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Fetal ultrasound measurements and associations with post natal outcomes in infancy and childhood - A systematic review of an emerging literature

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ABSTRACT

Background. Several hypotheses predict that faltering fetal growth is an antecedent for common non-communicable diseases. This is the first systematic review of an emerging literature linking antenatal fetal measurements to postnatal outcomes

Methods. Electronic databases (OVID, EMBASE and Google Scholar) and cohort study web sites were searched in July 2014. Studies were selected which examined associations between antenatal fetal ultrasound measurements to post natal outcomes. Neonatal outcomes, e.g. premature delivery, were not included.

Results. There were 23 papers identified from cohorts in Western countries, including 11 from a single cohort. Four papers reported outcomes in children aged over six years. Small, but not large, for gestational age (SGA) was associated with adverse outcomes except for one study where individuals with the lightest or heaviest estimated fetal weight risk were at increased risk for autistic spectrum disorder. The magnitude of associations was modest, for example each z score reduction in fetal size was associated with 10-20% increased risk for delayed development or a 1mmHg increase in blood pressure. Associations between decelerating in utero growth and outcomes were less consistent since growth acceleration and deceleration were both associated with adverse and advantageous outcomes.

Conclusions. There is consistency for antenatal SGA and growth deceleration being associated with adverse outcomes determined in early childhood. Accelerating fetal growth was associated with both advantageous and disadvantageous outcomes, and this is consistent with the concept of predictive adaptive responses where exposure to a post natal environment which was not anticipated predisposes the fetus to adverse health.

What this paper adds

What is already known on this subject. Poor fetal growth (as evidenced by low birth weight) is associated with adverse outcomes in childhood and adulthood. Hypotheses such as the fetal origins, developmental programming and predictive adaptive responses implicate deviations in fetal growth in causation of non communicable diseases.

What this study adds. Where associations were present, being small for gestational age was generally associated with adverse outcomes. There was evidence that both growth deceleration and acceleration were associated with adverse outcomes, and there were inconsistent associations between studies.

INTRODUCTION

Historically, before the 1990, the human fetus was considered as inhabiting a privileged environment where it was insulated from harm by the materno-placental unit[1], but this paradigm is no longer accepted. Cohort studies with extended follow up of the offspring of mothers exposed to starvation during pregnancy, such as during the Dutch Famine[1,2] and the Leningrad Siege [3], have demonstrated how this exposure was associated with both reduced birth weight and increased incidence of non-communicable diseases (NCD) or their physiological features[4]. A number of mechanisms have been proposed as explanations for associations between reduced fetal growth, as evidenced by reduced birth weight, and a broad spectrum of adult non-communicable diseases for which there is no cure including cardiovascular disease[5], type II diabetes[6], psychiatric diseases[7], chronic renal failure[8] and polycystic ovarian disease[9]. These mechanisms include the thrifty phenotype[10], the fetal origins hypothesis [5], developmental plasticity[11] and predictive adaptive responses[12] and collectively fall under the concept of developmental origins of disease[4](DOHaD). The thrifty phenotype and fetal origins hypotheses are focussed on fetal growth failure and predict that faltering fetal growth will be associated with adverse outcomes. The developmental plasticity and predictive adaptive responses theories would be less specific in predicting outcome but maintain that a single individual can achieve a number of phenotypes depending on the developmental milieu and that both fetal growth deceleration and acceleration may be beneficial or harmful to the individual depending on the postnatal environment.

Understanding the developmental mechanisms associated with faltering fetal growth and non-communicable diseases will inform antenatal preventative interventions which will ultimately improve the health of the population and reduce burden on healthcare resources [13]. A major challenge to understanding fetal origins of non-communicable diseases in humans is measuring fetal well being. Fetal anthropometry, as evidenced by ultrasound measurement, has been used as an index of fetal well being and related to risk for outcomes in childhood. There is now emerging

literature relating antenatal fetal measurements to childhood outcomes including asthma, allergy, obesity and hypertension and it is possible to determine whether the literature refutes or supports previous theoretical work. The present systematic review was designed to answer the question "are there consistent associations between antenatal size (e.g. small for gestational age) and faltering fetal growth and post natal outcomes?" The focus was on postnatal outcomes where DOHaD may be important and we set out to determine which of the different developmental theories best fitted the summation of the evidence identified.

METHOD

Search Methodology

The database search was carried out in July 2014 using OVID and also EMBASE and Google Scholar databases. The following terms were used for the search and were identified after reviewing relevant publications already known to the authors (also see online supplement for search strategy used): "Child", "Follow-up/Cohort/Epidemiological/Cross-sectional/Prospective Studies", "Fetal growth/development", "Infant/Infant New-born" and "Humans". Abstracts were reviewed independently by two researchers (FA and AE) and studies which potentially related antenatal fetal outcomes to postnatal outcomes identified. Eligible papers had to include fetal anthropometric ultrasound measurements representative of overall fetal size (i.e. crown rump length, biparietal diameter, head circumference, femur length, abdominal circumference and estimated fetal weight) as the predictive variable and postnatal outcomes determined ≥1 week after birth as the outcome. Studies which described outcomes of antenatal fetal congenital anomalies, eg echogenic bowel, congenital heart disease, cystic lesions in brain, lung and kidney, were not eligible since these fetal measurements were not representative of overall fetal size. Studies which related fetal measurements to perinatal outcomes (e.g. prematurity, increased/reduced birth weight and complications of delivery) or maternal exposures during pregnancy (e.g. maternal smoking or ambient air quality), were not eligible since our research question was focussed on the relationship

between antenatal measurements and post natal outcomes which were or might be pre-clinical indices for non-communicable disease. Three authors (FA, AE and ST) then agreed on the abstracts where full papers should be accessed. Further papers were identified by searching reference lists of identified papers and also from the websites for three key cohorts where fetal measurements were known to have been linked to post natal outcomes: Generation R (http://www.erasmusmc.nl/epi/research/Generation-R/?lang=en), Southampton Women's Survey (http://www.leu.soton.ac.uk/sws/) and "Raine Cohort (http://www.rainestudy.org.au/). Outcomes were sought for (i) size for gestational age (including small for gestational age) and (ii) fetal growth trajectory (including growth deceleration).

Description of fetal measurements. The variables included were: Crown rump length (CRL), biparietal diameter (BPD) and abdominal circumference (AC) were measured in the first trimester (i.e. up to 12 weeks gestation). In the second trimester (i.e. 13 to 27 weeks gestation) and third trimester (i.e. 28 weeks and beyond) head circumference (HC), femur length (FL) and BPD and AC were measured; estimated fetal weight (EFW) was derived from HC, AC and FL measurements.

Quality assessment

Quality assessment of all the included papers was carried out using a standard tool developed for use in any public health topic area (http://www.ephpp.ca/Tools.html). This process provides the reader with a global score as to the quality of evidence provided plus each study is rated over six domains (selection bias, study design, confounders, blinding, data collection methods and withdrawals and drop outs). Each domain is scored 1-3 and from these scores the global score is derived (1=strong study design, 2=moderate and 3=weak). Each paper was scored independently by two of the authors and a final score agreed.

RESULTS

The OVID search identified 450 study abstracts, 33 full texts were retrieved and 19 of these papers were ultimately included (see figure 1). The EMBASE and Google scholar searches produced 36 and 4074 abstracts respectively, none of which yielded additional papers. A paper which described associations between antenatal and postnatal echocardiographic outcomes was not included[14]. Four further papers were identified from previously described cohort web sites. Of the 23 papers included in this review[14-36], 11 arose from the Generation R cohort, four from Southampton Women Survey (SWS), three from the Raine cohort, two from the Study of Eczema and Asthma To Observe the influence of Nutrition (SEATON) cohort and three from other studies. Only four studies presented results in children aged more than six years [16,26-28]. All studies were from European or North American populations. Table 1 describes which fetal measurements were made in the five cohorts whose papers were included. Table 2 gives an overview of associations between small for gestational age and post natal outcome while table 3 describes associations between changing fetal size and postnatal outcomes. Table E1 on the on line data supplement presents fuller description of the study design and magnitude of the associations reported in individual papers. For each study, outcomes were first related to fetal size for a given gestation and then to fetal growth. Outcomes were categorised into: respiratory, allergy, obesity, neurodevelopmental, autistic spectrum disorders, febrile seizures, cardiovascular, renal and bone mineralisation. One of the studies achieved a strong global rating[15], 12 received a moderate rating (most failed to gain strong rating by not demonstrating how non participation affected the population demographics) and the remainder were given a weak rating (most failed to gain moderate rating by not demonstrating whether/how confounders such as maternal smoking and socioeconomic status were considered), see online data supplement table E2. Of the 6 studies which found no evidence of association between small fetal size and post natal outcome, 4 were of poor quality study design [23,3526] and 2 of moderate quality [17,31]. Among the 4 studies which found no association between changing fetal size and outcomes, 3 were of moderate quality design [21,24,31] and the fourth of poor quality [32].

Respiratory outcomes

There were four studies identified including two from the SEATON cohort. In the SEATON cohort, being small for gestational age(SGA) in the first trimester was associated with higher risk for doctor confirmed asthma and lower Forced Expiratory Volume in one second (FEV_1) at five[15] and ten years of age[16]. Second trimester SGA (here BPD was the measurement) was associated with higher asthma risk[15] at five and lower FEV_1 and Forced Expiratory Flow at 25-75% of Forced Vital Capacity(FEF_{25-75}) at ten years[16]. Fetal measurements were not associated with bronchodilator response at five years, bronchial hyperreactivity at ten years, or exhaled nitric oxide at five or ten years. Growth acceleration between the first and second trimesters was associated with lower FEF_{25-75} at five and ten years but lower asthma risk at ten years compared with persistent high growth[15]. Growth acceleration between the first and second trimesters was also associated with lower risk for wheeze at three years of in the SWS[18]; here children were stratified by skin prick positivity and increasing HC between 11 and 19 weeks was associated with lower risk for non-atopic wheeze. Increasing AC growth between 19 and 34 weeks was also associated with lower risk for atopic wheeze[18]. In the Generation R Cohort[17] there were no associations between fetal measurements or growth and respiratory outcomes at four years but postnatal weight gain was positively associated with risk for symptoms, regardless of antenatal size or growth.

Allergy outcomes

There were four papers identified. In the SEATON study, fetal size for a given gestation was not associated with risk for hayfever or eczema at ten years[16] (results not presented at five years) nor with skin prick reactivity five[15] or ten[16] years. When compared to persistent high growth, accelerated fetal growth size during first and second trimesters was associated with higher eczema risk and decelerating fetal growth with lower hay fever risk at ten years[16]. In SWS[18], increasing AC growth between weeks 11 and 19 was also associated with higher risk for atopy but increasing AC growth between 19 and 34 weeks gestation was associated with decreased risk for atopy in three-

year-olds[18]. In contrast, in the Generation R cohort[17] increasing AC between the 2nd and 3rd trimesters was associated with higher risk for eczema at four years.

Obesity

Obesity outcomes were reported in five studies, four from Generation R. In the Generation R Cohort, absolute measurements of second and third trimester EFW were not related to fat mass at age 6 months (calculated by dual-energy X-ray absorptiometry, DEXA)[20] but a relative increase in EFW z score of >0.67 was associated with higher fat mass. In a second paper from Generation R, SGA for third (but not second) trimester EFW was associated with an increase of borderline significance in ultrasound-determined abdominal fat deposits at age two years[21]; the change in EFW between second and third trimesters was not associated with abdominal fat measurements[21]. In the third paper, first trimester CRL and second and third trimester FL and EFW were linked to peak velocities in height, weight and body mass index (BMI) up to four years of age[22]. There was no association between first trimester CRL and outcomes. There were positive associations between second (but not third) trimester EFW and peak weight velocity and FL and peak height velocity. Second and third trimester EFW and relative growth between these times were all positively related to body mass index at adiposity peak. In the final paper from the Generation R cohort, first trimester size was related to total body fat at a median age of six years and each increase in z score in CRL was associated with a 0.3% reduction in total body fat [95% CI 0.03, 0.57] [36]. In the Project Viva cohort[19], individuals in the highest quartile for EFW had higher BMI z score at three years and were at higher risk for obesity (defined as ≥95th centile) when compared to the lowest quartile[19]. Compared to individuals in the lowest EFW and birth weight quartiles, those in the highest EFW and birth weight quartiles had higher BMI at three years of age. There were no associations between EFW and birth weight and skinfold thickness at three years of age, i.e. an index of adiposity[19].

Plasma lipid outcomes

In a recent paper from the Generation R cohort[36] each z score increase in CRL was linked to a mean reduction of 0.05 mmol/L cholesterol [95% CI 0, 0.10] in six year olds. There was also a trend which approached significance for an inverse relationship between CRL and plasma low density lipoprotein but no association was apparent for triglycerides.

Neurodevelopment

There were three studies to consider neurodevelopment. One Generation R Cohort paper described associations between SGA for second and third trimester AC, EFW and ratio of AC:HC (but not HC *per se*) and higher risk for being in the lowest tertile for Touwen's Neurodevelopmental Examination at 9 to 15 weeks of age[24]. A second Generation R cohort publication related SGAfetal HC measurements in early, mid and late pregnancy to increased risk for delayed social development at twelve months, SGA HC in late pregnancy was also associated with increased risk for delays in self help and fine motor skills. Reduced relative size in HC between early and mid pregnancy (i.e. IUGR) was associated with higher risk for delayed fine motor development and SGA HC growth in later pregnancy with higher risk for delayed self-help abilities, gross and fine motor and language development at 12 months[25]. A case-control study from the Raine cohort related FL and HC at 18 weeks and HC at delivery to Specific Language Impairment[23] and there were no differences in fetal measurements between the 30 case and 30 controls. The prevalence of microcephaly (i.e. HC at birth <-1.67 z score) was higher among cases (40%) compared to controls (10%)[23].

Autistic spectrum disorders (ASD)

There were three case-control studies. A study from the Raine cohort found no difference in head circumference at 18 weeks gestation and birth between 14 cases with ASD and 56 matched control[27]. A study from America [26] also found no difference in second trimester BPD, AC and FL between 45 cases and 222 controls. In a post hoc analysis, cases were subcategorised as multiplex autism (i.e. autism occurring in association with schizophrenic symptoms, n=8) or simplex autism (n=33); multiplex autism was associated with SGA AC compared with simplex autism and also with

controls[26]. A third study from Sweden compared second trimester EFW between 4283 children with ASD and 36,588 controls[28]. ASD risk was higher for the smallest and largest EFW, ie both small and large for gestational age. When individuals were subcategorised as ASD with or without intellectual disability, the associations with EFW were similar.

Febrile seizures

The Generation R cohort team related SGA second and third trimester fetal transverse cerebellar diameter [TCD] to risk for febrile seizures by two years of age[29]. There were 67 cases among the 3372 children studied. Individuals in the lowest tertile of third trimester EFW, AC and FL (but not HC) measurements were also at higher risk for febrile seizures compared to the highest tertile. Cases had EFW similar to controls at 16 weeks gestation but by 34 weeks gestation, EFW was -0.4 z scores relatively lower for cases suggesting IUGR rather than SGA was important.

Cardiovascular Outcomes

Four reports considered cardiovascular outcomes. A study from the Raine Cohort related FL, AC and HC measured between 18 and 38 weeks gestation to systolic blood pressure (SBP) at age six years in 707 individuals[30] and observed an inverse association between FL and SBP. A similar finding was seem in the Generation R cohort where SGA FL at 30 (but not 20) weeks gestation was associated with increased SBP at age two years[31]. A second Generation R study reported a mean reduction in diastolic (but not systolic) blood pressure at six years of age of 0.43 mmHg [0.01, 0.84] for each z score increase in first trimester CRL but this association was not significant when the child's weight was considered[36]. In the project Viva cohort [19], relative to individuals in the lowest quartiles for both EFW and birth weight, elevated SBP at three years was present among those who were (i) in the highest EFW quartile and second lowest birth weight quartile (ii) in the second lowest quartile for both and (iii) in the second lowest EFW quartile and second highest birth weight quartile.

Renal Outcomes

In the one paper identified, third (but not second) trimester HC and AC were positively associated with kidney volume at the age of 2 years[32]. There was no association between growth in HC and AC between second and third trimesters and kidney volume[32].

Bone mineralisation

There were four studies identified. In the first of three studies from the SWS, FL measurements at 19 and 34 weeks and growth between these gestations were positively associated with bone mineral content and skeletal size (expressed as bone area) in four year olds[33]; bone outcomes were determined by whole-body DEXA scan. There were less convincing positive associations between AC and bone mineralisation. Femoral neck section modulus, an index of bending strength and relevant to fractures in the elderly, was determined in 493 six year olds in SWS and increasing FL growth between 19 and 34 weeks (and to a lesser degree between 11 and 19 weeks) was positively associated with this outcome [37]. In the second study, growth in FL and AC between the 11th and 19th weeks of pregnancy was positively associated with bone area and bone mineral content at birth and four years of age[34]. In the Generation R Study[35], second and third trimester EFW were positively associated with bone mineral density (BMD) and content (BMC) in six month olds; some associations were only present for either lumbar spine only or total body BMD and BMC. Change in EFW between 20 and 30 weeks, but not between 30 weeks and term, were also positively associated with BMD for TB.

DISCUSSION

This is the first systematic review of the literature relating antenatal fetal size and growth to postnatal outcomes. We considered a broad spectrum of post natal outcomes since some organs pass through important developmental stages at the same gestation and an antenatal exposure at a given time might affect more than one organ. Equally, different organs develop at different gestations and serial fetal ultrasound measurements can give insight into the developmental origins

of different health outcomes. The first main finding was that when associations were present, it was small for a given gestational age (and not large) that was linked to adverse outcomes with the exception of one study which found higher risk for autistic spectrum disorder among the smallest and largest second trimester fetuses[28]. The second notable finding was that growth deceleration was associated with some unfavourable outcomes although there were some inconsistencies between studies. The final important finding was that in utero growth acceleration was associated with adverse and beneficial outcomes (e.g. higher risk for asthma, obesity and atopy but also higher bone mineral density, table 3). The magnitude of associations between fetal measurements and outcomes, when present, was generally modest for an individual, but these associations may be relevant to public health where small changes in risk may lead to large absolute number of individuals with incurable outcomes such as coronary artery disease, type II diabetes and asthma. Our conclusions are based on studies from Europe, North America and Australia this adds a limitation that the results may not be generalisable to other populations where different genetic, environmental and socioeconomic influences may be present. We point out that causation cannot be implied from the associations we describe from the observational studies identified. The cohort members are still young, some of the associations described may resolve over time and it will be many years before follow up will be able to link fetal measurements to outcomes such as cardiovascular disease[5] and type II diabetes[6].

Most studies found small for gestational age to be associated with a higher risk for “adverse” outcomes, and included birth weight and postnatal measurements in the analyses indicating that the “adverse outcomes” were not simply small fetuses becoming small infants and children. Inclusion of birth weight as a confounder does determine whether antenatal or neonatal measurement is more relevant to the outcome. Inclusion of birth weight might be a case of over adjustment since this birth weight is on any causal pathway between fetal measurements and post natal outcome and

therefore unlikely to be a confounder. Moreover adjustment for birth weight may inadvertently adjust for a mediator/exposure which affects fetal growth in later pregnancy.

Developmental pauses at critical stages of development might explain these associations, for example the association between small for gestation and lower lung function was apparent from the first trimester [16] suggesting a problem in development occurring in very early pregnancy whereas associations with higher blood pressure were more apparent at 30 weeks gestation than at 20 weeks [30,31]. During the embryonic and fetal periods, organs develop according to different timetables; for example in the lungs airway division occurs by 16 weeks gestation[38] whereas in the kidneys, glomerulogenesis occurs between 7 and 35 weeks gestation[39]. In this context, a transient exposure before 16 weeks might lead to a life-long aberration in airway function but not adversely affect renal function and the fetus will achieve a normal/near normal birth weight.

There was some consistency between studies for associations between change in fetal size and outcomes, for example (i) accelerated growth during early pregnancy associated with higher risk for eczema[16] and atopy[18] (ii) accelerated growth during later pregnancy associated with increased fat mass[20], body mass index[22] and bone mineral density[33,35]. There were also some apparent inconsistent associations between studies, for example (i) accelerated growth during late pregnancy and higher risk for eczema[17] but also lower risk for atopy[18] and hayfever[16] (ii) accelerating [19] and decelerating[19] growth during later pregnancy associated with higher systolic blood pressure or not at all[31]. These different outcomes may reflect differences in ages at postnatal assessment, different methodologies used to measure outcomes and differences between study populations. These different outcomes might also reflect genuine differences in determinants of antenatal growth in different populations.

The “fetal origins” hypothesis proposed that faltering growth during mid gestation was associated with higher risk for cardiovascular disease and we found evidence of faltering fetal growth being

associated with higher blood pressure (table 3) and also with other unfavourable outcomes including lower lung function and developmental delay. We also found evidence for increasing growth during early and late pregnancy being associated with higher risk for adverse outcomes in young children including lower lung function, increased asthma and adiposity (table 3). Associations between relative acceleration and deceleration in growth and "advantageous" and "disadvantageous" outcomes are not consistent with the fetal origins hypothesis but are in keeping with the predictive adaptive response hypothesis[12] where fetal growth anticipates the post natal environment, and inappropriate (positive or negative) fetal growth may be disadvantageous. The relationship between fetal growth and post natal outcomes may be modified by post natal growth trajectories, as was found in some studies included in this review[17 20]. Large cohorts with detailed follow up and advanced statistical approaches are required to understand the complex relationship between antenatal growth and postnatal morbidity.

There are a number of limitations to this review. First, there was considerable heterogeneity between study designs and meta analysis of data was not possible, furthermore outcomes measured within studies sometimes varied as the study participant became older, eg obesity and neurodevelopmental outcomes, and this limits direct comparison of results from the same cohort. Second, gestational age certainty is crucial to the accurate interpretation of fetal measurements[40] and there is inevitable inaccuracy regardless of whether date of last menstrual period or first trimester fetal measurement is used (or combination of these), however this inaccuracy is not likely to alter the direction of any associations between fetal size and outcome within a population but is likely to reduce the true magnitude of any associations. A third factor to consider is that fetal measurements may not be an accurate index of fetal wellbeing, although the evidence from this review does support the role of fetal measurements as a surrogate for fetal wellbeing. Statistical points to note are that false positive results with borderline p values may have arisen due to multiple testing within studies and also due to post hoc analyses. Fourth, our quality control found that only one study had strong design; although blinding and data collection methods were strong,

details were missing for how representative cohorts were of the general population, how incomplete participation at post natal follow up might bias the population studies and the confounders adjusted for. Perhaps most importantly there were no intervention studies included and causation can only be determined from such studies and not from observational studies such as we describe here. Nutritional interventions aimed preventing impaired fetal growth, but where antenatal fetal measurements were not made, have met with limited success [41] and might offer a mechanism to alter antenatal growth.

In conclusion, this review of the literature has identified evidence that small fetal size and changes in fetal growth trajectory may be important to post natal outcomes. These associations do not prove causation but do suggest that antenatal interventions might be one option of preventing non-communicable diseases in adulthood. The associations reported here require replication in non-Western populations to confirm world-wide generalizability. Future research might look at intervention strategies aimed at preventing small for gestational age and growth failure but avoid stimulating fetal growth acceleration since this may lead to unwanted outcomes (table 2).

Table 1. Details of the five cohorts which have linked antenatal fetal measurements to post natal outcomes.

Cohort	Country	Years of recruitment	Number recruited	Fetal measurements available	Rationale for recruiting cohort	Inclusion and exclusion criteria
Generation R[42]	Netherland	2002-2006	9778 mothers and details from 5125 offspring including more detailed assessment in ≤1232	T1: CRL (used for dating) T2+3: BPD, HC, AC FL, EFW, transverse cerebellar diameter	To identify early environmental and genetic causes of normal and abnormal growth, development and health from fetal life until young adulthood	Delivery date April 2002-January 2006. Recruitment any time during pregnancy (ideally <18 weeks). Living within Rotterdam area. No exclusion criteria stated.
Southampton Women's Survey[43]	UK	1998-2002	12579 women (75% of all women approached) of whom 2567 became pregnant and delivered live born infant by 2005	Weeks 11, 19 and 34: FL, AC	To learn more about the dietary and lifestyle factors that influence the health of women and their children	Women aged 20-34 years recruited between 1998 and 2002. Infant born <37 weeks gestation were excluded.
Raine cohort[44]	Australia	1989-1991	2876	Weeks 18, 24, 28, 34 and 38 (in 1415*): AC, HC and FL	To determine whether use of multiple ultrasound assessments improved pregnancy	Mothers 16-20 weeks pregnant. Fluent in English and expected to deliver

					outcomes	in the recruiting hospital
SEATON study[45]	UK	1997-1999	2000 mothers (of 2690 invited to take part) who delivered 1924 live born singleton infants	T1 CRL, T2 BPD and FL no antenatal T3 measurements	To detect associations between maternal diet during pregnancy and childhood asthma and eczema	Mother 10-12 weeks pregnant. Other exclusion and inclusion criteria not described
Project Viva[46] http://dacp.org/viva/index.html	USA	1999-2002	2671 mothers (64% of eligible) of whom scan details were used in 772 and of these 438 were followed up at 3 yrs	T2 (18 weeks) BPD, FL, AC and EFW	To find ways to improve the health of mothers and their children by looking at the effects of mother's diet as well as other factors during pregnancy and after birth	Mothers recruited after initial clinical prenatal visit (≤22 weeks gestation). Exclusion criteria included multiple pregnancy, not fluent in English,

T1, 2 and 3 = first, second and third trimesters. CRL=crown rump length, BPD=biparietal diameter, HC=head circumference, FL=femur length, AC=abdominal circumference, EFW=estimated fetal weight (derived from HC, FL and AC).*The Raine cohort was designed to determine whether regular antenatal ultrasounds were associated with higher risk of harm to the fetus, mothers were randomised to have either one or five assessments.

Table 2. Summary of associations between being small for gestational age in the first, second and third trimester and outcomes in post natal life. SWS=Southampton Women's Study, CRL=Crown Rump Length, BPD=BiParietal Diameter, SGA=Small for Gestational Age, EFW=Estimated Fetal Weight, FL=Femur Length, AC=Abdominal Circumference, HC=Head Circumference.

		Associations with being small for gestational age		
Outcome	Cohort	First trimester (approximately 10 weeks)	Second trimester (approximately 20 weeks)	Third trimester (approximately 30 weeks)
Respiratory	SEATON[15,16]	Higher risk for asthma at 10 yrs (CRL) Lower lung function at 10 yrs (CRL)	Higher risk for asthma at 10 yrs (BPD) Lower lung function at 10 yrs (BPD)	Scan not done
	SWS[18]	Outcomes with SGA not reported		
	Generation R[17]	No association with symptoms at 4yrs	Outcomes with SGA not reported	
Allergy	SEATON[15,16]	No associations apparent between SGA and eczema, hayfever, skin prick reactivity or exhaled nitric oxide		
	SWS[18]	Outcomes with SGA not reported		
	Generation R[17]	Outcomes with SGA not reported		
Obesity	Generation R[20-22]	Not associated with peak growth velocities (PGV)	No relationship with EFW and fat mass at 6mo or abdominal fat mass (AFM) at 2 yrs. EFW associated with lowerweight PGV and body mass index at adiposity peak. FL inversely associated with height PGV.	No relationship with EFW and fat mass at 6mo but borderline association with AFM at 2 yrs and body mass index at adiposity peak
	Project Viva[19]	Scan not done	Reduced EFW associated with lower body mass index and obesity at 3 yrs	Scan not done
Neurodevelopment	Generation R[24,25]	Higher risk for delayed fine motor development at 12 mo (HC)	SGA AC, EFW and AC:HC (not HC) and neuromotor developmental delay at 9-15 weeks. SGAHC associated with delayed fine motor development at 12 mo	SGA AC, EFW and AC:HC (not HC) and neuromotor developmental delay at 9-15 weeks. SGA HC associated with global developmental delays at 12 mo
	Raine[23]	Scan not done	No association with specific language impairment at 10yrs	Association not reported
Autism	Raine[27]	Scan not done	No association with HC and	Association not reported

			autism at 16 yrs	
	Hobbs *et al*[26]	Scan not done	No association with BPD, AC or FL and autism (mean age 7 years)	Scan not done
	Abel *et al* [28]	Scan not done	Group with lowest (and also highest) EFW at highest risk for autism by 17 yrs	Scan not done
Febrile convulsion	Generation R[29]	Association not reported	SGA trans cerebellar diameter associated with higher risk	SGA for trans cerebellar diameter, EFW, AC and FL (not HC) associated with higher risk
Blood pressure	Raine[30]	Scan not done	SGA for FL (not AC or HC) at 24 weeks (not 18) associated with higher systolic blood pressure (SBP) at 6 yrs	SGA for FL (not AC or HC) throughout associated with highersystolic blood pressure at 6 yrs
	Generation R[31]	Association not reported	No association between FL, AC, HC or EFW and SBP at 2 yrs	SGAFL associated with higher SBP at 2 yrs
	Project Viva[19]	Scan not done	No association between EFW and SBP at 3 yrs	Scan not done
Renal	Generation R[32]	Association not reported	No association between HC and AC and kidney volume at 2 yrs	No association between HC and AC and kidney volume at 2 yrs
Bone mineralisation	SWS[33,34]	Outcomes with SGA not reported		
	Generation R[35]	Association not reported	SGA for EFW associated with lower bone mineral density and content at 6 mo	SGA for EFW associated with lower bone mineral density and content at 6 mo

Table 3. Summary of adverse outcomes associated with increasing or decreasing growth in fetal measurements during the first or second half of pregnancy. *In this paper growth acceleration was linked to reduced risk for hayfever but growth failure not linked to increased risk for hayfever. CRL=Crown Rump Length, BPD=Biparietal Diameter, AC=Abdominal Circumference, EFW=Estimated Fetal Weight, HC=Head Circumference

	Growth before 20 weeks gestation (fetal outcome measured)	Antenatal growth after 20 weeks gestation (fetal outcome measured)
Accelerating growth	Lower spirometry at five[15] and ten years[16](CRL and BPD) Higher asthma risk at ten years[16](CRL and BPD) Higher eczema risk at ten years[16](CRL and BPD) Higher atopy at three years[18] (AC) Higher non atopic wheeze at three years[18] (HC)	Lower spirometry at ten years[16] (BPD and birth weight) Higher asthma risk at ten years[16] (BPD and birth weight) Lower hayfever risk at ten years[16] (BPD and birth weight)* Higher eczema risk at four years[17] (AC) Higher fat mass at six months[20] (EFW) Higher body mass index at adiposity peak[22] (EFW)
Decelerating growth	Lower spirometry (FVC) at ten years[16](CRL and BPD) Lower risk for hayfever at ten years[16](CRL and BPD) Higher risk for delay in fine motor development at 12months[25] (HC) Lower bone mineral content at birth and four years[34](FL and AC) Lower femoral neck section modulus (FL) [37]	Higher risk for several developmental outcomes[25] (HC) Higher risk for febrile convulsions [29] (EFW) Lower systolic blood pressure at three[19] years (FL) Lower bone mineral density at six months[35] (EFW) Lower bone mineral content at four years[33] (FL) Higher systolic blood pressure at three[19] and six[30] years (FL) Higherrisk for atopy at three years[18] (AC) Higher risk for atopic wheeze at three years[18] (AC) Lower femoral neck section modulus (FL) [37]

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FIGURE LEGEND

Figure 1. Quorum diagram showing how the papers included in this review were identified

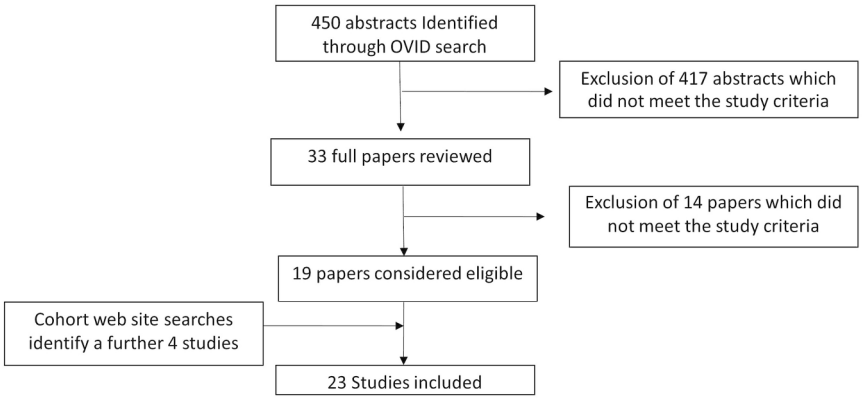

Figure 1. Quorum diagram showing how the papers included in this review were identified
190x142mm (300 x 300 DPI)

Fetal ultrasound measurements and associations with non-communicable diseases in childhood - A systematic review of an emerging literature

Farah AlKandari, Awaiss Ellahi, Lorna Aucott, Graham Devereux, Steve Turner

On line data supplement

Table E1. A summary of the findings of the papers included in this review. 95% confidence intervals are presented in square brackets.

Study	Outcome	Cohort name and inclusion/exclusion criteria	Sample size, age when outcome measured	Outcomes for size for a given gestation	Outcomes for change in fetal measurements
Associations between fetal size, maternal alpha-tocopherol and childhood asthma [1]	Respiratory and allergy	SEATON	578 five year olds	Inverse association between CRL (4%[0,9] risk reduction per mm) and BPD (12%[3, 20] risk reduction per mm) and asthma risk at five years. Positive association CRL and FEV_1 at five years (increase 4mls [1,7] per mm).	Change from "small" to "large" between 1st and 2nd trimester associated with reduced FEV_1 (73ml [19, 127]) and FEF_{25-75} (-0.12 l/s [0.003, 0.25]) at five years compared to persistently "large" group).
First and second trimester fetal size and asthma outcomes at age ten years [2]		SEATON	449 ten year olds	Inverse association between CRL and asthma risk at ten years (6% [1, 11] risk reduction per mm). Positive association between CRL (increase 6ml [0, 11] per mm) and BPD (increase 21ml [9, 33] per mm) and FEV_1 at ten years.	Change from "small" to "large" between 1st and 2nd trimester associated with reduced FEF_{25-75} (-0.21 l/s [0, 0.43]) and increase risk for symptomatic asthma (OR 5.1 [1.4, 19.2]) and eczema (OR 2.5 [1.2, 5.3]) at ten years. Converse change associated with reduced FVC (116mls [7, 225]) and reduced risk for hayfever (OR 0.10 [0.01, 0.82]).
Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years [3]		SWS	1184 three year olds	Associations with absolute size not reported	Increased BPD between 11 and 19 weeks associated with reduced non-atopic wheeze (10% reduced risk for each z score increase). Increased AC between 19 and 34 weeks associated with reduced risk for atopic wheeze and atopy (20% [0, 35] reduction in risk for both outcomes for each z score increase CI [0, 35] and [6, 31] respectively). Increased AC growth between 11 and 19 weeks associated with increased risk for atopy (risk increased by 46% [11, 93] for each z score increase)

Fetal and infant growth and asthma symptoms in preschool children: the Generation R Study [4]	Obesity	Generation R	5125 four year olds	No associations between absolute fetal measurements and symptoms identified.	No associations between change in fetal measurements and respiratory symptoms identified. Each z score increase in AC between 20 and 30 weeks associated with 5% [1,10] increased risk for eczema.
Fetal and postnatal growth and body composition at 6 months of age [5]		Generation R	252 six month old infants	No associations between fetal measurements and outcome detected	Increased EFW between 20 and 30 weeks associated with ~1% increase in fat mass at six months
Growth in foetal life and infancy is associated with abdominal adiposity at the age of 2 years: the Generation R study [6]		Generation R	481 two year olds	Reduced EFW at 30 weeks associated with increased abdominal fat deposition at two years of age (each z score reduced EFW associated with 3.7% [0.1, 7.2] increase in preperitoneal fat area)	No associations between change in fetal measurements and outcome detected
Fetal and infant growth and the risk of obesity during early childhood: the Generation R Study [7]		Generation R	6267 children where data collected in first four years was analysed	Second trimester EFW positively associated with peak weight velocity (PWV, 12.02 kg/year for lowest EFW quintile and 12.16 for highest quintile, $p<0.05$). Second trimester FL positively associated with peak height velocity (PHV, for highest quintile for FL 49.28 cm/year compared to 48.89 for the shortest FL quintile, $p<0.05$.	Increase in EFW between second and third trimester associated with increased body mass index at adiposity peak (17.68 and 17.52 kg/m^2 for the groups in the highest and lowest quartiles for EFW growth respectively)
First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study [8]		Generation R	1184 children, median age 6.0 years	Each increase in first trimester CRL z score was associated with a mean reduction in total fat mass of 0.3% [0.03, 0.57]. This association became non significant when the child's current weight was considered.	Associations with change in size not reported

Second trimester estimated fetal weight and fetal weight gain predict childhood obesity[9]		Project Viva	438 three year olds	Highest EFW quartile at 16 weeks had increased BMI z score at three years compared to lowest EFW quartile (mean 0.34 [0.07, 0.61] z score)	Associations with change in size not reported
Fetal head circumference growth in children with specific language impairment[10]	Neurodevelopmental outcomes	Raine	30 cases, 30 controls aged ≤10 years	No association between BPD and risk for outcome	Associations with change in size not reported
Fetal programming of infant neuromotor development: the generation R study [11]		Generation R	2965 infants aged 9-15 weeks	Reduced AC and EFW associated with increased risk for being in tertile with "poorest" neuromotor outcome (11% [3, 18] increased risk for each z score reduction in growth)	No association between change in fetal measurements and risk for outcome
Fetal growth from mid- to late pregnancy is associated with infant development: the Generation R Study[12]		Generation R	>3045 12 month olds	Reduced HC after 25 weeks gestation was associated with increased risk for delayed social development (18% [7, 23] increase risk per z score)	Reduced HC growth early-mid pregnancy associated with increased risk for delayed fine motor development (15% [2, 27] increased risk per z score reduction). Reduced HC growth from mid-late pregnancy associated with increased risk for delay in the following domains: social, self-help and fine motor. Risk for overall developmental delay increased l 15% [-13, +36] per z score reduction in HC and 35% [13, 51] per z score reduction in EFW.
Brief report: a preliminary study of fetal head circumference growth in autism spectrum disorder[13]	Autistic spectrum disorders (ASD)	Raine	14 cases and 56 controls in a population aged up to 16 years	No association between second trimester HC and risk for ASD	Associations with change in size not reported
A retrospective fetal ultrasound study of brain size in autism[14]		No cohort	45 cases 222 controls, mean age 7 years	No association between second trimester BPD, AC or FL and risk for ASD	Associations with change in size not reported

Deviance in fetal growth and risk of autism spectrum disorder[15]		No cohort	4283 cases and 36588 controls in a population aged 0-17 years	Highest risk for individuals EFW <-2 or >+2 z scores in second trimester (increased risk 70% [44, 101] and 49% [46, 76] respectively)	Associations with change in size not reported
Fetal growth retardation and risk of febrile seizures[16]	Febrile convulsions	Generation R	3372 (including 67 with febrile seizure) followed up to two years of age	Small transverse cerebellar diameter (ie lowest tertile) in second and third trimester associated with increased risk (OR 2.9 [1.3, 6.3] for second trimester measurement when compared to highest tertile). No association with HC. Small third trimester EFW, AC, BPD and FL associated with similar magnitude of increased relative risk.	Febrile seizures associated with reduced EFW after 16 weeks (-0.4 z score [CI not presented] ireduction in EFW between 16 and 34 weeks for cases compared to controls).
Prenatal ultrasound biometry related to subsequent blood pressure in childhood[17]	Blood pressure	Raine	707 six year olds	Inverse association between FL between 24 and 38 weeks and systolic blood pressure (SBP, each z score increase associated with mean reduction of 1-2mmHg)	Each z score increase in FL growth between 18 and 38 weeks was associated with a 0.7mmHg (standard error 0.5) reduction in SBP
Second trimester estimated fetal weight and fetal weight gain predict childhood obesity[9]		Project Viva	438 three year olds	No association between absolute second trimester size and systolic blood pressure	Compared to those in the lowest quartile for second trimester EFW and birth weight, there were reductions in the following groups growth deceleration (highest to second lowest quartile, 5.5 mmHg [1.1, 10.0]), growth acceleration (second lowest to second highest quartile, 4.6mmHg [0.1, 9.0]) and remaining in the second lowest tertile (5.0 [0.3, 9.7]
Fetal and postnatal growth and blood pressure at the age of 2 years. The		Generation R	566 two year olds	Association between increased FL at 30 weeks (but not 20 weeks) and reduced SBP at two years (mean	No association between SBP at two years and change in FL between 20 and 30 weeks gestation. Each z score increase in

