

2019

The placenta and cardiovascular disease: A meta-analysis

Ruben Phillips
Edith Cowan University

Follow this and additional works at: <https://ro.ecu.edu.au/theses>



Part of the [Medicine and Health Sciences Commons](#)

Recommended Citation

Phillips, R. (2019). *The placenta and cardiovascular disease: A meta-analysis*. Edith Cowan University.
Retrieved from <https://ro.ecu.edu.au/theses/2267>

This Thesis is posted at Research Online.
<https://ro.ecu.edu.au/theses/2267>

Edith Cowan University

Copyright Warning

You may print or download ONE copy of this document for the purpose of your own research or study.

The University does not authorize you to copy, communicate or otherwise make available electronically to any other person any copyright material contained on this site.

You are reminded of the following:

- Copyright owners are entitled to take legal action against persons who infringe their copyright.
- A reproduction of material that is protected by copyright may be a copyright infringement. Where the reproduction of such material is done without attribution of authorship, with false attribution of authorship or the authorship is treated in a derogatory manner, this may be a breach of the author's moral rights contained in Part IX of the Copyright Act 1968 (Cth).
- Courts have the power to impose a wide range of civil and criminal sanctions for infringement of copyright, infringement of moral rights and other offences under the Copyright Act 1968 (Cth). Higher penalties may apply, and higher damages may be awarded, for offences and infringements involving the conversion of material into digital or electronic form.

The placenta and cardiovascular disease: A meta-analysis

A thesis submitted in partial fulfilment of the requirements for the degree of

Master of Science (Human Biology)

Ruben Phillips

Edith Cowan University

School of Medical and Health Sciences

2019

Abstract

The uterine environment in which a fetus grows and develops is now recognised as a risk factor for the development of adult diseases such as cardiovascular disease (CVD). A fetus relies on the nutrients and conditions delivered via the placenta, and as such the placenta plays a vital role in the establishment and maintenance of appropriate uterine conditions. Unfavourable uterine conditions such as an inadequate resource flow from the placenta can lead to diminished growth of the fetus and may ultimately result in both short and long-term increases in risk of CVD for the baby. This has been demonstrated in large observational cohort studies and has been corroborated in animal experiments. Despite these findings, there remains significant variability in the association between the fetal environment and adult disease risk in observational data across human populations. Moreover, the size of the association between the placenta, as master of the uterine environment, and CVD is yet to be quantified. In order to bridge this knowledge gap, the present study conducted a systematic literature search and meta-analysis of published data examining the effects of the placenta on cardiovascular outcomes across the life course.

A systematic search was carried out and results were collated and assessed, with records which met the selection criteria then entered in to a meta-analytical process which included a funnel plot, calculation of Egger's Regression Intercept and estimation of effect size. The results of the search indicated that the association between placental weight and CVD risk had been investigated in a total of 109,721 participants across eight countries. The meta-analytical process initially indicated that higher blood pressure was related to a lighter placenta. On further inspection of the funnel plot, a distinct outlier was detected. This outlier was removed and the remaining records were analysed again. This second analysis indicated that higher

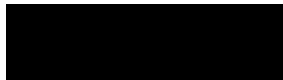
blood pressure was related to a heavier placenta. This process demonstrated that a single large study can substantially alter the results of a meta-analysis. Further, the variety of confounding variables which a study can adjust for demonstrates that placental weight cannot be viewed in isolation. None of the placenta studies relating placental weight to cardiovascular outcomes (such as mortality and morbidity) were comparable in this meta-analysis, indicating that there needs to be some guide to uniformity in the data collection and analysis. Such a guide would lead to better reporting and comparability between studies enabling new knowledge to build on previous research in this field. Ultimately, improved comparability of these studies, along with the transition of this field towards more complex measures of the placenta such as thickness, circumference and volume as well as the use of real-time imaging of the placenta, as the fetus develops in-utero, will contribute another dimension to our understanding of the relationship between placental function and adult disease risk.

Declaration

I certify that this thesis does not, to the best of my knowledge and belief:

- i. incorporate without acknowledgment any material previously submitted for a degree or diploma in any institution of higher education;
- ii. contain any material previously published or written by another person except where due reference is made in the text of this thesis; or
- iii. contain any defamatory material;

Signature of Candidate:

A black rectangular box redacting the signature of the candidate.

Date: 14 October 2019

Acknowledgements

I wish to acknowledge my supervisors who have generously supported and directed me through this Master by Research journey, A/Prof Peter Roberts who has shared his experience of over 20 years of research supervision and Dr. David Coall who is a well-respected researcher in this field. My sincere thanks for your advice and guidance.

To the reviewers, both formal and informal, thank you for your comments and suggestions, they have been helpful in shaping my thoughts and developing my research project.

To all my colleagues and fellow students, I am deeply grateful for your words of encouragement and for sharing your research stories which maintained my interest in doing research.

I wish to acknowledge the senior management team at the School of Medical & Health Sciences, Edith Cowan University, for supporting me through this research journey and for granting me study leave to carry out my research.

To my family, my wife Ellen, who has been very patient though this and my children, Atticus and Charlotte, who were born while I was on this research path, thank you for inspiring me.

Table of Contents

Abstract.....	ii
Declaration.....	iv
Acknowledgements.....	v
Table of Contents.....	vi
List of Figures	viii
List of Tables	ix
List of Acronyms.....	x
1. Introduction.	11
1.1 Hypertension and Cardiovascular Disease.....	13
1.2 Developmental Origins of Health and Disease (DOHaD).	15
1.3 Birth Weight, Fetal Growth and Cardiovascular Disease.....	18
1.4 Placental Weight, Placental Efficiency and Cardiovascular Disease.	21
1.5 Birth weight, placental weight and cardiovascular disease: Summary.	25
1.6 Animal Models	27
1.7 Epigenetics and DOHaD.	32
2. Materials and Methods.....	35
2.1 Systematic Literature Search	35
2.2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). 37	
2.3 Statistical Analysis.....	38
2.4 Examination of Geographical Locations Studied.	41
2.5 Grey Literature.....	41
2.6 Selection Criteria.....	41
2.7 Analysis of Study Quality Using the Newcastle-Ottawa Scale.	42
3. Results.....	45
3.1 PRISMA Flow Diagram.....	45
3.2 Meta-Analysis of Records	48
3.3 Records Related to Blood Pressure: Qualitative Synthesis.....	56
3.4 Records Related To Mortality or Morbidity.....	62
3.5 Records With Defining Statements But No Data.	67
3.6 Characteristics of The Studies.....	69
3.7 Age of Participants.....	71

3.8	Geographical Focus.....	72
4.	Discussion.	73
4.1	Inspection of Funnel Plots, Meta-Analysis Results and Outlier.	74
4.2	Placental Weight and Blood Pressure and Sex.	75
4.3	Placental Weight and CVD, CHD, IHD and Stroke.	77
4.4	Variation, Study Characteristics and Measured Outcomes.	78
4.5	Age of Participants.	81
4.6	Geographical Focus.....	81
4.7	NOS Analysis of Quality.....	82
4.8	U shaped curve	83
5.	Conclusion.....	86
6.	Limitations.	87
7.	References.	88
8.	Appendix A Extracted Data From Records.....	96
9.	Appendix B NOS Quality Assessment Form for Cohort Studies.....	109

List of Figures

Figure 1. PRISMA Flow Diagram displaying the number of records at of the four stages of the prescribed PRISMA process.....	47
Figure 2. Funnel plot of standard error by standard difference in means, output from CMA. A record highlighted (red dot) was identified as an outlier.	48
Figure 3. Funnel plot of standard error by standard difference in means, output from CMA. This plot has omitted the outlier from fig 1, Whincup et al. (1997).	49
Figure 4. Results of literature search. Articles are ranked using the Newcastle Ottawa Scale (NOS).	70
Figure 5. Different types of cardiovascular characteristics reported in the articles found.	71
Figure 6. Age of participants in records found through the search.	69
Figure 7. Heat map displaying the locations of the studies found in the search.	70

List of Tables

Table 1. Egger's Regression Intercept and p-value scores for the Egger's test performed in conjunction with the funnel plots.....	50
Table 2. Results of meta analysis performed.	52
Table 3. Results of meta analysis omitting Whincup et al. (1997).....	53
Table 4. Results of literature search. Articles listed have reported placental weights measured and association with blood pressure.....	58
Table 5. Results of literature search. Articles listed have reported placental weights measured and association with cardiovascular morbidity and mortality.	63
Table 6. Results of literature search. Articles listed have not reported any data. Authors made a summary statement of the relationship in the text of the article.	68

List of Acronyms

AGA	Appropriate for Gestational Age
AHRQ	Agency for Health Research and Quality
CHD	Coronary Heart Disease
CI	Confidence Interval
CMA	Comprehensive Meta-Analysis
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DOHaD	Developmental Origins of Health and Disease
FGR	Fetal Growth Restriction
HR	Hazard Ratio
ICD	International Classification of Diseases
IHD	Ischaemic Heart Disease
IUGR	Intrauterine Growth Restriction
NHFA	National Heart Foundation of Australia
NOS	Newcastle-Ottawa Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Risk Ratio
SMR	Standardised Mortality Ratio
SGA	Small for Gestational Age
SBP	Systolic Blood Pressure
WHO	World Health Organisation

1. Introduction.

Cardiovascular Disease (CVD) is a major chronic, non-communicable disease and in 2015 the World Health Organisation (WHO) reported that CVD accounted for 31% of all global deaths and 45% of deaths caused by non-communicable diseases (WHO, 2017). The burden of CVD is seen not only in mortality rates, but also in ongoing symptom control and treatment. In Australia, it was estimated that in 2013-2014, the Pharmaceutical Benefits Scheme (PBS) provided payments totalling AUD\$1.7 Billion (17% of total payments) for cardiovascular related medications (Nichols et al., 2016). Major dietary, lifestyle, and metabolic risk factors for CVD have been identified (e.g. hypertension, high blood cholesterol, smoking, sedentarism, and obesity), however, the majority of these manifest in adult life and for some people these signs and symptoms come too late to allow for any meaningful lifestyle change.

The Developmental Origins of Health and Disease (DOHaD) paradigm suggests that the early environment, specifically the uterine environment, may have an effect on cardiovascular morbidity and mortality. DOHaD is a new health and research paradigm that was born in the 1980s from a growing body of evidence indicating that poor fetal growth can have life-long consequences for chronic health conditions (Barker, 1994). Longitudinal studies in humans and experimental studies using animal models (see section 1.5) have since supported and refined the concept that insults in early life influence subsequent mortality in adulthood from diseases including cardiovascular disease (CVD) and stroke (Baird et al., 2016).

Within the DOHaD paradigm, there has been a strong research emphasis on birth weight as the independent variable representing the quality of the uterine environment the developing fetus has experienced. This has proven fruitful with a consistent association between reduced birth weight (or fetal growth) and increased risk of hypertension and CVD. This consistent inverse relationship has been evident

in times where infant and maternal mortality were low, as found in The Aberdeen Children of the 1950s study cohort (Lawlor et al., 2005). This cohort of 10,803 singleton births lived through a time of profound improvements in infant and maternal health, therefore, factors other than the quality of healthcare, namely, genetics and variations in placental function were implicated (Lawlor et al., 2005).

Focusing on birth weight as the main measure of the early environment, however, has misdirected the research focus to some extent. Birth weight is an outcome of the uterine environment rather than a cause of CVD. Birth weight is at the end of a long nutrition and oxygen supply line from the mother via the placenta to the fetus. Because of this relationship, the uterine environment, placenta and fetal growth are inextricably linked. Therefore, examining an alternative measure of the early environment – placental weight – and its association with subsequent cardiovascular health may provide additional insights. This is of particular interest when it is recognised that a range of proposed cues (e.g. oxygen and nutrient levels, stress, and hormone levels) present during pregnancy are either influenced or regulated by the placenta and it is this which ultimately determines the physiological fitness of the heart (Thornburg et al., 2010). It has been calculated, from a sample of 24,152 singleton liveborn children from the Collaborative Perinatal Project, that placental weight alone accounted for 36.6% of birth weight variation (Salafia et al., 2008).

In order to quantify the strength of the association between placental weight and cardiovascular disease risk, the present study will synthesise published research and conduct a meta-analysis to provide a deeper and more complete understanding of the association between placental weight and CVD.

The aim of this project is to bring together and evaluate the placental weight and cardiovascular health literature and attempt to quantify this relationship through the calculation of an effect size. This knowledge will contribute to our understanding of

the significance of the early environment for CVD and potential interventions aimed at improving placental and fetal growth and development.

1.1 Hypertension and Cardiovascular Disease.

Chronic non-communicable diseases exhibit an increasing health burden on the world's population. Cardiovascular disease (CVD) is a major chronic, non-communicable disease and the World Health Organisation (WHO) reported that globally in 2015, there were 17.7 million deaths attributed to CVD (equating to 31% of all global deaths or 45% of deaths by non-communicable diseases) and Australia is no exception (WHO, 2017). Nichols et al. (2016), reported that CVD was responsible for 45,392 deaths in Australia in 2015 (nearly 30% of all deaths). The burden of disease is seen not only in mortality, but also in ongoing treatment as our health services improve. It was estimated that in 2013-2014, the Pharmaceutical Benefits Scheme (PBS) in Australia provided AUD\$1.7 Billion worth of payments (17% of total payments) for cardiovascular related medications (Nichols et al., 2016).

The WHO defines CVD as diseases of the heart, vascular diseases of the brain and diseases of blood vessels, and categorises all CVDs into two groups, CVDs due to atherosclerosis and CVDs due to other causes. CVDs such as ischaemic heart disease (IHD) or coronary heart disease (CHD, of which 'heart attacks' are listed as a prime example), cerebrovascular disease (stroke), disease of the aorta and arteries, including hypertension and peripheral vascular disease, are all in the first category. The second category includes congenital heart disease, rheumatic heart disease, cardiomyopathies and cardiac arrhythmias (WHO, 2011).

The WHO lists hypertension as a leading cause of CVDs as it is a key metabolic risk factor for atherosclerosis. Hypertension as a risk factor is recognised through the measurement of systolic and diastolic blood pressures (reported in mm Hg as SBP/DBP e.g. 120/80 is a SBP of 120 mm Hg and a DBP of 80 mm Hg). The risk of

CVD may double for each incremental increase of 20/10 mm Hg beginning at 115/75 mm Hg, leading to CHD and cerebrovascular disease. Furthermore, uncontrolled hypertension contributes to heart failure, renal impairment and peripheral vascular disease, as well as visual impairment as it may damage retinal blood vessels (WHO, 2011).

According to both the WHO and the National Heart Foundation of Australia (NHFA), hypertension is intrinsically linked to CVD. The WHO released a “Global Brief on Hypertension” in 2013 naming it the ‘silent killer’ and a ‘global public health crisis’ (WHO, 2013; Nichols et al., 2016). Hypertension contributes to the burden of CVD, stroke and kidney failure and in many cases leads to premature mortality (WHO, 2013). Of the 17.7 million deaths due to CVD worldwide in 2017, it was estimated that hypertension was responsible for at least 45% of coronary heart disease deaths and 51% of deaths due to stroke (WHO, 2017).

The NHFA and the WHO recognise that the majority of deaths due to CVD are in low to middle socio-economic regions of the world. In the more developed regions the outlook for CVD is positive due to improved health and medical services (WHO, 2013; Nichols et al., 2016). The knowledge base regarding CVD risk factors has developed largely from the Framingham Heart Study, which began in 1948, and was conducted by the National Heart, Lung, and Blood Institute (NHLBI) of the United States (Franklin & Wong, 2013). The Framingham Heart Study has led to the identification of the major CVD risk factors - high blood pressure, high blood cholesterol, smoking, obesity, diabetes, and physical inactivity. In addition, a great deal of valuable information has been collected on the effects of related factors such as blood triglyceride and High Density Lipoprotein (HDL) cholesterol levels, age, gender, and psychosocial issues (Franklin & Wong, 2013). These risk factors manifest in adult life and for some these signs and symptoms may come too late to allow for any meaningful life change.

The known modifiable risk factors for CVD are largely based on lifestyle and nutrition. Danaei et al. (2009) estimated the mortality effects of twelve modifiable dietary, lifestyle, and metabolic risk factors in the United States of America (USA) and identified that smoking together with high blood pressure were responsible for the most deaths in the USA. Sedentary behaviour is another risk factor that is currently receiving attention, after Wilmot et al. (2012) performed a systematic review and meta-analysis which identified that more sedentary time was associated with a significantly increased risk of cardiovascular disease (RR=2.47; 95% CI: 1.44, 4.24) and cardiovascular mortality (HR=1.90; 95% CI: 1.36, 2.66).

The Developmental Origins of Health and Disease (DOHaD) paradigm suggests that the early environment, specifically the uterine environment, may have an effect on cardiovascular morbidity and mortality (Baird et al., 2016). Thus, understanding the risk factors for CVD in the early years, particularly during gestation and at birth has the potential to provide long-term benefits in reducing the burden of CVD.

1.2 Developmental Origins of Health and Disease (DOHaD).

DOHaD is a new health and research paradigm that was born in the 1980s from a growing body of evidence indicating that poor fetal growth can have life-long consequences for chronic health conditions (Barker, 1994). Longitudinal studies in humans and experimental studies using animal models (see section 1.5) have since supported and refined the concept that insults in early life influence subsequent mortality in adulthood from diseases including cardiovascular disease (CVD) and stroke (Baird et al., 2016).

The DOHaD paradigm highlights the importance of the early environment for health. The premise is that certain diseases (including cardiovascular disease, obesity, type 2 diabetes and metabolic disturbances, osteoporosis, chronic obstructive pulmonary disease, some forms of cancer, and mental illnesses) have their origins in the very

early stages of life (conception, pregnancy, infancy and early childhood) (Barker, 2003). Initial studies that generated the original Barker Hypothesis, and the idea of uterine programming, which later became DOHaD, were conducted by David Barker in Hertfordshire, England. Thanks to the meticulous records of midwives in the county under the leadership of Ethel Margaret Burnside, Barker was able to follow up these babies 50 years later and found an association between their birth records and adult disease patterns (Barker, Bull, Osmond, and Simmonds, 1990).

There had been concern at the start of the 20th Century that the health of the British population was in decline and it was decided in 1903 to vigorously preserve the life of every infant born. In 1911, Ethel Burnside was appointed “chief health visitor and lady inspector of midwives” in Hertfordshire. She proceeded to organise and train midwives of the county to educate new mothers on ways to keep their newborns healthy. Part of her duties was to keep records of infant birth weight plus weight at 1 year (Barker, 2003).

In the 1980s at Southampton University, David Barker and his research group began the search for maternity and infant health records from the early 20th Century. Many had been destroyed but some had been preserved and although the quality of the observations was inconsistent, varying from county to county, the largest and most complete set of recordings were those of Ethel Burnside and her team in Hertfordshire (Barker, 2003).

From this point Barker & Osmond (1986) could see that there was an association between infant mortality, childhood nutrition and ischaemic heart disease. They found a strong correlation between the rate of infant mortality at the time of birth and the development of ischaemic heart disease in the surviving babies later on in life. The records showed that a birth cohort with a high infant mortality rate, most likely due to poor nutrition, were more likely to develop ischaemic heart disease. They

investigated the causes of infant mortality only to find that it was largely due to adverse environmental conditions (poor living standards) (Barker & Osmond, 1986). Barker and Osmond's early work was shaped by Chapin's 1909 ideas that the nutrient intake of infants has a bearing on their metabolism later in life. It was surmised that since fat is the major source of energy in human milk and has a correlation to ischaemic heart disease (IHD), it could be that fat metabolism is the associating factor between early life nutrition and adult disease (Barker & Osmond, 1986). Although they could not measure the early uterine environment in this instance, birth weight was used as a proxy for the supply of nutrients to the fetus.

As nutrition was central to Barker and Osmond's concerns, it is important to consider both the nutrition of the mother and that of the fetus. Intrauterine growth of the fetus is both a function of the mother's health and nutritional status and the fetal supply line including the efficiency of the placenta that ultimately nourishes the fetus. Barker et al. (1990, 1993) found that it is placental efficiency (how many grams of baby are produced per gram of placenta), which leads to a healthy birth weight. In turn, it is *placental insufficiency* that leads to intrauterine growth restriction (IUGR) which is now recognised as one of the markers of the early environment that subsequently contributes to an increased risk of adult disease.

Barker (2003) stated that being small at birth or during infancy is a key indicator that sets people on developmental trajectories for the rest of their lives, with altered physiology that may ultimately increase their disease risk. He listed the following observed characteristics which set these people apart.

They have higher blood pressures and are more likely to develop type 2 diabetes. They have different patterns of blood lipids, reduced bone density, altered stress responses, thicker left ventricular walls, less elastic arteries, and different hormonal profiles, and they are ageing more rapidly. Out of these observations has arisen the fetal origins hypothesis, which proposes that cardiovascular disease originates through the responses of a fetus or infant to undernutrition that permanently change the structure and function of the body.

(Barker, 2003, p. 1430)

1.3 Birth Weight, Fetal Growth and Cardiovascular Disease.

Nutrition from birth through to adulthood has been identified as a contributing factor to high blood pressure and cardiovascular disease, therefore consistent with the DOHaD paradigm, it is likely that the nutritional status of an individual before birth will also be a significant factor. For many years, the nutritional status during gestation was summarised as the birth weight of the individual, which is routinely measured. Intuitively and empirically, a low birth weight is understood to be a poor outcome of gestation and depending on the severity it can reduce the individual's survival probability.

The WHO defines low birth weight (LBW) as less than 2500 grams and recognises that LBW is a significant public health matter by setting a 30% reduction target of LBW by 2025 (WHO, 2014). This target is focused on reducing preterm births in developing countries by improving antenatal care, nutrition and education. This is an admirable goal, however, not all low birth weight babies are preterm and not all preterm babies are of low birth weight (Wilcox, 2001). Therefore, reducing preterm birth may result in even more low birth weight babies being born. We are then faced with a situation where term babies have experienced their entire gestation under

restricted conditions, which may sometimes be diagnosed as intrauterine growth restriction. Intrauterine growth restriction (IUGR) has been defined as a rate of fetal growth that is less than normal for the growth potential of the fetus for that gestational age (Blair et al., 2005; Longo et al., 2013). The crucial mediator between the maternal environment, fetal growth and intergenerational health is the placenta, which is not as well studied.

