Offspring size at birth and maternal risk for cardiovascular disease: a systematic review and meta-analysis

Prabha Andraweera[1], Zohra Lassi[2], Maleesa Pathirana[1], Anna Ali[3], Gus Dekker[4], Claire Roberts[5], and Margaret Arstall[6]

[1]The University of Adelaide
[2]Robinson Research Institute
[3]Basil Hetzel Institute for Medical Research
[4]The University of Adelaide Adelaide Medical School
[5]University of Adelaide
[6]Lyell McEwin Hospital

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Abstract

Background: Offspring size at birth is known to be associated with maternal cardiovascular disease (CVD) risk. Low birthweight (LBW), small for gestational age (SGA) and intrauterine growth restriction (IUGR) are all used to define infants considered small at birth. Objectives: To determine whether women who give birth to SGA/LBW/IUGR infants have higher levels of cardio-metabolic risk factors compared to women who give birth to average for gestational age infants or women. Search strategy: We performed a systematic literature search using PubMed, Embase and CINAHL. Selection criteria: Studies that compared cardio-metabolic risk factors in women who gave birth to SGA/LBW/IUGR infants compared to a control group. Data collection and analysis: Two independent authors screened and extracted data. Meta-analysis was performed on Review Manager 5.3. Main results: The meta-analysis showed a significantly increased CVD mortality among women who gave birth to SGA infants compared to AGA infants (relative risk 1.45, 95% confidence interval (CI) 1.40 to 1.52; 2,584,533 participants, three studies; heterogeneity: Chi2 P=0.48; I2=0%). Women who gave birth to growth restricted infants had significantly higher mean BMI (1.72kg/m2, 95% CI 0.97 to 2.47; 77 participants, two studies; heterogeneity: Chi2 P=0.35; I2=0%), and higher total mean cholesterol levels (0.32mmol/l, 95% CI 0.13 to 0.50; 77 participants, two studies; heterogeneity: Chi2 P=0.69; I2=0%) compared to women who had uncomplicated pregnancies. Conclusions: Women who give birth to small infants are at increased risk of CVD. Postpartum screening for CVD risk factors will help identify those at risk.

INTRODUCTION

Increasing evidence demonstrates an association between offspring size at birth and maternal cardiovascular disease (CVD) risk. A meta-analysis of six studies, published in 2007, showed an inverse relationship between offspring weight at birth and maternal CVD mortality (pooled adjusted hazard ratio (aHR) of 0.75 (95% confidence interval (CI): 0.67 to 0.84) for 1-standard deviation (SD) increase in offspring birthweight)[1]. A subsequent study of 1,400,383 women showed 1.8 times higher risk of mortality from CVD among women who gave birth to low birth weight (LBW, birthweight <2500g) infants compared to those who gave birth to normal birthweight (2500-3999g) infants (aHR: 1.85; 95% CI 1.57 to 2.18)[2]. Recent studies have shown similar associations for women who give birth to infants diagnosed as small for gestational age (SGA) at birth compared to women who give birth to average for gestational age (AGA) infants[3, 4]. The terms "LBW" and "SGA" are both used to define infants considered small at birth. Although many infants classified as SGA or LBW have intrauterine growth restriction (IUGR) and many growth restricted infants are born with LBW

or are classified as SGA, the three terms are not synonymous[5]. LBW simply means birthweight < 2.5 kg and at present, the definition is mostly used in developing countries where gestational age is often uncertain, and reliable population centiles let alone customized centiles are not available. SGA means birthweight < 10^{th} centile for a given gestational age. Population centiles use birthweight centiles on a whole population, irrespective of maternal ethnicity, height and weight and customized centiles provide birthweight centiles customized for maternal ethnicity, height, weight and parity. Infants with IUGR are those that do not achieve full*in utero* growth potential because of genetic or environmental factors and are at increased risk for significant morbidity and mortality compared to infants with normal *in utero* growth. Infants born growth restricted are at increased risk of CVD and type 2 diabetes mellitus in adulthood and "programming in response to an adverse intrauterine environment" as well as genetic and environmental influences are proposed to contribute to the risk. However, associations between offspring SGA/LBW and maternal CVD risk cannot be explained to a large extent by programming. This, however, can be explained by the presence of genetic polymorphisms that influence both fetal growth and CVD as well as by adverse environmental influences that operate across the parental life course and affect both offspring and adult health. To our knowledge there is no systematic review and meta-analysis that has assessed maternal risk for CVD using data from studies reporting on the three common classifications of offspring size at birth. Therefore, the aim of this study was to identify the relationship between offspring size at birth and maternal CVD risk based on different classifications of offspring size at birth.

