancy BMI and household social class.
[c]Adjusted for offspring sex; nulliparity, maternal prepregnancy BMI and socioeconomic position.
PIH: pregnancy induced hypertension; CI: confidence interval; LDL: low-density lipoprotein; HDL: high-density lipoprotein; IQR: interquartile range

Table 4. Studies on the association between preeclampsia and systolic blood pressure or diastolic blood pressure (mmHg).

					PE		Normotensive pregnancy			
Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	(Sub)group	Mean (SD)	*N*	Mean (SD)	*N*	Mean difference	95% CI or *p*-value[a]
Systolic blood pressure										
4	24	Kvehaugen (2010)	5–8	All children	Median (25,75 pct): 100.0 (95.0, 105.0)	23	Median (25,75 pct): 100.0 (92.5, 103.0)	17	Median: 0[b]	$p = 0.210$
	25	Kvehaugen (2011)	5–8	All children	99.8 (6.7)	26	98.2 (5.7)	15	1.6[b]	$p = 0.4$
5	26	Palti (1989)	6	All children	101.3 (10.2)	94	99.8 (9.5)	94	1.5	$p =$ n.s.
				Boys	103.8 (9.9)	45	99.8 (9.3)	45	4.0	$p = 0.05$
				Girls	99.1 (10.0)	49	99.8 (9.8)	49	0.7	$p =$ n.s.
14	36	Belfort (2012)	6.5	All children	Not reported	112	Not reported	582	Crude: not reported	Not reported
									Adjusted[c]: −0.7	−2.4, 1.0
7	28	Langford (1980)	7–11	Boys	100.9 (11.3)	59	100.0 (12.6)	164	0.9[b]	$p =$ n.s
				Girls	103.3 (13.5)	56	100.4 (12)	134	2.9[b]	$p = 0.08$
15	37	Staley (2015)	7	All children	Not reported	117	Not reported	5.295	Crude: 1.45	−0.39, 3.29
									Adjusted[d]: 1.22	−0.52, 2.97
	38	Geelhoed (2010)	9	All children	104.5 (8.8)	205	102.2 (9.1)	5.345	Crude: 2.36	1.09, 3.64
									Adjusted[e]: 2.05	0.72, 3.38
	10	Lawlor (2012)	10–11	All children	107 (11)	143	104 (9)	5.367	Crude: not reported	Not reported
									Adjusted[f]: geometric mean: 1.82	0.03, 3.62
	39	Fraser (2013)	17	All children	120.2 (10.1)	53	117.6 (40.4)	2.404	Crude: 2.6[b]	$p = 0.03$
									Adjusted[g]: 1.12	−0.89, 3.12
9	30	Øglaend (2009)	11–12	All children	115.3 (9.8)	181	113.5 (8.5)	356	Crude: 1.8	0.2, 3.5
									Adjusted: 0.4	−1.2, 2.0
10	31	Tenhola (2003)	12	All children	116.4 (95% CI 114.1, 118.7)	59	113.2 (95% CI 110.9, 115.5)	60	3.2[b]	*Adjusted:* $p = 0.021$

(continued)

Table 4. Continued

Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	(Sub)group	PE		Normotensive pregnancy		Mean difference	95% CI or *p*-value[a]
					Mean (SD)	*N*	Mean (SD)	*N*		
	32	Tenhola (2006)	12	All children	116.8	57	113.0	57	3.8[b]	Not reported
11	33	Jayet (2010)	13–14	All children	108 (9)	48	110 (11)	90	Crude: −2.00	−5.41, 1.41
12	34	Vatten (2003)	13–19	All children	122.4 (95% CI 121.1, 123.8)	220	119.5 (95% CI 119.2, 119.9)	3.479	2.9[b]	*Adjusted:* $p=<0.001$
16	40	Miettola (2013)	16	All children	Geometric mean: (IQR): 116 (108, 125)	197	Geometric mean: (IQR): 114 (106, 123)	5.045	Crude: 2[b]	$p=0.145$
									Adjusted[h]: % difference: 0.7	−0.8, 2.1
				Boys	Geometric mean: (IQR): 121 (114, 131)	Not reported	Geometric mean: (IQR): 120 (113, 128)	Not reported	Crude: 1.0[b]	$p=0.496$
				Girls	Geometric mean: (IQR): 110 (104, 116)	Not reported	Geometric mean: (IQR): 109 (103, 117)	Not reported	Crude: 1.0[b]	$p=0.534$
Diastolic blood pressure										
4	24	Kvehaugen (2010)	5–8	All children	Median (25,75 pct): 60.0 (55.0, 65.0)	23	Median (25,75 pct): 60.0 (55.0, 60.0)	17	Median: 0[b]	$p=0.604$
	25	Kvehaugen (2011)	5–8	All children	60.0 (55.0 to 64.0)	26	60.0 (55.0 to 60.0)	17	0.0[b]	$p=0.7$
5	26	Palti (1989)	6	All children	66.2 (8.3)	94	63.9 (8.0)	94	2.3	$p=0.03$
				Boys	68.3 (8.5)	45	64.6 (7.8)	45	3.6	$p=0.04$
				Girls	64.3 (7.8)	49	63.2 (8.2)	49	0.8	p=n.s.
7	28	Langford (1980)	7–11	Boys	58.6 (16.5)	59	58.4 (13.7)	164	0.2[b]	p=n.s
				Girls	63.7 (12.5)	56	57.9 (13.0)	134	5.8[b]	$p=0.05$
15	37	Staley (2015)	7	All children	Not reported	117	Not reported	5.295	Crude: 0.84	−0.50, 2.18
									Adjusted[d]: 0.80	−0.53, 2.13

