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ORIGINAL RESEARCH

Multi-Organ Phenotypes of Offspring Born Following Hypertensive Disorders of Pregnancy: A Systematic Review

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BACKGROUND: Hypertensive pregnancies are associated with an increased risk of cardiovascular and neurological diseases in the offspring during later life. However, less is known about the potential impact on multi-organ phenotypes in offspring before disease symptoms occur. The objective of this systematic review was to determine the associations of fetal exposure to maternal hypertensive pregnancy with multi-organ phenotypes across developmental stages.

METHODS AND RESULTS: Ovid MEDLINE, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials), WoS, Scopus, CINAHL, and ClinicalTrials.gov were systematically searched until February 2024. Records were independently screened by 2 authors. Studies reporting on the structure or function of the heart, blood vessels, brain, liver, and kidneys in offspring of hypertensive pregnancies compared with a normotensive control population were included. Risk of bias was assessed using the Newcastle-Ottawa Scale. Extracted data were presented using harvest plots. Seventy-three studies including 7091 offspring of hypertensive pregnancies and 42 164 controls were identified that met the inclusion criteria. Thirty-two studies were investigations in fetuses, 24 in neonates and infants, 12 in children, 2 in adolescents, and 3 in adults. Offspring of hypertensive pregnancies had structural and functional changes in the heart compared with controls in some studies across developmental stages. Offspring of hypertensive pregnancies also had smaller occipital and parietal vessels, higher aortic intima-media thickness, and lower retinal arteriolar-to-venular ratio. Some conflicting evidence existed for other phenotypical alterations.

CONCLUSIONS: There is still inconsistent evidence of multi-organ structural and functional differences in offspring of hypertensive pregnancies. The evidence base could therefore be further strengthened through well-designed and conducted prospective studies.

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Hypertensive disorders of pregnancy represent a spectrum of pregnancy complications, including chronic hypertension, gestational hypertension, preeclampsia, eclampsia, and the syndrome of hemolysis, elevated liver enzymes, and low platelets.[1] These disorders affect 5.2% to 8.2% of all pregnancies globally.[2] Hypertensive pregnancies are associated with multi-organ changes[3] and increased risks of cardiac and cerebrovascular disease later in life in the mother.[4] Recent evidence suggests their offspring also have a

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RESEARCH PERSPECTIVE

What Is New?

- This systematic review revealed that offspring born to hypertensive pregnancies are, to some extent, at greater risk of developing subtle structural changes in the heart and impaired measures of ventricular systolic and diastolic function.
- Offspring of hypertensive pregnancies also had smaller occipital and parietal vessels, higher aortic intima-media thickness, and lower retinal arteriolar-to-venular ratio, although there were some inconsistent findings for other structural and functional alterations at different developmental stages.

What Question Should Be Addressed Next?

- Larger scale, longitudinal cohort studies are needed to better characterize subclinical structural and functional organ changes in offspring born to hypertensive pregnancies.

Nonstandard Abbreviations and Acronyms

LVM	left ventricular mass
LVMi	left ventricular mass indexed
PI	pulsatility index
PWV	pulse wave velocity
RAAS	renin-angiotensin-aldosterone system
RI	resistive index
RVM	right ventricular mass

26% increased risk for all-cause mortality.[5] Adult offspring of hypertensive pregnancies have both an increased cardiovascular risk[6] in later life and higher risk for neurological diseases.[7] Events in utero, including hypertensive pregnancies, influence fetal development with long-term health consequences that may persist after birth.[8]

Hypertensive pregnancies are multifactorial diseases, caused by genetic and environmental factors and the interplay of these factors between the mother, placenta, and fetus. Transcriptomic studies have revealed that the placenta has specific molecular subtypes: (1) a "canonical" subtype in typical preeclamptic pathways, involving altered secretion and hypoxia, (2) an "immune" subtype representing immune response genes related to poor placental immune tolerance and infectious pathology, and (3) a "maternal" subtype with normal placental gene expression that might be related to maternal cardiovascular dysfunction.[9] This placental insufficiency contributes to the adverse intrauterine environment and affects fetal developmental programming, though the unique impact on fetal physiology of the placental molecular subtypes remains unknown.

Developmental programming in fetuses of hypertensive pregnancies is also affected by the modification of enzymes, transcription factors, oxidative stress markers, methylation, and DNA histone modification.[10] Alterations specific to the renin-angiotensin-aldosterone system (RAAS) may play an important role in fetal programming of cardiovascular diseases and hypertension in offspring from hypertensive pregnancies, with evidence that epigenetic changes to RAAS genes contribute to hypertension in the offspring later in life.[10] An exaggerated inflammatory response leading to endothelial dysfunction is also a known pathophysiologic mechanism in hypertensive pregnancies, particularly in preeclampsia, that may affect fetal developmental programming[11] and influence the offspring's future health.

A narrative review of preclinical studies revealed that offspring of hypertensive pregnancies have cardiac structural and functional changes compared with offspring of normotensive pregnancies.[12] In 5-month-old rodent models, corresponding to adult age rats, in utero exposure to hypoxia resulted in cardiac hypertrophy and higher expression of collagen I and II in the offspring's left ventricle (LV) with a normal size of cardiomyocytes.[13] Hypertensive pregnancies are also associated with altered endothelial function[14] and systemic microvasculature changes[15] that may impact LV afterload and contribute to increased LV mass (LVM).

Because hypertensive pregnancies frequently exhibit increased placental resistance, right ventricular (RV) afterload in the fetus may increase as a consequence. The RV may be more susceptible than the LV because of the RV dominant circulation in fetuses,[16] leading to potential adverse changes in right ventricular mass (RVM).

Previous systematic reviews have shown that offspring born to hypertensive pregnancies had higher blood pressure and body mass index (BMI) compared with offspring of normotensive pregnancies.[17,18] Increased blood pressure from childhood can lead to cardiovascular remodeling, particularly in those with higher vascular stiffness.[19] Elevated blood pressure is also associated with arterial remodeling in young adulthood as demonstrated by greater carotid-femoral pulse wave velocity (PWV) and carotid intima-media thickness.[20]

Although guidelines currently include hypertensive pregnancies as a risk-enhancing factor for future cardiovascular disease in women,[4] they do not currently mention risk of later disease in their offspring. However, the potential impact of hypertensive pregnancies on

multi-organ phenotypes in the offspring before any cardiovascular and neurological symptoms occur remains unknown. Investigating such organ changes may help to increase our understanding of how and why cardio- and cerebrovascular diseases develop in offspring of hypertensive pregnancies, ultimately contributing to targeted secondary prevention, such as screening using multi-organ imaging approaches, and treatment strategies. This systematic review examines the available evidence for associations between hypertensive pregnancies and structural and functional changes in the heart, blood vessels, brain, liver, and kidneys in the offspring. We hypothesized that offspring of hypertensive pregnancies have adverse multi-organ structural and functional differences compared with offspring born to normotensive pregnancies, particularly higher LVM and RVM.

OBJECTIVE

Our objective was to provide an evidence-based consensus as to whether a history of fetal exposure to maternal hypertensive pregnancies is associated with multi-organ structural or functional changes across developmental stages by comparing offspring from hypertensive pregnancies to offspring from normotensive pregnancies.

