

Article Type: Original

Fetal growth trajectory and risk for eczema in a Saudi population

Amel AlMakoshi^{1,2}, Awaiss Ellahi¹, Bala Sallout³, Graham Devereux¹, Steve Turner¹

¹Child Health, University of Aberdeen, Aberdeen, UK

²General Administration of Research and Studies, Ministry of Health, Riyadh, Saudi Arabia

³Maternal-Fetal Medicine Department, Women`s Specialized Hospital, King Fahad Medical City, Riyadh, Saudi Arabia

⁴Department of Clinical Biochemistry, King Fahad Medical City, Riyadh, Saudi Arabia

Running title: Late fetal growth and early eczema

Correspondence to: Dr Turner, Child Health, Royal Aberdeen Children`s Hospital, Aberdeen, AB25 2ZG, UK. Tel +44 1224 438470. s.w.turner@abdn.ac.uk

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ABSTRACT

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Pediatr Allergy Immunol

Background. Recent studies in Western cohorts have identified associations between increasing fetal abdominal circumference (AC) during mid-pregnancy and increased risk for eczema and atopy. We sought to replicate these findings in a Saudi population where antenatal environmental exposures are different compared to Western countries

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12380

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Methods. A Saudi birth cohort was recruited to relate maternal dietary intake and fetal growth to wheeze, eczema and rhinitis in the first two years. Fetal size was determined from routine ultrasound scan measurements in the second and third trimester and birth weight was noted. Parent-reported outcomes during the first two years were acquired by telephone administered questionnaire.

Results. There were 1076 mothers recruited. AC was determined in 562 for the second, in 632 for the third and 281 for both second and third trimesters. A history of eczema was determined in 814 children at two years of age. There was an inverse relationship between change in abdominal circumference between the second and third trimesters for eczema (OR 0.66 per z score increase in AC [95% CI 0.49, 0.89]), and the quartile with the greatest faltering growth were at increased risk compared to other groups ($p \leq 0.045$). Change in fetal size between the third trimester and birth was not associated with altered eczema risk. There were no associations between fetal growth and wheeze at age two years.

Conclusions. Our findings contrast observations made in Western populations but nonetheless suggest that factors associated with changing fetal growth trajectory in the second half of pregnancy is also relevant to atopy development on the global setting.

Key words. Eczema, Fetus, In utero growth retardation, Saudi Arabia

Requests for offprints should be sent to Dr Turner, Child Health, Royal Aberdeen Children's Hospital, Aberdeen, AB25 2ZG, UK. Tel +44 1224 438470. s.w.turner@abdn.ac.uk

INTRODUCTION

Eczema is a non-communicable disease whose prevalence approaches 30% in some populations and where many factors are implicated in causation (1). The signs and symptoms of eczema are apparent from early infancy in the majority of individuals and this implicates mechanisms acting in early in life in the underlying aetiology (1). Genetic factors such as filaggrin(2) and environmental

Accepted Article

exposures to parental smoking(3), cows' milk infant formula(4) and early weaning diet (5) have all been associated with increased eczema risk. Increased birth weight is associated with increased risk for eczema (6) and recent studies have found associations between accelerating fetal size after the first trimester and increased the risk for eczema in childhood(7, 8). Accelerated growth between the first and second trimesters(7) and a relative increase in abdominal circumference between the second and third trimesters(8) have been associated with increased risk for eczema. In keeping with the findings previously described, a third cohort has observed associations between accelerating abdominal circumference before and after the second trimester and increased risk for skin prick positivity (9) whilst faltering growth by the second trimester is associated with reduced risk for hayfever in ten-year-olds(7).

The mechanism underlying the associations between accelerating fetal growth and increased risk for eczema (and atopy and hayfever) is likely to be complex and might involve predictive adaptive responses(10), a paradigm where there is mismatch between the environment anticipated, and prepared for, by the fetus (as determined by antenatal cues) and the actual post natal environment leads to increased risk for non-communicable disease such as eczema. Importantly, the observations to date linking antenatal fetal growth to outcomes such as eczema risk, are limited to populations in Australia, the Netherlands, the USA and UK where the antenatal environment and potential confounders are similar. Studies in non-Western populations, where antenatal environmental cues may differ, may give new understanding of the developmental origins of disease(11).