METHODS

Data sources and Search strategy

This systematic review and meta-analysis was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines[6]. The review protocol is registered with PROSPERO (CRD42019138399). We searched the electronic databases, MEDLINE, EMBASE, CINHAL, and Web of Science with an end of search date of May 6, 2019. Subsequently, we updated the literature search to include all relevant articles published until May 31, 2020. The search was conducted by ZL. The search strategy is detailed in the supplementary file. Bibliographies of previously conducted systematic reviews and meta-analyses on closely related topics, and eligible studies were checked for additional studies. Two reviewers independently screened the titles and abstracts of studies (PA, MP, AA, ZL). Data extraction was also conducted by two reviewers independently (PA, ZL). Disagreements were resolved by discussion within the team.

Study selection and data extraction

Studies were considered eligible if they compared CVD risk factors between the following comparison groups: (1) women who gave birth to SGA infants compared to women who gave birth to AGA infants, (2) women who gave birth to LBW infants (birthweight [?]2500g) compared to women who gave birth to normal birthweight (birthweight >2500g) infants, (3) women who gave birth to infants diagnosed with IUGR with women who gave birth to non-IUGR infants. Studies that reported an association between maternal CVD mortality/CVD occurrence and offspring size at birth were also included. SGA was defined as birthweight below the 10^{th} population or customised birthweight centile; LBW was defined as birthweight below 2500g; and IUGR was defined as true documented intrauterine growth restriction or an accepted surrogate diagnosis of IUGR, i.e. birthweight <5^{th}population or customised birthweight centile and abnormal umbilical artery Doppler results. Definitions of SGA/LBW and IUGR used in the included studies are detailed in table 1. The outcomes assessed were systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), triglycerides, fasting blood glucose (BG), fasting insulin, and CVD mortality. Data from studies classifying infants as SGA, LBW and IUGR were analysed as separate groups. Studies that did not have the above definitions, those that did not define the comparison groups and those that compared women who gave birth to small babies with another risk group were excluded. All selected studies were published in peer-reviewed journals, undertaken in humans, and published in English.

Statistical analysis

The meta-analysis was performed using the RevMan software (Review Manager Version 5.3). For the outcomes of SBP, DBP, BMI, and lipids, Mean Difference (MD) and the 95% confidence interval (CI) were calculated using a fixed effects or random effects model. Where heterogeneity was substantially high (Chi^2 P value of <0.1 and I^2 value of >30%), we reported the outcomes using random-effect mode, otherwise the outcomes were reported using a fixed effect model. When standard error of the mean (SEM) or CI of means were reported instead of the SD, the SEM/CI were converted to SD. When median and intra-quartile range (IQR) were reported, the results were extracted as reported and are detailed in table 1. For the meta-analyses on CVD mortality, the number of deaths due to CVD and the total number of participants were used in the meta-analysis to analyse the risk difference. If the study reported the number as a percentage, then the number of participants/events was calculated based on the total sample size for each group. The methodological quality was assessed using the National Heart, Lung and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

RESULTS

A total of 21,884 articles were identified by the search, of which 520 were eligible for full text review (Figure 1) and a further 11 were identified from bibliographic searches. Of these, 18 studies were included in the review, and seven were included in the meta-analysis. The reasons for excluding 513 papers are detailed in figure 1. The quality assessment showed that no studies were of low quality.

Maternal CVD risk factors according to the delivery of a SGA vs AGA infant

Four studies reported on conventional CVD risk factors between women who gave birth to SGA compared to AGA infants (table 1)[7-10]. Two studies classified SGA as birthweight $<10^{th}$ population centile[7, 10], one as birthweight $<5^{th}$ population centile[9] and the other as birthweight $<10^{th}$ customised birthweight centile[8]. Two studies were conducted on normotensive women who gave birth to SGA infants[8, 9]. Four studies compared SBP and DBP between women who gave birth to SGA infants compared to those who gave birth to AGA infants. Of these, two studies reported significantly higher SBP[7, 9] and one study reported significantly higher DBP[7] among women who gave birth to SGA infants after adjusting for confounding factors (table 1). BMI was reported in one study which found no significant difference between the two comparison groups[7]. Three studies compared lipids between the two study groups[7, 9, 10]. Of these, two reported significantly higher serum triglycerides[9, 10] and one significantly higher LDL cholesterol[9] among women who gave birth to SGA infants compared to those who gave birth to AGA infants (table 1). Blood glucose was reported in three studies[7, 9, 10] and insulin level in one study[9]. All results on blood glucose and insulin were not statistically significantly different between the two comparison groups (table 1). Results of two studies were included in the meta-analyses on SBP and DBP[7, 8]. The pooled analyses did not show a significant difference in SBP or DBP between women who gave birth to SGA compared to AGA infants (Supplementary figures 1 and 2).