METHODS

Institutional board or ethics committee review was not required. This is a systematic review and does not involve new recruitment of participants. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[21] as well as the Synthesis Without Meta-analysis[22] reporting guidelines. The review protocol was registered with PROSPERO (CRD42023387550). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Search Strategy and Selection Criteria

The search strategy was developed by combining key terms and medical subject headings related to phenotypic outcomes of offspring born to hypertensive pregnancies (Tables S1). Electronic database searches were performed in MEDLINE and EMBASE (via Ovid), CENTRAL (Cochrane Central Register of Controlled Trials), Web of Science Core Collection, Scopus, and The Cumulative Index to Nursing and Allied Health Literature. All publications from inception until February 8, 2024, were searched by 1 reviewer (P.D.S.) without any language or article type restrictions. Bibliographies of retrieved articles and relevant systematic reviews were manually reviewed for potentially eligible studies. Additional searches were conducted on ClinicalTrials.gov registry on February 8, 2024, to identify ongoing studies.

Exposure and Outcomes

Populations included in this review were fetuses, neonates, infants, children, adolescents, and adults. Exposed groups consisted of offspring born to mothers with hypertensive pregnancies, whereas non-exposed (or control) groups consisted of offspring born to mothers with normotensive pregnancies. These normotensive pregnancies represent healthy pregnancies, including uncomplicated or uneventful pregnancies.

Primary outcomes included cardiac left and right ventricular mass, either absolute values or indexed to body surface area or height. Additional outcomes related to the structure or function of the heart, blood vessels, brain, liver, or kidneys were extracted and evaluated as well. No restrictions were applied to the type of imaging modality. Whenever available, Z score data or data standardized to body surface area were included.

Study Selection

Records identified through database searches were imported into the Systematic Review Accelerator for deduplication.[23] After manual removal of remaining duplicates, all unique abstracts were independently screened by at least 2 authors (P.D.S., A.S., H.R.C., M.A.) using Rayyan software.[24] Inter-rater reliability for title/abstract screening was assessed (Data S1).

Abstracts fulfilling inclusion criteria were selected for full text review. Prospective or retrospective studies evaluating offspring of hypertensive pregnancies were selected with the following inclusion criteria: (1) original research articles in humans; (2) research reporting on the structure or function of the heart, blood vessels, brain, liver, or kidneys in offspring; and (3) papers with availability to compare against those born to normotensive pregnancies. We excluded studies with unavailable outcome data of interest. Abstracts with selection discrepancies were evaluated by independent authors (A.J.L., V.Y.A., D.S.N.).

Selected full texts were evaluated according to the eligibility criteria to identify studies reporting on organ structure or function in offspring of hypertensive pregnancies compared with controls. Any disagreements for inclusion following a full-text review were resolved through discussion.

Data Extraction

Data were extracted using a standardized extraction form by a single reviewer (P.D.S.) and independently verified by other reviewers (A.S., H.R.C., M.A.) for accuracy

and completeness. Any disagreement was resolved by discussion. The following data were extracted: first author, publication year, country of study conduction, study design, setting, age at measurement, the total number of offspring of hypertensive pregnancies and controls, outcome measures, and the severity and gestational age at hypertensive pregnancies onset if available. When the required data could not be extracted, authors of the relevant studies were contacted. First or last authors of 19 relevant studies, including conference abstracts, were contacted. This resulted in the retrieval of unpublished data from 2 publications.[25,26]

Risk of Bias Assessment

Risk of bias in each study was assessed independently by at least 2 authors (P.D.S., A.S., H.R.C., M.A.) using the Newcastle–Ottawa Scale for observational studies (Data S2).[27] Studies were assessed based on the methods that were used to measure a particular study outcome, whether by taking serial measurements (cohort) or snap-shot data (cross-sectional), regardless of the predefined overall study design. The cohort studies were evaluated by: (1) the representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at start of study; (5) comparability of exposed and unexposed cohorts on the basis of the design or analysis; (6) assessment of outcome; (7) whether follow-up was long enough for outcomes to occur; and (8) adequacy of follow-up of cohorts. To provide a quality assessment of the included studies with cross-sectional data, the scale was adapted from the Newcastle–Ottawa Scale for cohort studies to evaluate the cross-sectional studies[28] by considering: (1) representativeness of the sample; (2) sample size; (3) ascertainment of exposure; (4) nonrespondents; (5) comparability of groups on the basis of the design or analysis; (6) assessment of outcome; and (7) statistical test. Each domain can be awarded a maximum of 1 star, except for comparability (for both cohort and cross-sectional studies) and ascertainment of exposure (for cross-sectional studies only), which were allowed a maximum of 2 stars. Any discrepancies were addressed by a re-evaluation of the original article. The total score for each study was obtained by summing all domain scores; a final score of 1 to 3 stars indicated high risk of bias, 4 to 6 stars indicated medium risk, and 7 to 9 stars indicated low risk. Inter-rater reliability for risk of bias assessment is reported in Data S1. A quality check for predatory behavior of publishers of included studies was also performed (Data S3).

Data Synthesis and Analysis

Findings were organized according to developmental stages (eg, fetuses, neonates and infants, children, adolescents, and adults) and outcome measures. Meta-analysis cannot be performed in this systematic review because of the unavailability of Z-score data, the expected heterogeneity of the included observational studies, and the limited number of studies for the outcomes of interest. Because meta-analysis relies on the degree of homogeneity between studies, another method of evidence synthesis needed to be considered.[22] Instead, we presented the extracted data using harvest plots, which provide a mean to synthesize the available evidence for a given exposure-outcome relationship by grouping studies based on the direction of their reported effects.[29] To this end, each study's direction of effect was extracted for each outcome, and the category of effect was defined as a "favorable outcome," "no difference" ($P>0.05$), or "unfavorable outcome" toward offspring of hypertensive pregnancies compared with controls (Table S8). If outcome measurements deviated from normal values and were generally considered to lead to negative health impacts (eg, higher LVM), they were considered "unfavorable outcomes." Studies in the harvest plots are represented by the bars, the color of the bar codes the developmental stage, the height of the bar describes the sample size of the exposed group, and the asterisk above the bar represents the study with low risk of bias.

Sample sizes were defined, based on the number of participants included in the exposed group, as small (n≤25), medium (n=26–100), or large (n>100). When multiple publications originated from the same study, all publications were reported but only the study with the most comprehensive data was included for evidence synthesis. Evidence was synthesized from all these studies with low to moderate risk of bias.