Many investigations into the association between the uterine environment and subsequent health outcomes have focused exclusively on birth weight. In a study of 12,150 births from The Aberdeen Children of the 1950s study (born 1950-1956), Lawlor et al. (2005) investigated the association between birth weight of 10,803 singleton births and vascular outcomes. The incidence of coronary heart disease and stroke were measured by way of hospital admissions or fatalities from these diseases, and an inverse relationship between birth weight and both these diseases was found. Furthermore, the authors stated that this was significant in times where infant and maternal mortality were low, indicating that this association held even when environmental circumstances were favourable to both the mother and child (Lawlor et al., 2005). The authors further state that the relationship was very strong and it is also independent of a number of factors, including adjustment for size in later childhood, social class and maternal and pregnancy characteristics. In addition, as the The Aberdeen Children of the 1950s study cohort lived through a time of profound improvements in infant and maternal health, Lawlor et al. (2005) noted that factors other than the quality of healthcare were at work, namely, genetics and variations in placental function. In their findings, Lawlor et al. (2005) surmised that the discovery of an inverse relationship between birth weight and incidence of cardiovascular disease at a time when there was low infant mortality strengthened the argument that birth weight could be an important predictor of cardiovascular disease.

This inverse association between birth weight and CVD mortality is also found when birth weight and subsequent blood pressure are investigated in observational studies, further supporting the link between birth weight, hypertension and CVD. A meta-analysis of 20 articles (reporting 27 original studies) showed that the inverse relationship was present with babies born of low birth weight (< 2500g) showing an increased risk of hypertension (OR=1.21; 95% CI: 1.13, 1.30) compared to a birth weight greater than 2500g. Similarly, mean systolic blood pressure (SBP) was shown to increase by 2.28 mm Hg (95% CI: 1.24, 3.33) in the low birth weight group. Conversely, babies of high birth weight (> 4000g) had a 2.08 mm Hg decrease in mean SBP compared to babies with birth weights less than 4000g (95% CI: -2.98, -1.17) (Mu et al., 2012).

Whether birth weight increased the risk of death generally or was specific to CVD was also explained. A meta-analysis that investigated 36,834 deaths using birth weight as the key predictor, has provided some insight into all-cause mortality, CVD mortality and cancer mortality, by calculating hazard ratios (HRs) and 95% confidence intervals (95% CI). From the 22 studies analysed, it was calculated that CVD mortality had a stronger inverse association with birth weight (HR=0.88; 95% CI: 0.85-0.91) than all-cause mortality (HR=0.94, 95% CI: 0.92-0.97) (Risnes et al., 2011). Other mortality categories which were not consistently predicted by birth weight include cancer, cirrhosis of the liver, diabetes, diseases of the nervous system, lung diseases and mental disorders (Risnes et al., 2011).

Evidence also suggests that the association between birth weight and vascular health varies between males and females. Gamborg et al. (2007), on behalf of the NordNet Study Group, performed a meta-regression analysis of 20 Nordic studies that synthesised the data from 197,954 births and found an inverse relationship between birth weight and systolic blood pressure (SBP) and a linear association with males and females having a birth weight greater than 4 kg. They estimated the effect

of birth weight on SBP at age 50 years for men to be -1.53 mm Hg/kg (95% CI: -2.27, -0.77) and for women -2.80 mm Hg/kg (95% CI: -3.85, -1.76). The effect on women was nearly twice that of men. Due to these sex differences, this present study has attempted, where possible, to explore the evidence of an association between placental ratio and CVD for women and men separately.

This strong research emphasis on birth weight has consistently shown an association between blood pressure and CVD, however, this has misdirected the focus to some extent. Birth weight is an outcome of the uterine environment rather than a cause of CVD. To further our understanding of the uterine environment, the relationship between the placenta and birth weight needs to be considered at the gross level as can be seen in a sample of 24,152 singleton liveborn children of the Collaborative Perinatal Project, where it was found that placental weight alone accounted for 36.6% of birth weight variation; the six other placental measures accounted for 28.1%. Combined, all placental measures accounted for 39.1% of birth weight variation (Salafia et al., 2008). The current study will establish the pooled effect size of placental weight and contribute to the future understanding of the predictive power of the early environment, specifically the placental weight and the subsequent development of CVD and hypertension.

1.4 Placental Weight, Placental Efficiency and Cardiovascular Disease.

As the growth of the fetus is determined to a large extent by the uterine environment, it can be seen that fetal growth, LBW and IUGR and the placenta, are inextricably linked. Fetal growth is dependent on the uterine conditions as nutrients are transported from the mother to the fetus via the placenta (Godfrey & Barker, 2000). Indeed, the importance of birth weight as a proxy for the end product of a long oxygen and nutrition supply line, has been questioned. For example, studies such as

those using data from the Dutch Hunger Winter Famine, suggest that early life exposures (predominantly maternal undernutrition) may not affect size at birth, yet still influence chronic disease risk (Barker, 1993; Ravelli et al., 1998; Lunney, 1998; Roseboom, 2011). As such, it may be that we need to look beyond birth weight and focus on attempting to identify additional factors that influence fetal growth (Whincup & Owen, 2006; Salavati et al., 2019).

The most common pathophysiological mechanism for fetal growth restriction (FGR) is placental insufficiency. FGR fetuses are seen to occur in all fetal weight categories (small, appropriate and large for gestational age), however, there are limited studies focusing on placental morphometry and FGR. A recent review conducted by Salavati et al. (2019) indicated that morphometric data such as placental dimensions/shape and weight should be further explored as they contribute to placental insufficiency and can help to identify FGR. Moreover, placental conditions are the most frequent aetiology of IUGR (Mandrizzato et al., 2008). Key placental characteristics such as chorioangioma, infarction, circumvallate placenta, confined placental mosaicism and obliterative vasculopathy of the placental bed are all possible causes of IUGR. Therefore, examination of placental characteristics is a worthwhile activity to understand FGR and IUGR and provides an additional predictive factor for the risk of both reduced fetal growth and premature cardiovascular disease. If reliable predictors can be found, the potential to reduce the consequences of poor in-utero growth exist (Mandrizzato et al., 2008).

A gross estimate of placental efficiency is calculated from its weight and the relationship between placental weight and birth weight has been demonstrated on several occasions in various cohorts around the world (Barker et al., 1990; Whincup et al., 1995; Godfrey & Barker, 2000). In a review of the placental origins of chronic diseases, Burton et al. (2016) defines one measure of placental efficiency to be the amount of fetal body mass accumulated per gram of placenta, as the key indicator of

the offspring's resilience and susceptibility to chronic disease in later life. Burton et al. (2016) note that based on this measure of placental efficiency, the human placenta is relatively inefficient, suggesting that other evolutionary selective pressures have been more significant, namely, the placenta's ability to mitigate maternal and environmental stressors through its endocrine and epigenetic adaptability.

In recent times, larger longitudinal studies have added to the evidence base supporting the predictions of DOHaD and highlighted the importance of the placenta's role in the uterine environment. Analysis of the Trondheim Cohort from Norway, a study of 31,307 Norwegians born between 1934 and 1959, found that the placental weight to birth weight ratio (placental ratio) was positively associated with cardiovascular disease mortality (Risnes et al., 2011). They concluded that either a disproportionately large placenta or a relatively growth restricted fetus increases the amount of work a fetus' cardiovascular system needs to do and that this has consequences for development, specifically of the fetal cardiomyocytes. This, in turn, may limit capillary formation in the myocardium and lead to a poorly developed and susceptible cardiovascular system (Risnes et al., 2011).

The consistent nature of these findings is further supported by the presence of similar associations in populations from developing countries. This is exemplified by the Mysore Parthenon study in Southern India with which Winder et al. (2011) investigated the factors that influence placental morphology. The authors concluded that the mother's nutritional status and body size (mother's height was measured in this study) were associated with greater placental efficiency. The neonates in this cohort are too young to follow up for cardiovascular mortality at present; however, an analysis of the 9.5 year blood pressure data concluded that the children's blood pressure at 9.5 years can be predicted by the size and shape of the placental surface (Winder et al., 2011). This demonstrates the value of understanding factors

that influence the development of an efficient placenta and confirms that they apply in different environments and cross-culturally. Examination of the published evidence and estimating effect sizes in the current study should not only develop our understanding of associations between fetal growth, placental weight and cardiovascular disease, but may also contribute to the knowledge of which populations are more susceptible and require increased monitoring.

In addition, other anthropomorphic markers of the uterine environment have also been used. Measures such as ponderal index, head to chest circumference ratio and placental ratio may be more sensitive indicators of restricted growth rather than birth weight and their association with CVD needs to be investigated. Using data from the Collaborative Perinatal Project in the United States, Hemachandra et al. (2006) examined 29,710 births between 1959 and 1965. At birth, anthropomorphic measurements such as birth weight, placental weight, and head and chest circumference, were obtained, and from this data they calculated the placental ratio, ponderal index and head to chest circumference ratios. The placental ratio is a common proxy for placental efficiency and is defined as the amount of fetus (in grams) produced per gram of placenta. The subjects were followed up and in their seventh year, their blood pressures were taken. Of all the measurements available, it was the placental ratio percentage, that is the weight of the placenta expressed as a percentage of the birth weight (calculated by dividing the placental weight by birth weight then multiplying by 100), that was associated with an increased risk for high systolic blood pressure and pulse pressure at seven years of age (Hemachandra et al., 2006).

Although hypertension is rare among children, Misra and colleagues (2010) noted that blood pressure does track from childhood into adulthood. Several longitudinal studies have found that if a child has blood pressure at the higher end of the distribution, they are more likely to have hypertension as adults. They further

commented that there is a considerable amount of effort in place, focusing on nutrition and physical activity, which targets children at risk of developing hypertension in adult life. If we follow the DOHaD paradigm, there is considerable evidence supporting the idea that factors prior to the birth of the child are also at work. A subset of the Collaborative Perinatal Project (15,902 births) was analysed and it was found that birth weights smaller or larger than the predicted placental weight have a predictive effect on future blood pressure and body mass index (BMI). This effect was found to be independent of other measurements (Misra et al., 2010). The placenta gives unique insight into intrauterine conditions and placental growth may be linked to an increased life-time risk of hypertension and cardiovascular disease. Through calculating effect sizes, this present study aims to quantify the influence of the early environment more accurately in order to provide the evidence base for or against early interventions.

1.5 Birth weight, placental weight and cardiovascular disease:

Summary.

In summary, the association between the uterine environment and its subsequent health consequences in humans has produced mixed findings, particularly with regard to the role of the placenta. This relationship was further investigated in relation to blood pressure and Barker (1997) discovered that at any given birth weight, blood pressure rose as placental weight increased. He suggested that people with the highest blood pressures as adults were in-utero, sacrificing their own growth to support placental growth, resulting in an increased placental ratio: a larger placenta with a smaller baby (Barker, 1997). This highlights how valuable placental growth is and that the placenta plays a key role in the uterine environment. Development of the fetus and birth weight are outcomes of this uterine environment and understanding the effect of the placenta on them and cardiovascular morbidity and mortality is crucial.

Although some studies find evidence for an important role of the placenta beyond that of birth weight (e.g. Hemachandra et al., 2006; Misra et al., 2010), others find birth weight is the key predictive factor (e.g. Blake et al., 2001; Huang et al., 2007; Lawlor et al., 2005). For example, Blake et al. (2001) studied 2,507 births between 1989 and 1992 and recorded blood pressure at age 1, 3 and 6 years. In contrast to Barker (1997), they concluded that there was an inverse relationship between placental weight and blood pressure at 1, 3 and 6 years. However, there was no consistent relationship between placental weight and later blood pressure within birth weight categories and based on this finding, they surmised that it was not clinically significant.

What we do know is that it is generally accepted that birth weight has been a long standing predictor of infant mortality and FGR (Wilcox, 2001; Salavati et al., 2019). It is reasonable to link fetal nutrition with fetal growth and ultimately birth weight. The ease of measurement and attainment of birth weight records has fostered a huge body of data examining birth weight and numerous infant and adult health outcomes (Wilcox, 2001). Birth weight itself, however, does not wholly explain the developmental consequences of placental insufficiency, IUGR or FGR, which does indicate that birth weight should be related as an outcome of placental insufficiency rather than a cause of future disease (Wilcox, 2001). It has been noted recently that in a normally nourished population, the small for gestational age (SGA) group may include those exhibiting placental insufficiency, those in which no signs of placental insufficiency have been detected or represent unknown or undetected causes of placental insufficiency or those with congenital malformations or infections (Figueras & Gratacos, 2017). In order to separate out the cause, that is, maternal and fetal nutrition from the effect, which is measured as placental and fetal growth, animal models have been utilised.

1.6 Animal Models

Animal models have been usefully applied in biology and medicine to investigate potential mechanisms underlying associations seen at the group level. These models are particularly useful for investigating the mechanisms behind DOHaD effects, consequently, a number of small and large animal models as well as novel models have been developed for this purpose (Bertram & Hanson, 2001). Animal models have long been used to demonstrate that maternal nutrition may program adult disease (Bertram & Hanson, 2001). Indeed the first experiments relating to the current DOHaD concept may have been run over 50 years ago by Winick & Noble (1966). The association between birth weight and CVD noted by Barker and colleagues (1990, 1993, 1994, 1997) worldwide have been supported through the use of animal models. Therefore, the following section will discuss the use of animal models to investigate mechanisms underlying the DOHaD phenomenon. These models have been used to develop the knowledge base of DOHaD and continue to refine our understanding of the effect the placenta has in animal populations.

These models indicate that insults during critical periods of embryonic and fetal development can have permanent long-term effects on organ structure and function, and regulatory systems of the body, which ultimately impact adult health (Jones et al., 2012). Collectively, it has been shown that effects on the placenta or fetal heart depend on the nature of the challenge and the duration, severity and timing in relation to the development of the heart and placenta (Camm et al., 2018).

Presently, there are a number of established animal models used with some being less invasive, for example, using dietary protein restriction or global nutrient restriction to induce IUGR (McMullen & Mostyn, 2009; Jones et al., 2012). Others are more invasive, using techniques such as uterine ligation or the in-utero removal of part of the placenta (Bertram & Hanson, 2001; McMullen & Mostyn, 2009). These animal models demonstrate that IUGR offspring develop post-natal hypertension, a

known contributing factor to cardiovascular disease. Small animal models, such as mice, rats and guinea pigs, also have a number of benefits including shorter gestation times and short lifespans which affords us the opportunity to investigate the DOHaD concept in ways that cannot be done in humans (Jansson & Lambert, 1999; Bertram & Hanson, 2001; Symonds, et al., 2007; Wyrwoll et al., 2007; McMullen & Mostyn, 2009; Camm et al., 2018).

A range of animal models have been used to investigate environmental factors that link the phenotypic characteristics of the placenta to those of the heart. These models comprise three broad groups: 1) Those that reduce oxygen and nutrient delivery to the fetus (these include various forms of ligation of the key arteries and veins); 2) Those that reduce oxygen availability for transfer to the fetus (these include various forms of inhalation hypoxia); and 3) Those that alter nutrient availability for the fetus (these include maternal dietary restrictions) (Camm et al., 2018). The methods employed in these three categories cannot be ethically replicated in randomised trials of human populations, therefore, for human populations, it is left to observational studies or studies based on natural experiments (e.g. the Dutch Famine and other factors which may impose a dietary restriction) or in cases of clinical placental pathology such as abnormal umbilical cord insertion (Camm et al., 2018). A fourth group does exist as the administration of glucocorticoids (usually synthetic) in experimental animal models and in humans to hasten development in pre-term birth. Due to the weight of evidence from animal experiments it is generally accepted that the efficiency of the placenta is associated with the efficiency of the cardiovascular system.

Furthermore, animal models have the added dimension of experiments conducted on genetically modified organisms. In describing the relationship between placental formation and fetal heart development, findings from genetically modified mouse experiments suggest that fetal heart development requires several genes which also

regulate the development of the placenta (Camm et al., 2018). This adds further evidence to the causal nature of the association between placental function and heart development.

A search of The Mouse Genome Informatics database, conducted in February 2018 by Camm et al., identified 329 genes with both placental morphology and cardiovascular defects (2018). 24 of these genes were included in a review of placenta and fetal heart interactions and all of these genes highlight the impact of placental development on fetal heart formation and growth, with malformations of the heart and placenta cited as the most common cause for mid-gestational lethality in mice (Camm et al., 2018). Furthermore, the previous focus was largely centred on assessing the impact of a genetic manipulation rather than the interaction between placental formation and cardiac development (Camm et al., 2018).

The physiological relevance of some animal models is questioned, often cited differences include the dietary requirements and the physiology and reproductive capacity, particularly of small animal models, as negatives (Bertram & Hanson, 2001). It is true that rats or mice have different diets to humans, different disease profiles and their offspring are born with immature nervous systems in litters rather than singleton births with relatively mature nervous systems (a functioning Hypothalamic–Pituitary–Adrenal axis or HPA axis) common in humans. The guinea pig model has been used as the invasiveness of the placenta is significant and their offspring are relatively mature at birth, however, the other drawbacks of dietary and disease profile still remain (Bertram & Hanson, 2001; McMullen & Mostyn, 2009). Even in the face of these drawbacks, rat and mouse models using uterine artery and vein ligated placenta have been shown to result in hypertensive offspring in rats and mice (Bertram & Hanson, 2001).

Large animal models which are less like the rat and mouse model, are used by researchers as some are perceived to be closer to humans in physiology. Three large animal models considered are the sheep, the pig and non-human primates, all of which have offspring born with a functioning HPA axis. Non-human primates afford us the greatest insight, however, ethically, morally and financially the use of such a model is controversial and restricted. There are other factors that impact on the use of non-human primates such as the age at reproductive maturity, which could be between 4 and 7 years. This incurs a further increase in costs for care in captivity, as well as our responsibility for their physical and mental well-being requiring many resources and expertise. In most countries, these factors are prohibitively expensive (McMullen & Mostyn, 2009).

Natural experiments in pig and sheep populations occurring on farms, have provided supporting anecdotal evidence for the relationship between the placenta and fetal development, and these results are anecdotally referred to as the 'runt of the litter' effect (Bertram & Hanson, 2001). In a commercial age where every animal born needs to provide a monetary return to the farmer, it is considered an important factor to study in order to avoid financial loss. Natural experiments in pigs occur due to the anatomy of the pig's uterus, as it is 'U' shaped, the fetus attached to the ends of the arms of the 'U' have a natural restriction and it is easily a demonstration of how a naturally restricted placenta results in poor birth outcomes such as LBW.

Experiments in sheep in which ligation of placentae are easily done due to the bi-lobed nature of the sheep's placenta reduced the overall size of the ligated placenta by half, and the resulting offspring exhibit IUGR characteristics (McMullen & Mostyn, 2009).

Where the sheep fails to match humans in dietary intake, the pig matches a human's omnivorous diet and so, a porcine model for DOHaD is emerging. In the porcine model, due to the large litter size and variability in uterine environment, piglets of the

same litter may have up to a 3-fold difference in birth weight. It is this unique feature of the pig and the fact that they can be assessed within litters which provides a natural model of variable fetal growth conditions (McMullen & Mostyn, 2009).

With regard to the investigation of DOHaD and cardiovascular disease, animal models routinely demonstrate that IUGR results in hypertensive offspring. Alexander (2003) conducted an experiment on rats whereby placental perfusion was reduced to induce IUGR and observed that the IUGR rats had a marked elevation in mean arterial pressure at four, eight and twelve weeks of age when compared to controls. Furthermore, at twelve weeks of age, the rats showed a differentiation based on sex, with IUGR male rats showing an increased mean arterial pressure vs male controls (158 ± 1 versus 135 ± 2 mm Hg, $P < 0.01$), whereas female IUGR rats showed an increase that was not significant (139 ± 4 versus 126 ± 3 mm Hg; IUGR versus control, respectively, no p-value supplied) (Alexander, 2003). Ojeda et al. (2008) states that animal models have been used to demonstrate how an environment of under nutrition, by reducing uteroplacental perfusion during late gestation, leads to hypertension in the IUGR offspring. Findings such as these in animal models parallel human epidemiological studies where reduced placental efficiency is related to cardiovascular mortality and morbidity in the offspring.

Animal models have also afforded proof of concept for DOHaD by allowing investigations into specific causal mechanisms. They provide an analogy enabling us to study the DOHaD concept and allow us to experiment in ways that would be unethical, immoral or unfeasible in a human population. Bilateral uterine blood vessel ligation in rat models has been used to induce uteroplacental insufficiency and this has been associated with reduced birth weights and increased systolic blood pressure and pulse pressure in adult rats (Schreuder et al., 2006). One of the most likely mechanisms appears to be a reduced number of nephrons in the kidneys of these growth restricted animals. This appears to hold for several animal models

including diet restriction (Woods et al., 2004). This association between lower birth weight, a reduced nephron number and increased blood pressure is also supported by human data (Hughson et al., 2003; Manalich et al., 2000). Animal models continue to be refined with new guidelines specific to their use in DOHaD research in order to continue accumulating knowledge into the effects of genome, environment and epigenetics (Dickinson, 2016).

1.7 Epigenetics and DOHaD.

The role epigenetics play in the DOHaD paradigm has also been investigated using animal models. This is of particular interest as the paradigm views the fetal insult as a 'programming' process implying the embodiment of the stressor as a precondition for disease in later life. A mouse model showed that there are at least two global epigenetic reprogramming events which can be related to the DOHaD concept, the first being the mass deletion of the parental genome followed by a selective epigenetic re-programming of the gametes during gametogenesis while the second occurs after fertilisation within the zygote which enables the pluripotency of the cells (Symonds et al., 2007).

The mouse model provides support that in humans, following fertilisation, maternal and paternal genomes (excluding the imprinted genes) of the developing zygote undergo demethylation in order to ensure that the cells are pluripotent. This demethylation is undone in 70% of Cytosine-phosphate Guanine dinucleotides (CpGs) prior to implantation, but following implantation, DNA methylation continues to be vital in cell differentiation as it silences the expression of specific genes during the development of tissues and organs. This results in a window of opportunity, where if an insult were to occur during this time, then variations in gene expression can result (Godfrey et al., 2007; Einstein et al., 2010).

In addition to the effect on the offspring's genome, epigenetic regulation is a significant factor in the development of the placenta and its function. Nelissen et al. (2010) reviewed the literature on epigenetics in relation to placental development and function in order to further examine this claim. It was noted that the proper epigenetic regulation of both imprinted and non-imprinted genes is crucial to placental development and this, in turn, is key to a developing fetus (Nelissen et al., 2010). Showing further support for the DOHaD paradigm, Nelissen et al. (2010), concluded that various environmental factors can disturb the epigenetic regulation process leading to abnormal placental development with possible consequences to the offspring's susceptibility in later life.

Banister and colleagues (2011) examined 206 human placentae for genome wide DNA methylation patterns and found that it is possible to use patterns of DNA methylation to classify IUGR and small for gestational age (SGA) placentae from appropriate for gestational age (AGA) placentae. A significant difference ($p = 0.0007$) in the prevalence of IUGR or SGA placentae was found, which led them to conclude that DNA methylation profiles and IUGR or SGA placentae are significantly associated (Banister et al., 2011). This adds a further factor to the complexity of the placental influence on the growth and development of the fetus. Through epigenetic modifications of the placenta and its function a complex array of alterations to the DNA have specific roles in the phenotype. Coall et al. (2015) proposed that methylation can occur in response to the external environment and this may be reversible, hence the changes are prime candidates for developmental adaptations as seen in DOHaD.