Maternal CVD risk factors according to the delivery of a low birth weight vs normal birth weight infant

Two studies reported on maternal CVD risk factors based on birthweight of offspring[11, 12] (table 1). Catov and colleagues compared blood pressure, BMI, lipids, fasting blood glucose and fasting insulin between women who gave birth to low birth weight vs normal birthweight infants and reported significantly higher SBP and significantly lower BMI among women who gave birth to LBW infants[11] (table 1). Lawlor and colleagues assessed the relationship between birthweight of offspring and age adjusted BMI, SBP, LDL, HDL and triglyceride levels in a cohort of 3265 women[12]. Their study demonstrated that for each increase of 1kg in offspring birthweight, the logarithm of SBP decreased by 1.79 and BMI increased by 0.74[12] (table 1). The results of the two studies reporting on maternal CVD risk factors based on birthweight of offspring could not be included in the meta-analyses.

Maternal CVD risk factors according to the delivery of an infant with intrauterine growth

restriction vs women who experienced uncomplicated pregnancies

Two studies compared maternal CVD risk factors between women who gave birth to growth restricted infants and women who had uncomplicated pregnancies[13, 14] (table 1). Of these one study was conducted on normotensive women who gave birth to growth restricted infants[14]. Manten and colleagues reported a significantly higher serum total cholesterol level among women who gave birth to infants diagnosed as having IUGR compared to women who had uncomplicated pregnancies but the difference was not significant after excluding women with chronic hypertension, smokers and those with BMI > 30kg/m^2[13] (table 1). Yinon and colleagues compared BMI, total cholesterol, LDL, HDL, blood glucose and insulin in women who gave birth to growth restricted infants and those who had uncomplicated pregnancies[14]. Both studies were included in meta-analyses on BMI, total cholesterol, HDL cholesterol and triglycerides[13, 14]. The pooled analyses showed that women who gave birth to infants diagnosed as having IUGR had significantly higher mean BMI (1.72kg/m^2, 95% CI 0.97 to 2.47; 77 participants, heterogeneity: Chi^2 P 0.35; I^2 = 0%, figure 2A), and higher total mean cholesterol levels (0.32mmol/l, 95% CI 0.13 to 0.50; 77 participants, heterogeneity: Chi^2 P 0.69; I^2 = 0%) compared to women who had uncomplicated pregnancies (figure 2B)[13, 14].

Association between offspring size at birth and maternal cardiovascular disease mortality

Nine large data linkage studies assessed the association between offspring birthweight/SGA and maternal cardiovascular disease mortality[1, 2, 4, 15-20] and one assessed the association between delivery of a SGA infant and the occurrence of maternal CVD[3] (table 2). Of the studies reporting on maternal CVD mortality, two studies demonstrated aHRs of 2.0 and 2.2 for each 1kg decrease in offspring birthweight[15, 18] and five studies demonstrated aHRs between 0.75 and 0.89 for each 1 SD increase in offspring birthweight[1, 2, 4, 19, 20](table 2). Four studies assessed maternal CVD mortality in relation to giving birth to a SGA vs AGA infant and reported aHRs between 1.31 – 3.5 among women who gave birth to SGA compared to AGA infants[2-4, 16] (table 2). A large data linkage study of 812,732 women demonstrated that, compared to women who gave birth to non-SGA infants, the aHR for first occurrence of CVD among women who gave birth to moderately SGA infants (birthweight between 3rd – 10th percentile) was 1.36 (95% CI, 1.23 to 1.49) and among women who gave birth to severe SGA infants (birthweight <3rd centile) was 1.66 (95% CI, 1.47 to 1.87)[3] (table 2). That study also showed a linear increase in aHR for first occurrence of CVD of 1.42 (95% CI, 1.30 to 1.54), 1.65 (95% CI, 1.34 to 2.03) and 2.42 (95% CI, 1.52 to 3.85) for women who gave birth to one SGA infant, two SGA infants and three SGA infants respectively, compared to women who gave birth to non-SGA infants[3] (table 2). Three studies were included in the meta-analysis on CVD mortality among women who gave birth to SGA compared to AGA infants, providing data on 2,584,533 individuals (figure 3) [2, 4, 16]. The pooled data shows a significantly increased CVD mortality among women who gave birth to SGA infants compared to those who gave birth to AGA infants (RR 1.45, 95% CI 1.40 to 1.52); heterogeneity: Chi^2 P 0.48; I^2 = 0%)

DISCUSSION

This systematic review demonstrates an inverse relationship between offspring birthweight and maternal CVD mortality. Our meta-analysis shows an approximately 1.5 times increased risk of death from CVD among women who gave birth to SGA infants compared to women who gave birth to AGA infants. The meta-analyses also demonstrated that BMI and total cholesterol levels were higher among women who gave birth to infants diagnosed as having IUGR compared to women who experienced uncomplicated pregnancies.

The evidence for the association between offspring birthweight and maternal CVD mortality was provided by eight large data linkage studies conducted in six countries[1, 2, 4, 15-20]. All studies provided consistent findings and showed a reduction in offspring birthweight associated with increased maternal CVD mortality or an increase in offspring birthweight associated with a reduction in maternal CVD mortality. All of these results were shown to be significant after adjusting for relevant confounding factors. All studies that compared CVD mortality among women who gave birth to SGA vs AGA infants demonstrated a HR between 1.31-3.5 for women who gave birth to SGA infants after adjusting for relevant confounding factors[2, 4, 16] while the pooled analysis showed a RR of 1.45 with no significant heterogeneity among the three studies (Chi^2 P 0.48,

$I^2 = 0\%$).

A few mechanistic pathways could be implicated in the association between offspring size at birth and maternal CVD risk. One plausible mechanism is the genetic contribution. CVD has a substantial genetic component, and polymorphisms in several genes encoding glucokinase[21], angiogenic pathway[22], angiotensinogen[23], clotting factors[24] are associated with both restricted fetal growth and risk of CVD. The evidence for a genetic link between offspring birthweight and maternal risk for CVD is supported by studies that have shown an association between offspring birthweight and parental CVD risk. Li and colleagues (2010) in a data linkage study of 1,400,383 primigravida and their spouses demonstrated an adjusted HR of 1.13 (95% CI: 1.03 to 1.24) among fathers of low birth weight infants[2]. Consistent with the above findings, Davey Smith and colleagues reported an adjusted HR of 0.94 (95% CI: 0.89 to 0.99) for CVD mortality among fathers for each one SD increase in offspring birthweight[1]. The theory for a genetic association is further strengthened by a number of multigenerational studies, reporting a strong association between birthweight of grandchild and CVD mortality in grandparents (HR of 0.86, 95% CI: 0.83 to 0.89 for 1kg increase in birthweight [25] and HR between 0.95-0.99 for one quintile increase in birthweight)[26]. The genetic theory is further supported by a recent study of 1,353,956 births that showed an association between offspring birthweight and CVD mortality among aunts and uncles (HRs between 0.90 (95% CI 0.86 to 0.95) and 0.93 (95% CI 0.91 to 0.95) for one SD increase in offspring birthweight)[4].

Another plausible mechanism linking offspring size at birth with maternal CVD risk is shared environmental and behavioural factors. For example, smoking is a risk factor for both low birthweight and CVD. Women who smoke during pregnancy are at a higher risk of giving birth to growth restricted infants. These women are likely to continue smoking, increasing their subsequent risk of CVD. Partners of women who smoke are likely to be smokers themselves and hence would also be at higher risk of developing CVD. Hence, the association between offspring size at birth and paternal CVD risk could also be explained by environmental and behavioural factors shared by both parents.

The third plausible theory on the association between offspring size at birth and maternal CVD risk suggests maternal/fetal nutritional factors and intrauterine programming as a potential contributor. Women who themselves had poor intrauterine growth and LBW tend to give birth to SGA infants[27]. This association may be mediated via poor placentation or effects of intrauterine programming. Pregnancy may also act as a "second hit" for women who were born small[28]. Pregnancy is increasingly being considered as a physiological stress test for the female cardiovascular system and those who were born "small", when exposed to a second hit of pregnancy, may develop pregnancy complications including intrauterine growth restriction[28].

This systematic review and meta-analysis demonstrates evidence of an association between offspring size at birth and maternal CVD mortality. However, there was insufficient data to compare conventional CVD risk factors among women who gave birth to small babies compared to women who have birth to AGA infants due to the limited number of studies reporting on the outcomes. Pooled evidence from two small studies demonstrate higher BMI and higher serum total cholesterol levels among women who gave birth to growth restricted infants compared to women who had uncomplicated pregnancies. However, the sample sizes in these analyses were very small. Hence, larger studies are required for meaningful comparisons. In addition, only few studies reported on cohorts of normotensive women who gave birth to small infants, hence, confounding due to maternal gestational hypertension and preeclampsia is a real possibility. Another limitation in the current literature is the paucity of information on women's age in studies reporting on the associations between offspring size at birth and maternal CVD mortality. The reported follow up periods of the included studied varied from 4 years to ˜47 years postpartum. Hence, some of the studies reported CVD mortality among old aged women.

Overall, this systematic review and meta-analysis shows that women who give birth to SGA infants are at higher risk of CVD mortality compared to women who give birth to AGA infants. Genetic, environmental and behavioural factors could all contribute to this association. Larger well characterised cohorts with the ability to distinguish CVD risk factor profiles at a young age between normotensive and hypertensive women who give birth to SGA infants are required to identify the true association between offspring size at birth

and maternal risk for CVD.

Disclosure of interests

The authors declare no conflicts of interest

Contribution to authorship

PHA, ZSL, MAA, CTR and GAD conceived and designed the study. ZSL conducted the search. PHA, ZSL, MMP and AA screened the papers and extracted data. ZSL conducted the meta-analysis. PHA wrote the manuscript. All authors read and approved the final version of the manuscript.

Details of ethics approval

Since this study was a systematic review and meta-analysis, ethics approval was not required.

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Figure Legends

Figure 1: PRISMA flow diagram of study selection process

Figure 2: Cardio-metabolic risk factors between women who gave birth to infants with IUGR and women who had uncomplicated pregnancies

Figure 3: Cardiovascular disease mortality between women who gave birth to SGA infants and women who gave birth to AGA infants

Table 1 Published studies of the association between offspring size at birth and maternal cardiovascular disease risk factors

Study	Study design	Country	Age	Post partum follow up time	Inclusion criteria: Cases	Inclusion criteria: Controls	Exclusion criteria	Birthweight Cases/Control (g), Gestational age Cases/Contr (wks)	Fi *S ra fin
Small for gestational age (SGA) Hillman *et al.* 2017	**Small for gestational age (SGA)** Case Control	**Small for gestational age (SGA)** UK	**Small for gestational age (SGA)** Approx.33-38	**Small for gestational age (SGA)** 6 - 9 months	**Small for gestational age (SGA)** Women who gave birth to infant with a BW <10th customised centile (n=15)	**Small for gestational age (SGA)** Women who gave birth to infant with a BW between the 10th and 95th centile (n=29)	**Small for gestational age (SGA)** Fetal anomaly, smoking, pregnancy complicated by preeclampsia or gestational hypertension	**Small for gestational age (SGA)** BW Case:2254 ± 547 Con:3566 ± 350 Cus centiles: Case:1.9 ± 2.3 Con:47.5 ± 26.3 GA Case:268 ± 19.4 Con:285 ± 9.6	**Sm for ge tic ag (S** Wo wh SG inf wo wh AG inf Re me SD 10 vs 7.9 0.1 64. 7.6 63. 7.6 0.1

Study	Study design	Country	Age	Post partum follow up time	Inclusion criteria: Cases	Inclusion criteria: Controls	Exclusion criteria	Birthweight Cases/Control (g), Gestational age Cases/Contr (wks)	Fi *S ra fin
Kanagalingam *et al.* 2009	Case Control	UK	29-48	4 years	Women who gave birth to a first child with a BW below the 5th centile at 36-43 weeks gestation (n=28)	Women who gave birth to a first child with a BW between the 25th and 90th centile (n = 29)	Pre-existing hypertension, DM, gestational hypertension, preeclampsia, genetic anomaly Cases and controls were matched for age at index pregnancy, parity, BMI at booking, GA at booking and delivery	BW Case:2.47 (2.24-2.62) Con:3.43 (3.35-3.61) Cus centiles: Case:1.0 (0-3) Con: 47 (36-74) GA Case: 40 (39-40) Con: 40 (39.5-40)	Wo wh SG inf wo wh AC inf Re me (in ter ran SB (m 120 (11 vs (10 p = 0.0 DE (m 70 vs (60 = (m 4.5 (3. vs (3. 4.5 0.0 (m 1.4 (1. vs (1. 1.9 0.1 (m 2.3 (1. vs (1. 2.0 0.0 (m 0.9 (0. vs (0

Study	Study design	Country	Age	Post partum follow up time	Inclusion criteria: Cases	Inclusion criteria: Controls	Exclusion criteria	Birthweight Cases/Control (g), Gestational age Cases/Contr (wks)	Fi *S ra fin
King *et al.* 2013	Cohort	Ireland	27-37	6 weeks	Women who gave birth to an infant with a BW <10th centile (n=23) Subsequently classified as Preeclampsia/ GH = 3	Women who gave birth to an infant with a BW [?] 10th centile (n = 23) Subsequently classified as Preeclampsia/GH = 2	Pre-existing diabetes mellitus, hypertension, CVD GDM, smoking, significant medical/psychiatric illness	BW Case:2.34 (2.13-2.65) Con:3.6 (3.17-3.85) GA Case:271 (260-278) Con:278 (270-286)	Wo wh SG inf wo wh AC inf Re me (in ter ran SB (m 110 (11 vs (10 p = DE (m 72 vs (70 = TC (m 5.5 5.8 5.1 (4. p = HI (m 1.6 (1. vs (1. 2.0 0.3 (m 3.0 (2. vs (2. 3.1 0.2 (m 0.9 (0. vs (0

