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

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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]		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]	Obesity	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

REFERENCES

1. Turner SW, Campbell D, Smith N, et al. Associations between fetal size, maternal alpha-tocopherol and childhood asthma. *Thorax* 2010;**55:**555-61.
2. Turner S, Prabhu N, Danielian P, et al. First and second trimester fetal size and asthma outcomes at age ten years. *Am J Respir Crit Care Med* 2011;**184:**407-413.
3. Pike KC, Crozier SR, Lucas JS, et al. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. *Thorax* 2010;**65:**1099-1106.
4. Sonnenschein-van der Voort AM, Jaddoe VW, Raat H, et al. Fetal and infant growth and asthma symptoms in preschool children: the Generation R Study. *Am J Respir Crit Care Med* 2012;**185:**731-7.
5. Ay L, Van Houten VA, Steegers EA, et al. Fetal and postnatal growth and body composition at 6 months of age. *J Clin Endocrinol Metabol* 2009;**94:**2023-30.
6. Durmus B, Mook-Kanamori DO, Holzhauer S, et al. Growth in foetal life and infancy is associated with abdominal adiposity at the age of 2 years: the generation R study. *Clin Endocrinol* 2010;**72:**633-40.
7. Mook-Kanamori DO, Durmus B, Sovio U, et al. Fetal and infant growth and the risk of obesity during early childhood: the Generation R Study. *Eur J Endocrinol* 2011;**165:**623-30.
8. Jaddoe VW, de Jonge LL, Hofman A, Franco OH, Steegers EA, Gaillard R. First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. *Brit Med J* 2014;**348:**g14.
9. Parker M, Rifas-Shiman SL, Oken E, Belfort MB, Jaddoe VW, Gillman MW. Second trimester estimated fetal weight and fetal weight gain predict childhood obesity. *J Pediatr* 2012;**161:**864-70.
10. Whitehouse AJ, Zubrick SR, Blair E, Newnham JP, Hickey M. Fetal head circumference growth in children with specific language impairment. *Arch Dis Child* 2012;**97:**49-51.
11. van Batenburg-Eddes T, de Groot L, Steegers EA, et al. Fetal programming of infant neuromotor development: the generation R study. *Pediatr Res* 2010;**67:**132-7.
12. Henrichs J, Schenk JJ, Barendregt CS, et al. Fetal growth from mid- to late pregnancy is associated with infant development: the Generation R Study. *Dev Med Child Neurol* 2009;**52:**644-51.
13. Whitehouse AJ, Hickey M, Stanley FJ, Newnham JP, Pennell CE. Brief report: a preliminary study of fetal head circumference growth in autism spectrum disorder. *J Autism Dev Disord* 2011;**41:**122-9.
14. Hobbs K, Kennedy A, Dubray M, et al. A retrospective fetal ultrasound study of brain size in autism. *Biological Psychiatry* 2007;**62:**1048-55.
15. Abel KM, Dalman C, Svensson AC, et al. Deviance in fetal growth and risk of autism spectrum disorder. *Am J Psychiatry* 2013;**170:**391-8.
16. Visser AM, Jaddoe VW, Hofman A, et al. Fetal growth retardation and risk of febrile seizures. *Pediatr* 2010;**126**.
17. Blake KV, Gurrin LC, Beilin LJ, et al. Prenatal ultrasound biometry related to subsequent blood pressure in childhood. *J Epidemiol Comm Health* 2002;**56:**713-8.

18. van Houten VA, Steegers EA, Witteman JC, Moll HA, Hofman A, Jaddoe VW. Fetal and postnatal growth and blood pressure at the age of 2 years. The Generation R Study. *J Hypertension* 2009;**27:**1152-7.
19. Geelhoed JJ, Verburg BO, Nauta J, et al. Tracking and determinants of kidney size from fetal life until the age of 2 years: the Generation R Study. *Am J Kidney Dis* 2009;**53:**248-58.
20. Harvey NC, Mahon PA, Robinson SM, et al. Different indices of fetal growth predict bone size and volumetric density at 4 years of age. *J Bone Miner Res* 2010;**25:**920-7.
21. Harvey NC, Mahon PA, Kim M, et al. Intrauterine growth and postnatal skeletal development: findings from the Southampton Women's Survey. *Paediatr Perinatal Epidemiol* 2012;**26:**34-44.
22. Ay L, Jaddoe VW, Hofman A, et al. Foetal and postnatal growth and bone mass at 6 months: the Generation R Study. *Clin Endocrinol* 2011;**74:**181-90.
23. Harvey NC, Cole ZA, Crozier SR, et al. Fetal and infant growth predict hip geometry at 6 y old: findings from the Southampton Women's Survey. *Pediatr Res* 2013;**74:**450-6.