It has been observed that the key regulators of growth and development of blood vessels within the placental villi are members of the Vascular Endothelial Growth Factor (VEGF) family (David, 2017). These include VEGF-A, or the processed forms of VEGF-C and VEGF-D which bind to VEGF receptor 2 (VEGFR-2) which result in

vasculogenesis and angiogenesis in the placenta, increasing placental efficiency. In IUGR mice models, this is inhibited and a soluble form of VEGF-2 is formed which binds VEGF-A, subsequently inhibiting its actions (David, 2017).

The preceding reviews of human studies and animal models strongly advocate for the existence of a link between the placenta and the offspring's subsequent cardiovascular health. Thus it can be seen that the DOHaD paradigm is well supported, however, the mechanism adopted to describe the uterine environment is not clearly defined. There is a large body of evidence in support of the use of birth weight while other data shows support for the placental ratio percentage as a marker of the uterine environment. A range of proposed haemodynamic, growth factor, stress and nutrient or oxygen cues before birth are either influenced or regulated by the placenta and it is this that determines the ultimate physiological fitness of the heart (Thornburg et al., 2010). The next step is to quantify the strength of the association between placental weight and cardiovascular disease risk. The current study is a synthesis of the published data and a meta-analysis to provide a deeper and more complete understanding of the association between placental weight and CVD. Therefore, generating an effect size from a meta-analysis of observational data in human populations may contribute further to our understanding of and the value of potential interventions aimed at improving placental growth, development, and structure and ultimately function.

This project will:

- 1) Examine the published evidence on the associations between in-utero growth of humans (focusing on placental weight measurements and the placental ratio percentage) on cardiovascular outcomes (hypertension and cardiovascular morbidity as defined by the WHO ICDs) in adult life by performing a systematic review.

- 2) Use meta-analytical techniques to synthesize the information found through the systematic review.
- 3) Use the PRISMA statement to report the findings from the published data on human studies.

2. Materials and Methods.

2.1 Systematic Literature Search

To examine the published data describing the effect of placental weight on cardiovascular outcomes, a broad and as complete as possible range of published work was assessed. To access this work, the search terms were carefully selected taking into account different spelling, word combinations, research and disease terms. Search terms included the following and/or combinations of, 'birth weight', 'birthweight', 'IUGR', 'fetal weight', 'foetal weight', 'placental weight', 'placental weight ratio', 'placental ratio', 'hypertension', 'high blood pressure', 'stroke' and 'cardiovascular disease'. The search was restricted to studies on human, singleton births and articles written in English published up to and including the 30 December 2017. These search terms have been chosen using key definitions set out by the WHO and are in line with the original findings underlying the Developmental Origins of Health and Disease paradigm.

A systematic search of the following databases, PubMed, EMBASE and ISI Web of Science, was conducted and the results recorded in the PRISMA flow chart (Figure 1; Chapter 3 below) and a spreadsheet (Appendix A). Searching the PubMed database was considered valuable as it covers publications in the biomedical and life sciences fields of research and is linked to the US National Library of Medicine. This enabled the search to cover the MEDLINE database (in total PubMed covers 27 million references) and in addition, the database is indexed using a controlled

vocabulary termed MeSH - Medical Subject Headings. MeSH suggested search terms which are approximates to the original terms entered for example, 'placenta weight' was recommended by MeSH in lieu of 'placental weight'. Searching the Web of Science database, expanded the literature search to include books and conference proceedings. In addition to journals, this maximised the probability of accessing grey literature, that is, data which may have been discussed as part of a conference or book chapter but was not published in a journal. To broaden the scope of the search further, the EMBASE database was searched as it covers journals that are not included in the MEDLINE database (searched through PubMed).

The database searching was conducted as follows. First, the BMJ, PLoS One and PLoS Medicine journals were searched in full, as these are journals of quality where significant research groups in the field of DOHaD have published repeatedly. Second, the databases (PubMed, EMBASE and ISI Web of Science) were searched followed by a Google Scholar search. The Google Scholar search was employed as an additional layer to maximise reach and diversity as it employs meta-searches rather than direct database searches. A detailed list of the articles found was maintained in order to avoid duplicates.

When the systematic literature search was carried out, the relationship between the placenta and the cardiovascular system was investigated, the most common placental measures being used were placental weight and placental weight to birth weight ratio (sometimes referred to as the placental ratio). It is becoming more apparent that other placental measures such as volume, surface area, length and breadth are increasingly being used. As more studies using these measurements are published a better understanding of the placenta's role in CVD will emerge. As this is emerging literature, the search criteria for this thesis was focused on placental weight measurements. In the original defining work by Barker and colleagues (1986), placental weights were measured in imperial pounds, whereas subsequent

investigations used metric measurements (grams). The cardiovascular outcomes have been defined by the WHO using the International Classification of Diseases (ICD) codes to identify cardiovascular diseases such as ischaemic heart disease (IHD), coronary heart disease (CHD) and stroke. In addition, blood pressure was investigated alongside hypertension as blood pressure was sometimes measured in children and this was seen as separate to diagnosed hypertension in adults.

2.2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

The best practice guidelines for conducting and reporting meta-analyses and systematic reviews are provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, developed and published by The PRISMA Group. This statement was released via simultaneous publications in the British Medical Journal (BMJ), Annals of Internal Medicine, PLoS Medicine, Journal of Clinical Epidemiology, Open Medicine and the International Journal of Surgery. This statement recognised that while meta-analyses and systematic reviews are essential tools used to provide a reliable and accurate view of published data, there is evidence that the published works resulting from a systematic review and/or meta-analysis are often less useful than expected because the key information is not reported well (The PRISMA Group, 2009). This was most likely due to the lack of a standard protocol for reporting systematic reviews and meta-analyses. The PRISMA statement introduced a means for standardised reporting in order to provide a guide on how to report the findings (The PRISMA Group, 2009). In the current project, the PRISMA statement guidelines were followed, and in doing so, the transparent and complete reporting of key information was ensured (The PRISMA Group, 2009), see Figure 1 for this study's PRISMA 2009 Flowchart.

2.3 Statistical Analysis.

Through a systematic review of the published works, a list of studies was created as displayed in appendix A. The studies were examined and data was extracted from them in these eleven fields: 1) Publication details (e.g. authors, date and title of publication), 2) Setting or cohort studied, 3) Recruitment location, 4) Method of measurement, 5) Diagnostic criteria to determine CVD, 6) Age at outcome, 7) Number of subjects, 8) Placental weight categories, 9) Other placenta data, 10) Key findings and 11) Comments.

The studies were grouped according to the type of cardiovascular outcome measure (e.g. hypertension, coronary heart disease and cerebrovascular disease), and further stratification was made based on geographical regions and/or population. If data was available on sex this was also used to group data. Once the groupings were set up, meta-analytical techniques (as defined by the PRISMA statement) were performed.

To analyse the data a specialised meta-analysis package, Comprehensive Meta-Analysis (CMA) software from <https://www.meta-analysis.com/> was used. CMA was chosen as it does not restrict the type of data entered for the calculation of effect size and variance to one format, for example, means and standard deviations. The CMA software accepts more than one hundred formats including the more frequently used, mean and standard deviation, odds ratio and confidence intervals, increasing the number of studies that can be incorporated into the analysis.

The first technique was the examination of publication bias which was done through the use of funnel plots. Publication bias was first formalised by Dickersin & Min (1993) as a tendency for articles not to be published based on the direction and strength of the results of a study. It is now one of several biases related to meta-analyses, collectively termed reporting biases (Sedgwick, 2013). A funnel plot is a plot of the estimated effect size of each trial against its sample size. By including a

funnel plot we visualised how the individual studies found, through the systematic review, were related to each other and explored the implications for data heterogeneity, publication bias and chance (Liu, 2011; Sedgwick, 2013). Of specific concern was the shape of the plot, as in the absence of bias, the plot resembles an inverted funnel indicating a balance between positive and negative results exists in the published literature. The shape comes from the commonly held statistical understanding that results from studies of smaller sample size will scatter widely across the bottom of the funnel plot because a smaller sample size lends itself to greater variability and this spread of effect sizes will narrow as the sample sizes increase (Egger et al., 1997).

Symmetry can be assessed visually providing a quick method to determine if publication bias exists, however, to be certain, calculated statistics are employed. In this instance an Egger's test was performed. The null hypothesis for Egger's test is that symmetry exists in the funnel plot, with the alternative indicating that asymmetry is present and there is evidence of publication bias (Egger et al., 1997; Sedgwick, 2013). When the Egger's test was applied, if the resulting p-value was greater than 0.05 it indicated that there was no evidence to reject the null hypothesis in favour of the alternative, indicating that symmetry was present and there is no evidence of publication bias. This indicated that at the 5% level of significance it could be concluded that symmetry exists in the funnel plot. Calculated p-values for the Egger's test are recorded in Table 1.

The meta-analysis consisted of three main parts. First, a pooled estimate and confidence interval for the condition's effect size was calculated after combining all the studies. Second, a test for whether the condition's effect size was statistically significant or not (i.e. does the effect differ from no effect more than would be expected by chance?). Third, a test for heterogeneity of the effect on outcome

between the included studies (i.e. does the effect vary across the studies more than would be expected by chance?).

Discussion on the value of effect sizes by Sullivan and Feinn (2012) indicated that p-values are not enough on their own. P-values are greatly influenced by sample size, with large sample sizes (which are common in this field of research) increasing the likelihood of a small effect size being statistically 'significant' without any clinical meaning. Therefore, an examination of each study in light of the calculated p-value and effect size was carried out, with the calculated effect sizes reported whenever possible. Cumming (2013) stated that effect sizes and confidence intervals provide the basis for estimation and the use of estimation is superior to null hypothesis testing. Meta-analytical techniques used in the current project are the key tool in synthesizing the records found through the systematic literature search. Effect sizes will quantify the placental risk factor enabling comparisons to other early (e.g. birth weight) and adult (e.g. hypertension) risk factors for CVD.

Using the CMA software, the relevant data from the records were extracted and entered in the required fields and then the I^2 statistic was calculated. The I^2 statistic is a useful summary of the impact of heterogeneity in a data set as it describes the proportion of total variation that is due to heterogeneity (Higgins & Thompson, 2002). An I^2 of less than 25% indicates that the studies should be combined using a fixed-effects model as they are homogenous. Alternatively scores of greater than 75% for an I^2 indicate that the studies are highly heterogeneous and a mixed-effects model should be used (Fernandez & Tran, 2009). After determining that a mixed-effects model should be used in this study (an I^2 more than 25% was reported in section 3.2), a meta-analysis was run and results displayed in Tables 2 and 3. The results included lower and upper limits for 95% CI, standard difference in means and variance of each study. These statistics provide a broader picture of the data and an estimate of the effect of each study on the overall calculated effect size.

2.4 Examination of Geographical Locations Studied.

Records that satisfied the selection criteria were coded on a heat map of the world in order to generate a view of the most common locations where these studies were carried out. A further examination of these records in light of the geographic region was conducted and this is discussed in section 4.6.

2.5 Grey Literature.

Several records which were found through the search process did not satisfy the selection criteria and were deemed inappropriate for further analysis. These records were thoroughly searched and were found to cite two potentially unexplored links to the topic.

The two possible links were:

1. Eight groups identified by McNamara et al. (2012) who studied early life influences on cardio-metabolic health in aboriginal populations.
2. A research group working out of the King Saud University who investigated changes in the placenta during and around Ramadan (Alwasel et al., 2011; Harrath et al., 2014).

They were searched independently using Google Scholar and PUBMED. In addition, the corresponding authors were contacted via email as they may also have collected data which has not been published.

2.6 Selection Criteria.

On completion of the literature search the resulting studies were systematically reviewed. Search results which did not fulfil the above criteria (in addition to reporting on placental weights and CVD) were excluded from further analysis, but retained to provide possible insight and a search of their reference lists was conducted to extract relevant studies.

Records were screened using the following criteria:

- 1) Records were written in English or a duplicate published translation.
- 2) Records were an original report on the relationship between human placental weight and blood pressure, hypertension, cardiovascular disease, ischaemic heart disease, stroke or coronary heart disease. Studies were considered irrespective of the definition of cardiovascular disease (definitions used included those of the World Health Organisation and the National Heart Foundation).
- 3) Records studied subjects of singleton births, born at full term.
- 4) Records reported placental weight and the incidence of cardiovascular disease as described in point 2.
- 5) Records indicated the geographical and/or ethnic group of the cohort studied

If a record did not fulfil criteria 1, 2, 3 and 4, it was excluded from further analysis as the record was not usable. The records were retained in order to provide further insight and for a search of the reference list. Records that did not satisfy criteria 5 were retained and included in the meta-analysis as this criterion did not impact on the record's suitability for this meta-analysis.

2.7 Analysis of Study Quality Using the Newcastle-Ottawa Scale.

After the search was conducted and analysis was performed, it became apparent that further examination of the search results was required to provide additional evidence by which the quality of each study could be evaluated. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the articles reported in this study and to examine outliers in the data. The NOS was developed in conjunction with the University of Newcastle (Australia), The University of Ottawa (Canada) and The Ottawa Hospital Research Institute. It has been used extensively at the University of Ottawa and the Ottawa Hospital Research Institute, most notably in a

project assessing the association of CHD with hormone replacement therapy in postmenopausal women (Wells et al., 2000). The Cochrane Collaboration and the Agency for Health Research and Quality (AHRQ) have identified the value of the NOS (AHRQ, 2010; Singh et al., 2015). It is noted that users who are unfamiliar with the field of research tend to require more training than those who are familiar with the field (Singh et al., 2015). Therefore, in order to maintain consistency, a systematic review and meta-analysis that employed the NOS was used as a guide to the ranking process. The article by Zhang et al. (2013) on, "The Associations of High Birth Weight with Blood Pressure and Hypertension in Later Life" ranked 30 articles that had a range of scores from four to nine stars. The author of this thesis read and ranked the articles according to the NOS and the scores were compared in order to develop consistent scoring. The present study used the NOS criteria specifically designed for cohort studies and this is reported in appendix B.

Using the NOS, studies are ranked on three domains: Selection, Comparability and Outcome, with a maximum of nine stars to be awarded (these ratings are displayed in Figure 4). Domains for the NOS scale were defined on the basis of the search criteria of the present study. For example, in the first NOS Domain for 'Selection' under the heading, 'Representativeness of the Cohort' both the exposed and non-exposed cohort was set to be of all singleton, full term babies in the community studied. Therefore, a star was awarded if there was 'full representation' (all singleton, full term babies in that population, sample, or hospital) or 'somewhat representative' and no stars were awarded if the study was restricted to one sex, for example. Under the NOS domain for 'Comparability', it was noted that as every article found reported a study which controlled for some factors, such as birth weight or age, it was deemed that although this was not consistently the same factor, there was an awareness that some factors in each study were acting as confounders and so one star was awarded to each study in this domain. According to the NOS guidelines,

another star was awarded if the study specifically controlled for age, sex and marital status. The final NOS domain was for 'Outcome', and it required an indication of the median duration of follow-up and it was defined that any study which included rates of mortality from CVD or incidence of hypertension or CVD was awarded a star indicating that the duration of follow-up was adequate. Studies which examined blood pressure (without the key diagnosis of hypertension) were not given a star.

In relation to the NOS scoring system, the Agency for Healthcare Research and Quality (AHRQ) has indicated that there are three standards, Good, Fair and Poor.

Good quality is defined as: Three or four stars in the 'Selection' domain, and one or two stars in the 'Comparability' domain and two or three stars in the 'Outcome' domain. **Fair quality** is defined as: Two stars in the 'Selection' domain and one or two stars in the 'Comparability' domain and two or three stars in the 'Outcome' domain. **Poor quality** is defined as: None or one star in the 'Selection' domain or no stars in the 'Comparability' domain or none or one star in the 'Outcome' domain. One article, Barker (1997) indicated with an asterix (*) in Figure 4 was ranked but it reported on data previously published and so was not counted as an original article for the purposes of the meta-analysis. This is further discussed in section 4.7.

3. Results.

3.1 PRISMA Flow Diagram.

The process and results of the search of the published literature is detailed in Figure 1. This figure outlines the stages of 'Identification', 'Screening', 'Eligibility' and 'Inclusion' with the appropriate number of records and details the prescribed steps at each stage as outlined by the PRISMA statement. The search identified 826 potential articles through the database search and 18 articles from other sources such as the reference lists of relevant articles. After removing duplicates, 724 records remained. An initial screening process found that the majority of these records were reporting on similar cohorts or were responses to the editor and/or authors of published articles and these 592 records were subsequently removed from the list. In addition, several records were reference texts, established procedural guidelines (e.g. guidelines for the pathological examination of the placenta) or recommendations for changes to the guidelines, which were also removed. Following this initial screening process, 132 records remained. A further 103 records were excluded as they did not completely fulfil the selection criteria (as outlined in section 2.5). Although excluded, these 103 records were retained, their full texts obtained and searched in detail in order to extract any information which may have been overlooked. Three records were of use as they indicated:

1. Eight groups identified by McNamara et al. (2012) who studied early life influences on cardio-metabolic health in aboriginal populations.
2. A research group working out of the King Saud University who investigated changes in placenta during and around Ramadan (Alwasel et al., 2011; Harrath et al., 2014).

The appropriate correspondence authors were contacted via the email address supplied and a detailed search of their reference lists was conducted for potentially useful records.

The full texts of the remaining 29 records were assessed and 3 were found to be unsuitable as they either used placental weights as part of a cluster analysis which analysed Percentage of Expected Birth Weight (PEBW), measured placental weights as an outcome of exposure to famine or the record was an analysis of a cohort which was previously included. The remaining 26 records were included in subsequent analyses. Of the 26, four records were found to reported sufficient data to enter into the meta-analysis in this study. The results of this meta-analysis are shown in Tables 2 and 3.

On entering the data into the CMA program it became apparent that the various combinations of data type (e.g. SBP, DBP, diagnosed hypertension, OR, RR, HR, SMR), placental weight groupings (grouping placentae into three, four and five groups) and use of differing methodologies (e.g. meta-regression or adjustments for different variables) would cause the data reported in the records to be incompatible. To gain a greater understanding of the quality and potential variability between studies, further analysis of the records was also employed. This included:

- 1) To examine difference in geographical origins of the cohorts.
- 2) To examine the quality of the studies using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies.



PRISMA 2009 Flow Diagram

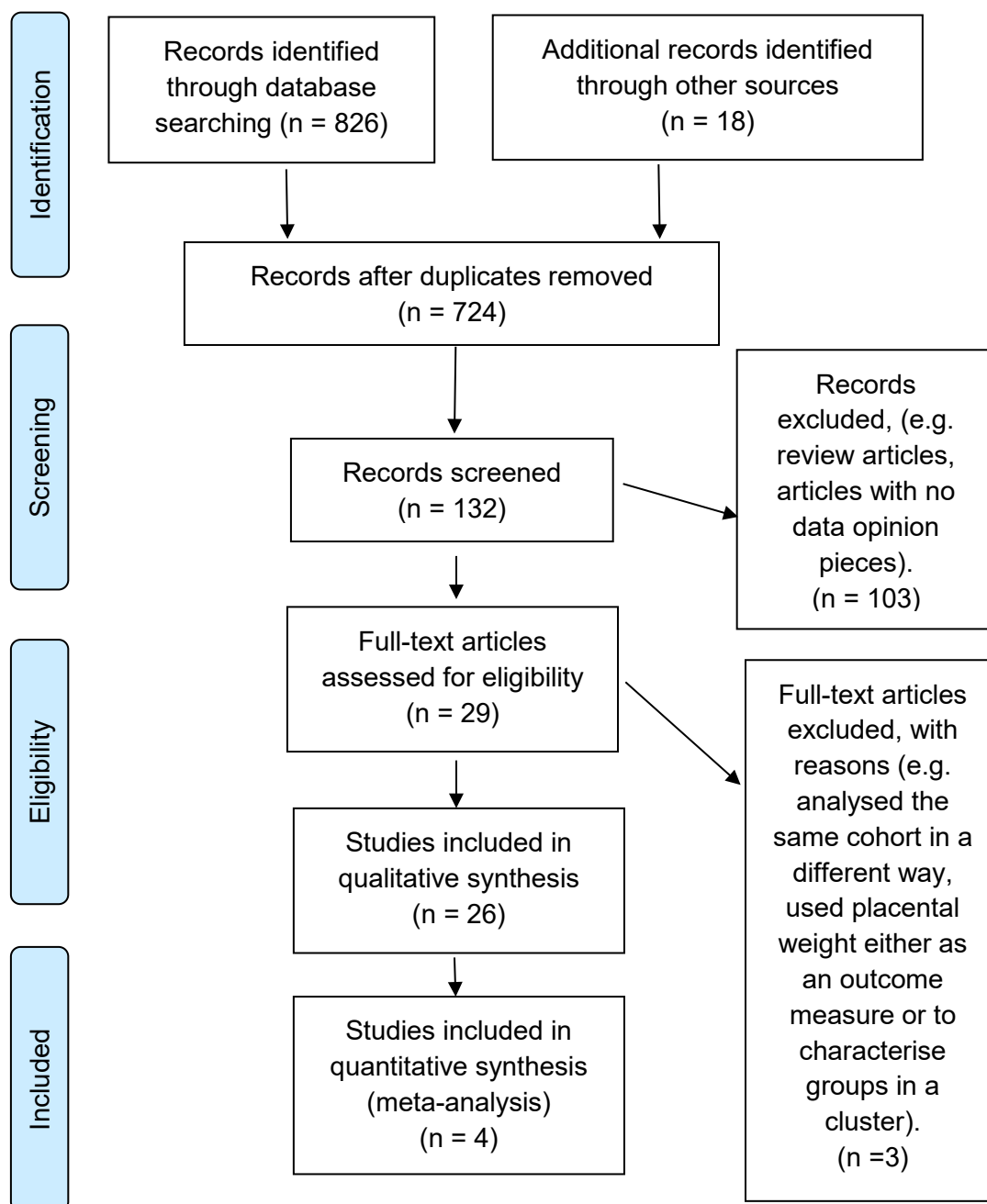


Figure 1. PRISMA Flow Diagram displaying the number of records at each stage of the four stages of the prescribed PRISMA process.

3.2 Meta-Analysis of Records

Of the 26 records, four supplied data in a compatible format which allowed a meta-analysis to be performed and all four records focused on blood pressure as an outcome measure. One record collected blood pressure readings at three age points (1, 3 and 6 yrs) and this data was entered as three individual cohorts. The funnel plot for these records is displayed in Figure 2.

One record (Whincup et al., 1995) was identified (shown as a red dot in Figure 2) as an outlier and the data was analysed again without this record, with the funnel plot for the repeat analysis shown in Figure 3.