Study	Study design	Country	Age	Post partum follow up time	Inclusion criteria: Cases	Inclusion criteria: Controls	Exclusion criteria	Birthweight Cases/Control (g), Gestational age Cases/Contro (wks)	Fi *S ra fin
Fraser *et al.* 2012	Cohort	UK	Approx. 42-52	18 years	Women who gave birth to an infant with a BW <10th centile (n = 262)	Women who gave birth to an infant with a BW between 10^{th} – 90^{th} centile (n = 2630)	N/A	N/A	Wo wh SG inf wo wh AC inf Re age adj me for vs gro an dif (co de int BM (kg (0. 29 (0. -0. (-0 0.2 (m 105 (2. 10 (2. 1.9 3.4 DI (m 70 (1. 68 (1. 1.7 2.7 HI (m 0.8 vs (0. 0.0 (-0 0.0 (m

Study	Study design	Country	Age	Post partum follow up time	Inclusion criteria: Cases	Inclusion criteria: Controls	Exclusion criteria	Birthweight Cases/Control (g), Gestational age Cases/Contr (wks)	Fi *S ra fin
Low birth-weight (LBW)	Low birth-weight (LBW)	Low birth-weight (LBW)	Low birth-weight (LBW)	Low birth-weight (LBW)	Low birth-weight (LBW)	Low birth-weight (LBW)	Low birth-weight (LBW)	Low birth-weight (LBW)	Lo bi we (L

Study	Study design	Country	Age	Post partum follow up time	Inclusion criteria: Cases	Inclusion criteria: Controls	Exclusion criteria	Birthweight Cases/Control (g), Gestational age Cases/Contr (wks)	Fi *S ra fin
Catov *et al.* 2007	Cohort	USA	70-79	Approx. 47-51 years	Women who gave birth to first born LBW <2500g (n=56) **18/56 preterm**	Women who gave birth to first born Normal BW [?] 2500g (n=390) **12/390 preterm**	Hypertension, preeclampsia	N/A	Ma cha ist ac to de a I No BV Re ar ad for BM SB (m 14 13 0.0 DE (m 73 72 0.3 (k 26 28 0.0 (m 21 22 0.6 (m 12 12 0.7 HI (m 61 60 0.6 (m 14 12 0.0 (m 99 97 0.7 Ins ((I 8.1

Study	**Study design**	**Country**	**Age**	**Post partum follow up time**	**Inclusion criteria: Cases**	**Inclusion criteria: Controls**	**Exclusion criteria**	**Birthweight Cases/Contro (g), Gestational age Cases/Contr (wks)**	**Fi *S ca fin**
Lawlor *et al.* 2002	Cross sectional survey	UK	68.1 – 69.4	N/A	3265 randomly selected women. Details of pregnancy obtained at interview and blood samples taken for assessment of insulin. Women groups according to BW of first child as 1.56-2.94kg, 2.95-3.26kg, 3.27-3.58kg, 3.59-4.98kg	3265 randomly selected women. Details of pregnancy obtained at interview and blood samples taken for assessment of insulin. Women groups according to BW of first child as 1.56-2.94kg, 2.95-3.26kg, 3.27-3.58kg, 3.59-4.98kg	3265 randomly selected women. Details of pregnancy obtained at interview and blood samples taken for assessment of insulin. Women groups according to BW of first child as 1.56-2.94kg, 2.95-3.26kg, 3.27-3.58kg, 3.59-4.98kg	3265 randomly selected women. Details of pregnancy obtained at interview and blood samples taken for assessment of insulin. Women groups according to BW of first child as 1.56-2.94kg, 2.95-3.26kg, 3.27-3.58kg, 3.59-4.98kg	Re are rat age adj dif pe off BW (m -1. (-3 -0. = BM (kg 0.7 to p< LD (m -0. 0.1 p = HI (m 0.0 (-0 0.0 TC (m -0. (-0 0.0
Intrauterine growth restriction (IUGR)	**Intrauterine growth restriction (IUGR)**	**Intrauterine growth restriction (IUGR)**	**Intrauterine growth restriction (IUGR)**	**Intrauterine growth restriction (IUGR)**	**Intrauterine growth restriction (IUGR)**	**Intrauterine growth restriction (IUGR)**	**Intrauterine growth restriction (IUGR)**	**Intrauterine growth restriction (IUGR)**	**In gr re st tio (I**

Study	Study design	Country	Age	Post partum follow up time	Inclusion criteria: Cases	Inclusion criteria: Controls	Exclusion criteria	Birthweight Cases/Control (g), Gestational age Cases/Contr (wks)	Fi *S ra fin
Manten *et al.* 2007	Case Control	The Netherlands	Approx. 27-37	3 – 25 months	Women who gave birth to an infant with BW <5th percentile for the Dutch population and delivery < 34 weeks' gestation due to fetal distress (n=59) Chronic hypertension = 5	Women who had uncomplicated pregnancies (n=53)	N/A	BW Case: 972 ± 763 Con: 3635 ± 462 GA Case: 210 ± 37 Con: 283 ±10	Wo wh bir inf wit IU wo wh un cat pre cie Re are exp as (SI (m 12 vs (14 (m 79 75 BM (kg 25 23 (m 5.3 vs (0. HI (m 1.3 vs (0. (m 1.1 -3. 1.0 (0. *N sig aft exc wo wit chr hy sio sm