Generation R Study[18]				reduction 1.2 mmHg [0.3, 2.1] per increased in z score). No association with HC, AC or EFW.	weight between 20 weeks and 2 years associated with increased SBP (mean increase 0.7 mmHg [0.01, 1.3]). Each z score increase in length between 30 weeks gestation and 2 years associate with increased SBP (mean increase 1.0[0.3, 1.7] mmHg)
First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study[8]		Generation R	1184 children, median age 6.0 years	Each increase in first trimester CRL z score was associated with a mean reduction in diastolic BP of 0.43 mm Hg [0.01, 0.84]. This association became non significant when the child's current weight was considered.	Associations with change in size not reported
First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study[8]	Metabolic outcomes	Generation R	1184 children, median age 6.0 years	Each increase in first trimester CRL z score was associated with a mean reduction in cholesterol of 0.05 mmol/L [0, 0.10] and of low density lipoprotein by mean 0.04 mmol/L [0, 0.09].	Associations with change in size not reported
Tracking and determinants of kidney size from fetal life until the age of 2 years: the Generation R Study[19]	Renal size	Generation R	688 two year olds	Increased third (but not second) trimester HC and AC were positively associated with kidney volume at two years of age, e.g. each z score increase in HC associated with mean increase in renal volume of 1.3 cm^3 [0.2, 2.4]	No association between change in fetal measurements between second and third trimester and renal size.
Intrauterine growth and postnatal skeletal development: findings from the Southampton Women's Survey[20]	Bone mineralisation	SWS	380 four year olds	FL at 19 and 34 weeks positively associated with increased bone mineral content (BMC, association expressed as correlation coefficients, 0.13 and 0.31 respectively). Associations with AC	Change in FL between 19 and 34 weeks positively associated with increased BMC (association expressed as correlation coefficient, 0.29)

				of lesser and sometimes non-significant magnitude	
Different indices of fetal growth predict bone size and volumetric density at 4 years of age[21]		SWS	628 four year olds	Associations with absolute measurements and BMC not reported	Growth in FL and AC between 11th and 19th gestational weeks positively associated with BMC at birth and at four years of age (regression coefficient approximately 0.25-0.35 for all comparisons)
Foetal and postnatal growth and bone mass at 6 months: the Generation R Study[22]		Generation R	252 six month old infants	EFW at 30 weeks gestation was positively associated with total body bone mineral density at six months of age (2% [0.1, 0.3*, increase per kg increase in EFW) *as reported in paper, presumed to be 3.0	Increasing EFW between 20 and 30 weeks (but not 30 weeks and term) associated with total body bone mineral density at six months of age (mean increase 0.5% [0.1, 0.8] per z score increased EFW)
Fetal and infant growth predict hip geometry at 6 y old: findings from the Southampton Women's Survey[23]	Hip geometry	SWS	493 six year olds	Association with size not reported	Increasing FL between 19 and 34 weeks associated with femoral neck section modulus (an index of bending strength) – regression coefficient 0.26 cm^3 per z score increase.

SWS=Southampton Women's Study, FEV1=forced expired volume in one second, CRL=crown rump length, BPD=biparietal diameter, HC=head circumference, FL=femur length, AC=abdominal circumference, EFW=estimated fetal weight

Table E2. Quality control. For each component and the global score, 1=strong, 2=moderate and 3=weak design.

Study	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawals and Drop outs	Global Rating
Associations between fetal size, maternal alpha-tocopherol and childhood asthma [1]	2	2	2	1	1	2	1
First and second trimester fetal size and asthma outcomes at age ten years [2]	2	2	2	1	1	3	2
Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years [3]	3	2	2	1	1	2	2
Fetal and infant growth and asthma symptoms in preschool children: the Generation R Study [4]	3	2	2	1	1	2	2
Fetal and postnatal growth and body composition at 6 months of age [5]	3	2	3	1	1	2	3
Growth in foetal life and infancy is associated with abdominal adiposity at the age of 2 years: the Generation R study [6]	3	2	2	1	1	2	2
Fetal and infant growth and the risk of obesity during early childhood: the Generation R Study [7]	3	2	2	1	1	2	2
Second trimester estimated fetal weight and fetal weight gain predict childhood obesity [9]	3	2	2	1	1	2	2
First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study [8]	3	2	2	1	1	2	2
Fetal head circumference growth in children with specific language impairment [10]	3	2	3	1	1	2	3
Fetal programming of infant neuromotor development: the generation R study [11]	3	2	2	1	1	2	2

Fetal growth from mid- to late pregnancy is associated with infant development: the Generation R Study[12]	3	2	2	1	1	2	2
Brief report: a preliminary study of fetal head circumference growth in autism spectrum disorder[13]	3	3	3	1	1	2	3
A retrospective fetal ultrasound study of brain size in autism[14]	3	3	3	1	1	2	3
Deviance in fetal growth and risk of autism spectrum disorder[15]	2	2	2	1	1	2	2
Fetal growth retardation and risk of febrile seizures[16]	3	2	2	1	1	2	2
Prenatal ultrasound biometry related to subsequent blood pressure in childhood[17]	3	2	3	1	1	2	3
Fetal and postnatal growth and blood pressure at the age of 2 years. The Generation R Study[18]	3	2	2	1	1	2	2
Tracking and determinants of kidney size from fetal life until the age of 2 years: the Generation R Study[19]	3	2	3	1	1	2	3
Intrauterine growth and postnatal skeletal development: findings from the Southampton Women's Survey[20]	3	2	3	1	1	2	3
Different indices of fetal growth predict bone size and volumetric density at 4 years of age[21]	3	2	3	1	1	2	3
Foetal and postnatal growth and bone mass at 6 months: the Generation R Study[22]	3	2	3	1	1	2	3
Fetal and infant growth predict hip geometry at 6 y old: findings from the Southampton Women's Survey[23]	3	2	3	1	1	2	3

Case-control studies[13-15] were given a weak rating due to study design. Cohort studies other than SEATON were given a weak rating since evidence on the effect of drop outs was not presented. For selection bias, only the SEATON study presented details of mothers who did and did not participate (moderate rating), the remaining studies scored weak rating. The SEATON cohort received a weak rating for withdrawal and drop outs due to a <50% follow up at ten years[2]. Blinding was assumed to be strong since the ultrasound measurements were made before postnatal outcomes were known. Data collection methods were all valid.

Table E3. Search terms used and number of results.

Search Number #	Searches	Results	Search Type
1	Only Child/ or Child/ or Child, Preschool/ or Child Development	1560833	Advanced
2	Follow-up Studies/ or Cohort Studies/ or Cross-sectional studies/ or Longitudinal studies/ or Prospective studies/ or Epidemiological studies/	1001238	Advanced
3	fetal growth.mp or Fetal Development/	22848	Advanced
4	Infant/ or Infant, Newborn/	936554	Advanced
5	humans/	13588386	Advanced
6	1 + 2 + 3 + 4 + 5	450	Advanced

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