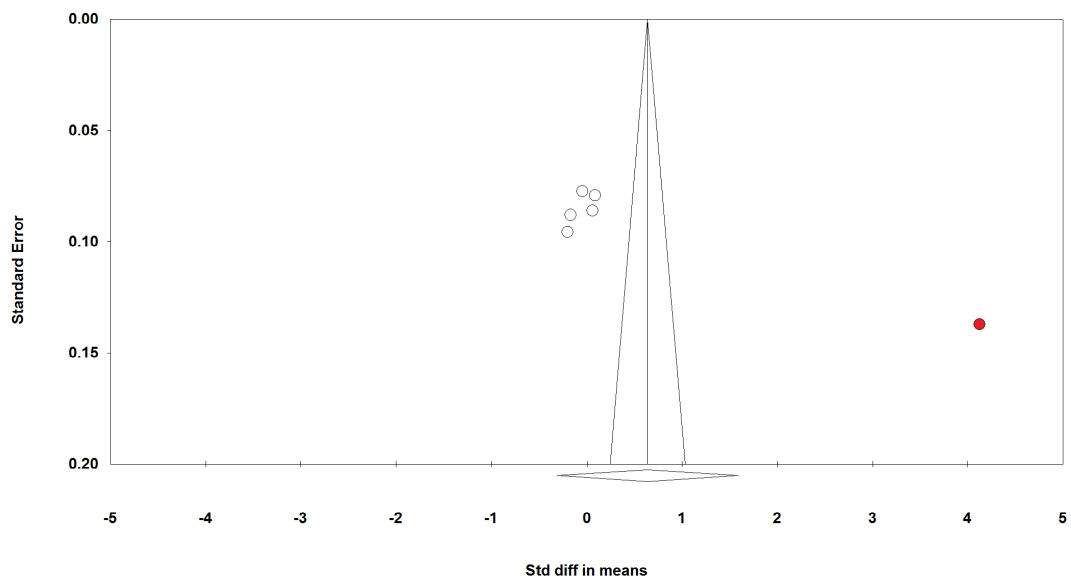


Figure 2. Funnel plot of standard error by standard difference in means, output from CMA. A record highlighted (red dot) was identified as an outlier. The diamond on the horizontal axis indicates the spread of the effect size as calculated by standard difference in means.

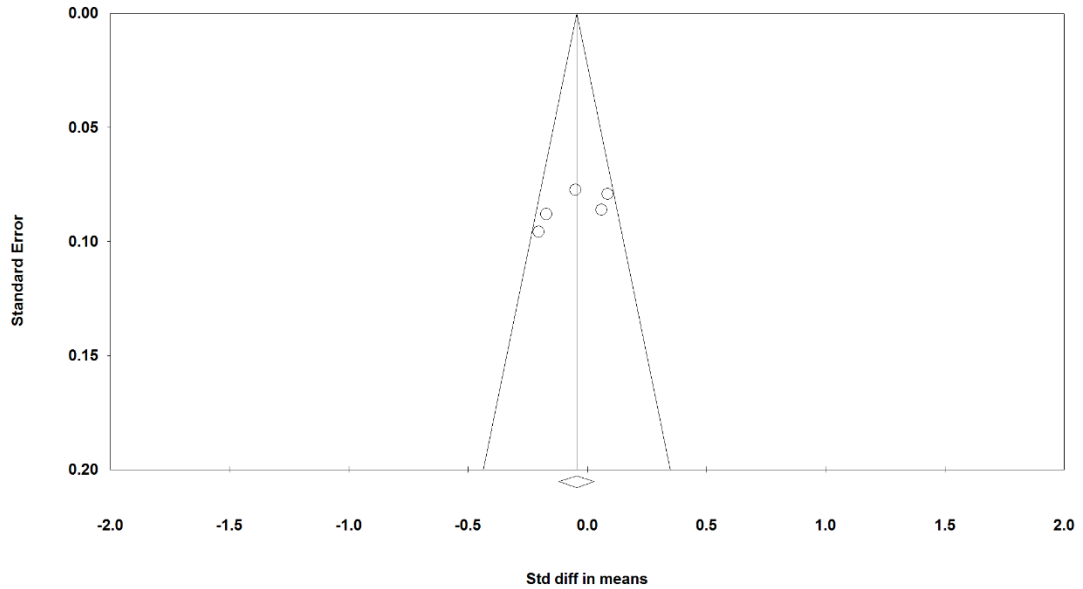


Figure 3. Funnel plot of standard error by standard difference in means, output from CMA. This plot has omitted the outlier, Whincup et al. (1995), from Figure 2. The diamond on the horizontal axis indicates the spread of the effect size as calculated by standard difference in means.

Through visual examination of the plot an outlier was expected. An Egger's test was performed to determine the level of heterogeneity in the studies, which leads to the selection of a mixed-effects or a fixed-effects model. The results of the Egger's test are displayed in Table 1, with both 1-tailed and 2-tailed p-values affected by the removal of the outlying record. In the original analysis (Figure 2), both p-values indicated that asymmetry existed and after removing the record (Figure 3) the p-values indicated that symmetry does exist ($p > 0.05$)

Table 1. Egger's Regression Intercept and p-value scores for the Egger's test of the funnel plots with and without the outlier.

	For all records (Figure 2).	Omission of outlier (Figure 3).
Intercept	63.239	-11.604
Standard Error	17.267	7.722
95% CI lower limit (2 tailed)	15.297	-36.180
95% CI upper limit (2 tailed)	111.180	12.972
t-value	3.662	1.503
df	4.000	3.000
p-value (1-tailed)	0.011	0.115
p-value (2-tailed)	0.022	0.230

The results from the meta-analysis including Whincup et al. (1995) can be seen in Table 2 while Table 3 displays the results from the meta-analysis omitting it.

An I^2 value of 99.4 was calculated and as it was greater than 75% it was determined that a mixed-effects model was appropriate, because, as noted by Fernandez & Tran (2009) mixed-effects models are usually reserved for I^2 scores of greater than 75%. As displayed in Table 2, p-values indicate significant results from the Barker et al. (1990) and Whincup et al. (1995) records. One other record, Moore et al. (1996), had a p-value of 0.05. All three cohorts from the Blake et al. (2001) record are not significant.

In this analysis (Table 2), the combined effect favoured a lighter placenta, indicating that higher blood pressure was related to a lighter placenta (Effect size = 0.250; p-value < 0.0005). An outlier (Effect size = 4.125; p-value < 0.0005) which distinctly favoured a lighter placenta (Whincup et al., 1995) was noted.

Once the outlier was removed, the analysis was re-run. Removing the outlier generated an I^2 value of 55.5, and as it was greater than 25% it was determined that a mixed-effects model was appropriate, however, it is not greater than 75% and therefore an analysis was run using both fixed and random effects models. The

results are displayed in Table 3 and no difference was found between the fixed and random effects models in the calculated results.

As displayed in Table 3, the effect sizes and p-values for individual studies remained the same as in Table 2. P-values indicate significant results from the Barker et al. (1990) and Whincup et al. (1995) records. The Moore et al. (1996) study retained the p-value of 0.05 and all three cohorts from the Blake et al. (2001) record are not significant.

The combined effect however, is no longer significant and has changed to indicate that a higher blood pressure is related to a heavier placenta (Effect size = -0.044; p-value = 0.24).

Table 2. Results of the meta-analysis performed. Blake et al. (2001) included subjects from three age categories and therefore each age category was treated as an individual cohort. Standard Difference in Means, Standard Error, Variance and Relative Weights were calculated and Lower and Upper limits are reported for 95% CI. The plot shows that overall the condition favours a lighter placenta, indicating that higher blood pressure is related to a lighter placenta.

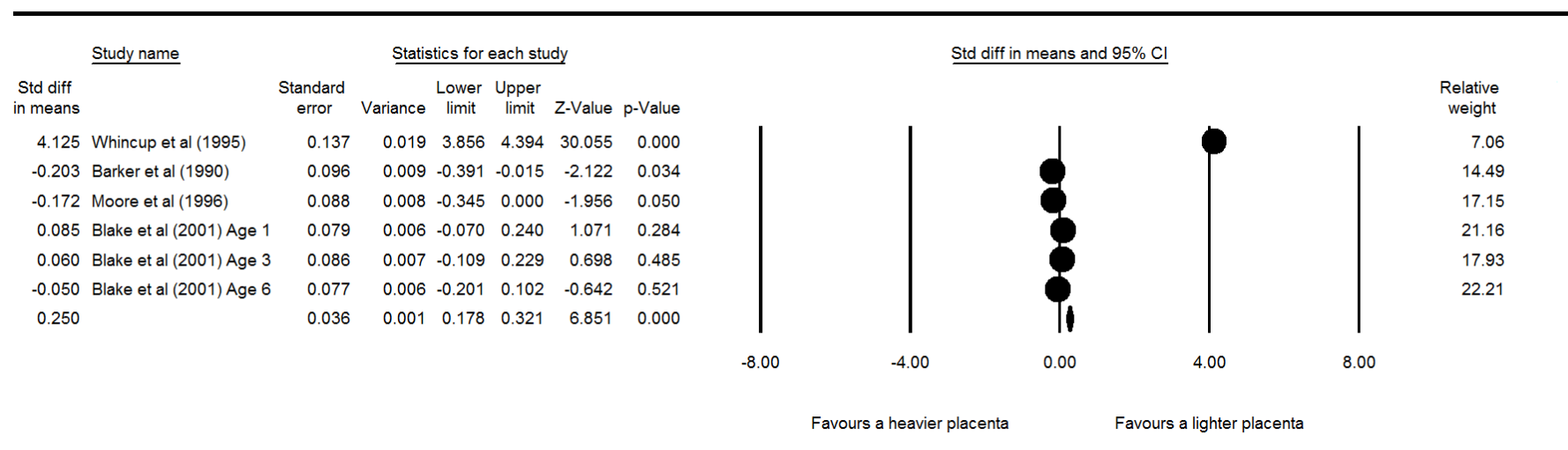
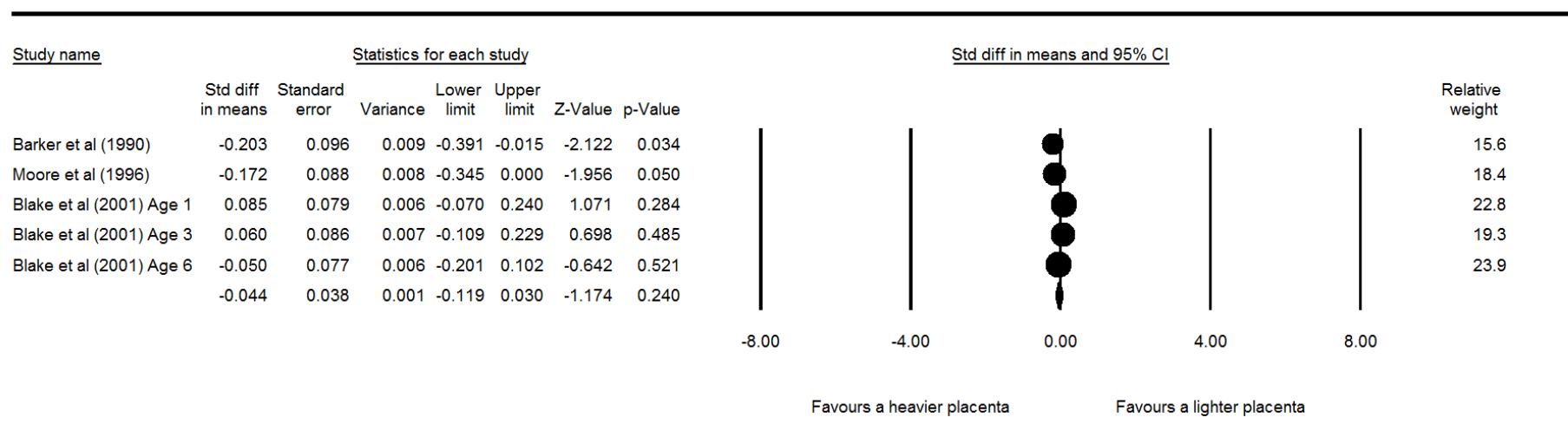


Table 3. Results of the meta-analysis omitting the outlier (Whincup et al. (1995)), performed on 3 records. Blake et al. (2001) included subjects from three age categories and therefore each age category was treated as an individual cohort. Standard Difference in Means, Standard Error, were calculated and Lower and Upper limits are reported for 95% CI. The plot shows that overall the condition favours a heavier placenta, indicating that a higher blood pressure is related to a heavier placenta although it is not significant.



To further understand the quality of the research articles being assessed and further evaluate the removal of the outlier, an additional analysis of the quality of the studies was undertaken.

The Newcastle-Ottawa Quality Assessment Form for Cohort Studies was employed and the results of the ranking are displayed in Figure 4. Of the 26 records ranked, 20 (77%) were of good quality, three (12%) were ranked as borderline Good/Fair and another three were ranked as borderline Fair/Poor.

The borderline Good/Fair ranking was used as these three records received only 1★ in the Outcome domain (placing them in the Poor Category), however, they received sufficient scores in the other two domains to place them in the Good category. This meant that they were in the Good category for two out of three domains, but placed in the Poor category for one domain. Similarly, the Fair/Poor ranking was used because the three records in this category received 3★ in the Selection Domain (placing them in the Good Category) and 1★ in both the Comparability and Outcome Domains, which places them in the Poor Category.

The Whincup et al. (1995) article which was originally identified as an outlier was one of two articles that received the highest possible score (nine out of nine ★), therefore, it is not likely that it was an outlier or an error. The other records in the meta-analysis are not as highly ranked, with Barker et al. (1990) scoring 8★, Moore et al. (1996) and Blake et al. (2001) both scoring 6★. The other article which scored 9★ (Risnes et al., 2009) found that death by CVD had an increase in HR per SD (120g) of placental weight (HR 1.13, 95% CI 1.00, 1.28). Death by CHD had an increase in HR per SD (120g) of placental weight (HR 1.13, 95% CI 0.97, 1.33) and death by stroke Death had a decrease in HR per SD (120g) of placental weight (HR

0.083, 95% CI 0.87, 1.58). Therefore, the two highest ranked studies, both with 9★, found diverging associations between placental weight and cardiovascular health.

Authors	Design	Selection				Co mpa rabi lity		Outcome			Total	Quality
		★	★	★	★	★	★	★	★	★		
Whincup et al. (1995)	CH	★	★	★	★	★	★	★	★	★	9	Good Quality Selection: 3 or 4 ★ Comparability: 1 or 2 ★ Outcome: 2 or 3 ★
Risnes et al. (2009)	CH	★	★	★	★	★	★	★	★	★	9	
Barker et al. (1990)	CH	★	★	★	★		★	★	★	★	8	
Barker et al. (2009)	CH	★	★	★	★		★	★	★	★	8	
Eriksson et al. (2011)	CH	★	★	★	★		★	★	★	★	8	
Eriksson et al. (2000)	CH	★	★	★	★		★	★	★	★	8	
Fan et al. (2009)	CH	★	★	★	★		★	★	★	★	8	
Hesmati & Koupil (2014)	CH	★	★	★	★		★	★	★	★	8	
Leon et al. (1998)	CH	★	★	★	★		★	★	★	★	8	
Taylor et al. (1997)	CH	★	★	★	★		★	★	★		7	
Eriksson et al. (2010)	CH	★	★	★	★		★	★	★		7	
Barker (1997) *	CH	★	★	★	★		★	★	★		7	
Burke et al. (2004)	CH	★	★	★	★		★	★	★		7	
Barker et al. (1992)	CH		★	★	★		★	★	★	★	7	
Campbell et al. (1996)	CH		★	★	★		★	★	★	★	7	
Forsen et al. (1997)	CH		★	★	★		★	★	★	★	7	
Martyn et al. (1994)	CH	★	★	★	★		★	★	★		7	
Law et al. (1991)	CH		★	★	★		★	★	★		6	
Martyn et al. (1996)	CH		★	★	★		★	★	★		6	
Forsen et al. (1999)	CH		★	★	★		★	★	★		6	
Whincup et al. (1999)	CS	★	★	★	★	★	★	★			7	Good/Fair Quality. Selection: 4★ Comparability: 1 or 2★ Outcome: 1★
Blake et al. (2001)	CH	★	★	★	★		★	★			6	
Moore et al. (1996)	CH	★	★	★	★		★	★			6	
Moore et al. (1999)	LS		★	★	★		★	★			5	Fair/Poor Quality: Selection: 3★ Comparability: 1★ Outcome: 1★
Winder et al. (2011)	CH		★	★	★		★	★			5	
Forrester et al. (1996)	CH		★	★	★		★	★			5	

Figure 4. All 26 articles from the qualitative synthesis ranked from highest quality (9★), to lowest quality (5★). The Newcastle Ottawa Scale (NOS) the Quality Assessment Form for Cohort Studies.

Note: A study can be given a maximum of nine stars across the three sections of Selection, Comparability and Outcome. The Agency for Healthcare Research and Quality (AHRQ) has indicated that there are three standards, Good, Fair and Poor. These are defined as **Good quality**: 3 or 4 ★ in selection domain AND 1 or 2 ★ in comparability domain AND 2 or 3 ★ in outcome/exposure domain. **Fair quality**: 2 ★ in selection domain AND 1 or 2 ★ in comparability domain AND 2 or 3 ★ in outcome/exposure domain. **Poor quality**: 0 or 1 ★ in selection domain OR 0 ★ in comparability domain OR 0 or 1 ★ in outcome/exposure domain. One article, Barker (1997), indicated with an asterisk (*) was ranked but it reported on data previously published and so was not counted as an original article.

3.3 Records Related to Blood Pressure: Qualitative Synthesis.

To further understand the relationship between placental weight and CVD outcomes, the studies related to each outcome were analysed separately. Of the 26 records, 12 focused on blood pressure, of which four (Barker et al., 1990; Whincup et al., 1995; Moore et al., 1996; Blake et al., 2001) were compatible for the meta-analysis. In this group of 12, two reported mean diastolic and systolic blood pressures (DBP and SBP), four reported mean SBP only (two reported group SD only and they were found to be reporting on the same cohort, the duplicate article is indicated with an * in Table 4) one used a calculation of mean difference and one reported incidence of diagnosed hypertension, one record reported only a p-value for linear trend while no records used DBP exclusively. In addition, there are four records which used either SBP or DBP as a factor in regression model analysis. These records are listed along with key information such as the placental weight categories used, direction of relationship and p-value for linear trend (where reported) in Table 4. Five records (42%) reported a positive relationship between placental weight and blood pressure (i.e. the condition favours a heavier placenta or a heavier placenta is associated with higher blood pressure). Four (33%) reported a negative relationship and two were mixed, with Winder et al. (2011) reporting a positive relationship for girls and a negative relationship for boys, conversely, Taylor et al. (1997) reported a negative relationship for girls and a positive one for boys. One article was the duplicate study indicated with a asterix.

Of the four records which reported mean SBP and DBP, one record reported the mean and a group standard deviation for the entire cohort, another record reported means only without standard deviations or confidence intervals or a similar statistic. One did not report any data but provided a descriptive statement on the relationship between placental weight and blood pressure. Two records split the cohort to compare boys and girls, one used means and standard deviations of SBP and DBP

and the other used regression modelling with SBP and DBP as factors. Table 4 displays more detail for each study such as the reported regression coefficients, p-values and direction of relationship.

Table 4. Results of literature search. Articles listed have reported both placental weights and an association with blood pressure. Placental weight categories, mean Systolic Blood Pressure (SBP), mean Diastolic Blood Pressure (DBP), direction of relationship (positive trend denotes an increase in blood pressure between lightest to heaviest placental weight categories), p-values for linear trends are listed when available in the published article. In some cases, SD, R² and 95% CI were available and this has been noted in the table below. Of the twelve articles, five articles demonstrated a positive relationship, four demonstrated a negative relationship, two articles examined boys and girls separately, one found a negative trend for girls and a positive trend for boys, the second found a negative trend for girls DBP, boys SBP and DBP and a positive trend for girls SBP, the remaining article shared data from another study indicated with *.