RESULTS

Study Selection and Characteristics

The search strategy identified 7987 unique records, of which 7835 were excluded during initial abstract screening. The remaining 152 articles were carried forward for full text review, resulting in 75 articles being excluded (Table S9) and 77 included in our final review (Figure 1). Among 77 (Table S10) included articles, 73 were unique studies collectively including 49 255 offspring (hypertensive pregnancies offspring: n=7091; controls: n=42 164) (Figure 2). Studies were conducted in the following geographical regions: Europe (n=27), Asia (n=34), North America (n=3), South America (n=5), Oceania (n=3), and Africa (n=1). Stratified by developmental stages, there were 32 studies investigating fetuses, 24 investigating neonates and infants (birth to ≤1 year), 12 investigating children (>1 to ≤14 years), 2 investigating adolescents (>14 to <18 years), and 3 investigating adults (≥18 years). Ongoing studies were

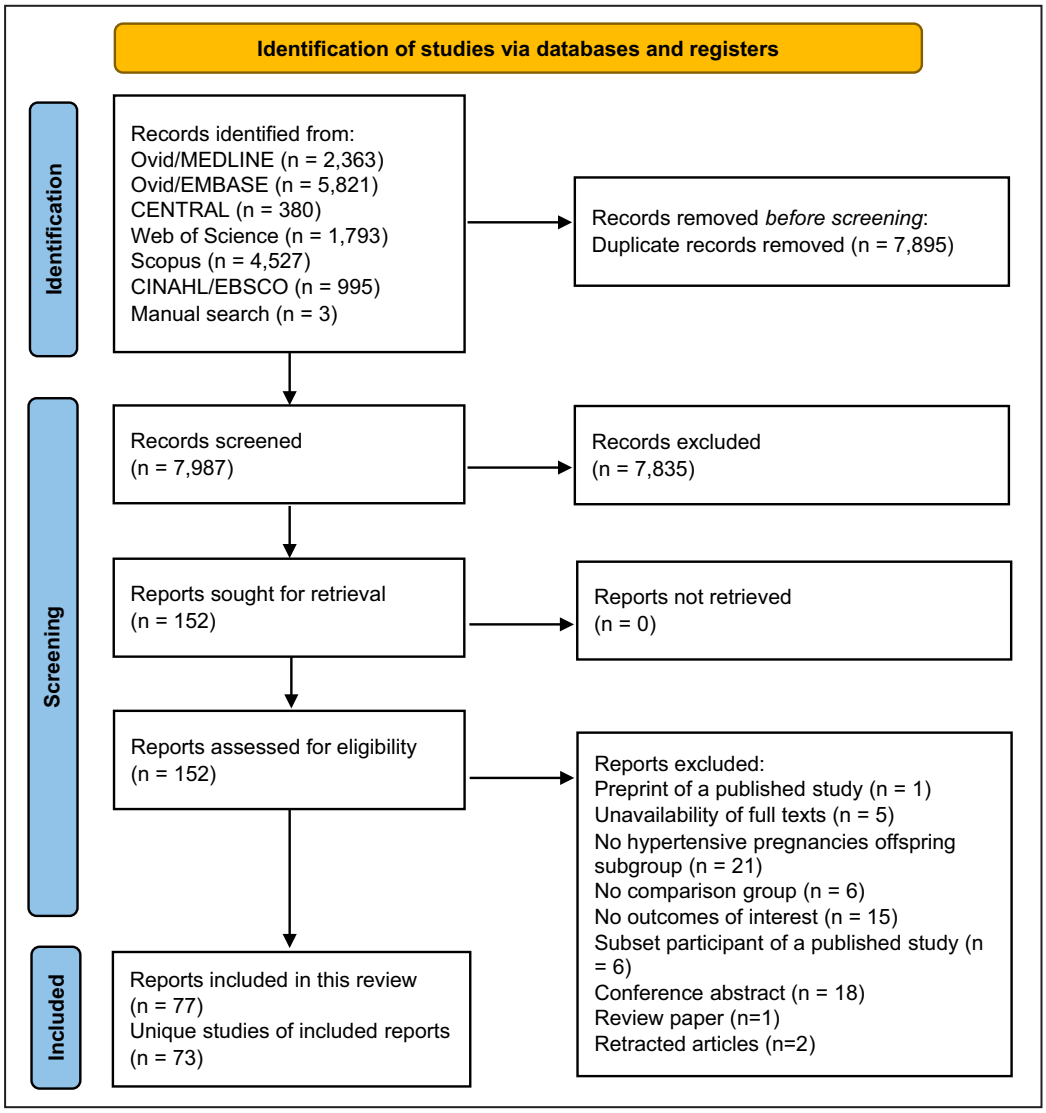

Figure 1. Flow diagram of the study selection process.
CENTRAL indicates Cochrane Central Register of Controlled Trials; CINAHL, The Cumulative Index to Nursing and Allied Health Literature; EBSCO, Elton Bryson Stephens Company; EMBASE, Excerpta Medica Database; and MEDLINE, Medical Literature Analysis and Retrieval System Online.

searched through ClinicalTrials.gov to identify potential reports on offspring of hypertensive pregnancies investigating organ phenotypes. There were 533 registers found, and only 1 study fulfilled the eligibility criteria.

Risk of Bias of Included Studies

Based on the Newcastle–Ottawa Scale, 20 studies were graded as low risk, 52 as moderate risk, and 2 studies were deemed high risk of bias (Table S10). In terms of participant selection, most studies (n=57/73) had exposed and control participants that were representative of the general population. There were 45 studies that did not provide adequate sample size calculations. All included studies confirmed maternal hypertensive pregnancies history through medical records or registry data, leaving no studies with increased risk of bias because of the ascertainment of exposure. Only 13 of 73 studies provided detailed information on recruitment processes (eg, using flowcharts), leading to a risk of bias on the selection of participants. For the outcome assessment, 40 studies did not provide a statement on the blinding of the assessor toward the exposure of hypertensive pregnancies. Nevertheless, the included studies were all low to moderate risk of bias and 2 were deemed high risk of bias.

Cardiac Structure and Function

Figure 3 depicts the included studies with reported outcomes on cardiac structure and function.[25,26,30-57] A total of 38 studies reported on cardiac structure or function in