(continued)

Table 4. Continued

Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	(Sub)group	PE		Normotensive pregnancy		Mean difference	95% CI or *p*-value[a]
					Mean (SD)	*N*	Mean (SD)	*N*		
	38	Geelhoed (2010)	9	All children	58.6 (6.6)	205	57.2 (6.4)	5.345	Crude: 0.99 Adjusted[e]: 1.00	0.10, 1.89 −0.01, 2.01
	10	Lawlor (2012)	10–11	All children	62 (8)	143	60 (8)	5.367	Crude: not reported Adjusted[f]: geometric mean: 1.40	Not reported −0.17, 2.98
	39	Fraser (2013)	17	All children	66.6 (7)	53	64.5 (6.8)	2.404	Crude: 2.1[b] Adjusted[g]: 1.71	$p = 0.006$ 0.23, 3.17
9	30	Øglaend (2009)	11–12	All children	66.4 (6.8)	181	65.3 (7.0)	356	Crude: 1.0 Adjusted: 0.0	−0.2, 2.3 −1.3, 1.4
10	31	Tenhola (2003)	12	All children	73.9 (95% CI 72.1, 75.7)	59	70.3 (95% CI 68.2, 72.4)	60	3.6[b]	*Adjusted:* $p = 0.022$
	32	Tenhola (2006)	12	All children	74.3	57	70.5	57	3.8[b]	Not reported
11	33	Jayet (2010)	13–14	All children	73 (7)	48	73 (7)	90	Crude: 0.0	−3.0 to 4.0
12	34	Vatten (2003)	13–19	All children	65.3 (95% CI 64.3, 66.3)	220	63.6 (95% CI 63.4, 63.9)	3.479	1.7[b]	*Adjusted:* $p = 0.001$
16	40	Miettola (2013)	16	All children	Geometric mean (IQR): 68 (64, 74)	197	Geometric mean (IQR): 67 (62, 72)	5.045	Crude: 1[b] Adjusted[h]: % difference: 1.6	$p = 0.020$ $p = -0.01$, 3.3

(continued)

Table 4. Continued

Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	(Sub)group	PE		Normotensive pregnancy		Mean difference	95% CI or *p*-value[a]
					Mean (SD)	*N*	Mean (SD)	*N*		
				Boys	Geometric mean (IQR): 69 (65, 74)	Not reported	Geometric mean (IQR): 68 (63, 73)	Not reported	Crude: 1.0[b]	$p = 0.066$
				Girls	Geometric mean (IQR): 67 (62, 72)	Not reported	Geometric mean (IQR): 66 (62, 71)	Not reported	Crude: 1.0[b]	$p = 0.347$

[a]*p*=n.s., not statistically significant.
[b]We calculated the mean difference if this was not reported by the authors.
[c]Adjusted for offspring sex, height z-score, age, blood pressure measurement method, child behavioural state at outcome measurement; maternal age, maternal education, annual household income and ethnicity.
[d]Adjusted for offspring sex, body mass index, height at outcome measurement; maternal age, prepregnancy body mass index (BMI), parity, smoking during pregnancy, education and head of household social class.
[e]Adjusted for offspring sex, BMI, height, age at outcome measurement; and calcium supplement status during pregnancy.
[f]Adjusted for offspring sex body mass index, height, height-squared, age and dietary sodium at outcome measurement; maternal age, prepregnancy BMI, nulliparity, smoking during pregnancy, education and head of household social class.
[g]Adjusted for offspring sex and age; maternal age, prepregnancy BMI, parity, smoking during pregnancy and household social class.
[h]Adjusted for offspring sex; nulliparity, maternal prepregnancy BMI and socioeconomic position.
PE: preeclampsia; pct: percentiles; CI: confidence interval; IQR: interquartile range

Table 5. Studies on the association between preeclampsia and cholesterol, triglycerides and glucose (mmol/L).