Authors	Placental Weight categories	Measure (SBP, DBP or both)			Direction of relationship	P-value for linear trend	Other measures/ statements
Blake et al. (2001)	<540g 541-640g >640g	Mean SBP (95% CI)			All regression coefficients for placental weight and SBP were negative.	None reported	The child's current weight was the concurrent variable most strongly correlated with blood pressure. Placental weight was positively associated with current weight. No consistent pattern was seen in the relationship between placental weight and SBP within birth weight groups or overall. The highest SBP at age 6 years was in those children with the highest placental weight and lowest birth weight and the lowest SBP was in those with the lowest placental and highest birth weight
		1 yo	3 yo	6 yo			
		98.3	99.6	104.3			
		97.9	99.1	104.8			
Moore et al. (1996)	≤500g 510-600g >600g	Mean SBP and DBP at age 8 no SD reported			Positive (SBP & DBP)	None reported	Placental weight alone was not related to systolic pressure. There was a positive but not statistically significant relationship between placental weight and diastolic pressure.
		SBP		DBP			
		100.6		60.1			
		101.5		60.7			
		102.2		62.3			

Barker et al. (1990)	Placental weights in pounds (converted to grams) ≤1.0 (≤454g) 1.01-1.25 (458.54-567.5) 1.26-1.5 (572.04-681) >1.5 (>681)	RR SBP>160 mm Hg and RR Treatment for Hypertension		Positive	None reported	Systolic and diastolic blood pressure were strongly related to placental weight. Mean differences were also calculated with 95% CI 1st cohort Mean difference pw ≤1.5 lb and >1.5 lb, 11 mm Hg, 4 to 18) 2nd cohort 7, 0 to 14 Combined 9, 4 to 14 The highest pressures were among people who had been small babies with large placentae and the lowest were among people who had been large babies with small placentae.
		SBP >160 mm Hg	Treatment for Hypertension			
		1.0 (ref) 1.3	1.0 (ref) 1.1			
		2.4	1.2			
		3.0	2.5			
Barker et al. (1992)	Placental weights in pounds (converted to grams) ≤1.0 (≤454g) 1.01-1.25 (458.54-567.5) 1.26-1.5 (572.04-681) >1.5 (>681)	Mean SBP group SD 20.2 age 46-54 144 148 148 156		Positive	None reported	
Barker (1997) *	Same cohort and data as Barker (1992)					

Law et al. (1991)	≤550g 650g 750g >750g	Mean difference SBP mm Hg and 95% CI age 4 years. 0 (ref) -0.1 0.6 2.6				Positive	None reported	
Winder et al. (2011)	≤350g 400g 450g >450g	Mean SBP and DBP and SD Age 9.5 yr				Negative (Boys – SBP and DBP, Girls DBP)	0.15 (Boys SBP)	Length, breadth and area of placenta.
		Boys		Girls				
		SBP	DBP	SBP	DBP	Positive (Girls – SBP)	0.24 (Boys DBP)	
		102.5	58.5	99.4	58.6			
		101.1	58.7	99.6	58.6			
103.6	59.4	100.1	57.9	0.8 (Girls SBP)				
100.6	57.5	100.6	56.6		0.02 (Boys DBP)			
Burke et al. (2004)	None used	Regression Modelling age 8 years Coefficient 0.003 95% CI -0.001, 0.007				Positive	0.169	R ² 0.001
Campbell et al. (1996)	None used	Regression modelling Statement only				Negative	0.2	Low placental weight was associated with a higher blood pressure in the offspring though this was not statistically significant(regression coefficient -9.2 mm Hg/kg; 95% CI - 22.6 to 4.1

Taylor et al. (1997)	None used	Regression modelling SBP and DBP boys and girls 8-11 yr				Negative (Girls) Positive (Boys)	0.01 (Girls SBP)	Difference in coefficients between boys and girls P value 0.002 (SBP), 0.05 (DBP)
		Girls		Boys			0.37 (Girls DBP)	
		SBP -7.74	DBP -1.79	SBP 4.27	DBP 3.21		0.09 (Boys SBP)	
						0.05 (Boys DBP)		
Whincup et al. (1995)	Low ≤589g Middle 590 – 689g High ≥690g	Mean SBP and SE age 9-11yr 108.6 105.6 105.3				Negative		
Whincup et al. (1999)	None used	Regression Modelling SBP and DBP SE and p value SBP Coefficient -0.007 SE 0.003 p value 0.01 DBP Coefficient -0.005 SE 0.002 P value 0.02				Negative	0.01 (SBP) 0.02 (DBP)	Effect of adjustment for birth weight examined

3.4 Records Related To Mortality or Morbidity.

Of the 26 records inspected, ten investigated the association between placental weight and the risk of mortality by coronary heart disease (CHD), ischaemic heart disease (IHD), stroke, cardiovascular disease (CVD) and diagnosed hypertension. Table 5 lists these records and provides further details along with key information such as the placental weight categories used, measure of risk (e.g. odds ratio), direction of relationship and p-value for linear trend. Of the ten records, three used hazard ratios (HR), three used odds ratios (OR), two used standardised mortality ratios (SMR), one used a rate per 100,000 of population and one used cumulative incidence (percentage). Three records (30%) focused on diagnosed hypertension, one record observed the risk of death by stroke, CHD, and non-CVD causes, four records focused on CHD, one used CVD and one used IHD. Of the ten records in this section, six (60%) reported a negative relationship between placental weight and mortality and morbidity (i.e. a lighter placenta is associated with an increased mortality risk), three (30%) reported a positive relationship (i.e. a heavier placenta is associated with increased mortality risk) and one (10%), Martyn et al. (1996), had mixed results, reporting a negative relationship for stroke, and a positive relationship for CHD and for non-CVD related deaths.

Table 5. Results of literature search. Articles listed have reported both placental weights and an association with cardiovascular morbidity and mortality. Placental weight categories, measure of cardiovascular morbidity and mortality such as odds ratio (OR), hazard ratio (HR), standardised mortality ratio (SMR), risk ratio (RR), direction of relationship (positive trend denotes an increase in risk between lightest to heaviest placental weight categories and a negative denotes a decrease in risk between the lightest to heaviest placental weight categories), p-values for linear trends are listed when available in the published article. In some cases, SD, R^2 and 95% CI were available and this has been noted in the table below. Of the ten articles, three articles showed a positive relationship, six showed a negative relationship and Matryn et al. (1996) demonstrated a negative result for stroke but a positive result for coronary heart disease.

Authors	Placental Weight categories	Measure (eg OR, HR, RR, SMR)	Direction of relationship	P-value for linear trend	Other measures
Eriksson et al. (2011)	≤550g 650g 750g >750g	HR for coronary heart disease 1.2 1.1 1.3 1.0 (ref)	Negative	0.1	In men whose mother's BMI was above the median, coronary heart disease was associated with low placental weight and small placental area.
Barker et al. (2009)	≤550g 650g 750g >750g	OR for diagnosed hypertension 1.8 1.3 1.3 1.0 (ref)	Negative	<0.001	Diagnosed hypertension OR increased as placental weight, area and the two diameters decreased. Hypertension was associated with both reduced placental weight and with increased placental weight in relation to birth weight.
Fan et al. (2009)	<450g 560g 670g ≥675g	OR for coronary heart disease 1.0 (ref) 0.69 0.5 0.47	Negative	0.05	Subjects with CHD had lower birth-weight, placental weight, birth length, smaller head circumference, and birth-weight/length. Placental weights were low, 17.8% weighed less than 450g

Eriksson et al. (2010)	≤550g 650g 750g >750g	OR for diagnosed hypertension		Negative	0.06 (Men) <0.001 (Women)	OR per 100g 0.89 (Men) 0.80 (Women) Mean birth weight and placental weight were higher in boys. Hypertension in men was only weakly related to low placental weight. Women with low placental weight and area were at increased risk.
		Men	Women			
		1.6	2.0			
		1.1	1.6			
		1.2	1.3			
		1.0 (ref)	1.0			
Risnes et al. (2009)	Lowest - Median 560g Middle - Median 680g Highest - Median 800g	HR for cardiovascular disease		Positive	0.04	Birth weight included as a covariate in analysis of placental weight.
		1.0 (ref)				
		0.97				
		1.35				
Hesmati & Koupil (2014)	≤550g 650g 750g >750g	Rates per 100,000 for Ischaemic Heart Disease		Negative for all categories.	95% CI reported.	Negative trend found for both men and women. 4 multivariate models investigated
		Men	Women			
		1344	799			
		1320	705			
		1249	711			
		1232	682			

Eriksson et al. (2000)		Cumulative incidence (%) of hypertension (use of medication)			Negative for all categories.	0.07 (Men)	No statistically significant trend with placental weight and cumulative incidence of hypertension.
						0.91 (Women)	
						0.16 (All)	
	≤450g	Men	Women	All			
	550g	30.7	28.3	29.5			
	650g	28.8	27.8	28.3			
	750g	25.4	28.5	26.9			
		27.0	30.1	28.5			
	>750g	24.6	27.3	25.8			
Forsen et al. (1997)		SMR for coronary heart disease			Positive	0.004	Ponderal index was strongly associated with placental weight. Men who had a low placental weight had a low ponderal index at birth and raised death rates from coronary heart disease as adults.
	≤500g	111					
	600g	98					
	700g	76					
	>700g	67					
Forsen et al. (1999)		HR for coronary heart disease			Positive	Statement only Trend was not significant.	Hazard ratios tended to rise with increasing placental weight, although this trend was not significant. There was, however, a significant rise with an increasing ratio of placental weight to birth weight (P=0.01, adjusted for gestation). In a simultaneous analysis with birth weight, placental weight, and gestational age the hazard ratios fell with increasing birth
	≤500g	No data reported.					
	600g	Statement only					
	700g						
	>700g						

							weight (P=0.007) but rose with increasing placental weight (P=0.03). There were stronger trends in a simultaneous analysis of birth length, placental weight, and gestational age, the hazard ratios falling with increasing birth length (P>0.0001) and rising with increasing placental weight (P=0.02). The hazard ratios increased by 13.8% (7.5 to 19.6) for each cm decrease in length at birth and increased by 14.8% (2.6 to 28.3) for each 100 g increase in placental weight. The trends with length and placental weight were similar for fatal and non-fatal disease.
Martyn et al. (1996)	Placental weights in pounds (converted to grams) ≤1.0 (≤454g) 1.01-1.25 (458.54-567.5) 1.26-1.5 (572.04-681) >1.5 (>681)	SMR for stroke, CHD and non-CVD causes			Negative (Stroke) Positive (CHD) Positive (non-CVD causes)	Not stated.	U shaped variation noted. 5% of the population died from stroke, 35% died from coronary heart disease.
		Stroke	CHD	Non-CVD causes			
		147	93	101			
		125	108	103			
		96	97	106			
100	106	103					

3.5 Records With Defining Statements But No Data.

There were four records found through the search which made defining statements on the relationship (or lack of) between placental weight and either blood pressure or death by IHD. Table 6 lists the four records along with key information such as the defining statement. One record reported no evidence of an association between placental weight and mortality from IHD and three records reported on the association between placental weight and blood pressure. Of the three records reporting associations with blood pressure, one indicated no consistent relationship between placental weight and SBP or DBP, another reported that the placental weight was not associated with SBP, but had a correlation with DBP ($r=0.12$, $p=0.05$). The last record reported that an inverse relationship between SBP and placental weight existed ($p=0.003$) after adjustment for age, sex and current weight and this became non-significant in a simultaneous regression with birth weight. Therefore, it was deemed non-significant.

Table 6. Results of literature search. Articles listed have not reported any data. Authors made a summary statement of the relationship in the text of the article.

Authors	Placental Weight Categories	Measure used	Statement
Leon et al. (1998)	Not reported	Data not shown	There was no evidence of any association of placental weight with mortality from ischaemic heart disease.
Martyn et al. (1995)	Not reported	Data not shown SBP and DBP age 50-53 yr	No consistent relationship between adult blood pressure and placental weight or ponderal index (weight/length ³) of the infant for either systolic or diastolic pressure found.
Moore et al. (1999)	Not reported	Data not shown SBP DBP age 20 yr	Placental weight was not associated with systolic pressure when considered alone. Placental weight was correlated with DBP ($r=-0.12$, $p=0.05$) which did not persist after adjustment for gestational age.
Forrester et al. (1996)	Not reported	Data not shown SBP age 6-16	Placental weight was inversely related to systolic pressure after adjustment for age, sex, and current weight (test for trend $p=0.003$) This relationship became non-significant in a simultaneous regression with birth weight.

3.6 Characteristics of The Studies.

To further investigate the nature of these studies a range of characteristics that may influence the findings have been explored. Figure 5 displays the various characteristics of the records included in this study. Note that a total of six records are not included in Figure 5, these include the four records reported in Table 6. The other two records do not appear in this figure because they were either a record that measured placental weights and only related it to exposure to famine (Roseboom et al., 2011) and a record which measured placental weights and used them in a cluster analysis of Percentage of Expected Birth Weight (Huang, et al., 2007) or did not explicitly report any data.

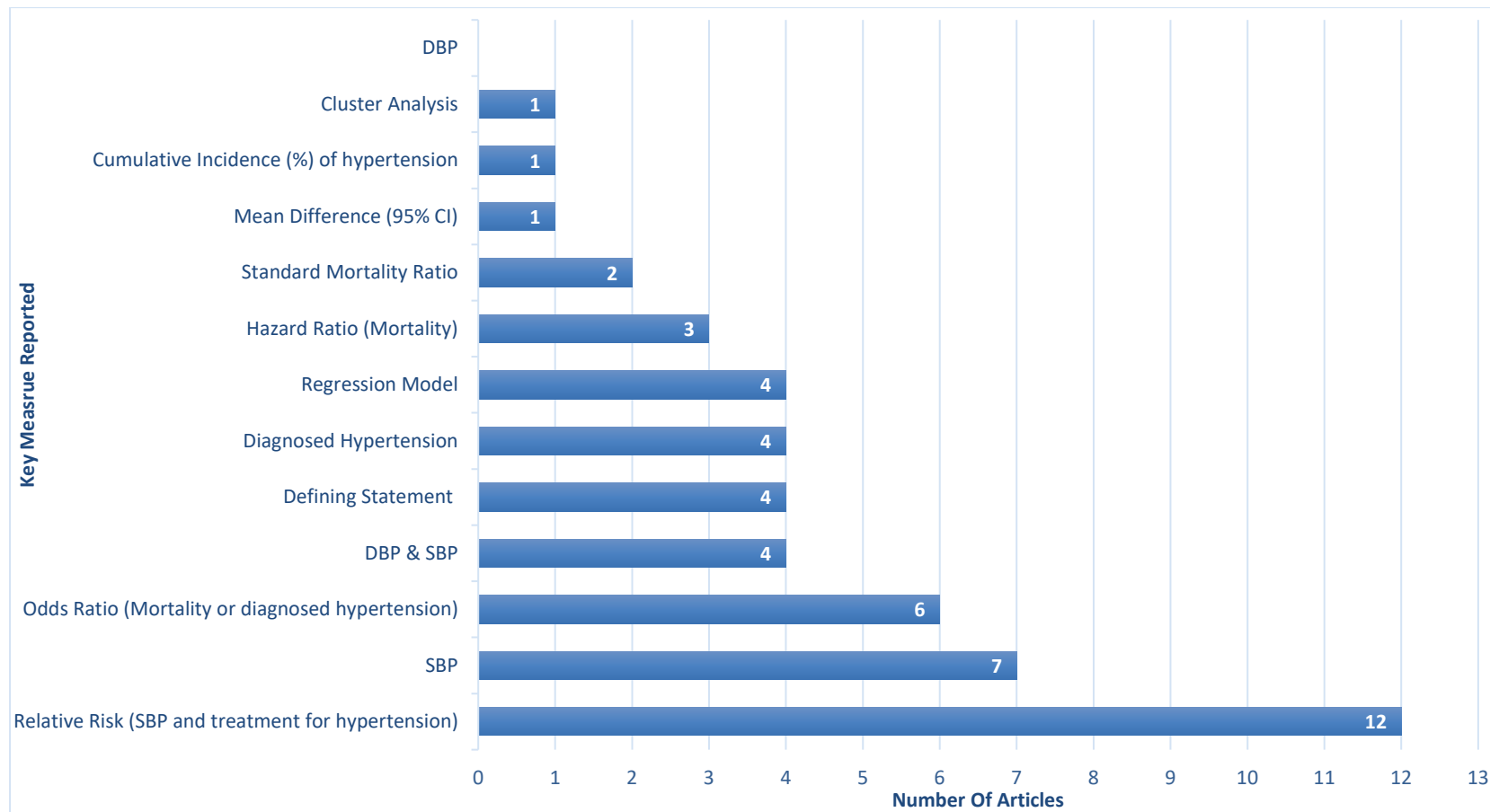


Figure 5. Different types of cardiovascular characteristics reported in the articles found. A score of 1 was allocated to each key measure e.g. a record that reported SBP and used a regression model would contribute a score of 1 to both the regression model and the SBP key measure.

Note: the four records reported in Table 6 do not appear in this figure.

3.7 Age of Participants.

The participants studied in the various records found ranged from 1 year to 69 years of age, Figure 6 graphs the range of ages, a score or 1 was given to each age category reported e.g. if the record stated that the cohort was between 6 and 16 years of age, then a score of 1 was allocated to each year from 6 through to 16. Although the range was from 1 year to 69 years of age, there appears to be a gap in the data available for participants 21-36 years, where there were no studies with any participants in that age range.

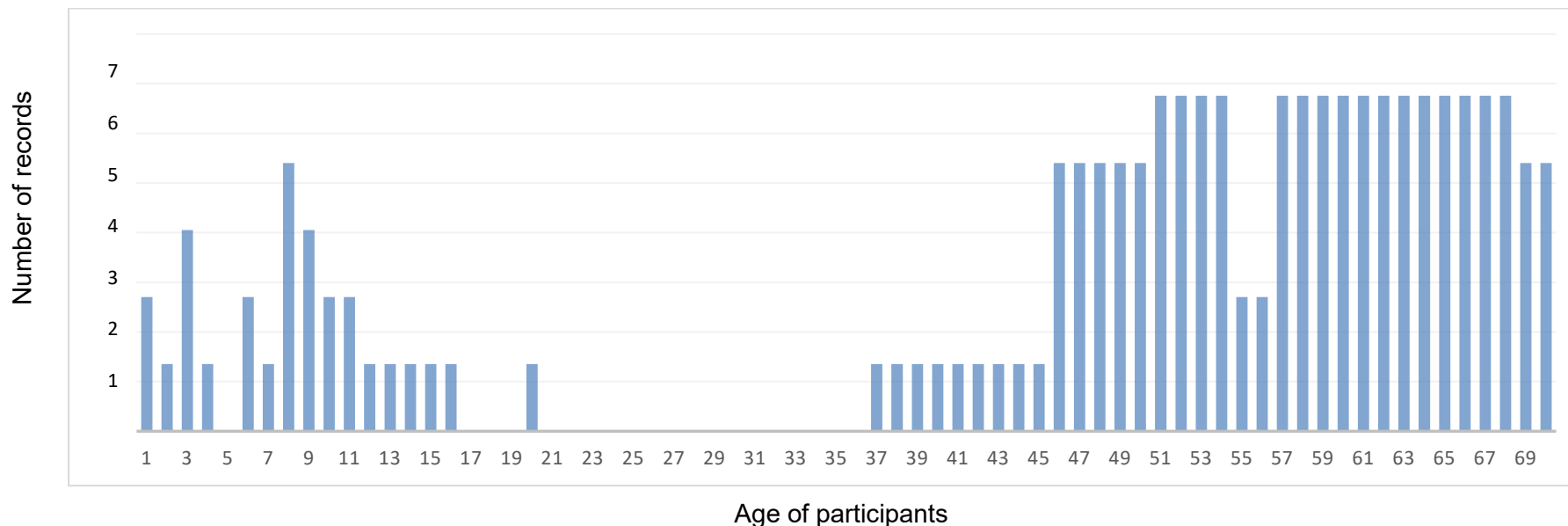


Figure 6. Age of participants in the 26 records identified.

Note: A score of 1 was allocated to each age category reported in the record such that a record stated that the cohort was between 6 and 16 years, a score of 1 was allocated to each year from 6 through to 16.

3.8 Geographical Focus

A geographical analysis of the 26 records is displayed in Figure 7, as a heat map of the world. The records clustered around specific areas of the world, namely the United Kingdom (10 records), followed by Finland (5), Australia (4) and Sweden (2). China, India and Norway all had 1 record each. The studies analysed in the meta-analysis focused on cohorts from the United Kingdom (Barker et al., 1990; Whincup et al., 1995) and Australia (Blake et al., 2001; Moore et al., 1996).

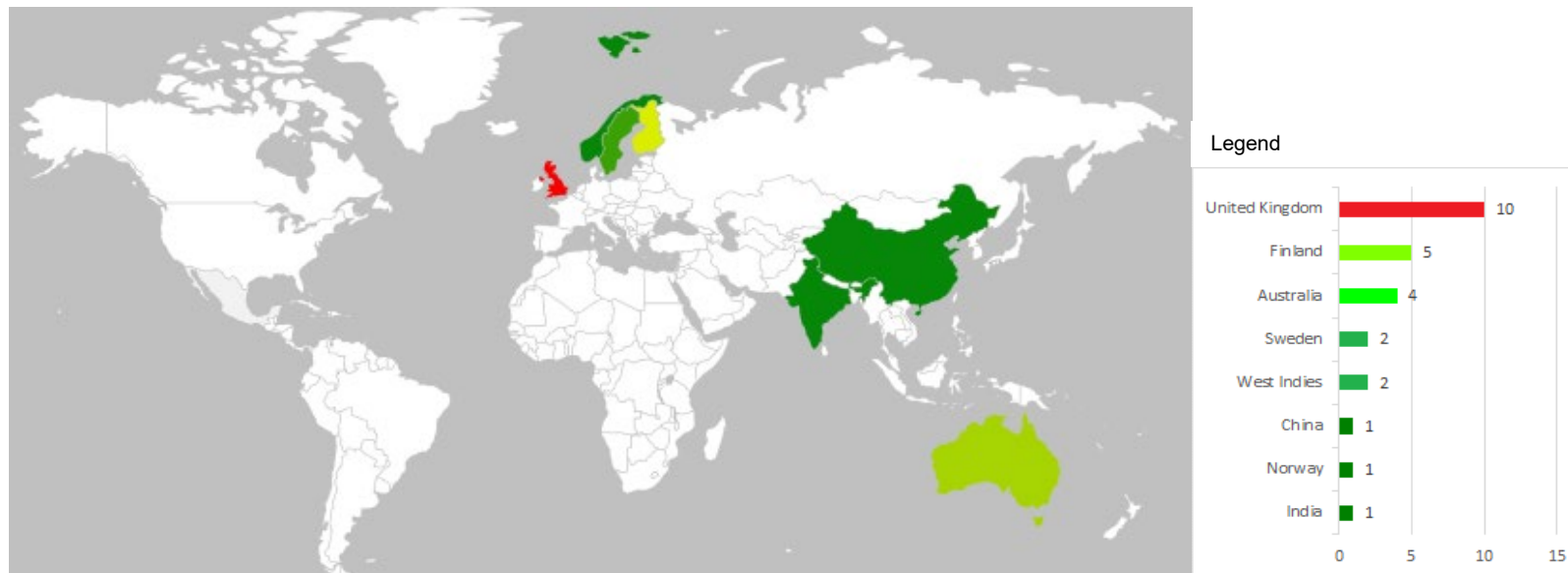


Figure 7. Heat map displaying the locations of the 26 studies identified.

4. Discussion.

Cardiovascular diseases are the leading non-communicable cause of mortality world-wide. The early environment, particularly the intrauterine environment, has been implicated as a risk factor and a potential target for intervention. However, the role of the placenta in this relationship is poorly understood.

This study used meta-analytical techniques to explore the association between placental weight and subsequent cardiovascular health outcomes in humans. The initial search process detailed in Figure 1 identified 844 records. Of these, 26 records, providing 6 data points in total, were analysed.

The systematic review identified 26 records which matched the selection criteria and these records had a combined cohort of 109,721 individuals, with 5,823 affected individuals. Four records reported compatible data that was adequate to perform a statistical meta-analysis (refer to Figure 4). Blake et al. (2001) reported data at age 1, 3 and 6 years of age and so each data set was treated as an individual study, providing six data points in total.

The meta-analysis showed that a lighter placenta was associated with a subsequent higher blood pressure. This association was greatly influenced by an outlier and once removed, the combined effect reversed direction to favour a heavier placenta. The only record which retained significance ($p=0.034$) was one of the original articles written by Barker et al. (1990). The remaining records displayed an effect which is not significant and very close to the line of no effect. This analysis suggests that the evidence relating specifically to placental weight and CVD is much more diverse than for birth weight. Currently a strong conclusion on the effect size cannot be made. Importantly, this analysis brings the placental weight research into focus and highlights methodological weakness, research gaps and future directions for study.