We have recruited a birth cohort in Saudi Arabia to relate maternal diet during pregnancy to postnatal asthma and eczema outcomes. We have retrospectively obtained routinely acquired fetal ultrasound measurements from this cohort and here test the primary hypothesis that accelerating growth in abdominal circumference is associated with increased risk for eczema. We have

previously observed a negative associations between maternal vitamin E intake during pregnancy and eczema risk at age two years in an Aberdeen cohort (12)and here tested a secondary hypothesis that reduced maternal intake of this nutrient would be associated with reduced eczema in a Saudi population.

METHODS

Study design

A birth cohort was recruited between February 2010 and January 2011 from pregnant mothers attending antenatal clinic in King Fahad Medical City Hospital in Riyadh. The cohort was designed to relate maternal dietary exposures to post natal allergy outcomes. There was no selection for maternal allergic conditions (i.e. asthma, eczema or hayfever). At recruitment, details of maternal and paternal allergic conditions, smoking status and socio-economic status were determined. Routinely acquired fetal ultrasound scan measurements were obtained retrospectively during 2013. At birth, the infant weight was recorded and a note was made of whether the birth occurred during the dust season (spring) when air quality is known to be poor. Telephone interviews were used to capture outcomes when the child was one and two years of age. The administered questionnaire was based on that used in the ISAAC studies translated into Arabic, the method of translation for the follow up questionnaires followed the guidelines recommended by the ISAAC programme for questionnaire translation. The study was approved by the ethics committee of King Fahad Medical City, Riyadh, Saudi Arabia.

Fetal ultrasound measurements

Gestational ascertainment was by date of last menstrual period or when these were uncertain, by first trimester ultrasound scan. First trimester scans were carried out in obstetrician's clinic and were not usually available on record at King Fahad Medical City (KFMC). Pregnant mothers are routinely referred to KFMC for fetal anomaly scans in the second or third trimester; the second trimester was defined as between 14 and 28 weeks and the third trimester >28 weeks gestation. Scans were also carried out in both the second and third trimester for clinical indications, eg breech presentation, low lying placenta, suspicion of small for gestational age. The iU22 xMATRIX ultrasound System (Phillips Healthcare, MA, USA) was used for fetal measurements which included: abdominal circumference (AC), head circumference (HC), femur length (FL) and estimated fetal weight (EFW, calculated from AC, BPD and FL by the method described by Hadcock (13). The ratio of HC:AC was also derived to give insight into asymmetrical fetal growth (14). Obvious outliers were removed after inspection of the plot of measurements against gestation. Z scores were created to standardise measurement against gestation. Inter- and intra-operator variability for ultrasound fetal measurements is less than 10% (15).

Maternal dietary intake

Maternal dietary intake was characterised using a validated semi-quantitative food frequency questionnaire (SFFQ). The SFFQ was designed and validated for use in Arab countries and previously used in a study conducted in Kuwait and the United Arab Emirates (16). The correlation coefficient of nutrient intake calculated against the FFQ with and without portion size taken into account was over 0.9. The correlation coefficients for individual nutrients was low and varied among nutrients, with the highest correlation being for vitamin C (0.23) and lowest was for total folate (0.16) The SFFQ questionnaire consisted of 164 questions divided into 12 sections covering 6 food groups, vitamin

and mineral supplementation, beverages and mixed dishes. The mothers were asked the frequency of consumption of the food groups in the last year. The frequency was divided by day, week and month and the number of times within that time frame based on portion size. Answer options were: No or less than once a month, 1-3/month, once a week, 2-4/week, 5-6/week, once a day, 2-3/day, 4-5/day or ≥ 6 /day. The SFFQ was slightly modified with 14 additional food items. The additional items were local dishes eaten in Riyadh with details of these items added (with their ingredients and measurements) to be included in the food frequency analyses database. Energy-adjusted dietary intakes were derived and expressed as quartiles. Based on our earlier work(12, 17), dietary vitamin E intake was the primary nutrient of interest.