						PE		Normotensive pregnancy			
Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	Outcome	(Sub)group	Mean (SD)	*N*	Mean (SD)	*N*	Mean difference	95% CI or *p*-value
Cholesterol											
4	24	Kvehaugen (2011)	5–8	Total cholesterol	All children	Median (IQR): 5.01 (4.44, 5.39)	20	Median (IQR): 4.43 (4.00, 5.00)	14	Median difference: 0.58[a]	$p = 0.04$
				HDL cholesterol	All children	1.60 (0.31)		1.41 (0.34)		0.19[a]	$p = 0.1$
				LDL cholesterol	All children	Median (IQR): 1.81 (1.20, 2.42)		Median (IQR): 1.53 (1.12, 2.26)		Median difference: 0.28[a]	$p = 0.3$
15	10	Lawlor (2012)	9–10	HDL cholesterol	All children	1.37 (0.30)	88	1.40 (0.31)	3.369	Crude: not reported	Not reported
										Adjusted[b]: −0.03	−0.11, 0.04
				Non-HDL cholesterol	All children	2.87 (0.59)	88	2.87 (0.65)	3.369	Crude: not reported	Not reported
										Adjusted[b]: −0.01	−0.16, 0.14
15	39	Fraser (2013)	17	Total cholesterol	All children	3.6 (0.6)	53	3.8 (0.7)	2.404	Crude: −0.2[a]	$p = 0.19$
										Adjusted[c]: −0.11	−0.29, 0.07
				HDL cholesterol	All children	1.2 (0.2)	53	1.3 (0.3)	2.404	Crude: −0.1[a]	$p = 0.17$
										Adjusted[c]: −0.03	−0.11, 0.05
				LDL cholesterol	All children	2.0 (0.6)	53	2.1 (0.6)	2.404	Crude: −0.1[a]	$p = 0.34$
										Adjusted[c]: −0.08	−0.24, 0.08
8	29	Alnes (2014)	10–11	Total cholesterol	Boys, mild preeclampsia	4.45 (0.12)	Not reported	4.35 (0.06)	383	Not reported	Boys, $p = 0.29$ for normotensive *vs.* all types of preeclampsia
					Boys, moderate preeclampsia	4.41 (0.15)	Not reported				
					Boys, severe preeclampsia	4.65 (0.15)	Not reported				

(continued)

Table 5. Continued

Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	Outcome	(Sub)group	PE		Normotensive pregnancy		Mean difference	95% CI or *p*-value
						Mean (SD)	*N*	Mean (SD)	*N*		
					Girls, mild preeclampsia	4.45 (0.13)	Not reported	4.42 (0.05)	383	Not reported	Girls, $p = 0.18$ for normotensive *vs.* all types of preeclampsia
					Girls, moderate preeclampsia	4.58 (0.09)	Not reported				
					Girls, severe preeclampsia	4.20 (0.15)	Not reported				
				HDL cholesterol	Boys, mild preeclampsia	1.70 (0.05)	Not reported	1.74 (0.03)	383	Not reported	Boys, $p = 0.26$ for normotensive *vs.* all types of preeclampsia
					Boys, moderate preeclampsia	1.66 (0.07)	Not reported				
					Boys, severe preeclampsia	1.84 (0.07)	Not reported				
					Girls, mild preeclampsia	1.57 (0.07)	Not reported	1.64 (0.03)	383	Not reported	Girls, $p = 0.40$ for normotensive *vs.* all types of preeclampsia
					Girls, moderate preeclampsia	1.69 (0.05)	Not reported				
					Girls, severe preeclampsia	1.71 (0.08)	Not reported				
				Non-HDL cholesterol	Boys, mild preeclampsia	2.76 (1.12)	Not reported	2.60 (0.06)	383	Not reported	Boys, $p = 0.31$ for normotensive *vs.* all types of preeclampsia

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Table 5. Continued

Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	Outcome	(Sub)group	PE		Normotensive pregnancy		Mean difference	95% CI or *p*-value
						Mean (SD)	*N*	Mean (SD)	*N*		
					Boys, moderate preeclampsia	2.77 (0.14)	Not reported				
					Boys, severe preeclampsia	2.81 (0.14)	Not reported				
					Girls, mild preeclampsia	2.88 (0.13)	Not reported	2.78 (0.05)	383	Not reported	Girls, $p = 0.11$ for normotensive *vs.* all types of preeclampsia
					Girls, moderate preeclampsia	2.89 (0.09)	Not reported				
					Girls, severe preeclampsia	2.49 (0.14)	Not reported				
10	31	Tenhola (2003)	12	Total cholesterol	All children	4.54 (95% CI 4.32, 4.76)	60	4.50 (95% CI 4.29, 4.71)	60	0.04[a]	Adjusted: $p = 0.618$
				HDL cholesterol	All children	1.31 (95% CI 1.24, 1.38)		1.36 (95% CI 1.29, 1.43)		−0.05[a]	Adjusted: $p = 0.468$
				LDL cholesterol	All children	2.82 (95% CI 2.63, 3.01)		2.75 (95% CI 2.57, 2.93)		0.07[a]	Adjusted: $p = 0.342$
16	40	Miettola (2013)	16	Total cholesterol	All children	Geometric mean (IQR):	174	Geometric mean (IQR):	4.518	Crude: 0.01[a]	$p = 0.979$
						4.19 (3.70, 4.70)		4.18 (3.70, 4.70)		Adjusted[d]: % difference: 0.4	−2.3, 3.3
					Boys	Geometric mean (IQR): 4.01 (3.50, 4.40)	Not reported	Geometric mean (IQR): 4.02 (3.60, 4.50)	Not reported	Crude: −0.01[a]	$p = 0.998$
					Girls	Geometric mean (IQR): 4.41 (3.85, 5.05)	Not reported	Geometric mean (IQR): 4.35 (3.90, 4.80)	Not reported	Crude: 0.06[a]	$p = 0.755$

(continued)

Table 5. Continued

Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	Outcome	(Sub)group	PE		Normotensive pregnancy			
						Mean (SD)	*N*	Mean (SD)	*N*	Mean difference	95% CI or *p*-value
				HDL cholesterol	All children	Geometric mean (IQR): 1.36 (1.17, 1.62)	174	Geometric mean (IQR): 1.38 (1.20, 1.59)	4.518	Crude: −0.02[a] Adjusted[d]: % difference: -0.1	$p = 0.777$ −3.2, 3.1
					Boys	Geometric mean (IQR): 1.27 (1.12, 1.47)	Not reported	Geometric mean (IQR): 1.29 (1.14, 1.48)	Not reported	Crude: −0.02[a]	$p = 0.706$
					Girls	Geometric mean (IQR): 1.47 (1.25, 1.72)	Not reported	Geometric mean (IQR): 1.46 (1.29, 1.66)	Not reported	Crude: 0.01[a]	$p = 0.942$
				LDL cholesterol	All children	Geometric mean (IQR): 2.18 (1.80, 2.60)	174	Geometric mean (IQR): 2.17 (1.90, 2.60)	4.518	Crude: 0.01[a] Adjusted[d]: % difference: 0.4	$p = 0.965$ −3.5, 4.4
					Boys	Geometric mean (IQR): 2.12 (1.80, 2.50)	Not reported	Geometric mean (IQR): 2.12 (1.80, 2.50)	Not reported	Crude: 0.00[a]	$p = 0.965$
					Girls	Geometric mean (IQR): 2.26 (1.95, 2.60)	Not reported	Geometric mean (IQR): 2.23 (1.90, 2.60)	Not reported	Crude: 0.03[a]	$p = 0.895$
Triglycerides											
4	25	Kvehaugen (2011)	5–8	Triglycerides	All children	Median (IQR): 0.60 (0.53, 0.73)	20	Median (IQR): 0.58 (0.53, 0.82)	14	0.02[a]	$p = 0.9$
15	10	Lawlor (2012)	9–10	Triglycerides	All children	Geometric mean (95%CI): 0.99 (0.91, 1.09)	70	Geometric mean (95%CI): 1.03 (1.01, 1.04)	2.869	Crude: not reported Adjusted[b]: ratio of geometric mean: 0.96	Not reported 0.85, 1.07
15	39	Fraser (2013)	17	Triglycerides	All children	Median (IQR): 0.7 (0.6, 1.1)	53	Median (IQR): 0.8 (0.6, 1.0)	2.404	Crude: −0.1[a] Adjusted[c]: % difference: −0.01	$p = 0.56$ −10.9, 10.8

(continued)

Table 5. Continued

Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	Outcome	(Sub)group	PE		Normotensive pregnancy		Mean difference	95% CI or *p*-value
						Mean (SD)	*N*	Mean (SD)	*N*		
10	31	Tenhola (2003)	12	Triglycerides	All children	0.90 (95%CI 0.80, 1.00)	60	0.86 (95%CI 0.78, 0.94)	60	0.04[a]	$p = 0.617$
16	40	Miettola (2013)	16	Triglycerides	All children	Geometric mean (IQR):	174	Geometric mean (IQR):	4.518	Crude: 0.0[a]	$p = 0.997$
						0.75 (0.56, 1.02)		0.75 (0.57, 0.97)		Adjusted[d]: % difference: −0.2	−6.5, 6.6
					Boys	Geometric mean (IQR): 0.76 (0.57, 0.99)	Not reported	Geometric mean (IQR): 0.74 (0.55, 0.95)	Not reported	Crude: 0.02[a]	$p = 0.809$
					Girls	Geometric mean (IQR): 0.74 (0.56, 1.05)	Not reported	Geometric mean (IQR): 0.77 (0.59, 0.98)	Not reported	Crude: −0.03[a]	$p = 0.739$
Glucose											
8	29	Alnes (2014)	10–11	Glucose	Boys, mild preeclampsia	4.88 (0.05)	Not reported	4.88 (0.03)	383	Not reported	Boys, $p = 0.51$ for normotensive *vs.* all types of preeclampsia
					Boys, moderate preeclampsia	4.92 (0.06)	Not reported				
					Boys, severe preeclampsia	4.79 (0.06)	Not reported				
					Girls, mild preeclampsia	4.81 (0.07)	Not reported	4.74 (0.03)	383	Not reported	Girls, $p = 0.45$ for normotensive *vs.* all types of preeclampsia
					Girls, moderate preeclampsia	4.83 (0.05)	Not reported				
					Girls, severe preeclampsia	4.76 (0.08)	Not reported				

(continued)