Study	Study design	Country	Age	Post partum follow up time	Inclusion criteria: Cases	Inclusion criteria: Controls	Exclusion criteria	Birthweight Cases/Control (g), Gestational age Cases/Contr (wks)	Fi *S ra fin
Yinon *et al.* 2010	Case Control	Canada	Approx. 31-36	6-24 months	Normotensive IUGR Women who gave birth to an infant with BW <5th percentile accompanied by abnormal umbilical artery Doppler (absence or reverse of end diastolic velocity) in the absence of hypertensive disease in pregnancy -n=9 All 9 had severe IUGR and were delivered <34 weeks' gestation	Women who had uncomplicated pregnancies (n=16)	Current or past hypertension, diabetes mellitus, pregestational renal disease, BMI >30kg/m2, multiple gestation in index pregnancy, smoking, those living with smokers, those using oral contraceptive pill	BW Case: 841 ± 133 Con: 3417 ± 88 GA Case: 29.2 ± 0.9 Con: 39.6 ± 0.3	Wo wh bir inf wit IU wo wh un cat pre cie Re are exp as (SI BM (kg 25. vs 0.6 (m 4.4 vs 0.1 (m 1.3 vs 0.1 (m 2.6 vs 0.1 (m 1.2 vs 0.1 (m 4.6 vs 0.1 (pr 45. vs 2.4

Study	Study design	Country	Age	Post partum follow up time	Inclusion criteria: Cases	Inclusion criteria: Controls	Exclusion criteria	Birthweight Cases/Control (g), Gestational age Cases/Contro (wks)	Fi *S ra fin

Table 2 Published studies of the association between offspring size at birth and maternal cardiovascular disease mortality

Study	Study design	Country	Follow up	Population	Outcome measures reported	Significant findings
Davey Smith *et al.* 1997	Record linkage study	Scotland	15 years	794 married couples from the west of Scotland	CVD mortality	For 1 kg decrease in offspring BW, HR = 2.0 (95% CI, 1.18, 3.33) For 1 quartile increase in offspring BW, HR = 0.83 (95% CI, 0.68, 1.02) Adjusted for offspring sex, parental age Adjustment for blood pressure, cholesterol, body mass index, smoking, social class, area deprivation, lung function, bronchitis, angina and ECG evidence of CHD at baseline had only modest effects on the point estimates but reduced the statistical significance

Study	Study design	Country	Follow up	Population	Outcome measures reported	Significant findings
Davey Smith *et al.* 2000	Record linkage study	UK	10 years	Information from birth registrations of infants during 1976-97 is linked to data from the census and death registration. Data from 44,813 women aged 15-45 years at birth registration.	CVD mortality	For 1kg decrease in offspring BW HR = 2.22 (95% CI, 1.46, 3.38) (adjusted for maternal age SES and marital status).
Davey Smith *et al.* 2000	Record linkage study	Finland	34 years	3706 women who gave birth to live born singletons between 1954 – 1963 and followed up through the Finnish Central population and cause of death registries	CVD mortality	For 1SD increase in offspring BW HR = 0.77 (95% CI, 0.65, 0.90) Adjusted for maternal age, height, marital status, use of private health care during pregnancy, use of hormones during pregnancy and offspring sex

Study	Study design	Country	Follow up	Population	Outcome measures reported	Significant findings
Smith *et al.* 2001	Record linkage study	Scotland	N/A	Routine discharge data of all singleton births in Scotland between 1981-1985 linked to mothers' subsequent admissions and deaths at 15-19 years follow up (129, 920 women)	CHD mortality	For CHD mortality comparing the lowest fifth of offspring BW with the highest four fifth: HR = 2.8 (95% CI, 1.5, 5.2) Adjusted for maternal age, height, social class and preeclampsia and offspring sex and pre term birth HR = 2.4 (95% CI, 1.3, 4.4)
Davey Smith *et al.* 2005	Record linkage study	Sweden	Average 20.4 years	Data from the Swedish Medical Birth register for all 783,814 children born in Sweden between 1973 - 1980 were linked with parents' death records (783,340 women)	CVD mortality CHD mortality	For 1SD (0.53kg) increase in offspring BW, Gestational age adjusted CVD mortality, HR = 0.75 (0.70 – 0.80) Gestational age adjusted CHD mortality, HR = 0.72 (0.65 – 0.80)

Study	Study design	Country	Follow up	Population	Outcome measures reported	Significant findings
Davey Smith *et al.* 2007	Record linkage study	UK	26.2-27.5	12,086 women from the 1958 British Birth Cohort	CHD mortality	CHD mortality For a 1-SD increase in BW; HR = 0.80 (95% CI: 0.74, 0.87) After adjustment for: birth year, offspring gestational age, social class in 1958, maternal parity, preeclamptic pregnancy, maternal height and BMI in 1958, maternal smoking during pregnancy HR = 0.84 (95% CI: 0.77, 0.91)

Study	Study design	Country	Follow up	Population	Outcome measures reported	Significant findings
Li *et al.* 2010	Record linkage	Taiwan	30 years	Linkage of data of 1,400,383 women with singleton births recorded in the Taiwan Birth Registry between 1978-2006 with mortality data recorded in the Taiwan Death Registry	CVD mortality	CVD mortality for: (a)1 SD increase in offspring BW: HR[a] = 0.89 (95% CI, 0.85, 0.94) (b)Offspring BW<2500g HR = 1.93 (95% CI, 1.65, 2.27) HR[a] = 1.85 (95% CI, 1.57, 2.18) (c) SGA Offspring HR = 1.38 (95% CI, 1.19, 1.59) HR[a] = 1.31 (95% CI, 1.13, 1.52) [a]Adjusted for gestational age, year of offspring birth, urbanization of residential area and parental ages, education levels, employment status, marital status at the time of offspring birth

Study	Study design	Country	Follow up	Population	Outcome measures reported	Significant findings
Pariente *et al.* 2013	Record linkage study	Israel	N/A	Perinatal database of women who delivered between Jan 1988-Dec 1998 was linked with hospitalization data collected up until 31 Dec 2010. SGA was defined as BW below the 10^{th} population centile Risk for mortality due to CVD among those who delivered SGA infants (n=4414) was compared with those who delivered non-SGA infants (n=47612)	CVD mortality	After adjusting for diabetes, preeclampsia obesity, maternal age, and ethnicity, SGA was associated with increased cardiovascular mortality (adjusted HR 3.5, 95% CI, 1.5-8.2

Study	Study design	Country	Follow up	Population	Outcome measures reported	Significant findings
Ngo *et al.* 2015	Record linkage	Australia	Median 7.4 years	Linkage of data of 812,732 women using four databases: Perinatal data collection (birth data), admitted patient data collection (hospital data), registrar of births, deaths and marriages (death data), Australian Bureau of Statistics (cause of death data)	CVD occurence	Compared to women of non-SGA infants, first occurrence of CVD among women of (a) Moderate SGA infants (3^{rd} -10^{th} percentile) HR[a] = 1.36 (95% CI, 1.23, 1.49) (b)Severe SGA infants ($<3^{rd}$ percentile) HR[a] = 1.66 (95% CI, 1.47, 1.87) (c) One SGA infant HR[a] = 1.42 (95% CI, 1.30, 1.54) (d) Two SGA infants HR[a] = 1.65 (95% CI, 1.34, 2.03) (e) [?] three SGA infants HR[a] = 2.42 (95% CI, 1.52, 3.85) [a]Adjusted for maternal age at index birth, parity, country of birth, socioeconomic status, chronic and pregnancy hypertension, pre-gestational and gestational diabetes, maternal smoking during pregnancy

Study	Study design	Country	Follow up	Population	Outcome measures reported	Significant findings
Shaikh *et al.* 2019	Record linkage study	Norway	Mean follow up time 47 ± 5 years Mean age at follow up 55 ± 10.4 years	Linkage of data from cardiovascular health surveys, the medical birth registry, the cause of death registry, the educational registry and a multigenera-tional database containing information on familial relationships for the whole population of Norway. Offspring born between 1967-2012 were included	CVD mortality	(a) CVD mortality for 1 SD increase in offspring BW (b) CVD mortality in women who had SGA vs AGA offspring Model 1: adjusted for maternal age at offspring birth (a) HR = 0.72 (95% CI, 0.69, 0.75) (b) HR = 2.02 (95% CI, 1.85, 2.21) Model 2: adjusted for model 1 + offspring year of birth, mother's parity, mother's diseases before and during pregnancy, diseases in offspring (a) HR = 0.74 (95% CI, 0.71, 0.78) (b) HR = 1.87 (95% CI, 1.71, 2.05) Model 3: adjusted for model 1+2 + parental marital status, educational level in parents (a) HR = 0.77 (95% CI, 0.74, 0.80) (b) HR = 1.74 (95% CI, 1.59, 1.91)

Study	Study design	Country	Follow up	Population	Outcome measures reported	Significant findings

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Figure 1 PRISMA flow diagram of study selection process.docx available at https://authorea.com/users/351873/articles/476315-offspring-size-at-birth-and-maternal-risk-for-cardiovascular-disease-a-systematic-review-and-meta-analysis

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Figure 2 Cardio-metabolic risk factors between women who gave birth to infants with IUGR and women who
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Figure 3 Cardiovascular disease mortality between women who gave birth to SGA infants and women who gav
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