Analysis

Differences between groups were compared using chi square test, student's t-test or Mann Whitney U test where appropriate. The primary outcomes were history of eczema by two years (defined as an affirmative answer at one or two years, or both, to the question "has your child been diagnosed with eczema by a doctor?) and a history of wheeze by the second birthday (defined as an affirmative answer to the question asked in the questionnaire at one or two years, or both, "has your child wheezed in the last year?"). The primary predictor variable was change in AC between second and third trimester. Logistic regression models were used to relate the outcomes to change in fetal size (i.e. z scores for measurements in the second and third trimester and z scores in the third trimester and birth weight) adjusting for sex, presence of maternal condition (i.e. maternal eczema for childhood eczema and maternal asthma for childhood wheeze), being first born, maternal smoking and monthly household income (used as an index of socioeconomic status). The same approach was used to relate outcomes to absolute fetal size. Standard statistical software was used (SPSS version 22.0.0) and significance was assumed when $p < 0.05$.

RESULTS

Study Subjects

There were 1076 mothers recruited and 1063 live born infants delivered. AC was determined in the 913 pregnancies including during the second and third trimester in 562 and 632 pregnancies and at both gestation in 281 pregnancies. The mean (standard deviation) gestation for second trimester scan was 21.2 (3.4) weeks and for the third trimester was 33.8 (2.9) weeks. Vitamin E intake was highest among the lower income groups ($p=0.031$, see table 1 in supplementary material) but was not related to fetal measurements or early childhood eczema or wheeze. Questionnaire data were available at two years of age for 814 children. Table 1 presents details of the whole population and for subgroups where AC was available in the second, third and both trimesters; the subgroup where data were available in both second and third trimesters were more likely to have mothers with eczema and less likely to be born during the dust season. Table 2 compares details between the 154 children with a history of eczema and the 660 without a history of eczema, those with a maternal history of eczema were at increased risk for eczema (odds ratio 2.2 [95% confidence interval 1.2, 4.1] $p=0.009$).

Fetal growth and risk for outcomes

Increasing AC between the second and third trimesters was associated with reduced risk for eczema (OR 0.65 per z score increase [0.48, 0.89] $p=0.007$), and the quartile with most faltering AC growth were at increased risk for eczema compared to other groups, figure 1. There was no difference in gestational age at second or third trimester ultrasound scan when individuals were stratified by quartile of growth in AC (see table 2 in supplementary material) Eczema risk increased with increasing HC:AC ratio between the second and third trimesters (mean increase in z score HC:AC 1.54 [1.09, 2.19] $p=0.014$) The risk of eczema increased across quartile in growth for HC:AC but was

not significant (data presented in table 3 in the supplementary material). There was no association between risk for eczema and (i) change in other fetal measurements between the second and third trimester (ii) change in third trimester EFW and birth weight or (iii) change in third trimester HC and head circumference at birth. There were no associations between a history of wheeze and change in fetal size before or after the third trimester scan measurement.

Absolute fetal size and risk for outcomes

No second or third trimester fetal measurements or birth measurement were associated with altered risk for eczema or wheeze.

DISCUSSION

The aim of this study was to explore whether the association between change in fetal abdominal circumference and eczema risk, which has been reported in Western populations, can be replicated in a population from Saudi Arabia. The antenatal environment for fetuses in our cohort contrasts to Western cohorts in terms of the very low prevalence of maternal smoking, the low prevalence of maternal eczema and seasonal atmospheric pollution from dust storms. Additionally, the association between socio-economic status and maternal dietary vitamin E intake was the opposite to that observed in Western countries, i.e. Saudi women from the lower income bracket have a higher dietary intake vitamin E. The main finding was that we observed an association between change in fetal abdominal circumference between the second and third trimesters and eczema by two years of age, however the direction of the association in our population was the opposite to that observed in Western cohorts. These findings support the paradigm that factors affecting antenatal growth are also associated with the development of post natal eczema, but the direction of the association might depend on environmental cues.