Table 5. Continued

Study number	Reference number	First author (year)	Age at outcome measurement (range in years)	Outcome	(Sub)group	PE		Normotensive pregnancy		Mean difference	95% CI or *p*-value
						Mean (SD)	*N*	Mean (SD)	*N*		
10	31	Tenhola (2003)	12	Glucose	All children	4.3 (95% CI 4.2, 4.4)	60	4.4 (95% CI 4.3, 4.5)	60	−0.1[a]	$p = 0.371$
16	40	Miettola (2013)	16	Glucose	All children	Geometric mean (IQR):	174	Geometric mean (IQR):	4.518	Crude: 0.0[a]	$p = 0.993$
						5.14 (4.90, 5.50)		5.14 (4.90, 5.40)		Adjusted[d]: % difference: −0.3	−1.8, 1.2
					Boys	Geometric mean (IQR): 5.31 (5.10, 5.60)	Not reported	Geometric mean (IQR): 5.28 (5.00, 5.50)	Not reported	0.03[a]	$p = 0.793$
					Girls	Geometric mean (IQR): 4.95 (4.80, 5.30)	Not reported	Geometric mean (IQR): 5.02 (4.80, 5.30)	Not reported	−0.07[a]	$p = 0.509$
15	39	Fraser (2013)	17	Glucose	All children	5.1 (0.4)	53	5.1 (0.6)	2.404	Crude: 0.0[a]	$p = 0.65$
										Adjusted[c]: 0.001	−0.15, 0.16

[a]We calculated the mean difference if this was not reported by the authors.
[b]Adjusted for offspring sex, body mass index, height, height-squared, and age at outcome measurement; maternal age, prepregnancy body mass index (BMI), nulliparity, smoking during pregnancy, education and head of household social class.
[c]Adjusted for offspring sex and age; maternal age, prepregnancy BMI, parity, smoking during pregnancy and household social class.
[d]Adjusted for offspring sex; nulliparity, maternal prepregnancy BMI and socioeconomic position.
PE: preeclampsia; CI: confidence interval; LDL: low-density lipoprotein; HDL: high-density lipoprotein; IQR: interquartile range

were investigated varied strongly between studies. In general, BP levels increase from childhood into adolescence due to growth.[42] A mean difference in BP between HDP exposed and unexposed children observed in childhood can be similar to a mean difference in BP observed in adolescence, but the relative difference in BP would be larger in childhood due to the lower baseline BP at this age.

Possible underlying mechanisms

First, the higher BP in offspring exposed to PIH may be programmed via an intra-uterine mechanism. Miettola et al.[40] suggested a mechanism in which irregulation of maternal and foetal glucocorticoids is involved, but their hypothesis was based on evidence from animal studies investigating prenatal stress rather than PIH specifically. To our knowledge, there are no other studies in which intra-uterine mechanisms are described.

Second, HDPs are associated with adverse perinatal outcomes such as small for gestational age and preterm birth,[43] which in turn are associated with higher BP in children.[44] Only few studies in this review investigated the potential mediating effects of these perinatal factors in the association of PIH and offspring BP. In the ALSPAC study,[10,37,38] however, the association of PIH with offspring BP was not explained by birth weight, gestational age, method of delivery, breastfeeding or offspring BMI at outcome measurement.

Third, the higher BP in offspring exposed to PIH may reflect genetic susceptibility to develop high BP. Women who are genetically predisposed to develop hypertension are more likely to respond more extremely to physiological changes due to pregnancy, which may lead to endothelial dysfunction and PIH.[14] Pregnancy can thus be seen as a stress-test in which a genetic predisposition to CVD will be unmasked by an indication of HDP.[14] This genetic predisposition may be inherited by the mothers' offspring, independent of PIH-related conditions in utero.[15]

Last, shared environment and lifestyle, which on the one hand leads to the development of HDP and on the other hand increases the risk of adverse cardiometabolic outcomes in the offspring, may explain the association of PIH with BP. For instance, maternal obesity is an important risk factor for HDP,[43] but is also related to offspring BMI and BP.[45–47] Two studies in this review investigated whether maternal obesity amongst other potential confounders explained the association of PIH with offspring BP, and found that the association between PIH and higher SBP in childhood remained statistically significant after adjustment.[10,37–40] Nevertheless, obesity is known to interact with both environmental factors and a genetic component.[46] This well-known concept that offspring BP depends on both genetic and shared (familial) environmental factors is called familial aggregation of BP.[48] This is also supported by results from Miliku et al.[49] in which both higher maternal and higher paternal BP were associated with higher childhood BP.

In this systematic review most studies observed no association between preeclampsia and offspring BP. Exposure to preeclampsia would affect the development of organs and vascular structures in the foetus, thereby programming the child towards adverse cardiometabolic health. For example, microvascular adaptations,[50,51] endothelial dysfunction[25,33] and myocardial dysfunction[52] have been observed in the offspring of mothers with preeclampsia. A possible explanation for the lack of association in most of the studies is that exposure to preeclampsia in itself does not lead to higher BP in childhood. Preeclampsia is accompanied by an immunological response which induces different pathophysiological pathways in utero. It has been suggested that interaction between this in utero effect and adverse environmental factors (e.g. unhealthy lifestyle) during pregnancy leads to an increase in offspring BP.[53] Apart from data on smoking during pregnancy in the ALSPAC study,[10,36–38] data on adverse factors during pregnancy were lacking in the studies in this review, and thus we could not investigate this hypothesis.

Limitations

Our review has some limitations. First, due to the large variation in the children's ages at outcome measurement, we were not able to perform a meta-analysis and thus we could not provide a pooled estimate for the association between HDP and offspring BP. Instead, we counted the number of studies which did and did not observe a statistically significant association.

Second, there were few studies that investigated cardiometabolic outcomes other than BP in relation to HDP. We selected cardiometabolic outcomes which we expected to be available in epidemiological studies performed in children. For example, (carotid) intima-media thickness is increasingly studied as an endpoint in children. However, we found no study that investigated an association of exposure to HDP and (carotid) intima-media thickness. Possibly we have missed studies that selected other cardiometabolic outcomes.

Last, the studies in our review poorly reported on factors that might shed light on the possible underlying mechanisms. As mentioned earlier, data on perinatal factors were scarce, as well as data on adverse factors during pregnancy. In addition, we were not able to investigate whether BP lowering medication or severity of the HDP influence the association of HDP with offspring BP.

Relevance of findings and perspectives

HDP can be harmful for both the mother[54] and unborn child.[55] This systematic review shows that HDPs, in particular PIH, also have long term consequences for offspring BP. This is in line with the results of Tapp et al.;[56] they demonstrated an adverse cardiometabolic health (abnormalities of the retinal microvasculature, cardiac structure and increased BP) in adult offspring exposed to HDP in utero. It is known that BP tracks from childhood into adulthood.[57] Even small increases in BP, as observed in most of the studies in this review, may have a large impact on the cardiovascular health of the general population if those increases are widespread in the population.[58]

Perspectives

The exact underlying mechanisms – genetic susceptibility, shared familial environment, intra-uterine effects – of the association between PIH and offspring BP are puzzling. However, exposure to HDP, in particular PIH, leads to higher BP values in the offspring. Modifiable factors which could induce the development of high BP in the offspring should therefore be tackled. This stresses the importance of guiding (future) parents toward a healthier lifestyle before and during pregnancy, but also a healthy lifestyle of the whole family after pregnancy contributes to healthier BP levels in the offspring.

A higher BP was also found amongst women with a history of HDP: trajectories of classical CVD risk factors are altered and hypertension already occurs significantly more in the fourth decade.[59,60] Blood pressure seems to be the main driver of increased CVD risk both among women with a history of HDP and their offspring. Based on our findings and those of Groenhof et al., it could be argued that CVD prevention should begin earlier than currently practised in women with a history of HDP,[61] and should also be accessible to HDP exposed offspring.

Conclusions

Most studies in this systematic review showed that children exposed to PIH in utero have a higher BP than children who were not exposed to PIH. Most studies found no association between exposure to preeclampsia and BP in childhood. The studies in this review did not observe an association between HDP and blood cholesterol, triglycerides and glucose. We found no studies that investigated an association between HDP and HbA1c, diabetes mellitus type 2 or (carotid) intima media thickness.

Author contribution

MACJ and LPMP contributed equally to this work. MACJ, LPMP, HAS, GWD and LvR had the main role in research protocol design. MACJ and LPMP did the literature search, performed title and abstract screening, data extraction and drafted the manuscript. HAS additionally contributed to the screening and data extraction process. GWD, TKJG, CSPMU, HAS and LvR contributed to interpretation and participated in the critical revision of the article. All authors (MACJ, LPMP, GWD, TKJG, CSPMU, HAS and LvR) approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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References

1. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertens* 2014; 4: 97–104.
2. Bateman BT, Bansil P, Hernandez-Diaz S, et al. Prevalence, trends, and outcomes of chronic hypertension: A nationwide sample of delivery admissions. *Am J Obstet Gynecol* 2012; 206: 134.e131–138.
3. Klungsoyr K, Morken NH, Irgens L, et al. Secular trends in the epidemiology of pre-eclampsia throughout 40 years in Norway: prevalence, risk factors and perinatal survival. *Paediatr Perinat Epidemiol* 2012; 26: 190–198.
4. Lisonkova S and Joseph KS. Incidence of preeclampsia: Risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol* 2013; 209: 544.e541–544.e512.
5. Sebastian T, Yadav B, Jeyaseelan L, et al. Small for gestational age births among South Indian women: Temporal trend and risk factors from 1996 to 2010. *BMC Pregnancy Childbirth* 2015; 15: 7.

6. Wallis AB, Saftlas AF, Hsia J, et al. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987–2004. *Am J Hypertens* 2008; 21: 521–526.
7. World Health Organization. *WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia*. Geneva: World Health Organization, 2011.
8. Davis EF, Lazdam M, Lewandowski AJ, et al. Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: A systematic review. *Pediatrics* 2012; 129: e1552–1561.
9. Himmelmann A, Svensson A and Hansson L. Five-year follow-up of blood pressure and left ventricular mass in children with different maternal histories of hypertension: The Hypertension in Pregnancy Offspring Study. *J Hypertens* 1994; 12: 89–95.
10. Lawlor DA, Macdonald-Wallis C, Fraser A, et al. Cardiovascular biomarkers and vascular function during childhood in the offspring of mothers with hypertensive disorders of pregnancy: Findings from the Avon Longitudinal Study of Parents and Children. *Eur Heart J* 2012; 33: 335–345.
11. Rice MM, Landon MB, Varner MW, et al. Pregnancy-associated hypertension and offspring cardiometabolic health. *Obstet Gynecol* 2018; 131: 313–321.
12. Roberts JM, Pearson G, Cutler J, et al. Summary of the NHLBI Working Group on Research on Hypertension During Pregnancy. *Hypertension* 2003; 41: 437–445.
13. Davis EF, Newton L, Lewandowski AJ, et al. Pre-eclampsia and offspring cardiovascular health: Mechanistic insights from experimental studies. *Clin Sci (Lond)* 2012; 123: 53–72.
14. Sattar N and Greer IA. Pregnancy complications and maternal cardiovascular risk: Opportunities for intervention and screening? *BMJ* 2002; 325: 157–160.
15. Harrap SB. Hypertension: Genes versus environment. *Lancet* 1994; 344: 169–171.
16. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int J Surgery* 2010; 8: 336–341.
17. Stang A. Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; 25: 603–605.
18. Kotchen JM, Kotchen TA, Cottrill CM, et al. Blood pressures of young mothers and their first children 3–6 years following hypertension during pregnancy. *J Chronic Dis* 1979; 32: 653–659. 1.
19. Kotchen JM, McKean HE and Kotchen TA. Blood pressure of young mothers and their children after hypertension in adolescent pregnancy: Six- to nine-year follow-up. *Am J Epidemiol* 1982; 115: 861–867.
20. Bergel E, Haelterman E, Belizan J, et al. Perinatal factors associated with blood pressure during childhood. *Am J Epidemiol* 2000; 151: 594–601.
21. Svensson A and Sigstrom L. Blood pressure, erythrocyte sodium and potassium concentrations and Na+K+ATPase activity in children with hypertensive mothers. *J Hypertens* 1986; 4: 269–272.
22. Himmelmann A, Svensson A and Hansson L. Blood pressure and left ventricular mass in children with different maternal histories of hypertension: The Hypertension in Pregnancy Offspring Study. *J Hypertens* 1993; 11: 263–268.
23. Himmelmann A, Himmelmann K, Svensson A, et al. Glucose and insulin levels in young subjects with different maternal histories of hypertension: The Hypertension in Pregnancy Offspring Study. *J Intern Medic* 1997; 241: 19–22.
24. Kvehaugen AS, Andersen LF and Staff AC. Anthropometry and cardiovascular risk factors in women and offspring after pregnancies complicated by preeclampsia or diabetes mellitus. *Acta Obstet Gynecol Scand* 2010; 89: 1478–1485.
25. Kvehaugen AS, Dechend R, Ramstad HB, et al. Endothelial function and circulating biomarkers are disturbed in women and children after preeclampsia. *Hypertension* 2011; 58: 63–69.
26. Palti H and Rothschild E. Blood pressure and growth at 6 years of age among offsprings of mothers with hypertension of pregnancy. *Early Hum Dev* 1989; 19: 263–269.
27. Lazdam M, de la Horra A, Diesch J, et al. Unique blood pressure characteristics in mother and offspring after early onset preeclampsia. *Hypertension* 2012; 60: 1338–1345.
28. Langford HG and Watson RL. Prepregnant blood pressure, hypertension during pregnancy, and later blood pressure of mothers and offspring. *Hypertension* 1980; 2: 130–133.
29. Alsnes IV, Janszky I, Forman MR, et al. A population-based study of associations between preeclampsia and later cardiovascular risk factors. *Am J Obstet Gynecol* 2014; 211: 657.e1–7.
30. Oglaend B, Forman MR, Romundstad PR, et al. Blood pressure in early adolescence in the offspring of preeclamptic and normotensive pregnancies. *J Hypertens* 2009; 27: 2051–2054.
31. Tenhola S, Rahiala E, Martikainen A, et al. Blood pressure, serum lipids, fasting insulin, and adrenal hormones in 12-year-old children born with maternal preeclampsia. *J Clin Endocrinol Metab* 2003; 88: 1217–1222.
32. Tenhola S, Rahiala E, Halonen P, et al. Maternal preeclampsia predicts elevated blood pressure in 12-year-old children: Evaluation by ambulatory blood pressure monitoring. *Pediatr Res* 2006; 59: 320–324.
33. Jayet PY, Rimoldi SF, Stuber T, et al. Pulmonary and systemic vascular dysfunction in young offspring of mothers with preeclampsia. *Circulation* 2010; 122: 488–494.
34. Vatten LJ, Romundstad PR, Holmen TL, et al. Intrauterine exposure to preeclampsia and adolescent blood pressure, body size, and age at menarche in female offspring. *Obstet Gynecol* 2003; 101: 529–533.

35. Hiller JE, Crowther CA, Moore VA, et al. Calcium supplementation in pregnancy and its impact on blood pressure in children and women: Follow up of a randomised controlled trial. *Aust N Z J Obstet Gynaecol* 2007; 47: 115–121.
36. Belfort MB, Gillman MW and McCormick MC. Prenatal and perinatal predictors of blood pressure at school age in former preterm, low birth weight infants. *J Perinatol* 2012; 32: 265–269.
37. Staley JR, Bradley J, Silverwood RJ, et al. Associations of blood pressure in pregnancy with offspring blood pressure trajectories during childhood and adolescence: Findings from a prospective study. *J Am Heart Assoc* 2015; 4: e001422.
38. Geelhoed JJ, Fraser A, Tilling K, et al. Preeclampsia and gestational hypertension are associated with childhood blood pressure independently of family adiposity measures: The Avon Longitudinal Study of Parents and Children. *Circulation* 2010; 122: 1192–1199.
39. Fraser A, Nelson SM, Macdonald-Wallis C, et al. Hypertensive disorders of pregnancy and cardiometabolic health in adolescent offspring. *Hypertension* 2013; 62: 614–620.
40. Miettola S, Hartikainen AL, Vaarasmaki M, et al. Offspring's blood pressure and metabolic phenotype after exposure to gestational hypertension in utero. *Eur J Epidemiol* 2013; 28: 87–98.
41. Lazdam M, de la Horra A, Pitcher A, et al. Elevated blood pressure in offspring born premature to hypertensive pregnancy: Is endothelial dysfunction the underlying vascular mechanism? *Hypertension* 2010; 56: 159–165.
42. Falkner B and Daniels SR. Summary of the fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Hypertension* 2004; 44: 387–388.
43. Hutcheon JA, Lisonkova S and Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2011; 25: 391–403.
44. Huxley RR, Shiell AW and Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: A systematic review of the literature. *J Hypertens* 2000; 18: 815–831.
45. Ludwig-Walz H, Schmidt M, Gunther ALB, et al. Maternal prepregnancy BMI or weight and offspring's blood pressure: Systematic review. *Matern Child Nutr* 2018; 14: e12561.
46. Nielsen LA, Nielsen TR and Holm JC. The impact of familial predisposition to obesity and cardiovascular disease on childhood obesity. *Obes Facts* 2015; 8: 319–328.
47. Dolton P and Xiao M. The intergenerational transmission of body mass index across countries. *Econ Hum Biol* 2017; 24: 140–152.
48. Wang X, Xu X, Su S, et al. Familial aggregation and childhood blood pressure. *Curr Hypertens Rep* 2015; 17: 509.
49. Miliku K, Bergen NE, Bakker H, et al. Associations of maternal and paternal blood pressure patterns and hypertensive disorders during pregnancy with childhood blood pressure. *J Am Heart Assoc* 2016; 5: e003884.
50. Yesil GD, Gishti O, Felix JF, et al. Influence of maternal gestational hypertensive disorders on microvasculature in school-age children: The Generation R Study. *Am J Epidemiol* 2016; 184: 605–615.
51. Islam M, Jafar TH, Bux R, et al. Association of parental blood pressure with retinal microcirculatory abnormalities indicative of endothelial dysfunction in children. *J Hypertens* 2014; 32: 598–605.
52. Fugelseth D, Ramstad HB, Kvehaugen AS, et al. Myocardial function in offspring 5–8 years after pregnancy complicated by preeclampsia. *Early Hum Dev* 2011; 87: 531–535.
53. Stojanovska V, Scherjon SA and Plosch T. Preeclampsia as modulator of offspring health. *Biol Reprod* 2016; 94: 53.
54. Khan KS, Wojdyla D, Say L, et al. WHO analysis of causes of maternal death: A systematic review. *Lancet* 2006; 367: 1066–1074.
55. Basso O, Rasmussen S, Weinberg CR, et al. Trends in fetal and infant survival following preeclampsia. *JAMA* 2006; 296: 1357–1362.
56. Tapp RJ, Hughes AD, Kahonen M, et al. Cardiometabolic health among adult offspring of hypertensive pregnancies: The Cardiovascular Risk in Young Finns Study. *J Am Heart Assoc* 2018; 7: e006284.
57. Chen X and Wang Y. Tracking of blood pressure from childhood to adulthood: A systematic review and meta-regression analysis. *Circulation* 2008; 117: 3171–3180.
58. Rose G. Strategy of prevention: Lessons from cardiovascular disease. *Br Med J (Clin Res Ed)* 1981; 282: 1847–1851.
59. Groenhof TKJ, Zoet GA, Franx A, et al. Trajectory of cardiovascular risk factors after hypertensive disorders of pregnancy. *Hypertension* 2019; 73: 171–178.
60. Groenhof TKJ, van Rijn BB, Franx A, et al. Preventing cardiovascular disease after hypertensive disorders of pregnancy: Searching for the how and when. *Eur J Prev Cardiol* 2017; 24: 1735–1745.
61. Heida KY, Bots ML, de Groot CJ, et al. Cardiovascular risk management after reproductive and pregnancy-related disorders: A Dutch multidisciplinary evidence-based guideline. *Eur J Prev Cardiol* 2016; 23: 1863–1879.