4.1 Inspection of Funnel Plots, Meta-Analysis Results and Outlier.

On examination of the first funnel plot, (Figure 2) a clear indication of a publication bias related effect was noted, as there was a specific record (highlighted in red) which did not sit in the boundary of the funnel plot. This visual observation was supported by the Egger's p-values of 0.01 (1-tailed) and 0.02 (2-tailed). The clear outlier was removed and the plot re-drawn, with the resulting plot (Figure 3) being more consistent with the type of plot that demonstrates symmetry, that is all the records are plotted within the confines of the funnel plot boundaries. This is further supported by Egger's p-values < 0.05 (0.011, 1-tailed and 0.022, 2-tailed) indicating that publication bias was evident. The outlying record (Whincup et al., 1995) had such a large impact on the funnel plot and combined effect size because its cohort size was the largest of the records in this calculation (n=1,511 compared to n=1,039 for the next largest cohort) and therefore had more power in affecting combined effect size. Additionally, removing this outlier influenced the I^2 score (increasing it from 55.5% to 99.4%) which firmly set it in the category of a mixed effects model as it was above the 75% threshold prescribed by Fernandez & Tran (2009). In the original meta-analysis, the outlier was seen to have an effect size of 4.125 compared to the combined effect of 0.250 (as calculated by the Standard Difference in Means in Table 2), which further highlights the magnitude of the effect of this specific record.

To gain a better understanding of the quality and reliability of these findings, the effect of this outlier was investigated further using the NOS to examine and rank the records. The outlier returned a maximum score of nine out of nine stars, indicating that it was a high quality study. This score placed the outlier on par with a study by Risnes et al. (2009), which was the only other record to score nine stars.

Although the two studies measured different factors, Whincup et al. (1995) measured SBP and Risnes et al. (2009) measured mortality, it is useful to compare their findings. For Whincup et al. (1995) a heavier placenta was associated with a decrease in SBP whereas Risnes et al. (2009) found that a heavier placenta was associated with increased chance of death by CVD and CHD and a decreased chance of death by stroke and this further highlights to complications with studying the effect of placental weight on CVD, as increased SBP is noted as one of the risk factors for all CVD.

Therefore, the high quality of the Whincup et al. (1995) article does support its inclusion in the meta-analysis. However, its influence on the direction of the combined effect and presence of publication bias indicate that there needs to be more exploration of the data as well as unified reporting of the research which will facilitate the inclusion of other studies into future meta-analyses.

Moreover, this raises the issue of which additional articles that were excluded should be considered and contribute to the effect recorded.

4.2 Placental Weight and Blood Pressure and Sex.

Of the 12 records which examined placental weight and blood pressure, 5 reported a positive relationship for the entire cohort studied, indicating that as placental weight increased, so too did blood pressure (refer to Table 4 for further details). Four records reported a negative relationship for the entire cohort studied, two records split their cohorts into girls and boys and SBP and DBP. The remaining record (Barker, 1997) is not included as it referred to a cohort already studied (Barker, 1992).

Fundamental physiological differences between the sexes indicate that there is a need to examine the variation between sexes. Winder et al. (2011) and Taylor et al. (1997) split their cohorts into girls and boys and measured both SBP and DBP.

Winder et al. (2011) reported means and SD whereas Taylor et al. (1997) performed regression modelling. Winder et al. (2011) identified a negative trend for boys (both SBP and DBP) with the boys DBP being significant (p -value=0.02) and a negative trend for girls SBP which was not significant (no p -value reported). Taylor et al. (1997) identified a negative trend for girls (SBP and DBP) with only the girls SBP trend being significant (p -value=0.01) and a positive trend for boys (SBP and DBP) with only the boys (DBP) trend being significant (p -value=0.05). This variation between males and females has been attributed to key differences in hormone profiles, as demonstrated by experiments on IUGR rats where males showed significantly higher blood pressures compared to the female IUGR rats (Dasinger & Alexander, 2016). Here oestrogen is seen as a protective factor, which normalises blood pressure and provides protection for females from CVD, conversely, the male hormone, testosterone is seen as a cause for elevated blood pressure (Dasinger & Alexander, 2016). This is reflected in the human population where men usually display higher blood pressures and greater risk for CVDs than women of the same age (Dasinger & Alexander, 2016; WHO, 2011). Therefore a separate analysis for males and females may be necessary to clarify the relationship and may cancel each other out in studies that are included in the current meta-analysis.

Two of the most influential articles in the field of DOHaD which have been key references in the formation of this paradigm observed cohorts of adult age: Barker et al. (1990) and Barker et al. (1992). Barker et al. (1990), examined the Relative Risk (RR) of having a SBP greater than 160mm Hg and the RR of being treated for hypertension in doing so. The authors noted that SBP and DBP were strongly related to placental weight and that the highest pressures were measured in people who had been small babies with large placentae and conversely, the lowest pressures were measured in people who were large babies with small placentae (Barker et al., 1990). The second record, Barker et al. (1992), similarly found a positive trend with

mean SBP and placental weight although no significance measure was reported. The Barker et al. (1990) article noted that babies with placentae >1.5 pounds or >681 grams (SI unit conversion 1 pound = 454g) had a greater RR of having a SBP >160 mm Hg as well as a greater RR of being treated for hypertension than babies with a placental weight of ≤ 1.5 pounds. In further support the Barker (1992) article reported that babies with placental weights >1.5 pounds or >681 grams had higher mean SBP in adult life. This further highlights the complexity of the relationship, although, placental characteristics such as size, weight, volume and shape are all factors in determining the efficiency of a placenta. Ultimately, it is the amount of fetus which develops from a placenta that is the evidence of the efficiency of a placenta. Thus it may be inappropriate to consider placental weight as a predictor of CVD in isolation and it is its relationship with birth weight that provides more information. However, although the placental weight to birth weight ratio may in turn be limited, it is possible that a heavy placenta may be just as efficient as one of less weight simply because it has the same surface area (Salafia et al., 2008; Eriksson et al., 2011).

4.3 Placental Weight and CVD, CHD, IHD and Stroke.

Of the 10 records which examined the risk of developing or dying from CVD, CHD, IHD and Stroke, six (60%) reported that a heavier placenta was associated with a decreased chance of death. Of these six records, two reported that the linear trend was significant, one reported that it was significant only for women, three records reported a positive association and two indicated that it was significant. The last record by Martyn et al. (1996) split the cohort into three groups, a stroke group, a CHD group and a non-CVD group and they reported that a heavier placenta decreased the risk of stroke, but increased the risk of death by CHD and non-CVD causes. No p-values or any other measures of significance were reported although a U-shaped variation was observed in this study (Martyn et al., 1996).

When these studies are grouped by disease (e.g. diagnosed hypertension, CVD, CHD, IHD), there were no consistent findings. The majority of the studies reported a significant p-value for linear trend, however the direction of the relationship was almost evenly divided between studies showing that a heavier placenta is associated with decreased risk and a lighter placenta associated with increased risk.

4.4 Variation, Study Characteristics and Measured Outcomes.

It has been noted by the PRISMA group (2009) that variation in reporting does have a negative impact on the usefulness of systematic reviews and meta-analyses. This statement is clearly supported by the findings from the current study. In the 26 records identified, substantial variation has been apparent in the different methods of reporting. Figure 5 highlights the numerous items reported including odds ratios, hazard ratios and standardised mortality ratios. As well as the methods of measuring placental weight, one record indicated that the placentae were fixed in formalin (Whincup et al., 1999) compared to the other studies in which placentae are measured in an unfixed state.

Outcomes (conditions) are also measured in different ways where some report only the SBP while others used a diagnosis of hypertension, or treatment for CVD and others only looked at mortality rates. Further to this variability there is the rate of survival from a major CVD incident (e.g. myocardial infarction or stroke) or receiving treatment.

In addition to these variations, there are physiological and anatomical variations of the placenta, which is an organ that grows with the fetus and adjusts its growth patterns to match the environment as well as the demands from the fetus. Variations in the placenta can be affected by the environment through infections, anatomical differences in the point of attachment on the uterine surface as well as the level of remodelling of the spiral arteries. As the fetus develops, its nutritional demands are

served through the placenta and this is maintained via a delicate balance between growth of the fetus and growth of the placenta. Additionally, the fetal heart and the placenta share common developmental requirements, such as common genes and micronutrients (e.g. folate) regulating essential developmental steps (Burton & Jauniaux, 2018). Considering these factors, no two placentae should be alike, therefore, it is all the more important to systematically select and process placental measures in the future to standardise this field (Salafia & Roberts, 2019).

A key difference in the reporting and comparison of placental weights is the weight categories used by researchers. In summary, across all the records found, there was a broad range in the placental weights studied with the lightest placental weight group being $\leq 350\text{g}$ and the heaviest $>750\text{g}$ (there was another study reporting the highest group with a median placental weight of 800g). To further complicate matters, Barker et al.'s (1986, 1990, 1993) earlier work utilised imperial pounds as the standard measure and the lightest placental weight group was ≤ 1 pound or $\leq 454\text{g}$ and the heaviest group was >1.5 pounds or >681 grams (SI unit conversion 1 pound = 454g).

The cohorts studied were regularly divided into groups according to placental weight. Aside from the four records which made defining statements and the four records which used regression modelling, all other records (18), divided the cohorts into groups according to placental weight. The number of groups ranged from three to five with the most common being four groups (13 records). Of these 13 records that used 4 placental weight categories, the largest placental weight group was $>750\text{g}$ and the smallest was $\leq 550\text{g}$. Only one record used 5 placental weight groups, in this record, a $\leq 450\text{g}$ group was added to accommodate the lightest placentae in that study. Only one record reported median placental weight for the groupings and there were three groups in this record (Lowest group: median placental weight 560g ; Middle group: median placental weight 680g ; Highest group: median placental

weight 800g). The variety in these categories impacted on the ability to find comparable data to carry out a comprehensive meta-analysis. A more uniform reporting of this data would improve the comparability of the data for meta-analysis. Alternatively, if raw data sets were obtained, it may be possible to perform meta-regression analysis on these data sets as a whole in a similar way that Gamborg et al. (2007) used birth weights and systolic blood pressures from 20 Nordic studies.

This variance in placental weights, particularly the proportion of low weight placentae, was noted by Fan et al. (2009) as 17.8% of all placentae in their study (total n=2033) weighed less than 450g. More strikingly, Winder et al. (2011) studied a cohort where 74.9% of all placentae weighed less than 450g (total n=471). By contrast, Eriksson et al. (2000) reported figures showing only 7.2% of placentae in the same weight category (total n=7086). Exploring the mean weights of placentae, we find that in Fan et al. (2009) the mean placental weights were $539.1\text{g} \pm 103.1\text{g}$ (n=928 men) and $525.7\text{g} \pm 101.8\text{g}$ (n=953 women). Winder et al. (2011) reported mean placental weights for boys (n=228) of 410g (SD=81g) and 407g (SD=85g) for girls (n=243). At the opposing end of the scale, Forsen et al. (1997) reported the heaviest mean placental weight of 634g (SD=128g) and a placental weight range for men from 240g to 1440g (n=3302). Comparably, a study of 513 placentae found a mean placental weight (trimmed) of 538.3g (SD=95.3g) which was closer to Fan et al.'s (2009) cohort and a range of 261g to 877g (Coall et al., 2009).

In addition, the methodology used to weigh the placentae can make significant differences. Due to a range of factors, there has been measurement errors in the past, and even in the current research, uniform weighing of placentae within and between studies were not present, a key factor influencing placental weight being the time from birth to weighing of the placenta. (Coall et al., 2009).

It can be seen that extremes of placental weight exist in the various cohorts studied and unlike birth weight where 2.5 kg is seen as a critical cut off, there is no cut off for placental weight. Records which attempted to evenly distribute the cohort into groups were required to make arbitrary decisions on the groupings based on no defining evidence on what an adequate weight for a placenta is. This lends weight to the notion that placental weight cannot be used in isolation when examining its effects on cardiovascular outcomes of the baby until standardised advances in methodology have been agreed upon. Further investigation into what a 'standard placenta' is and a better understanding of what placental weight represents is essential for this research to progress.

4.5 Age of Participants.

As shown in Figure 5, the age range of participants was from 1 to 69 years old. There was, however, a gap between 21 and 36 years of age where there were no records found focusing on people of that age. It is understood that there is a paucity of information in that age bracket as it is an age group in which CVD is not seen as a major risk and deaths caused by CVD are rare and usually attributed to unusual circumstances. Likewise, hypertension and blood pressure in general is not a key concern for people in that age group and so it is not a widely studied factor. When considering age, it is also important to consider that the protective nature of oestrogen does diminish as women reach menopause and oestrogen production slows (Dasinger & Alexander, 2016). This variation and the underlying assumptions related to the relatively healthy age group may contribute to a lack of research in this age group.

4.6 Geographical Focus

When the records were compared according to country of focus, it was found that 38.5% (n=10) of the records focused on cohorts in the United Kingdom, followed by

19.2% (n=5) for Finland, 15.4% (n=4) for Australia, followed by 7.7% (n=2) for both Sweden and the West Indies (Jamaica), and 3.8% (n=1) for China, Norway and India. It is important to note that although Norway had one record, it was the largest of all the cohorts studied (n=31,307).

The most prolific author was Barker, who appeared in 12 records (46.2%), six focusing on cohorts in the United Kingdom, all of the five records focusing on Finland and the one record that focused on India.

4.7 NOS Analysis of Quality.

As the present study was not able to complete a comprehensive meta-analysis of the records identified, it was recognised that a tool to assess the quality of the articles should be employed to further investigate these results. The NOS scale was used to provide further analysis of the quality of the records found as it was previously used to investigate the outlier which was ranked the equal highest with the maximum score (nine stars). The remaining records in the meta-analysis scored eight stars (Barker et al., 1990) and six stars (Blake et al., 2001) and (Moore et al., 1996). This indicates that the studies included in the meta-analysis were of Good quality.

Further analysis of the records showed that the mode and median score were both seven stars and the mean was 6.9 stars (SD 1.1) with the range of scores from five to nine stars. There were three records scoring the lowest (five stars) which according to the AHRQ is a fair quality study. These articles were lacking in the 'Selection' domain under the "Representativeness of the Cohort" as they were subsets of larger cohorts such as in the Winder et al. (2011) study in which eligible participants attended the antenatal clinic at the Holdsworth Memorial Hospital in Mysore, South India and they didn't have diabetes before pregnancy. In addition, there was a 67% uptake by the eligible parties. Likewise, Moore et al. (1999) focused

on the cohort born at a single (unnamed) hospital in Adelaide, South Australia, furthermore, there was a 72% participation rate.

The 'Outcome' domain was another domain in which these records scored poorly (scoring one out of a possible 3 stars). It is noted that the adequacy of follow up may be a reflection of low participation rates as other studies with higher participation rates scored better in this domain. Finally, in the 'Comparability' domain, these three records failed to satisfy the criteria "Adjustment for age, sex and marital status", which was not a key issue as only three records were able to satisfy this.

The 'Outcome' domain was the domain which saw the greatest variability with the highest ranked records achieving a full 3★ and the lowest ranked records achieving 1 out of 3★, which was due to the impact of lower levels of follow up rates. Despite this the records achieved a mean of 6.9★ (SD1.1), which indicates how important complete and accurate data recording, as well as good follow up practices are, when conducting this research as those three articles ranked as Fair quality, would have been ranked as Good if the follow up rates were improved. All ten articles reporting rates of mortality and morbidity due to CVD were ranked in the Good category, and although 60% of the articles found a negative association, there was one record (Risnes et al., 2009) scoring the highest possible score of nine stars which found a positive trend. To further highlight the inconsistencies, for the articles reporting on blood pressure and hypertension, the highest ranked article (Whincup et al., 1995) reported a negative association.

4.8 U shaped curve

A possible explanation of the inconsistent nature of the findings may be due to the assumption made about the data and data analysis. It is evident that most articles assume the association between measures of the uterine environment such as placental weight and cardiovascular health is linear. However, because of the

adaptive reserve capacity of the placenta, there is no reason to assume an increasing placental weight is uniformly positive or negative. Therefore, it is important to explore curvilinear, particularly quadrilateral relationships.

Theoretically, the u-shaped curve association between the early environment and cardio-vascular health is likely to exist. In a study of 15,324 children, where SBP was measured, both the lower birth weight group (<2,000 g) and the higher birth weight group (3,500–3,999 g) and the highest birth weight group (>4,000 g) exhibited significantly higher SBP when compared to the median weight group (2500–2999 g) (Lai et al., 2019). The median birth weight group had the lowest SBP (103.56 ± 0.23 mm Hg) and was set as the reference group, the lower birth weight group had a mean SBP of 106.00 ± 0.72 mm Hg ($p=0.017$), and the higher birth weight group had a mean SBP of 105.13 ± 0.17 mm Hg ($p<0.001$). The highest group exhibited a mean SBP of 105.96 ± 0.27 mm Hg ($p<0.001$).

Moreover, there are recognised differences in male and female physiology which indicate that the association in males could be different to that in females. In a study using linear regression modelling, placental weight was shown to have a negative association in girls and a positive association in boys for both SBP and DBP, furthermore, the p values for differences in the regression coefficients (b) were seen to be significant ($p=0.002$ for SBP and $p=0.05$ for DBP) (Taylor et al., 1997). However, the majority of studies found through this meta-analysis fail to examine or do not report looking for this u-shaped relationship between placental weight and CVD.

In Thornburg et al.'s (2010) review of the placenta's role in programming subsequent cardiovascular disease, a U-shaped relationship was said to exist between the placental to fetal weight ratio and CVD. In the present study, one record, reported a U-shaped variation when describing the association between placental weight ratio

and risk of CVD (Martyn et al., 1996). Therefore, both a low and high placental weight ratio are associated with an increased risk of CVD. Consequently, the risk factor may not be the absolute birth weight or placental weight but the relative weight. This may more accurately reflect the challenges of the early environment and the placenta's capacity to adapt to insults. The placenta can adapt morphologically and functionally and these adaptations are a response to meet the demands of the developing fetus (Sferruzzi-Perri & Camm, 2016). These changes may be seen in changes to endothelial function, growth factors and angiogenesis that are then related to CV health. This provides strong evidence that the growth regulating abilities of the placenta may lead to reduced cardiovascular health in the offspring.

Therefore, future research and secondary data analysis should routinely explore the curvilinear, in addition to the linear, associations between the early environment and adult outcomes. Ultimately, this will advance the field and align the epidemiological associations with the underlying biological evidence.

5. Conclusion.

This study, through the meta-analysis of data points, found that a higher blood pressure was associated with a lighter placenta (a combined effect of 0.25 with a p-value <0.05). Due to the presence of an outlier, the analysis was repeated without the outlier and the combined effect indicated that a higher blood pressure was associated with a heavier placenta (combined effect of -0.044) but this was not significant (p-value=0.24).

Through this process of systematically searching the literature and conducting a meta-analysis, it has been shown that a large study such as that by Whincup et al. (1995) can alter the results of a meta-analysis greatly. The findings from this project further demonstrate the complexity of the field of study. There is a plethora of variation including study designs, measured outcomes and reporting criteria which may obfuscate the possible trends and observations. Further to this, the variety of confounding variables which a study can adjust for demonstrates that placental weight cannot be viewed in isolation. The field has moved towards more complex measures of the placenta such as thickness, circumference and volume. Furthermore, real time imaging of the placenta in-utero, as the fetus develops, will contribute another dimension to our understanding.

Future studies require standardised reporting of variables and measured outcomes as well as methodologies (e.g. standardised weighing of the placenta and reporting of weight categories). It is also recommended that retrospectively, raw data should be shared enabling the categorisation of variables to be matched and a large, more accurate and inclusive meta-analysis may be conducted. There is a need for uniformity in the data collection and analysis to enable a deeper understanding of the association between the early environment, particularly placental measurements, and the subsequent risk of adult disease.

In addition, future studies should attempt to capture the missing age groups (21 – 36 years of age) and include them in the analysis of the effect of placental weight on cardiovascular outcomes, this would further contribute to the field of research.

6. Limitations.

The author notes that the search concluded in 2017 and it has taken 17 months to complete this thesis, therefore, it is possible that articles published after 2017 were not included in this work. This was unavoidable, due to the nature of the full time work commitments of the author. To the best of my knowledge no pertinent research is available to include. However, it may be possible in future studies to redo the search with stricter time limits and using an independent searcher to verify the findings.

The systematic literature search itself was conducted by the author alone and it has been recommended by the PRISMA group as well as the Cochrane group that searches should be conducted in tandem at least for reliability. Information technologists at the ECU library were contacted to assist and while their advice was valuable, it was clear that it was an important factor, however, limited resources and capabilities meant that this was not possible. As with all systematic reviews and meta-analyses, the grey literature is a limitation. Every effort was made to search for grey literature and to contact likely authors who had published related work, however, communications to the corresponding authors were not successful.

7. References.

Agency for Health Research and Quality (AHRQ) (2010) Assessing the risk of bias of individual studies when comparing medical interventions. Accessed on 1st January, 2018. <https://www.ncbi.nlm.nih.gov/books/NBK115843/bin/appe-fm3.pdf>

Alexander, B. T. (2003). Placental insufficiency leads to development of hypertension in growth-restricted offspring. *Hypertension*. 2003; 41(3):457–462 DOI: 10.1161/01.HYP.0000053448.95913.3D

Alwasel, S. H., Abotalib, Z., Aljarallah, J. S., Osmond, C., Alkharaz, S. M., Alhazza, I. M., Harrath, A., Thornburg, K., & Barker, D. J. (2011). Secular increase in placental weight in Saudi Arabia. *Placenta* 2011 May; 32(5): 391-4. DOI:10.1016/j.placenta.2011.02.007.