Our findings confirm previously described association between change in abdominal circumference between the second and third trimesters and altered eczema risk (8) and atopy risk (9) but the novel finding is that the direction of the relationship is reversed in the Saudi population compared to populations in the Netherlands and UK. A recent systematic review has identified apparently inconsistent findings between antenatal growth and postnatal outcomes between different populations(11), for example blood pressure has been positively and negatively associated with femur length, and the results presented here compliment the findings of the systematic review and support the principle of predictive adaptive responses or developmental plasticity where a fetus might reach more than one post natal phenotype depending on the antenatal cues experienced at critical points of development.

This study was not designed to explain the mechanism(s) important to the association between fetal growth and eczema risk but our findings might give some insight. First, the lack of an association between growth between the third trimester and term and eczema suggests that growth after 33 week's gestation might not be important to eczema. Growth in abdominal circumference before the second trimester, which was not captured in the present study, has been previously linked to increased risk for eczema (7) and atopy (9) and together, the literature suggests that factors which influence fetal growth between 11 and 33 weeks gestation may also be important to the development of eczema. A second insight into the underlying mechanism(s) is that the association with increasing HC:AC ratio between the second and third trimesters and eczema risk, which suggests that asymmetrical fetal growth, and not a primary intra-abdominal process, may be relevant to eczema causation. The findings of our study might suggest that the "brain sparing effect", where cerebral growth is preferentially preserved at the expense of abdominal growth(18) leading to increased HC:AC ratio, also leads to increased risk for eczema. The opening of the ductus venosus to prioritise delivery of nutrients to the brain (19) results in depletion of liver glycogen

stores and reduced liver size may also lead to non-communicable diseases such as eczema but this would not explain the association between accelerated AC growth and eczema seen in Western cohorts(7). In a similar manner, the suggestion that increased thymic growth associated with the brain sparing effect might explain the association between accelerated fetal growth and increased risk for eczema in Western cohorts is not supported by our findings and furthermore there is no evidence of an association between thymic size at birth and later allergic symptoms (20). The mechanism for a non-communicable disease such as eczema will be complex, epigenetic factors are likely to be implicated(21), and our study adds to the evidence that the antenatal environment is important.

There are some factors which should be considered when interpreting these results. The main strength of this study is that it is the first to relate antenatal measurements to a post natal outcome in a non-Western population, and the findings exactly mirror findings in Western populations giving a novel insight into how different antenatal cues may have different implications for human non-communicable diseases. A striking difference between Western countries and the Saudi population is that vitamin E intake increases with increasing affluence in the former but the reverse association is seen for the Saudi population, where traditional foods rich in vitamin E, such as nuts, are more affordable and “Westernised” foods with lower vitamin E content are less available to low income households. A second strength is that those individuals followed were representative of the original cohort; drop out in Western populations is usually more prevalent among children from less affluent communities and whose parents smoke. Second trimester ultrasound examinations were only repeated in the third trimester in a minority of individuals, and due to clinical indications and this explains why paired AC measurements were available in relatively few pregnancies but we have demonstrated that antenatal and birth measurements were similar for pregnancies where second and third trimester measurements were available and the whole cohort. Infants where second and

third trimester measurements were available were more likely to have mothers with eczema and less likely to be born in the dust season, but these chance differences are not plausibly linked to fetal growth. One potential weakness to this study is that outcomes were ascertained by parent report via telephone questionnaire and eczema was not confirmed by a researcher or clinician but despite this we were able to link childhood eczema to both maternal eczema and antenatal growth in abdominal circumference and this suggests that we accurately identified the presence or absence of eczema with good precision.

In summary, we have tested our hypothesis that acceleration in growth in antenatal abdominal circumference was linked to increased eczema risk and we found that precisely the opposite was present in our population. Our study suggests that comparisons of the relationship between fetal growth and post natal outcomes between populations living in diverse environments will benefit understanding of the developmental origins of health and disease.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Abdulwahed AlDehaimi, Department of Clinical Biochemistry, King Fahad Medical City, for his assistance in plasma nutrient measurements.

REFERENCES

1. Bieber T. Atopic dermatitis. *N Engl J Med* 2008; 358: 1483-1494.
2. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; 38: 441-446.
3. Kramer U, Lemmen CH, Behrendt H, et al. The effect of environmental tobacco smoke on eczema and allergic sensitization in children. *Br J Dermatol* 2004; 150: 111-118.

4. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001; 45: 520-527.
5. Host A, Halken S, Muraro A, et al. Dietary prevention of allergic diseases in infants and small children. *Pediatr Allergy Immunol* 2008; 19: 1-4.
6. Panduru M, Salavastru CM, Panduru NM, Tiplica GS. Birth Weight and Atopic Dermatitis; Systematic Review and Meta-analysis. *Acta Dermatovenerol Croat* 2014; 22: 91-96.
7. Turner S, Prabhu N, Danielan P, et al. First- and second-trimester fetal size and asthma outcomes at age 10 years. *Am J Respir Crit Care Med* 2011; 184: 407-413.
8. 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: 731-737.
9. 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.
10. Gluckman PD, Hanson M, Spencer HG. Predictive adaptive responses and human evolution. *Trends Ecol Evol* 2005; 20: 527-533.
11. Alkandari F, Ellahi A, Aucott L, Devereux G, Turner S. Fetal ultrasound measurements and associations with postnatal outcomes in infancy and childhood: a systematic review of an emerging literature. *J Epidemiol Comm Health* 2015; 69: 41-48.
12. Martindale S, McNeill G, Devereux G, Campbell D, Russell G, Seaton A. Antioxidant intake in pregnancy in relation to wheeze and eczema in the first two years of life. *Am J Respir Crit Care Med* 2005; 171: 121-128.
13. Hadlock FP, Harrist RB, Carpenter RJ, Deter RL, Park SK. Sonographic estimation of fetal weight. The value of femur length in addition to head and abdomen measurements. *Radiology* 1984; 150: 535-540.
14. Campbell S, Thoms A. Ultrasound measurement of the fetal head to abdomen circumference ratio in the assessment of growth retardation. *Br J Obstet Gynaecol* 1977; 84: 165-174.
15. Sarris I, Ioannou C, Chamberlain P, Ohuma E, Roseman F, Hoch L, Altman DG, Papageorgiou AT. International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). Intra- and interobserver variability in fetal ultrasound measurements. *Ultrasound Obstet Gynecol* 2012; 39: 266-273.
16. Dehghan M, Al-Hamad N, McMillan CR, Prakash P, Merchant AT. Comparison of a semi-quantitative food frequency questionnaire with 24-hour dietary recalls to assess dietary intake of adult Kuwaitis. *Saudi Med J* 2009; 30: 159-161.
17. Turner SW, Campbell D, Smith N, et al. Associations between fetal size, maternal {alpha}-tocopherol and childhood asthma. *Thorax* 2010; 65: 391-397.

Table 1. Details of the whole cohort and subgroups where abdominal circumference was determined in the second and third trimesters. *p<0.05 compared to the whole cohort

		Whole cohort	Second trimester abdominal circumference determined	Third trimester abdominal circumference determined	Second and third trimester abdominal circumference determined
Mean maternal age (SD), years		28.3 (5.3) n=1076	28.1 (5.1) n=518	28.1 (5.3) n=629	28.0 (5.3) n=279
Monthly household income (Riyal)	<3000	10% (103/1076)	10% (57/558)	8% (53/629)	8% (24/279)
	3000-4999	20% (214/1076)	20% (106/558)	20% (127/629)	20% (55/279)
	5000-7999	32% (345/1076)	35% (194/558)	31% (197/629)	33% (92/279)
	8000-10000	20% (213/1076)	20% (91/558)	21% (131/629)	22% (61/279)
	>10000	18% (201/1076)	16% (91/558)	19% (121/629)	17% (47/279)
% Maternal history of eczema		6% (63/1076)	7% (41/558)*	5% (34/629)	8% (23/279)*
Median parity (interquartile range)		1 (0-9) n=878	1 (0-9) n=474	1 (0-9) n=505	1 (0-9) n=246
% born in dust season		31% (312/1012)	32% (168/529)	26% (152/595)*	22% (58/269)*
% maternal smoking during pregnancy		2.2% (24/1076)	2.7% (15/558)	1.9% (12/629)	1.4% (4/279)
Mean second trimester z score abdominal circumference (SD)		0.0 (1.0) n=562	0.0 (1.0) n=562	0.0 (1.0) n=292	-0.1 (0.9) n=281
Mean third trimester z score abdominal circumference (SD)		0.0 (1.0) n=632	0.0 (1.0) n=281	0.0 (1.0) n=632	0.0 (1.0) n=281
Mean birth weight z score (SD)		0.0 (1.0) n=961	0.0 (1.0) n=494	0.0 (1.0) n=563	0.0 (1.0) n=248

Mean birth length z score (SD)	0.0 (1.0) n=933	0.0 (0.9) n=480	0.0 (1.0) n=550	0.0 (1.1) n=244
Mean head circumference at birth (SD)	0.0 (1.0) n=917	0.0 (1.0) n=444	0.0 (1.0) n=536	0.0 (0.9) n=239
% male sex	52% (547/1063)	51% (284/552)	51% (315/624)	49% (135/278)
% with history of eczema ever	19% (154/814)	20% (83/419)	18% (87/489)	18% (39/219)
% with history of wheeze ever	44% (360/814)	44% (183/419)	44% (218/489)	45% (99/219)

18. Bellotti M, Pennati G, De Gasperi C, Bozzo M, Battaglia FC, Ferrazzi E. Simultaneous measurements of umbilical venous, fetal hepatic, and ductus venosus blood flow in growth-restricted human fetuses. *Am J Obstet Gynecol* 2004; 190: 1347-1358.

19. Godfrey KM, Haugen G, Kiserud T, et al. Fetal liver blood flow distribution: role in human developmental strategy to prioritize fat deposition versus brain development. *PLoS ONE [Electronic Resource]* 2012; 7: e41759.

20. Benn CS, Jeppesen DL, Hasselbalch H, et al. Thymus size and head circumference at birth and the development of allergic diseases. *Clin Exp Allergy* 2001; 31: 1862-1866.

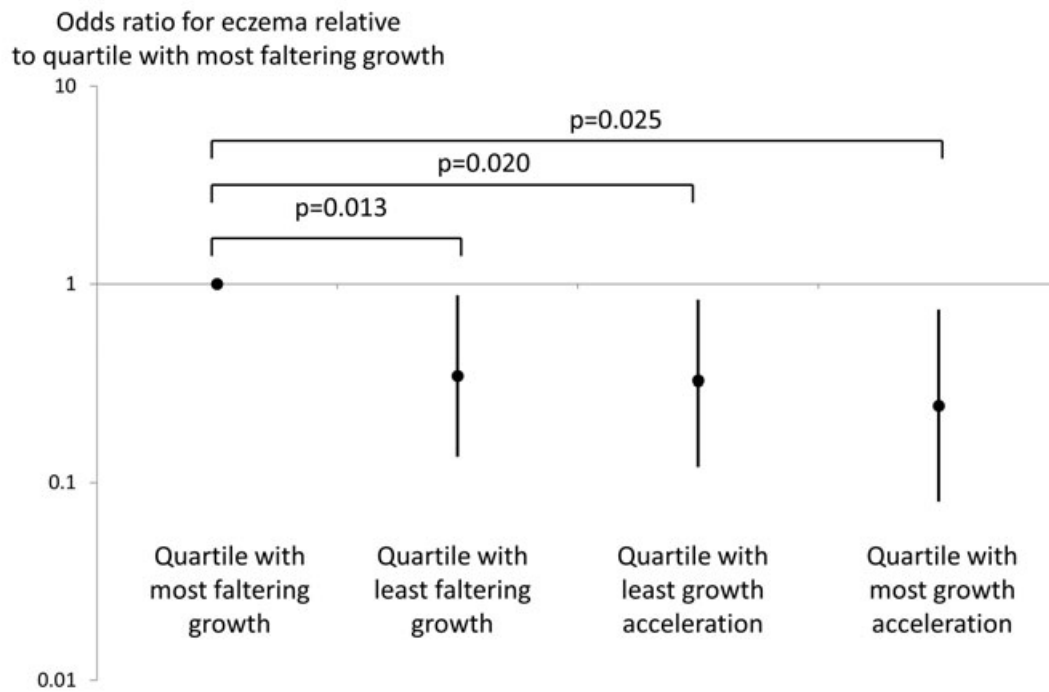
21. Gluckman PD, Hanson MA, Low FM. The role of developmental plasticity and epigenetics in human health. *Birth Defects Research.Part C, Embryo Today: Reviews* 2011; 93: 12-18.