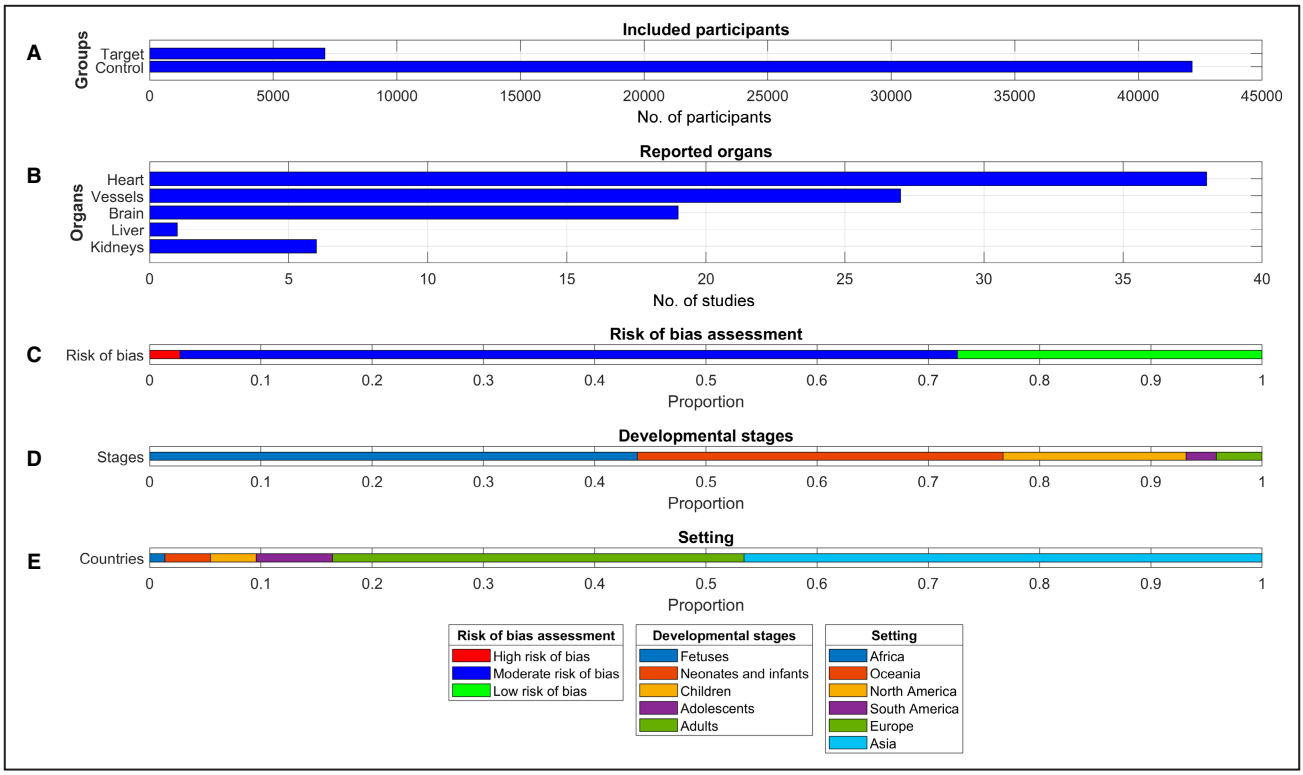

Figure 2. A statistical abstract illustrating the overall findings of literature search on the impact of hypertensive disorders of pregnancy on the offspring.

This systematic review included 73 unique studies, the majority with moderate risk of bias, performed mainly in Asia and Europe, that reported multi-organ structure and function using multimodal imaging across developmental stages. **A** indicates Included participants; **B**, Reported organs; **C**, Risk of bias assessment; **D**, Developmental stages; and **E**, Setting.

offspring of hypertensive pregnancies. The primary outcomes for this review were LVM and RVM, which were reported in 8 and 1 study, respectively (Figure 3). Included studies predominantly investigated cardiac structure and function using echocardiography, with 2 presenting magnetic resonance imaging (MRI)-derived data.[25,35]

Four studies reported LVM data (Table S11). Of the 6 included studies with LVM indexed (LVMi) data, 2 studies with low risk of bias reported higher LVMi in offspring of hypertensive pregnancies versus controls (Table S12).[32,54] A study performed in infancy showed that offspring of hypertensive pregnancies had similar LVMi at birth (20.6±4.0 versus 20.9±3.7 g/m^2, P=0.64) and then higher LVMi at 3-month follow-up (26.8±4.9 versus 24.9±4.6 g/m^2, P=0.04),[32] demonstrating a significant change during the first 3 months of life. The Avon Longitudinal Study of Parents and Children, with a follow-up performed during adolescence at age 17 years, reported a larger LVMi in offspring of gestational hypertension and essential hypertension compared with controls (30±7 and 31±7 versus 29±6 g/m$^{2.7}$, P=0.003).[54] However, the effect of increased LVM was not apparent in a children's MRI study.[35]

In addition to LVMi, the aforementioned study in infancy[32] also reported RVM indexed to body surface area in offspring of hypertensive pregnancies that showed similarity to controls (18.1±4.7 versus 17.5±3.7 g/m^2, P=0.57) at birth and a similar pattern of higher increase during the first 3 months of life (21.1±3.9 versus 17.1±4.2 g/m^2, P<0.001) (Tables S13 and S14). Relative LV wall thickness was reported to be higher in offspring from hypertensive pregnancies versus controls during the fetal period and adolescence; however, no difference was observed in other fetal, child, and adult studies (Table S15).

Tables S16 through S18 present LV ejection fraction, LV stroke volume, and RV ejection fraction reported in the included studies. There were 3 low-risk-of-bias, population-based cohort studies that reported findings related to cardiac volumes.[26,35,53] After adjusting for sex, gestational age, birth length, birth weight, and age, the Copenhagen Baby Heart Study reported LV remodeling in infants exposed to hypertensive pregnancies (n=1223) versus controls (n=17 384) in terms of higher LV end-systolic volume, higher LV internal diameter in diastole, thicker interventricular septum, and thicker LV posterior wall in diastole.[26] Using MRI, The Generation R Study demonstrated that children born to preeclamptic pregnancies (n=45) had lower

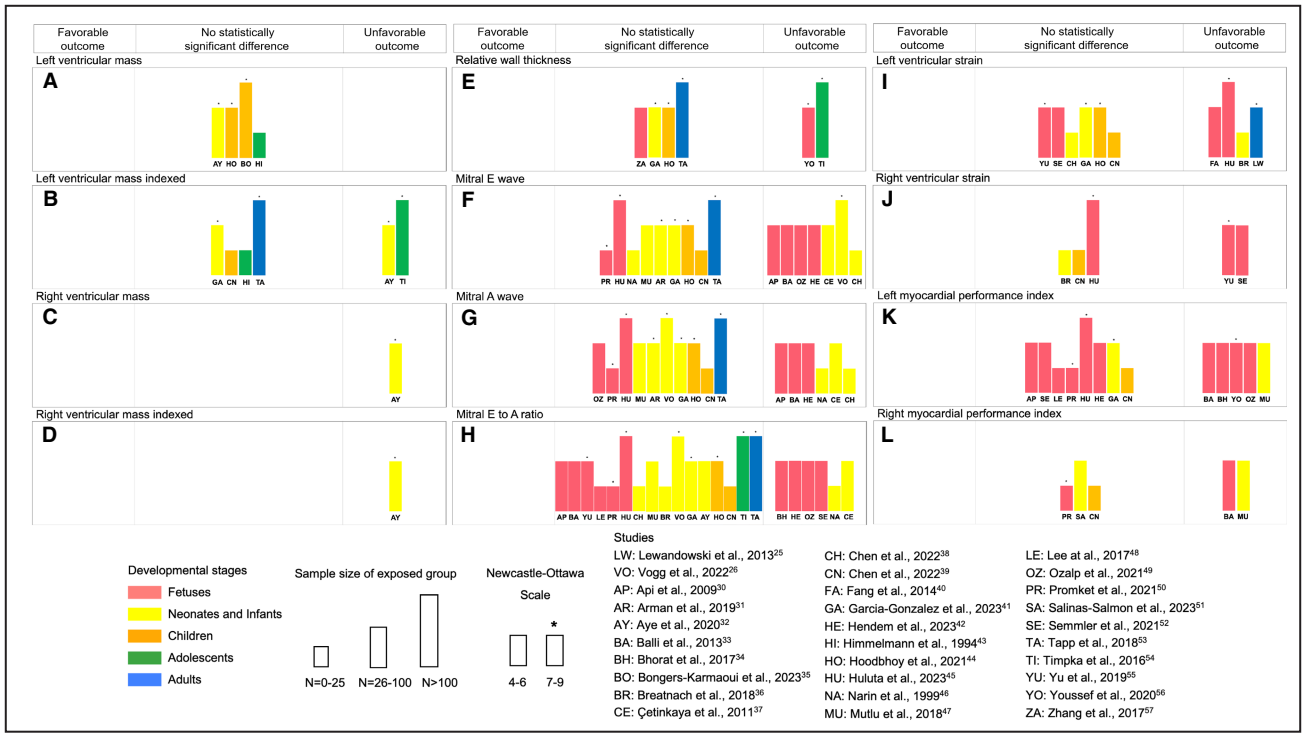

Figure 3. Harvest plot summarizing the effect of hypertensive pregnancies on the heart structure and function of the offspring.

The direction of effect was defined for each outcome and the type of effect size measure was classified as "no difference" or "unfavorable outcome." Studies are represented by the bars, the color of the bar codes the developmental stage, the height of the bar describes the sample size of the exposed group (N=number of participants), and the asterisk above the bar represents the study with low risk of bias. Included studies corresponding to each outcome are represented by the initials of the first author. **A** indicates Left ventricular mass; **B**, Left ventricular mass indexed; **C**, Right ventricular mass; **D**, Right ventricular mass indexed; **E**, Relative wall thickness; **F**, Mitral **E** wave; **G**, Mitral A wave; **H**, Mitral E to A ratio; **I**, Left ventricular strain; **J**, Right ventricular strain; **K**, Left myocardial performance index; and **L**, Right myocardial performance index.

RV ejection fraction compared with those born to gestational hypertension (n=87) and normotensive pregnancies (n=2322) with no structural differences among them.[35] Although no LV structural differences were reported from the Cardiovascular Risk in Young Finns Study, adult offspring of hypertensive pregnancies (n=129) have an increase in left atrial volume indexed to body surface area compared with controls (n=877).[53]

Offspring of hypertensive pregnancies had lower diastolic function in some, but not all, studies (Tables S19–S23). A total of 6 out of 16 studies reported a decrease in mitral E wave (Table S21) and 5 of 16 studies reported a decrease in mitral A wave (Table S22). A resultant decrease in mitral E to A ratio was reported in 3 of 22 studies (Table S23).[34,37,49] In contrast, 3 studies reported an increase in mitral E to A ratio.[42,46,52] Although 2 of 7 studies reported a decrease in mitral lateral e',[33,58] only 1 of the 8 studies reported significant differences in mitral E to e' ratio in preeclamptic fetuses.[45]

Particularly in fetal and infancy studies, offspring of hypertensive pregnancies had decreased ventricular function as shown by higher LV myocardial performance index in 5 of 13 studies (Table S24) and a higher RV myocardial performance index in 2 of 5 studies (Table S25). Compared with controls, offspring of hypertensive pregnancies had a lower LV strain in fetal,[40,45] neonate,[36] and adult studies[25] as well as a lower RV strain in 2 fetal studies.[52,55] The other studies reported nonsignificantly reduced LV strain (Table S26) in fetuses[52,55] and children[39,44] and nonsignificantly reduced RV strain (Table S27) in neonates[36] and children[39] born to mothers with hypertensive pregnancies compared with controls.

Vascular Structure and Function

Figure 4 presents the findings on vascular structure and function.[33,39,44,53,59-70] Offspring of hypertensive pregnancies showed significantly smaller aortic root inner diameters compared with controls in 1 infancy study (Table S28), although another fetal study did not reveal any statistical differences in aortic root diameter. Offspring of hypertensive pregnancies had a thicker aortic intima-media thickness in 1 fetal and 3 neonatal studies (Table S29). Although the young adult

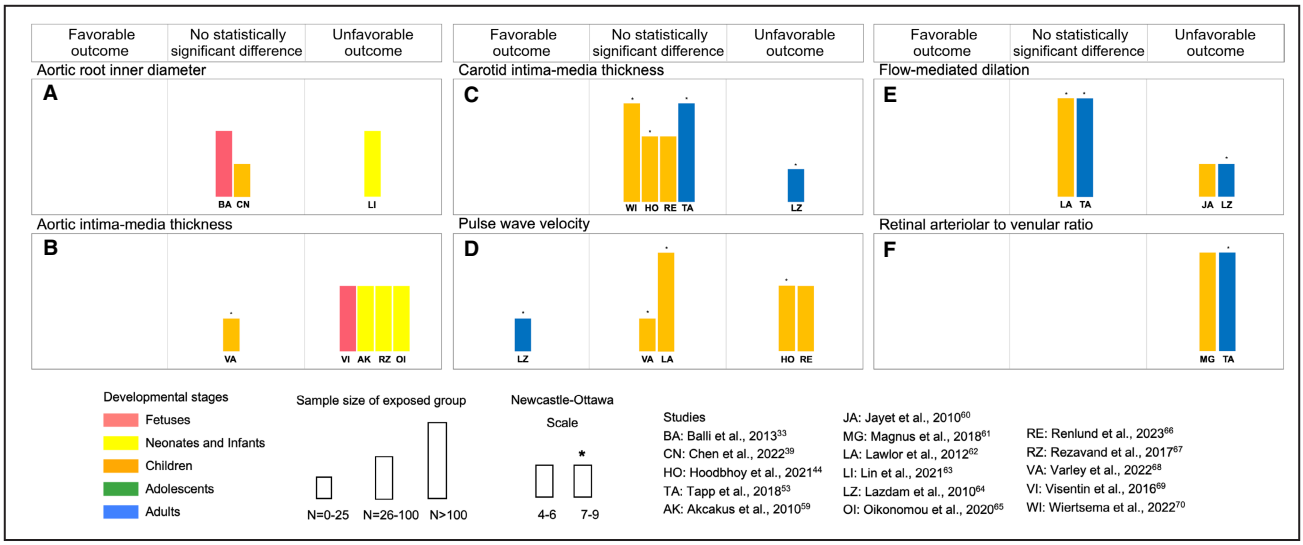

Figure 4. Harvest plot summarizing the effect of hypertensive pregnancies on the vascular structure and function of the offspring.

The direction of effect was defined for each outcome and the type of effect size measure was classified as "favorable," "no difference," or "unfavorable outcome." Studies are represented by the bars, the color of the bar codes the developmental stage, the height of the bar describes the sample size of the exposed group (N=number of participants), and the asterisk above the bar represents the study with low risk of bias. Included studies corresponding to each outcome are represented by the initials of the first author. **A**, Aortic root inner diameter. **B**, Aortic intima-media thickness. **C**, Carotid intima-media thickness. **D**, Pulse wave velocity. **E**, Flow-mediated dilation. **F**, Retinal arteriolar to venular ratio.

study found a thicker cIMT in preterm offspring of hypertensive pregnancies compared with both preterm and term controls,[64] other studies failed to demonstrate this difference in children and older adults (Table S30). Of 4 studies that reported PWV in offspring of hypertensive pregnancies, 2 studies showed higher PWV in childhood[44,66] and 1 study reported lower PWV in adulthood (Table S31).[64] Although no difference was shown in large-scale child[62] and adult studies,[53] flow-mediated dilation was >30% lower in the childhood of offspring of hypertensive pregnancies[60] and 30% lower in preterm young adult offspring of hypertensive pregnancies[64] compared with offspring of normotensive pregnancies (Table S32).

Children born to mothers with hypertensive pregnancies had a delay in the endothelial independent myogenic response and impaired post-ischemic vasodilation as reflected by the increased time to maximum perfusion without an increase in peak perfusion.[71] This study also reported different microvascular impairment patterns in offspring of hypertensive pregnancies in which female children showed impaired endothelial function, whereas male children showed increased vascular stiffness. Sex-specific alterations in microvascular function have also been demonstrated earlier during the first 3 days of life.[72] This peripheral microvascular blood flow was investigated on the lateral aspect of lower limb using laser Doppler flowmetry. At 6 hours of age, female infants of preeclamptic pregnancies had similar microvascular blood flow compared with offspring of normotensive pregnancies, followed by significantly greater blood flow by 72 hours. In contrast, male infants of preeclamptic pregnancies showed greater blood flow at 6 hours of life with no change until 72 hours.

Total vessel density reduced significantly between birth and 3 months postpartum in infants born to hypertensive pregnancies, with a significant lower total vessel density at 3 months old in the hypertensive pregnancy group.[15] Another study showed that term infants born to hypertensive pregnancies had significantly lower maximal capillary density compared with term infants of normotensive mothers.[73] Microvascular structure was also explored through retinal imaging in 2 population-based studies (Table S33). Although neither study found any difference in the retinal arteriolar and venular diameter, there was lower retinal arteriolar-to-venular ratio of gestational hypertension offspring aged 13 years[61] and hypertensive pregnancies offspring aged 34 to 49 years.[53]

Brain Structure and Function

Five of 9 fetal studies with data on middle cerebral artery pulsatility index (PI) reported lower values for those born after hypertensive versus normotensive pregnancies and lower resistive index (RI) in 1 fetal study (Tables S34 and S35). A fetal study revealed a lower total corpus callosum area in fetuses of hypertensive pregnancies with fetal growth restriction.[74] In terms of cortical development, fetuses from hypertensive pregnancies had reduced Sylvian fissure depth and greater insula depth (Table S36).[75]

Seven studies investigated offspring of hypertensive pregnancies using MRI, with 2 of them performed during the fetal period, 4 during infancy, and 1 during childhood. In 1 structural MRI infancy study, there were no differences in the global and regional brain volumes between offspring of hypertensive pregnancies and controls.[76] During infancy, diffusion tensor imaging examination showed that lagging brain development was detected using fractional anisotropy in the splenium of the corpus callosum, posterior limbs of the internal capsule, and superior frontal gyrus of offspring from hypertensive pregnancies.[77] Synthetic MRI performed in infants of hypertensive pregnancies demonstrated abnormal brain development with higher T1 and T2 values of the posterior limb of the internal capsule, parietal white matter, central semiovale white matter, ventral lateral nucleus of the thalamus, caudate nucleus, and cerebellum compared with controls.[78] In contrast, a hypertensive pregnancies infancy study indicated a favorable outcome of brain maturation and an increase in neuronal integrity of bilateral thalami explored using magnetic resonance spectroscopy.[79]

An exploratory MRI study performed in childhood showed that offspring of hypertensive pregnancies had enlarged regional volumes of the cerebellum, temporal lobe, brain stem, and right and left amygdala with reduced cerebral vessel radii in the occipital and parietal lobes.[80] Adverse hypertensive pregnancies exposure was further explored in those participants using resting-state functional connectivity, showing that offspring of hypertensive pregnancies had an altered resting-state functional connectivity between several brain areas.[81] A diffusion tensor imaging performed on the same participants showed increased fractional anisotropy in the caudate nucleus, increased volume of the tract for the superior longitudinal fasciculus and the caudate nucleus, and increased parallel diffusivity of the cingulate gyrus. This demonstrates that fetal exposure to hypertensive pregnancies affects microstructural properties in terms of myelination patterns and white matter connectivity (Table S37).[82]

Liver and Gastrointestinal Structure and Function

There were no differences in hepatic flow index, hepatic vascular index, or vascularization flow index in fetuses of hypertensive pregnancies compared to fetuses of healthy pregnancy (Table S38).[83] Regarding Doppler measurement of superior mesenteric artery blood flow velocity, infants of mothers with early-onset hypertensive pregnancies showed significantly lower values of peak systolic and end-diastolic velocity compared with controls.[84]

Renal Structure and Function

Although the volumes of kidneys did not differ between fetuses of hypertensive pregnancies and controls at gestational weeks 19 to 24 and 29 to 32, fetuses of hypertensive pregnancies had significantly 19.6% smaller kidney volumes at 34 to 37 gestational weeks (Table S39).[69] Five fetal studies investigated fetal renal artery PI and RI, which presented inconsistent results. Some studies showed that exposure to hypertensive pregnancies was associated with higher values for both indices, higher PI only, lower values for both indices, or lower RI only (Tables S40 and S41).

DISCUSSION

This is the first systematic review conducted to explore the impact of hypertensive disorders of pregnancy on the multi-organ structure and function in the offspring, providing the evidence that history of being born to hypertensive pregnancies may be associated with multi-organ phenotypic structural and functional changes compared with those born to normotensive pregnancies. Although a history of hypertensive pregnancies is now recognized as a cardiovascular risk factor in women, less has been explored about the impact on the affected offspring. Individuals born to mothers with hypertensive pregnancies are at increased risk for cardiovascular morbidity in later life.[85] Offspring of hypertensive pregnancies also had an increased risk for cardiovascular disease and neurological disease.[86,87] Nevertheless, our current systematic review shows that there is still inconsistent evidence on multi-organ structural and functional differences in offspring of hypertensive pregnancies.

Overexpression of soluble fms-like tyrosine kinase-1 (sFLT) in mouse models has been shown to increase systolic and diastolic blood pressure in male offspring.[88] Elevated blood pressure—a common risk factor for cardiovascular and neurological diseases—is often observed in individuals born to hypertensive pregnancies,[89] which may be partially driven by genetics or familial non-genetic risk factors. This may include shared genetic variants, common environmental exposures that predispose to hypertension, or direct intrauterine effects such as maternal inflammation, endothelial dysfunction, or poor placentation linked to preeclampsia.[90]

In fetuses of preeclamptic pregnancies, increased sympathetic tone leads to fetal cardiac dysautonomia[91] and an increase in the tone of fetal renal arteries.[92] Although RAAS may play a critical role in fetal developmental programming, it is unclear whether dysregulation of RAAS occurs as a consequence of placental insufficiency in hypertensive pregnancies or as a contributing factor in the development of

hypertensive pregnancies.[93] Additional to alterations in the sympathetic nervous system and RAAS, offspring of hypertensive pregnancies show an increase in hypothalamic–pituitary–adrenal axis activity, which contributes to increased blood pressure in the adolescence period.[94] All of these adaptations may increase the susceptibility to adverse cardiac remodeling in offspring of hypertensive pregnancies.

External stressors such as environmental and lifestyle factors during the developmental period are likely contributors to the increased adverse cardiovascular and metabolic risk profile. Blood pressure baseline data of offspring born to hypertensive pregnancies were available in 19 out of 73 studies in this review. Among those studies, 8 studies showed that offspring of hypertensive pregnancies had higher blood pressure compared with offspring of normotensive pregnancies (Table S10).

We found that, in some studies, fetal exposure to hypertensive pregnancies might be associated with higher offspring cardiac LVMi and RVM indexed, thicker relative wall thickness, more impaired mitral E to A ratio, lower LV strain, and higher biventricular myocardial performance index. The evidence of adverse cardiac remodeling in offspring of hypertensive pregnancies was supported by population-based prospective cohort studies in children where exposure to maternal preeclampsia was associated with lower RF ejection fraction[35] and in adolescence demonstrating that fetal exposure to hypertensive pregnancies was associated with a higher LV relative wall thickness and reduced LV end-diastolic volume.[54]

A preclinical study by Armstrong et al[95] demonstrated that LV remodeling may be attributable to the significant increase in Gata4, Gata6, and P300 gene expression, which are responsible for cardiomyocyte differentiation and cardiac development. The rodent model in this study showed that offspring of gestational hypertension, with chronically maternal hypertensive atrial natriuretic peptide knockout, had thicker relative wall thickness and restrictive filling patterns as a sign of diastolic dysfunction.[95] These mice had significant LV hypertrophy with no change in LV function, and subsequent cardiac stress resulted in significant LV diastolic dysfunction and interstitial myocardial fibrosis.

The pathophysiological changes in hypertensive pregnancies may be mediated by exposure to adverse intrauterine environments. The pathophysiological mechanism of preeclampsia includes angiogenic imbalance, excessive inflammation, ischemia/perfusion, and the production of oxidative stress.[96,97] Preeclamptic placentas release cytokines and circulating factors into the maternal circulation because of syncytiotrophoblast stress that results in excessive inflammation and formation of reactive oxygen species. All of these may mediate fetal and developmental programming by altering cell signaling and physiological conditions during a critical developmental window.[11,16,98]

The association between hypertensive pregnancy exposure and offspring cardiovascular disease risk may be explained by shared alleles between mothers and offspring as well as shared environmental and lifestyle factors.[11] Offspring of hypertensive pregnancies have more cardiovascular risk factors than controls, including higher blood pressure and BMI.[6,17] External stressors, as well as environmental and lifestyle factors during the developmental period, are likely contributory factors for the adverse cardio-cerebrovascular and metabolic risk profile in offspring of hypertensive pregnancies.

A lower mitral E to A ratio reported in offspring of hypertensive pregnancies might be related to impaired relaxation as can be seen in grade 1 diastolic dysfunction. In contrast, a higher mitral E to A ratio might reflect increased rapid early filling or decreased atrial contribution to LV diastolic filling. Ventricular function was also explored using global longitudinal strain, which represents the magnitude of myocardial deformation, in which lower strain implies reduced contractile function. This review demonstrated that offspring of hypertensive pregnancies had a lower LV and RV strain compared to controls. It is important to note that myocardial strain impairment has previously been reported in mothers with hypertensive pregnancies.[99] Furthermore, fetal and infant offspring of hypertensive pregnancies had a higher LV and RV myocardial performance index. Myocardial performance index increases under pathological conditions, such as an increase in cardiac afterload secondary to increased placental vascular resistance in hypertensive pregnancies.[100]

Changes in vascular structure and function of offspring born to hypertensive pregnancies may include arterial thickening and abnormal endothelial dilatation.[12] Endothelial dysfunction was evident in offspring exposed to preeclampsia in utero,[60,101] which represents an early biological marker of cardiovascular disease. From this review, offspring of hypertensive pregnancies in early years had higher aortic intima-media thickness compared with controls. Although greater cIMT is generally considered a surrogate marker of subclinical atherosclerosis, physiological adaptation might underlie the subtle change in cIMT involving the medial layer in young populations.[102] Changes in arterial stiffness represented by PWV can be observed since later childhood and adolescence. In a meta-regression analysis, increased PWV in later childhood and adolescence associated with early life factors including small gestational age and exposure to maternal diabetes, which associated with increased future cardiovascular disease risk.[103]

Offspring of hypertensive pregnancies also showed inferior vascular function during childhood that may support the hypothesis of endothelial dysfunction and less compliant microvasculature. Microvascular

changes may be identified decades before cardiovascular events. Retinal imaging is a noninvasive way to directly observe human microvasculature. Offspring of hypertensive pregnancies in later years were shown to have a lower retinal arteriolar-to-venular ratio,[53,61] which is predictive of cardiovascular events.

Offspring of hypertensive pregnancies also demonstrated lower adaptive functioning and mental well-being compared with normotensive offspring.[104] These observations may be linked to lower fetal tissue oxygenation in offspring of hypertensive pregnancies.[105] The Helsinki Birth Cohort showed that adult offspring of hypertensive pregnancies were at increased risk of stroke that might be attributable to a local disorder of cerebral blood vessels.[7] This review detected differences in cerebrovascular physiology on the fetal period, as fetuses born to hypertensive pregnancies showed a lower middle cerebral artery PI and lower RI in some studies. A pilot study investigating children born to hypertensive pregnancies revealed smaller occipital and parietal vessels, and enlarged regional volumes of the cerebellum, temporal lobe, brain stem, and right and left amygdala as well.[80] Collectively, these studies suggest an association of hypertensive pregnancies with modest alterations in offspring brain structure and function, which may persist from the fetal period into childhood.

Only 1 study investigated fetal liver blood flow, and no studies were performed after birth evaluating liver structure or function in offspring of hypertensive pregnancies. In hypertensive pregnancies, it is hypothesized that there is preferential blood shunting to the fetal brain at the expense of the fetal liver. However, 1 small-scale study failed to demonstrate this effect.[83]

One study investigating fetuses born to hypertensive pregnancies showed that they had smaller kidney sizes compared with controls.[69] Developing kidneys in the fetal period are susceptible to an adverse intrauterine environment, and reduced numbers of nephrons were demonstrated in preterm and low birth weight offspring, which often co-exist with hypertensive pregnancies.[106] During hypertensive pregnancies, fetal organs might adapt to hypoxic conditions to provide adequate blood supply to vital organs (eg, brain), by decreasing blood flow to other organs (eg, the kidneys). The included fetal studies showed conflicting results on whether hypertensive pregnancies would affect renal arteries' PI and RI. However, altered fetal renal artery blood flow was demonstrated as fetuses of hypertensive pregnancies had significantly lower vascularization index, flow index, and vascularization flow index.[107]

Abnormalities in utero-placental function during hypertensive pregnancies may result in fetal complications including preterm birth and intrauterine growth restriction. The association between preterm birth and cardiac structure and function has previously been demonstrated,[25,108] with the differences emerging since early life.[109] From this systematic review, we revealed that the differences in heart structure[32,54] and function[36,40] were also apparent in term offspring of hypertensive pregnancies, suggesting an independent impact of hypertensive pregnancies on cardiac development apart from prematurity.