Baird, J., Jacob, C., Barker, M., Fall, C. H. D., Hanson, M., Harvey, N. C., Inskip, H. M., Kumaran, K., & Cooper, C. (2016). Developmental origins of health and disease: a lifecourse approach to the prevention of non-communicable diseases. *Healthcare* 2017, 5, 14; DOI:10.3390/healthcare5010014

Banister, C., Koestler, D. C., Maccani, M. A., Padbury, J. F., Andres Houseman, E., & Marsit, C. (2011). Infant growth restriction is associated with distinct patterns of DNA methylation in human placentas *Epigenetics* 6(7): 920-927. DOI: 10.4161/epi.6.7.16079

Barker, D.J.P. (1994). *Mothers, babies, and disease in later life*. London: British Medical Journal Publishing Group. DOI: <https://doi.org/10.1002/ajhb.1310070520>

Barker, D. J. P. (1997) Fetal nutrition and cardiovascular disease in later life. *British Medical Bulletin* 53(1):96-108 DOI: <https://doi.org/10.1093/oxfordjournals.bmb.a011609>

Barker, D. J. P. (2003). The midwife, the coincidence, and the hypothesis. *British Medical Journal* 327: 1428-1430. DOI: 10.1136/bmj.327.7429.1428

Barker, D. J. P., Bull, A. R., Osmond, C., & Simmonds, S. J. (1990). Fetal and placental size and risk of hypertension in adult life. *British Medical Journal* 301: 259-262 DOI: 10.1136/bmj.301.6746.259

Barker, D. J.P., Gluckman, P. D., Godfrey, K. M., Harding, J. E., Owens J. A., & Robinson J. S. (1993). Fetal nutrition and cardiovascular disease in adult life. *The Lancet* 341(8850):938-41. DOI: 10.1016/0140-6736(93)91224-a

Barker, D. J. P., & Osmond, C. (1986). Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *The Lancet* 327(8489): 1077-1081 DOI: [https://doi.org/10.1016/S0140-6736\(86\)91340-1](https://doi.org/10.1016/S0140-6736(86)91340-1)

Barker, D. J. P., Osmond, C., Simmonds, S. J., & Wield, G. A. (1993) The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life *British Medical Journal* 306:422-6 DOI: 10.1136/bmj.306.6875.422

Bertram, C. E., & Hanson, M. A. (2001). Animal models and programming of the metabolic syndrome. *British Medical Bulletin* 60: 103-121. DOI: <https://doi.org/10.1093/bmb/60.1.103>

Blake, K. V., Gurrin, L. C., Beilin, L. J., Stanley, F. J., Landau, L. I., & Newnham, J. P. (2001). Placental weight and placental ratio as predictors of later blood pressure in childhood *Journal of Hypertension* 19(4): 697-702 DOI: 10.1097/00004872-200104000-00006

Burton, G. J., Fowden, A. L., & Thornburg, K. L. (2016) Placental origins of chronic disease *Physiology Reviews* 96: 1509–1565 DOI:10.1152/physrev.00029.2015

Burton, G. J., & Jauniaux, E. (2018). Development of the human placenta and fetal heart: Synergic or independent? *Frontiers in Physiology* 9: 373. DOI:10.3389/fphys.2018.00373

Camm, E. J., Botting, K. J., & Sferruzzi-Perri, A. N. (2018) Near to one's heart: The intimate relationship between the placenta and fetal heart. *Frontiers in Physiology*. DOI: 10.3389/fphys.2018.00629

Coall, D.A., Callan, A.C., Dickins, T.E., & Chisholm, J.S. (2015). Evolution and prenatal development: An evolutionary perspective (pp. 57-105). In M. E. Lamb (Vol. Ed.), R. M. Lerner (Series Ed.), *Handbook of child psychology and development science* (7th edition; Volume 3), *Social, emotional and personality development*. Hoboken NJ: Wiley.

Coall, D.A., Charles, A.K., & Salafia C.M. (2009) Gross placental structure in a low-risk population of singleton, term, first-born infants. *Pediatric and Developmental Pathology* 12, 200–210, 2009 DOI: 10.2350/08-02-0413.1

Cumming, G. (2013). Understanding the new statistics: Effect sizes, confidence intervals, and meta-analysis. Routledge.

David, A. L. (2017) Maternal uterine artery VEGF gene therapy for treatment of intrauterine growth restriction. *Placenta* 59(Supplement 1) S44-S50. DOI: <https://doi.org/10.1016/j.placenta.2017.09.011>

Danaei, G., Ding, E. L., Mozaffarian, D., Taylor, B., Rehm, J., Murray, C. J. L., & Ezzati, M. (2009). The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS Medicine* DOI: <https://doi.org/10.1371/journal.pmed.1000058>

Dasinger, J. H., & Alexander, B. T. (2016) Gender differences in developmental programming of cardiovascular diseases. *Clinical Science (London)* 2016 Mar;130(5):337-48. DOI: 10.1042/CS20150611.

Dickersin K., & Min, Y.I. (1993). Publication bias: the problem that won't go away. *Ann N Y Acad Sci* 1993;703:135–48. DOI: <http://dx.doi.org/10.1111/j.1749-6632.1993.tb26343.x>

Dickinson, H., Moss, T. J., Gatford, K. L., Moritz, K. M., Akison, L., Fullston, T., Hryciw, D. H., Maloney, C. A., Morris, M. J., Wooldridge, A. L., Schjenken, J. E., Robertson, S. A., Waddell, B. J., Mark, P. J., Wyrwoll, C. S., Ellery, S. J., Thornburg, K. L., Muhlhausler, B. S., & Morrison, J. L., for the ANZ DOHaD Animal Models of DOHaD Research Working Group. (2016) A review of fundamental principles for animal models of DOHaD research: an Australian perspective. *Journal of Developmental Origins of Health and Disease* 7(5):449–472. DOI:10.1017/S2040174416000477

- Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal* 315:629-34. DOI: <https://doi.org/10.1136/bmj.315.7109.629>
- Einstein F., Thompson R. F., Bhagat T. D., Fazzari M. J., Verma A., Barzilai N., et al. (2010). Cytosine methylation dysregulation in neonates following intrauterine growth restriction. *PLoS One* DOI: <https://doi.org/10.1371/journal.pone.0008887>
- Eriksson, J. G., Kajantie, E., Thornburg, K. L., Osmond, O., Barker, D. J. P. (2011) Mother's body size and placental size predict coronary heart disease in men. *European Heart Journal* 32(18): 2297–2303 DOI: <https://doi.org/10.1093/eurheartj/ehr147>
- Fernandez, R., S., & Tran, D. T. (2009) The meta-analysis graph: Clearing the haze. *Clinical Nurse Specialist* DOI: 10.1097/NUR.0b013e31819971fd
- Figueras, F., & Gratacos, E. (2017). An integrated approach to fetal growth restriction. *Best Practice & Research: Clinical Obstetrics & Gynaecology*. DOI: 10.1016/j.bpobgyn.2016.10.006.
- Forrester, T.E., Wilks, R.J., Bennett, F.I., Simeon, D., Osmond, C., Allen, M., Ching, A.P., & Scott, P. (1996). Fetal growth and cardiovascular risk factors in Jamaican schoolchildren *British Medical Journal* 312:156-160 DOI: <https://doi.org/10.1136/bmj.312.7024.156>
- Forsen, T., Eriksson, J.G., Tuomilehto, J., Teramo, K., Osmond, C., & Barker, D.J.P. (1997). Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow up study *BMJ* 315:837-40 DOI: <https://doi.org/10.1136/bmj.315.7112.837>
- Franklin, S. S., & Wong, N. D. (2013). Hypertension and cardiovascular disease: contributions of the Framingham Heart Study. *Glob Heart* 8(1):49-57. DOI: 10.1016/j.heart.2012.12.004.
- Gamborg, M., Byberg, L., Rasmussen, F., Andersen P. K., Baker, J. L., Bengtsson, C., Canoy, D., Drøgvold, W., Eriksson, J. G., Forsén, T., Gunnarsdottir, I., Järvelin, M-R., Koupil, I., Lapidus, L., Nilsen, T. I., Olsen, S. F., Schack-Nielsen, L., Thorsdottir, I., Tuomainen, T-P., & Sørensen, T. I., A, on behalf of the NordNet Study Group (2007). Birth weight and systolic blood pressure in adolescence and adulthood: Meta-regression analysis of sex and age-specific results from 20 Nordic studies. *American Journal of Epidemiology* 166(6): 634-645. DOI: <https://doi.org/10.1093/aje/kwm042>
- Godfrey, K. M., & Barker, D. J. P. (2000) Fetal nutrition and adult disease. *American Journal of Clinical Nutrition* 71(suppl):1344S-52S DOI: <https://doi.org/10.1093/ajcn/71.5.1344s>
- Godfrey, K. M., Lillycorp, K. A., Burdge, G. C., Gluckman, P. D., & Hanson, M. A. (2007). Epigenetic mechanisms and the mismatch concept of the developmental origins of health and disease. *Pediatric Research* 61: 5R-10R. DOI: <https://doi.org/10.1203/pdr.0b013e318045bedb>
- Harrath, A. H., Mansour, L., Al Omar, S., & Alwasel, S. (2014). The effect of food restriction on the expression of some placental proteins (LB24). *The FASEB Journal* 28(1_supplement):LB24 Accessed online https://www.fasebj.org/doi/abs/10.1096/fasebj.28.1_supplement.lb24

Hemachandra, A. H., Klebanoff, M. A., Duggan, A. K., Hardy, J. B., & Furth, S. L. (2006). The association between intrauterine growth restriction in the full-term infant and high blood pressure at age 7 years: results from the Collaborative Perinatal Project *International Journal of Epidemiology* 35(4): 871-877. DOI: <https://doi.org/10.1093/ije/dyl080>

Higgins, J. P. T., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;21:1539-1558. DOI: 10.1002/sim.1186

Huang, R. C., Burke, V., Newnham, J. P., Stanley, F. J., Kendall, G.E., Landau, L. I., Oddy, W. H., Blake, K. V., Palmer, L. J., & Beilin, L. J. (2007). Perinatal and childhood origins of cardiovascular disease. *International Journal of Obesity* 31: 236-244 DOI: <https://doi.org/10.1038/sj.ijo.0803394>

Hughson, M., Farris, A. B., Douglas-Denton, R., Hoy, W. E., & Bertram, J. F. (2003) Glomerular number and size in autopsy kidneys: The relationship to birth weight. *Kidney International* 63: 2113–2122, 2003 DOI: <https://doi.org/10.1046/j.1523-1755.2003.00018.x>

Jansson, T., & Lambert, G. W. (1999). Effect of intrauterine growth restriction on blood pressure, glucose tolerance and sympathetic nervous system activity in the rat at 3-4 months of age. *Journal of Hypertension* 17(9): 1239-1248. DOI: 10.1097/00004872-199917090-00002

Jones, J. E., Jurgens, J. A., Evans, S. A., Ennis, R. C., Van Anthony M. Villar, V. A. M., & Jose, P. A. (2012) Mechanisms of fetal programming in hypertension. *International Journal of Pediatrics* DOI:10.1155/2012/584831

Lai, C., Hu, Y.Y., He, D., Liang, L., Xiong, F., Liu, G. L., Gong, C. X., Luo, F. F., Chen, S. K., Wang C. L., & Zhu, Y. M. (2019). U-shaped relationship between birth weight and childhood blood pressure in China. *BioMed Central Pediatrics* 19(1): 264. DOI: <https://doi.org/10.1186/s12887-019-1638-9>

Lawlor, D.A., Ronalds, G., Clark, H., Smith, G.D., & Leon, D.A. (2005). Birth weight is inversely associated with incident coronary heart disease and stroke among individuals born in the 1950s. Findings from the Aberdeen children of the 1950s prospective cohort study. *Circulation* 112:1414-1418 DOI: <https://doi.org/10.1161/CIRCULATIONAHA.104.528356>

Leon, D.A., Lithell, H.O., Vagero, D., Koupilova, I., Mohsen, R., Berglund, L., Lithell, U.B., & McKeigue P.M. (1998). Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15,000 Swedish men and women born 1915-29 *British Medical Journal* 317:241-5 DOI: 10.1136/bmj.317.7153.241

Longo, S., Bollani, L., Decembrino, L., Di Comite, A., Angelini, M., & Stronati, M. (2013). Short-term and long-term sequelae in intrauterine growth retardation (IUGR). *Journal of Maternal-Fetal and Neonatal Medicine* 26: 222-225 DOI: <https://doi.org/10.3109/14767058.2012.715006>

Lunney, L.H. (1998) Compensatory placental growth after restricted maternal nutrition in early pregnancy. *Placenta* 19:105-111 DOI: [https://doi.org/10.1016/S0143-4004\(98\)90105-9](https://doi.org/10.1016/S0143-4004(98)90105-9)

- Manalich, R., Reyes, L., Herrera, M., Melendi, C., & Fundora, I. (2000) Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. *Kidney International* 2000; 58: 770–73. DOI: <https://doi.org/10.1046/j.1523-1755.2000.00225.x>
- Mandruzzato, G., Antsaklis, A., Botet, F., Chervenak, F. A., Figueras, F., Grunebaum, A., Puerto, B., Skupski, D., & Stanojevic, M. (2008). Recommendations and guidelines for perinatal practice - Intrauterine restriction (IUGR) *Journal of Perinatal Medicine*. 36: 277–281 DOI: <https://doi.org/10.1515/JPM.2008.050>
- Martyn, C.N., Barker, D.J., Jespersen, S., Greenwald, S., Osmond C., & Berry. C. (1994). Growth in- utero, adult blood pressure, and arterial compliance. *British Heart Journal* 73:116-121 DOI: 10.1136/hrt.73.2.116
- Martyn, C. N., Barker, D. J., & Osmond, C. (1996). Mother's pelvic size, fetal growth, and death from stroke and coronary heart disease in men in the UK. *The Lancet* 348:1264-68 DOI: [https://doi.org/10.1016/S0140-6736\(96\)04257-2](https://doi.org/10.1016/S0140-6736(96)04257-2)
- McMullen, S., & Mostyn, A. (2009). Animal models for the study of Developmental Origins of Health and Disease. *Proceedings of the Nutrition Society* 68: 306-320. DOI: <https://doi.org/10.1017/S0029665109001396>
- McNamara, B. J., Gubhaju, L., Chamberlain, C., Stanley, F., & Eades S. J. (2012) Early Life Influences on Cardio-Metabolic Disease Risk in Aboriginal Populations – What Is The Evidence? A Systematic Review of Longitudinal and Case-Control Studies. *International Journal of Epidemiology* 41:1661-1682 DOI: <https://doi.org/10.1093/ije/dys190>
- Misra, D. P., Salafia, C. M., Charles, A. K., & Miller, R. K. (2010). Birth weights smaller or larger than the placenta predict BMI and blood pressure at age 7. *Journal of Developmental Origins of Health and Disease* 1(2): 123-130 DOI: <https://doi.org/10.1017/S2040174410000139>
- Moher, D., Liberati A., Tetzlaff J., & Altman D.G., The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *British Medical Journal* 2009;339:b2535 DOI: 10.1136/bmj.b2535
- Moore, V.M., Cockington, R.A., Ryan, P., & Robinson, J.S. (1999). The relationship between birth weight and blood pressure amplifies from childhood to adulthood. *Journal of Hypertension* 17:883-888 DOI: 10.1097/00004872-199917070-00003
- Moore, V.M., Miller, A.G., Boulton, T.J., Cockington, R.A., Craig, I.H., Magarey A.M., & Robinson, J.S. (1996). Placental weight, birth measurements, and blood pressure at age 8 years. *Archives of Disease in Childhood* 1996,74:538-541 DOI: <http://dx.doi.org/10.1136/adc.74.6.538>
- Mu, M., Wang, S. F., Sheng, J., Zhao, Y., Li, H. Z., Hu, C. L., & Tao, F. B. (2012) Birth weight and subsequent blood pressure: A meta-analysis. *Archives of Cardiovascular Diseases* 105(2): 99-113 DOI: <https://doi.org/10.1016/j.acvd.2011.10.006>
- Nelissen, E. C. M., Montfoort, A. P. A., Dumoulin, J. C. M., & Evers, J. L. H. (2010). Epigenetics and the placenta. *Human Reproduction Update* 17(3): 397-417 DOI:10.1093/humupd/dmq052

Newcastle-Ottawa Quality Assessment Scale: Cohort studies. Available from:
http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.

Nichols, M., Peterson, K., Herbert, J., Alston, L., & Allender, S. (2016). Australian Heart Disease Statistics 2015. Melbourne: National Heart Foundation Australia

Organisation for Economic Cooperation and Development (OECD) List of OECD Member Countries Accessed on 1st January 2019

<http://www.oecd.org/about/membersandpartners/list-oecd-member-countries.htm>

Ojeda, N. B., Grigore, D., & Alexander, B. T. (2008). Developmental programming of hypertension: Insight from animal models of nutritional manipulation. *Hypertension* 52: 44-50. DOI: <https://doi.org/10.1161/HYPERTENSIONAHA.107.092890>

Ravelli, A. C. J., van der Meulen, J. H. P., Michels, R. P. J., Osmond, C., Barker, D. J. P., Hales, C. N., & Bleker, O. P. (1998) Glucose tolerance in adults after prenatal exposure to famine. *The Lancet* 351:173-77 DOI: [https://doi.org/10.1016/S0140-6736\(97\)07244-9](https://doi.org/10.1016/S0140-6736(97)07244-9)

Risnes, K. R., Vatten, L. J., Baker, J. L., Jameson, K., Sovio, U., Kajantie, E., Osler, M., Morley, R., Jokela, M., Painter, R. C., Sundh, V., Jacobsen, G. W., Eriksson, J. G., Sørensen, T. I. A., & Bracken, M. B. (2011). Birthweight and mortality in adulthood: a systematic review and meta-analysis *International Journal of Epidemiology* 40 (3): 647-661 DOI: <https://doi.org/10.1093/ije/dyq267>

Risnes, K. R., Romundstad, P. R., Nilsen, T. I. L., Esklid, A., & Vatten, L. J. (2009). Placental weight relative to birth weight and long-term cardiovascular mortality: Findings from a cohort of 31,307 men and women. *American Journal of Epidemiology* 170(5)622-631 DOI: <https://doi.org/10.1093/aje/kwp182>

Roseboom, T. J., Painter, R. C., de Rooij, S. R., van Abeelen, A. F. M., Veenendaal, M. V. E., Osmond, C., & Barker, D. J. P. (2011). Effects of famine on placental size and efficiency. *Placenta* 32:395-399. DOI: <https://doi.org/10.1016/j.placenta.2011.03.001>

Salafia, C. M., Zhang, J., Charles, A. K., Bresnahan, M., Shrout, P., Sun, W., & Maas, E. M. (2008). Placental characteristics and birthweight. *Paediatric and Perinatal Epidemiology* 22: 229-239. DOI: 10.1111/j.1365-3016.2008.00935.x

Salafia C., & Roberts D.J. (2019) Placental weight, shape and gross vascular morphology. In: Khong T., Mooney E., Nikkels P., Morgan T., Gordijn S. (eds) Pathology of the placenta. Springer, Cham DOI: https://doi.org/10.1007/978-3-319-97214-5_5

Salavati, N., Smies, M., Ganzevoort, W., Charles, A. K., Erwich, J. J., Plösch, T., & Gordijn, S. J. (2019) The Possible Role of Placental Morphometry in the Detection of Fetal Growth Restriction *Frontiers in Physiology*. DOI: 10.3389/fphys.2018.01884

Schreuder, M. F., van Wijk, J. A., & Delemarre-van de Waal, H. A. (2006) Intrauterine growth restriction increases blood pressure and central pulse pressure measured with telemetry in aging rats. *Journal of Hypertension* 24: 1337–1343, 2006 DOI: 10.1097/01.hjh.0000234114.33025.fd

Sedgwick, P. (2013) Meta-analyses: How To Read A Funnel Plot. *British Medical Journal* 2013; 346 DOI: <https://doi.org/10.1136/bmj.f1342>

Sferruzzi-Perri, A. N., & Camm E. J. (2016) The Programming Power of the Placenta. *Frontiers in Physiology*. 7:33. DOI: 10.3389/fphys.2016.00033

Singh, M., Kaur, J., Singh, S., Thumburu, K.K., Jaiswal, N., Chauhan, A., Agarwal, A., Paul, N., & Sagwal, S. (2015) Comparison of Newcastle Ottawa scale (NOS) and Agency for Health Research and Quality (AHRQ) as risk of bias assessment tools for cohort studies. In: Filtering the information overload for better decisions. Abstracts of the 23rd Cochrane Colloquium; 2015 3-7 Oct; Vienna, Austria. John Wiley & Sons; 2015

Sullivan, G. M., & Feinn, R. (2012) Using effect size - or why the P value is not enough. *Journal of Graduate Medical Education* 4(3), 279-282. DOI: <http://dx.doi.org/10.4300/JGME-D-12-00156.1>

Symonds, M. E., Stephenson, T., Gardner, D. S., & Budge, H. (2007) Long-term effects of nutritional programming of the embryo and fetus: mechanisms and critical windows. *Reproduction, Fertility and Development* 19(1): 53-63 DOI: <https://doi.org/10.1071/RD06130>.

Taylor, S.J.C., Whincup, P. H., Cook, D.G., Papacosta, O., & Walker, M. (1997) Size at birth and blood pressure: Cross sectional study in 8-11 year old children. *British Medical Journal (Clinical research ed.)*. DOI: 314. 475-80. 10.1136/bmj.314.7079.475.

Thornburg, K. L., O'Tierney, P. F., & Louey, S. (2010) Review: The placenta is a programming agent for cardiovascular disease. *Placenta* 31(Supplement): S54-59 DOI: <http://dx.doi.org/10.1016/j.placenta.2010.01.002>

Wells, G.A., Shea, B., O'Connell, D., et al. Newcastle Ottawa Quality Assessment Scale: Cohort studies. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed on 1st November, 2017.

Wilcox, A.J. (2001). On the importance-and the unimportance-of birthweight. *International Journal of Epidemiology* 30(6): 1233–1241 DOI: <https://doi.org/10.1093/ije/30.6.1233>

Wilmot, E. G., Edwardson, C.L., Achana, F.A., Davies, M. J., Gorely, T., Gray, L. J., Khunti, K., Yates, T., & Biddle, S. J. (2012) Sedentary time in adults and the association with diabetes, cardiovascular disease and death: Systematic review and meta-analysis. *Diabetologia* 55(11): 2895-905 DOI: 10.1007/s00125-012-2677-z.

Winick, M., & Noble, A. (1966). Cellular response in rats during malnutrition at various ages. *The Journal of Nutrition* 89(3): 300-306. DOI: <https://doi.org/10.1093/jn/89.3.300>

Whincup, P. H., Bredow, M., Payne, F., Sadler, S., Golding, S., & the ALSPAC Study Team. (1999). Size at birth and blood pressure at 3 years of age - The Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC). *American Journal of Epidemiology* 149(8):730-739 DOI: <https://doi.org/10.1093/oxfordjournals.aje.a009882>

Whincup, P. H., Cook, D., Papacosta, O., & Walker, M. (1995) Birth weight and blood pressure: cross sectional and longitudinal relations in childhood. *British Medical Journal* 311(7008):773-6 DOI: <https://doi.org/10.1136/bmj.311.7008.773>

Whincup, P. H., & Owen, C. G. (2006) Commentary: Early life determinants of blood pressure in childhood – where do we go from here? *International Journal of Epidemiology* 35:877-879 DOI: <https://doi.org/10.1093/ije/dyl150>

Winder, N. R., Krishnaveni, G. V., Hill, J. C., Karat, C. L., Fall, C. H., Veena, S. R., & Barker, D. J. (2011) Placental programming of blood pressure in Indian children. *Acta Paediatrica (Oslo, Norway: 1992)*, 100(5), 653–660. DOI: <http://doi.org/10.1111/j.1651-2227.2010.02102.x>

Woods, L. L., Weeks, D. A., & Rasch, R. (2004) Programming of adult blood pressure by maternal protein restriction: Role of nephrogenesis. *Kidney Int* 65: 1339–1348. DOI: <https://doi.org/10.1111/j.1523-1755.2004.00511.x>

World Health Organisation Eds Mendis, S., Puska, P., & Norrving, B. (2011) Global Atlas on Cardiovascular Disease Prevention and Control Accessed 23 May 2017 https://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/ Accessed 23 May 2017

World Health Organisation (2013) A Global Brief on Hypertension: Silent killer, Global Public Health Crisis. *WHO WHO/DCO/WHO/2013.2* https://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/ Accessed on 23rd May 2017

World Health Organisation (nd) Fact Sheet on Cardiovascular Diseases (CVD) <http://www.who.int/mediacentre/factsheets/fs317/en/> Accessed on 23rd May 2017

World Health Organisation. (2014) Global Nutrition Targets 2025: Low Birth Weight Policy Brief (WHO/NMH/NHD/14.5). Geneva: World Health Organisation https://www.who.int/nutrition/publications/globaltargets2025_policybrief_lbwt/en/ Accessed on 23rd May 2017

Wyrwoll, C. S., Mark, P. J., & Waddell, B. J. (2007) Developmental Programming of Renal Glucocorticoid Sensitivity and the Renin-Angiotensin System. *Hypertension* 50: 579-584. DOI: <https://doi.org/10.1161/HYPERTENSIONAHA.107.091603>

Zhang, Y., Li, H., Liu, S.J., Fu, G.J., Zhao, Y., Xie, Y.J., Zhang, Y., & Wang, Y.X. (2013) The associations of high birth weight with blood pressure and hypertension in later life: a systematic review and meta-analysis. *Hypertension Research* (2013) 36(8): 725–735. DOI: 10.1038/hr.2013.33.