Table 2. Details of children with and without a history of eczema. *p<0.05 compared to children with no history of eczema.

		Eczema at age two years	No eczema at age two years
Mean maternal age (SD), years		28.8 (4.8) n=154	28.3 95.4) n=660
Monthly household income (Riyal)	<3000	8% (12/154)	9% (62/660)
	3000-4999	16% (25/154)	21% (135/660)
	5000-7999	35% (54/154)	31% (204/660)
	8000-10000	25% (38/154)	19% (124/660)
	>10000	16% (25/154)	20% (135/660)
% Maternal history of eczema		11% (17/154)*	5% (35/660)
Median parity (interquartile range)		2 (0, 3)	1 (0, 3)
% born in dust season		28% (42/149)	31% (198/649)
% maternal smoking during pregnancy		2% (3/154)	2% (14/660)
Mean second trimester z score abdominal circumference (SD)		0.06 (0.91) n=86	-0.01 (0.98) n=352
Mean third trimester z score abdominal circumference (SD)		-0.15 (0.98) n=87	-0.04 90.97) n=402
Mean birth weight z score (SD)		0.0 (1.0) n=140	0.0 (1.0) n=603
Mean birth length z score (SD)		0.0 (1.0) n=138	0.0 (1.0) n=590
Mean head circumference at birth (SD)		0.0 (0.9) n=134	0.0 (1.0) n=582
% male sex		58% (90/154)	53% (347/660)
% with history of wheeze ever		45% (69/154)	44% (291/660)

FIGURE LEGEND

Figure 1. Odds ratio for a history of eczema by two years of age in groups stratified by quartile of change in estimated fetal weight between the second and third trimesters.



Supplementary material

Table 1. Relationship between maternal energy-adjusted dietary vitamin E intake and household income. Chi square $p=0.031$.

Monthly household income (Riyal)	Quartile of maternal dietary vitamin E intake			
	Lowest quartile	Next lowest quartile	Next highest quartile	Highest quartile
<3000	24% (24/99)	26% (26/99)	18% (18/99)	31% (31/99)
3000-4999	21% (42/205)	30% (62/205)	28% (57/205)	22% (44/205)
5000-7999	29% (95/324)	19% (61/324)	23% (75/324)	29% (93/324)
8000-10000	27% (55/206)	26% (53/206)	25% (51/206)	23% (47/206)
>10000	30% (55/183)	22% (40/183)	28% (51/183)	20% (37/183)

Table 2. Mean gestation at second and third trimester ultrasound assessment of fetal measurements stratified by quartile of growth in abdominal circumference. There were no differences between groups.

	Quartile of change in abdominal circumference			
	Lowest change (n=73)`	Next to lowest change (n=73)	Next to highest change (n=73)	Highest change (n=73)
Mean gestation and second trimester assessment (SD), weeks	21.6 (3.1)	21.0 (3.0)	22.0 (3.3)	21.8 (3.5)
Mean gestation and third trimester assessment (SD), weeks	34.4 (2.8)	33.6 (2.9)	33.6 (2.7)	34.0 (2.8)

Table 3. Risk for eczema across quartile of ratio of head circumference (HC) to abdominal circumference (AC) growth between the second and third trimesters. The logistic model adjusted for sex, maternal smoking, maternal eczema, parity, being first born and household income.

Quartile for HC:AC growth	Risk [95% confidence interval]
Lowest quartile	1
Second lowest quartile	1.9 [0.6, 6.1]
Second highest quartile	2.2 [0.7, 7.4]
Highest quartile	2.8 [0.8, 9.8]