Severe preeclampsia is associated with higher maternal cardiovascular disease risk and early onset preeclampsia (<34 gestational weeks) increases the risk for maternal cardiovascular disease.[110] Further work is needed to determine to what extent timing of onset and severity of maternal hypertensive pregnancies affect the future health status of the offspring. Nevertheless, neonates of early-onset preeclampsia were shown to have increased total cholesterol levels while those from late-onset preeclamptic pregnancies had reduced total cholesterol levels.[111] In a population registry study from Denmark and Sweden, children and adolescents born to mothers with preeclampsia had higher risk for neurodevelopmental disorders, with the greatest magnitude of effect in those born to early-onset and severe preeclamptic pregnancies.[112] Similarly, in a population registry study in adults born in Denmark, Sweden, and Finland, preeclampsia was associated with a higher risk for stroke in the offspring, with the greatest magnitude of effect in those born to early-onset and severe preeclampsia.[113] While some included studies in this current review provided information about the severity and onset of maternal hypertensive pregnancies (Table S10), there is not enough evidence to determine whether the severity and onset of maternal hypertensive pregnancies are associated with unfavorable organ changes in offspring.

In terms of ethnicity, participants in the included studies across developmental stages did not represent the worldwide population. Studies on adolescence and adulthood were only available from European countries. Therefore, there is no conclusive evidence of whether any particular structural and functional difference is experienced by certain ethnicities. Neonatal and childhood studies indicated sex-specific patterns of microvascular function alterations in offspring of hypertensive pregnancies.[71,72] Nonetheless, the effect of sex differences on other outcomes has not been investigated. Previous studies revealed that male and female offspring born to hypertensive pregnancies had similar risks for developing hypertension[89] and similar rates of cardiovascular mortality.[5] However, male offspring appear to have an increased risk for developmental programming changes.[114] Preclinical investigations showed this may relate to a protective effect of estrogen in female rodent offspring born to gestational hypertension-induced sensitization of angiotensin II hypertension.[115]

Offspring of hypertensive pregnancies have been demonstrated to have higher BMI compared with offspring of normotensive pregnancies,[18] with a retrospective cohort study showing offspring of hypertensive

pregnancies have an increased risk of being overweight and obese in adolescence.[116] It is plausible that the increased risk of obesity may share a common pathway with the greater risk of cardiovascular dysfunction in offspring born to hypertensive pregnancies.

Taken all together, the included studies produced inconsistent findings about the association of hypertensive pregnancies and structural or functional organ changes in offspring. The inconsistent cardiac findings may result from the imbalance of baseline data among participants, as in some studies, offspring of hypertensive pregnancies had higher systolic blood pressure. Perinatal characteristics may also influence these findings because genetic evidence suggests that perinatal risk factors (eg, low birth weight) have a direct adverse effect on cardiometabolic risk that goes beyond shared maternal alleles or the adverse intrauterine environment.[117] Nevertheless, the direction of effect for some studies showed unfavorable outcomes for offspring of hypertensive pregnancies.

Implications for Clinical Practice

Further work is needed to investigate the phenotypical differences (eg, using cardiac imaging across developmental stages) to identify key imaging features that might be affected by in utero exposure to hypertensive pregnancies. With the probable multi-organ structural and functional differences, offspring of hypertensive pregnancies may benefit from targeted primary cardiovascular disease preventive strategies. Further investigation is also needed to determine whether early screening for offspring of hypertensive pregnancies and closer monitoring in controlling traditional cardiovascular risk factors may reduce later-life cardiovascular disease risk. Imaging modalities can also be applied to investigate high-risk populations exposed to maternal hypertensive pregnancies[105] who may be at increased risk for cardiac and cerebrovascular diseases in the future.

Strengths and Limitations

This study used a robust search strategy to include a vast range of ages of offspring across developmental stages and capture important outcomes of interest. Additionally, the diagnosis of maternal hypertensive pregnancies was mainly ascertained through medical records that reduced possible information bias arising from self-report diagnosis.

Our review has limitations. First, there was a low number of available studies per developmental stage for evidence synthesis. Second, because of the nature of exploratory studies in most of the included studies, power calculations were not considered. The subtle structural and functional differences in offspring of hypertensive pregnancies and respective controls might fail to be detected from studies with lower statistical power. Third, most of the included studies did not report *Z*-score data or had different adjustments for confounding factors, meaning a meta-analysis could not be performed. In regard to included studies, cardiac structure and function were mostly explored using echocardiography. Advanced MRI with more in-depth structural and functional analysis and tissue characterization may help explore cardiac hemodynamic changes in offspring of hypertensive pregnancies.

Unanswered Questions and Future Research

The use of MRI to investigate multi-organ structure and function could reveal subclinical differences between offspring of hypertensive pregnancies and offspring of normotensive pregnancies. Particularly for the heart, elucidating the hemodynamic characteristics in offspring of hypertensive pregnancies may be performed using 4-dimensional flow MRI analysis to explore blood flow and myocardial function throughout the cardiac cycle.[118]

In addition, studies investigating the pathophysiological mechanisms underlying disease development following fetal exposure to hypertensive pregnancies are still limited and need to be further explored. While recent genetic analyses suggest early gestational age and low birth weight are causally associated with long-term cardiovascular remodeling,[119,120] any such associations remain to be tested for intrauterine exposure to hypertensive pregnancies. A longitudinal study with multiple follow-up time points may clarify observed inconsistencies in the literature by tracking trajectories of organ structural and functional changes over time in the same individuals. Lifestyle and environmental factors may also contribute to the variability in findings; for instance, blood pressure can drive some cardiovascular changes in the offspring. Therefore, a prospective cohort study with multiple data timepoints will be an important study design of consideration in this field to follow-up the individuals longitudinally from various socioeconomic status. Future studies should also focus on sex, race, and ethnicity differences in anatomy and physiology that may exist in offspring born to hypertensive pregnancies. This will better enable us to disentangle the causal effect of fetal exposure of hypertensive pregnancies from any confounding factors on multi-organ phenotype changes in the offspring.

Conclusions

Our systematic review revealed conflicting evidence of the extent that fetal exposure to hypertensive pregnancies is associated with multi-organ structural and functional changes in offspring of hypertensive pregnancies. Nevertheless, overall, offspring born to

hypertensive pregnancies tended to have unfavorable multi-organ structural and functional differences compared with their peers born to normotensive pregnancies. Thus, well-designed prospective cohort studies are needed to strengthen the current evidence base.

ARTICLE INFORMATION

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Prenali D. Sattwika and Adam J. Lewandowski designed the study. Prenali D. Sattwika, Art Schuermans, Winok Lapidaire, Paul Leeson, and Adam J. Lewandowski developed the search strategy. Prenali D. Sattwika searched the database. Prenali D. Sattwika, Art Schuermans, Hannah R. Cutler, Mohanad Alkhodari, Vita Y. Anggraeni, Detty S. Nurdiati, and Adam J. Lewandowski screened abstracts for inclusion. Prenali D. Sattwika, Art Schuermans, Hannah R. Cutler, and Mohanad Alkhodari assessed the risk of bias and extracted the data. Prenali D. Sattwika, Vita Y. Anggraeni, Detty S. Nurdiati, Art Schuermans, Winok Lapidaire, Paul Leeson, and Adam J. Lewandowski analyzed the data. Prenali D. Sattwika drafted the manuscript. All authors reviewed the final draft of the manuscript and approved it for submission.

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Disclosures

None.

Supplemental Material

Data S1.
Data S2.
Supplemental Methods, Tables S1–S41, References [121–162].

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