8. Appendix A Extracted Data From Records

Source	Setting/Cohort Studied	Recruitment Location	Method of Measurement	Diagnostic Criteria For Cardiovascular Disease	Age at Outcome (Years)	Total Number of Subjects (Number of subjects with Cardiovascular Effects)	Placental weight categories (if reported)	Other placenta data	Key findings related to placenta	Comments
Eriksson, Kajantie, Thornburg, Osmond & Barker. (2011) Mother's body size and placental size predict coronary heart disease in men. <i>European Heart Journal</i> 32:2297-2303	Men Helsinki Cohort, 1934-44	Details of birth records from University Central Hospital or the Maternity Hospital in Helsinki	Historical Medical Records HR (95% CI)	Death classified by International Classification of Disease (ICD) codes.	Not reported. Data reports death or hospital admission due to coronary heart disease (ICD-8, ICD-9 and ICD-10).	6975(655)	≤0.55kg 0.65kg 0.75kg >0.75kg	Placental surface area Placental/birth weight (%) Placental length minus breadth	Three combinations of maternal body size and placental size predict later coronary disease in men. 1) Oval placental surface in short mothers, 2) small placental surface in tall mothers whose body mass index was above the median. 3) Large placental surface in relation to birth weight. Men whose mother's BMI was above the median, coronary heart disease was associated with low placental weight and small placental area. HR 1.25 (1.10-1.42, P=0.0007) per 40 sqcm decrease in the surface area. Men whose mother's BMI was below the median coronary heart disease was related to a high ratio of placental weight to birth weight and a high ratio of placental area to	1934-44 Helsinki Cohort Women were excluded from the analysis as only 166 cases of coronary heart disease were reported in the cohort.

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

Heshmati & Koupil. (2014) Placental weight and foetal growth rate as predictors of ischaemic heart disease in a Swedish cohort <i>Journal of Developmental Origins of Health and Disease</i> 5(3): 164-170	Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen), 1915-1929.	Historical Medical Records from Uppsala University Hospital, Sweden.	Historical Medical Records HR (95% CI)	First recorded hospitalization or death from IHD, using International Classification of Disease (ICD) codes.	Not reported. Data reports death or hospital admission due to coronary heart disease (ICD-7, ICD-8, ICD-9 and ICD-10).	10503	≤0.55kg 0.551-0.65kg 0.651-0.75kg >0.75kg	Placental/birth weight (%)	Negative linear trend was observed between placental weight and IHD after adjustment for birth cohort, age, sex and parity, and the association appeared to be mediated by fetal growth rate. In the analysis stratified by social class at birth, a negative association between placental weight and IHD was observed among individuals from medium social class after adjustment for birth cohort, age and sex. Similarly, a negative association between placental weight and IHD was found for individuals who had a low education. Placenta/birth weight ratio showed no evidence of a significant association with IHD in our cohort. Hypertension was associated with both reduced placental weight and with increased placental weight in relation to birth weight. Both of these associations have been found before (Barker et al, 1990; Campbell et al, 1996; Eriksson et al, 2000). The association with low placental weight was
Barker, Thornburg, Osmond, Kajantie & Eriksson. (2010)	Subset of Helsinki Cohort (Men and Women) 1934-44.	University Central Hospital and infant welfare clinics in the city.	Historical Medical Records OR (95% CI)	Diagnosed with hypertension and been prescribed medication.	Not reported	2003(644)	≤0.55kg 0.65kg 0.75kg >0.75kg	Placental surface area. Maximal and lesser diameters	

									accompanied by reduced placental area but not reduced thickness.	
Risnes, Romundstad, Nilsen, Esklid & Vatten. (2009) Placental Weight Relative to Birth Weight and Long-term Cardiovascular Mortality: Findings From a Cohort of 31,307 Men and Women. <i>Am. J Epi</i> 170(5):622-631	Trondheim Cohort 1934-59	St Olav's University Hospital Trondheim Norway.	Historical Medical Records HR (95% CI)	Death classified by International Classification of Disease (ICD) codes. Cardiovascular disease, coronary heart disease and stroke	Mean age of mortality 51.3 yr	31307(382)	Low Med and High	Placental/birth weight (%)	A disproportionately large placenta relative to birth weight was associated with increased risk of cardiovascular disease death.	
Burke, Beilin, Blake, Doherty, Kendall, Newnham, Landau & Stanley. (2004) Indicators of Fetal Growth Do Not Independently Predict Blood Pressure in 8-Year-Old Australians <i>Hypertension</i> 43:208-213	Raine Cohort 1989	King Edward Memorial Hospital, Perth, Western Australia.	Historical Medical Records Regression coefficient R²	Systolic Blood Pressure age 8 yr.	8 yr.	1417	Not Used	Birthweight:placental weight.	BW/PW ratio significantly greater in boys. No significance found in neonatal measurements and SBP.	Study focused on BW and SBP, PW and BW:PW ratio were only considered in a regression model.

Whincup, Bredow, Payne, Sadler. Golding and the ALSPAC Study Team (1999) Size at birth and blood pressure at 3 years of Age The Avon Longitudinal study of Pregnancy and Childhood (ALSPAC) <i>Am J Epidemiol</i> 149(8):730-739 Barker (1997) Fetal nutrition and cardiovascular disease in later life <i>British Medical Bulletin</i> 53(1):96-108	Avon, England 1991-1992	Avon, Southwest Regional Health Authority 10% random sample from June 6 to December 11, 1992.	Historic Medical Records and longitudinal study with follow up every 4 months for first year and the every 6 months. Regression coefficient and SE with p-value for trend	SBP and DBP	3	660	Not used	Placental weight/Birth weight ratio	Placental weight showed to have a weak inverse relation with blood pressure. Which disappeared after inclusion of birth weight. Placental ratio also showed no relation with blood pressure	No data supplied only regression coefficients. Placenta were fixed in formalin prior to weighing.
	Summary article containing data from Preston cohort	N/A	Mean SBP		46-54 years				At any given birth weight, SBP rose as placental weight increased. Inverse relationships existed between both systolic and diastolic blood pressure and placental weight, adjusted for current weight at ages 1, 3 and 6 years. The relationships between placental weight and systolic blood pressure were statistically significant at ages 1 and 3 years. There was no consistent relationship between placental weight and later blood pressure within birth weight categories. No clinically or statistically significant association was seen between the	Sacrificing fetal growth for placental growth.
Blake, Gurrin, Beilin, Stanley, Landau & Newnham. (2001) Placental weight and placental ration as predictors of later blood pressure in childhood <i>Journal of Hypertension</i> 19:697-702	Raine Cohort 1989-1992	King Edward Memorial Hospital, Perth, Western Australia.	Prospective cohort study mean BP with 95% CI	Systolic Blood Pressure age 1, 3 and 6 yr.	Follow up at 1, 3 and 6 years	Age 1 - 964 Age 2 - 869 Age 3 - 1039	≤0.54kg 0.64kg >0.64kg			

Law, Barker, Bull & Osmond. (1991) Maternal and fetal influences on blood pressure <i>Archives of Disease in Childhood</i> 66:1291-1295	Salisbury Health District, UK. 1984-85	Hospital births in Salisbury Health District	Historical Medical Records. Mean Difference (95% CI)	BP	4 yr	405	placental ratio and either systolic or diastolic blood pressures at any age.	
							≤0.55kg 0.65kg 0.75kg >0.75kg	None reported
							BP rose with placental weight. Children whose placental weights were greater than 750g, had average pressures of 2.6mm Hg (95% CI -0.8 to 6.0) above those whose placental weights were 550g or less.	

Barker, Bull, Osmond & Simmonds. (1990) Fetal and placental size and risk of hypertension in adult life <i>BMJ</i> 301:259-62 Moore, Miller, Boulton, Cockington, Craig, Magarey & Robinson. (1996) Placental weight, birth measurements, and blood pressure at age 8 years. <i>Archives of Disease in Childhood</i> 1996,74:538-541.	Preston, Lancashire, UK. 1935-43	Sharoe Green Hospital Preston, Lancashire.	Historical Medical Records. Mean Difference (95% CI)	BP and treatment for hypertension.	46-54 yr	449(124)	In Pounds (lb) ≤1.0 1.25 1.5 >1.5 Converted to kg ≤0.45kg 0.57 0.68 >0.68	None reported	The highest pressures were among people who had been small babies with large placentae and the lowest were among people who had been large babies with small placentae.	Systolic and diastolic blood pressures were strongly related to placental weight.
Moore, Cockington, Ryan & Robinson. (1999) The relationship between birth weight and blood pressure amplifies from childhood to adulthood. <i>Journal of Hypertension</i> 17:883-888	Adelaide, South Australia. 1975-76	Queen Victoria Hospital, Adelaide, South Australia	Historical Medical Records Mean SD	BP	8 yr.	830	≤500g 501-600g >600g		Placental weight alone was not related to systolic BP. There was a positive but not statistically significant relationship between placental weight and diastolic BP. Placental weight alone was not related to systolic BP. A positive association with the ratio of placental weight to birth weight was seen, this was diminished on adjustment for gestational age. Correlation with placental weight was seen but did not persist after	At any birth weight BP tended to rise with increasing placental weight. At any placental weight BP tended to fall with increasing birth weight.
	Follow up of Adelaide cohort	Queen Victoria Hospital, Adelaide, South Australia	Longitudinal study correlation r	SBP DBP	20 years	584		None reported		

											adjustment for gestational age.
Forrester, Wilks, Bennett, Simeon, Osmond, Allen, Ching & Scott (1996) Fetal growth and cardiovascular risk factors in Jamaican schoolchildren <i>BMJ</i> 312:156-160	Kingston, Jamaica, West Indies nd.	University Hospital of the West Indies, Kingston, Jamaica. 27 surrounding schools.	Historical Medical Records and follow up	SBP	6-16 years	1610	Not reported	None reported	Placental weight was inversely related to systolic pressure after adjustment for age, sex, and current weight (test for trend p=0.003) There was no significant relation between the ratio of placental to birth weights and blood pressure. Hazard ratios tended to rise with increasing placental weight although this trend was not significant.	No data on placenta reported. Only defining statement.	
Forsen, Eriksson, Tuomilehto, Osmond & Barker. (1999) Growth in-utero and during childhood among women who develop coronary heart disease: longitudinal study. <i>BMJ</i> 1999;319:1403-7	Helsinki, Finland 1924-33 Women	Helsinki University Central Hospital, Finland.	Historic Medical Records HR	Hospital admission for or death from coronary heart disease.	Not reported	3447	500g 600g 700g >700g	Placental weight/Birth weight ratio	There was a significant rise with an increasing ratio of placental weight to birth weight (P=0.01, adjusted for gestation) Trends for fatal and non-fatal disease were similar. Ponderal index was strongly related to placental weight, mean with low placental weight had low ponderal index at birth and raised death rates from coronary heart disease as adults.	HR trends seen in simultaneous analysis between placental weight, birth length, birth weight, gestational age.	
Forsen, Eriksson, Tuomilehto, Teramo, Osmond & Barker. (1997) Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow up	Helsinki, Finland 1924-33 Men	Helsinki University Central Hospital, Finland.	Historic Medical Records SMR	Death by ICD code 8 or 9	mean age of death 57 years (range 37-70)	3302(286)	500g 600g 700g >700g	None reported		placental weight not investigated directly.	

study *BMJ*
315:837-40

Eriksson, Forsen, Tuomilehto, Osmond & Barker. (2000) Fetal and Childhood Growth and Hypertension in Adult Life <i>Hypertension</i> 36:790-794 Taylor, Whincup, Cook, Papacosta & Walker (1997) Size at birth and blood pressure: cross sectional study in 8-11 year old children. <i>BMJ</i> 1997;314:475 Whincup, Cook, Papacosta & Walker (1995) Birth weight and blood pressure: cross sectional and longitudinal relations in childhood. <i>BMJ</i> 311:773	Helsinki, Finland 1924-1933 still resident in Helsinki in 1971 10 towns across in England and Wales Guildford and Carlisle 1987 & 1991	Helsinki University Central Hospital, Finland. School based School based	Historic Medical Records p value for trend cumulative incidence (%) Cross sectional survey Linear regression model Cross sectional survey Regression coefficient and SE	Registered use of medication for hypertension SBP DBP BP	Not reported 8-11 years 	7086(1958) 3010 1511	≤450g 550g 650g 750g >750g Not used Low ≤589g Mid 590-689g High ≥670g	Placental weight/Birth weight ratio Placental weight/Birth weight ratio Placental ratio and placental weight is not related to blood pressure in children	No significant trend with either placental weight or the ratio of placental weight to birth weight. From men and women with both hypertension and NIDDM, cumulative incidence fell with increasing placental weight. Children with both had small placental size as well as small body size at birth. The association between placental weight and placental ratio and blood pressure in children 8-11 years is inconsistent Placental ratio and placental weight is not related to blood pressure in children	 Regression coefficients (b) reported Birth weight was based on maternal recall.
--	--	--	--	--	--	------------------------------------	---	---	--	--

Campbell, Hall, Barker, Cross, Shiell and Godfrey. (1996) Diet in pregnancy and the offspring's blood pressure 40 years later. <i>British Journal of Obstetrics and Gynaecology</i> 103:273-280	Aberdeen, Scotland. 1948-54	Aberdeen Maternity Hospital	Historic Medical Records. Longitudinal Regression Coefficient and 95% CI	SBP DBP Rose/WHO Chest Pain Questionnaire 12-lead ECG Defined CHD by the presence of 1 or more of the following: typical angina (according to the questionnaire); ECG Minnesota codes 1-1, 1-2 (Q and QS codes); more than 50% coronary artery stenosis on angiography, or a history of coronary artery revascularisation, either coronary by-pass graft or coronary angioplasty; or non-fatal myocardial infarction; further ECG changes or raised cardiac enzyme activities.	Mean age 40.6 yr	253	Not used	None reported	Placental weight was positively correlated with mother's weight (r=0.17) Low placental weight was associated with a higher blood pressure in the offspring though this was not statistically significant (r=-9.2 mmHg/kg; 95% CI - 22.6 - 41.; P=0.2	Diet was determined by a survey and follow was made 40 years later to measure BP
Fan, Zhang, Li, Wang, Xu, Gong, Zhou, Wen & Zeng. (2009) Relationship between birth size and coronary heart disease in China. <i>Annals of Medicine</i> 42(8): 596-602	Beijing, China. 1921-1954	Peking Union Medical College Hospital	Historic Medical Records. Retrospective randomly selected sub-cohort. Odds ratio 95%CI		Mean age (men) 59.9 ± 8.4 years Mean age (women) 59.9 ± 8.1 years	2033 (135)	≤450g 450 - 560g 560 - 670g ≥675g	None reported	Prevalence of CHD was inversely associated with placental weight (P < 0.05) Placental weights were low with 17.8% of all placenta weighing less than 450g Mean placental weight (male) 539.6 ± 103.1 g; Mean placental weight (female) 525.7 ± 101.8 g	Birth weights were especially low, 8% of births were less than 2500g.

Martyn, Barker & Osmond (1996) Mother's pelvic size, fetal growth, and death from stroke and coronary heart disease in men in the UK <i>The Lancet</i> 348:1264-68 Barker, Godfrey, Osmond & Bull (1992) The relation of fetal length, ponderal index and head circumference to blood pressure and the risk of hypertension in adult life. <i>Paediatric and Perinatal Epidemiology</i> 6:35-44	Hertfordshire and Sheffield, UK. 1907-1930	Jessop Hospital records & visiting midwife (Hertfordshire).	Historic Medical Records Retrospective cohort. SMR Observed number of deaths	ICD codes	Not reported	13249 (1639)	In Pounds (lb) ≤1.0 1.01 - 1.25 1.26 - 1.5 >1.5 Converted to kg ≤0.45kg 0.458 - 0.57 0.571 - 0.68 >0.68	Placental weight as % of Birth weight	SMR for stroke and CHD fell with increasing placental weight	Observed placental weight to head circumference as well as placental weight to mother's pelvis size.
Eriksson, Kajantie, Osmond, Thornburg & Barker (2010) Boys live dangerously in the womb. <i>Am J Hum Biol</i> 22(3):330-335	Preston, England 1935-1943	Sharoe Green Hospital	Historic Medical records and follow up mean systolic BP and SD	SBP	46-54 years	327	In Pounds (lb) ≤1.0 1.01 - 1.25 1.26 - 1.5 >1.5 Converted to kg ≤0.45kg 0.458 - 0.57 0.571 - 0.68 >0.68	None reported	Systolic pressure rose with increasing placental weight and PW:BW ratio	Placental weight to birth length. Split up in to two groups greater than and less than 1.25 pounds Placental weight to placental surface (calculated from diameters). Men with hypertension vs women with hypertension Men were born heavier than women but there was no significant difference in placenta.
Eriksson, Kajantie, Osmond, Thornburg & Barker (2010) Boys live dangerously in the womb. <i>Am J Hum Biol</i> 22(3):330-335	Helsinki, Finland 1934-1944	Helsinki University Central Hospital	Historic Medical Records and follow up diagnosis of hypertension Odds Ratios (split categories men and women) 95% CI	Diagnosed hypertension	mean 62 (range57-70 years)	2003(644)	≤0.55kg 0.65kg 0.75kg >0.75kg	Calculated surface area Diameter (greater and lesser)	In men, hypertension was only weakly correlated to low placental weight. In women, low placental weight predicted hypertension more strongly if their mothers were short.	

Barker, Thornburg, Osmond, Kajantie, Eriksson (2010) The surface area of the placenta and hypertension in the offspring in later life <i>Int J Dev Biol</i> 54:525-530	Helsinki, Finland 1934-1944	Helsinki University Central Hospital	Historic Medical Records and follow up diagnosis of hypertension Odds Ratios 95% CI	Diagnosed hypertension	mean 62 (range57-70 years)	2003(644)	≤0.55kg 0.65kg 0.75kg >0.75kg	Placental weight/Birth weight ratio Calculated surface area Diameter (greater and lesser)	Hypertension is associated with both reduced placental weight and increased placental weight in relation to birth weight Birth weight/placental ratio was lower in the high risk cluster supporting the role of antenatal influences. An association between the high BP with lower birth weight/placental ratio may be confounded by smoking.	Same Helsinki cohort 1934-44. Placental area and hypertension.
Huang, Burke, Newnham, Stanley, Kendall, Landau, Oddy, Blake, Palmer & Beilin. (2007) Perinatal and childhood origins of cardiovascular disease <i>Int. J. Obesity</i> 31:236-244 Thame, Osmond, Wilks, Bennett, McFarlane-Anderson & Forrester. (2000) Blood Pressure Is Related to Placental Volume and Birth Weight. <i>Hypertension</i> 2000;35:662-667. Leon, Lithell, Vagero, Koupilova, Mohsen, Berglund, Lithell & McKeigue (1998) Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15,000 Swedish men and	Subset of Raine Cohort 1989-1992	King Edward Memorial Hospital, Perth, Western Australia.	Longitudinal study Cluster analysis	BP	8 years	406		Birth weight/Placental ratio		High risk and low risk cluster analysis of subset of Raine cohort
	Kingston, Jamaica, West Indies nd.	University Hospital of the West Indies, Kingston, Jamaica.	Historical Medical Records	SBP	1, 2, 2.5, 3, 3.5 years	428	Not used	Placental volume		Placental weight not investigated directly.
	Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen), 1915-1929.	Historical Medical Records from Uppsala University Hospital, Sweden.	Follow up study	Death by ICD code 8 or 9		14611			No evidence of any association of placental weight with mortality from ischaemic heart disease.	No data on placenta reported. Only defining statement.

women born
1915-29 *BMJ*
317:241-5

Martyn, Barker,
Jespersen,
Greenwald,
Osmond & Berry.
(1995) Growth in-
utero, adult blood
pressure, and
arterial
compliance. *Br*
Heart J 73:116-
121

Sheffield, UK.
1939-40

Jessop Hospital

Historical Medical
Records

BP and Mean Pulse
Wave velocity

50-53 yr

337

Not used

None reported

No consistent
relations between
adult blood pressure
and placental weight.
No relation between
pulse wave velocity
and placental weight.

Not data.
Defining
statement only.

9. Appendix B NOS Quality Assessment Form for Cohort Studies.

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

- 1) Representativeness of the exposed cohort
 - a) Truly representative (*one star*)
 - b) Somewhat representative (*one star*)
 - c) Selected group
 - d) No description of the derivation of the cohort
- 2) Selection of the non-exposed cohort
 - a) Drawn from the same community as the exposed cohort (*one star*)
 - b) Drawn from a different source
 - c) No description of the derivation of the non-exposed cohort
- 3) Ascertainment of exposure
 - a) Secure record (e.g., surgical record) (*one star*)
 - b) Structured interview (*one star*)
 - c) Written self-report
 - d) No description
 - e) Other
- 4) Demonstration that outcome of interest was not present at start of study
 - a) Yes (*one star*)
 - b) No

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
 - a) The study controls for age, sex and marital status (*one star*)
 - b) Study controls for other factors (list) _____
(*one star*)
 - c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

- 1) Assessment of outcome
 - a) Independent blind assessment (*one star*)
 - b) Record linkage (*one star*)
 - c) Self-report
 - d) No description
 - e) Other
- 2) Was follow-up long enough for outcomes to occur
 - a) Yes (*one star*)
 - b) No

Indicate the median duration of follow-up and a brief rationale for the assessment above: _____

- 3) Adequacy of follow-up of cohorts
 - a) Complete follow up- all subject accounted for (*one star*)
 - b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (*one star*)
 - c) Follow up rate less than 80% and no description of those lost
 - d) No statement

E-17

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain