Full Title:

Fetal growth trajectories and measures of insulin resistance in young adults

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The authors have nothing to disclose.

ABSTRACT

Context

Events during gestation significantly influence the risk of cardiometabolic diseases including diabetes in the offspring during later life.

Objective

The study aimed to investigate relationships between serial ultrasound derived fetal growth trajectories and markers of insulin resistance in young adults in the Raine Study, an Australian pregnancy cohort.

Research Design and Methods

Linear mixed modeling examined the relationship between fetal growth trajectory groups, constructed using serial ultrasound-based abdominal circumference (AC), femur length (FL) and head circumference (HC) from 1333 mother-fetal pairs, and offspring Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), as a marker of diabetes risk, at 20 (n=414), 22 (n=385) and 27 (n=431) years. Analyses were adjusted for age, sex, ethnicity, socio-economic status, adult lifestyle factors and maternal factors during pregnancy.

Results

The study identified seven AC, five FL and five HC growth trajectory groups. Compared to the average-stable (reference) group, a low-falling AC growth trajectory (26%, P=0.005) and two low HC growth trajectories (20%, P=0.006 and 8%, P=0.021) associated with higher adult HOMA-IR. Trajectories representing a high-stable FL and a rising HC associated with 12%

(P=0.002) and 9% (P=0.021) lower adult HOMA-IR respectively, compared to the reference group.

Conclusions

Restricted fetal head and abdominal circumference from early pregnancy associate with higher relative insulin resistance in the offspring during adulthood. These data strengthen our understanding of the importance of the intrauterine environment and its effect on the risk of predisposition to adult diabetes and related metabolic disorders.

INTRODUCTION

Diabetes has emerged as a serious, life threatening and disabling chronic disease with more than 1 in 10 adults presently living with diabetes worldwide (1). In 2021, 536.6 million people, accounting for approximately 10.5% of the world's adult population, had either *type 1* or *type 2* diabetes which is projected to rise to 12.2% (783.2 million) in 2045 (1). An estimated 1.3 million Australians (4.9%) had diabetes in 2020 including 48,300 people newly diagnosed with *type 2* diabetes mellitus (T2DM) in the year 2020 (2). T2DM associates with a 2-3 times higher risk of premature death, compared to the general population (3,4). The rising prevalence over the past two decades has led to growing concerns and prompted research into the developmental and environmental factors that contribute to the onset and progression of T2DM (5-8). Sedentary lifestyle, consumption of energy-dense foods and rise in overweight and obesity associate with a greater risk of early onset T2DM (4,9).

There is considerable evidence that events during gestation may predispose to increased risk of adult cardiometabolic diseases including diabetes (10-12). Birthweight has been extensively studied as a surrogate marker of fetal growth; low birthweight closely associates with adult diabetes (5-7,13). However, birthweight does not necessarily provide an accurate measure of early fetal growth and development. In the Raine Study, an Australian longitudinal pregnancy cohort, we have shown a disassociation between birthweight and growth trajectories *in utero* (14). We have also reported significant associations between different intrauterine growth trajectories and offspring adult blood pressure (14), body-mass index (BMI), waist-circumference and high-sensitivity C-reactive protein (hs-CRP)(15).

The present study extends our recent findings and investigates the relationships between fetal growth trajectories and adult Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) as a marker of insulin resistance.

MATERIALS AND METHODS

The Raine Study enrolled 2900 pregnant women from 1989-91 in Perth, Western Australia. The study aimed to investigate the effect of ultrasound imaging on pregnancy outcomes and the role of early life events on subsequent childhood and adult health. Details on recruitment, randomization and data collection in the original trial are published (16). In brief, the study randomized pregnant women (Gen1) into two groups based on the number of ultrasounds administered during gestation. While the intervention arm had five imaging examinations at 18, 24, 28, 34 and 38-weeks gestation, the control arm had a single ultrasound at 18-weeks unless clinically required. Only participants from the intervention arm were selected for the current analysis as a minimum of two ultrasound measurements were needed to develop growth trajectories. Offspring (Gen2) (n=2868) have been prospectively followed up from birth to their current age of 27-years. Demographic, lifestyle, clinical and biochemical information has been collected at regular intervals through questionnaires and clinical assessments. The present analysis uses Gen2 cohort information at 20, 22, and 27-years. Informed, written consent was provided by the pregnant women during initial recruitment and the adult offspring at each follow-up. The Human Research Ethics Committees at King Edward Memorial Hospital and The University of Western Australia approved the study.

Gen1 (pregnancy) Demographic and Lifestyle Measures

Information on Gen1 maternal and paternal socio-demographic characteristics and ethnicity, mother's marital status, family income, maternal smoking and alcohol drinking was obtained by self-reported questionnaires at 16 and 34-weeks gestation. Annual family income during pregnancy was used to assess family income, low being <$24 000 (AUS) in 1989-91. Maternal medical records provided pregnancy characteristics including maternal weight, height and medical conditions. Gestational age was calculated from the date of the last menstrual period

and in case of discordancy, ultrasound estimation at 18-weeks. Maternal BMI was calculated at 16-weeks and pregnancy weight gain was calculated between 16 and 34-weeks gestation. Gestational weight gain during this period associates with *in utero* growth and birthweight. Smoking and alcohol drinking during pregnancy were assessed at 16 and 34-weeks and recorded as yes/no, yes being consumption at either or both time points. Self-reported gestational diabetes was recorded 2-days after delivery. All live births at <37 completed weeks were categorised as preterm. Standard blood pressure recordings during pregnancy obtained by midwives were used to establish pregnancy HTN, characterised as Uncomplicated-HTN or Complicated-HTN. History of HTN before pregnancy or HTN during pregnancy without proteinuria or preterm delivery was defined as Uncomplicated-HTN. Complicated-HTN was defined as HTN during pregnancy with proteinuria (>2+ on dipstix test) or 300mg on 24-hour urinary protein excretion or preterm delivery (17). Systolic blood pressure (SBP) >140mmHg and/or diastolic blood pressure (DBP) >90mmHg was classified as HTN during pregnancy (18). Birth weight of the offspring was extracted from hospital records. Breast feeding was coded as not breastfed, breastfed for <6-months or breastfed for ≥6-months.

Adult Offspring (Gen2) Measures

Wedderburn Chair Scales (to the nearest 100g) were used to measure body weight with participants dressed in light clothing. A Stadiometer (to the nearest 0.1cm) recorded height while a measuring tape was used to measure waist circumference (to the nearest 0.1cm). A halfway point between the lowest rib and the iliac crest was used to record waist circumference. Socio-demographic and lifestyle data at 20, 22 and 27-years were obtained from computer-based questionnaires. Smoking was coded as a binary variable (yes/no) with participants categorised as smokers if they smoked a cigarette in the past 1-month. Total ethanol consumption in g/week was obtained for alcohol intake, with 1-standard drink equivalent to

10g ethanol. Information included the amount and type of alcoholic beverage consumed daily over the past 7-days. In females, current use of any hormonal contraceptive pill, injection, implants or intrauterine device determined the status of hormonal contraceptives (yes/no). Offspring were categorised as Caucasian if both parents were Caucasians. Socioeconomic indexes for areas (SEIFA) scores were used as a continuous variable to quantify the socio-economic status (SES) of Gen2 participants. Education was categorised as completing high school (level-1), apprenticeship or vocational training (level-2), or university (level-3). Metabolic equivalents (MET-minutes/week) were used to measure physical activity; one MET defined as the amount of oxygen consumed during rest (3.5ml/kg/min). MET-minutes/week were obtained using the International Physical Activity Questionnaire (IPAQ-short/long) as per a standardized protocol (19). BMI was coded as a continuous variable (bodyweight in kg/height in m^2). Fasting plasma glucose (mmol/L) was assayed by standard spectrophotometer (Abbott Diagnostics, Abbott Laboratories, USA). Serum insulin was measured by the immunoassay technique (Abbott Diagnostics, Abbott Laboratories, USA). HOMA-IR was calculated according to the formula: [fasting insulin (mIU/mL) x fasting glucose (mmol/L)]/22.5. Waist-to-height ratio (WHtR) was calculated as waist circumference divided by height (both in cm). Prediabetes was defined as fasting plasma glucose ≥5.6 and <7 mmol/L (20). T2DM was diagnosed on the basis of self-reporting or fasting plasma glucose ≥7 mmol/L.

Antenatal data and fetal growth trajectories

Serial ultrasound measurements of abdominal circumference (AC), femur length (FL) and head circumference (HC) from 1333 mother-fetal pairs were used to develop fetal growth trajectories as described in detail previously (14). Briefly, linear regression models predicted standard deviation scores (SDS) for the three fetal anthropometric markers (AC, FL and HC), adjusting for physiological factors influencing fetal growth (sex and ethnicity of the fetus,

maternal height and parity). Seven AC, five FL and five HC trajectory groups were identified (Supplementary Figure-1) (new ref 21) by group-based trajectory modelling using a Stata plug-in (14).

Statistical Analysis

Fetal growth trajectories and Gen2 adult measures of insulin resistance and adiposity

The relationship between fetal growth trajectory groups and adult HOMA-IR at 20, 22 and 27-years, was examined using random coefficient mixed-effects linear regression. Bootstrapping with 500 replications minimised outlier influence and generated robust estimates. Data for trajectory groups and Gen2 adult lifestyle information were available for 414, 385 and 431 participants at 20, 22 and 27-years, respectively, representing 641 individuals who attended at least one follow-up. (Figure-1). Statistical reasoning, scientific evidence and availability of data were used to select the final set of confounders. Age at each follow-up, sex, ethnicity, alcohol intake, smoking, adult SES, educational status and physical activity constituted the adult covariates. Maternal covariates included family income during pregnancy, smoking, alcohol drinking, weight gain, maternal BMI at 16-weeks, preterm pregnancy, gestational diabetes mellitus (GDM), family history of diabetes, Uncomplicated-HTN, Complicated-HTN and breastfeeding. Family history of diabetes in the participants was examined using two variables: family history of diabetes in the grandparents of Gen2 (both maternal and paternal; self-reported by Gen1 parents; n=164) and history of maternal diabetes in Gen1 before pregnancy (self-reported by mothers; n=22). Log-transformation of HOMA-IR and insulin was performed due to evidence of significant skewing. Use of the mixed modelling technique and bootstrapping accounted for missingness of data at one or more timepoints and for non-normality. Selection of the most parsimonious model was based on a P-value threshold, change in model estimates and *a priori* knowledge of the risk factors. Mixed model results were

interpreted using a conservative approach based on both the global and local P-value for the trajectory variable. SES, physical activity and gestational age (for birthweight analyses) were normalized by z-score standardization techniques. Model-1 examined the outcome variable (HOMA-IR) and trajectory groups adjusted for age, sex, female hormonal contraceptive use, ethnicity, SES and adult lifestyle factors. Model-2 additionally adjusted for pregnancy covariates including uncomplicated hypertension during pregnancy, maternal alcohol drinking, and maternal BMI at 16-weeks. Both Model-1 and -2 were adjusted for either BMI or WHtR (as a measure of adult adiposity) with results presented separately. BMI was centered at 25 kg/m^2 and a second order polynomial was used in some models. Sex-trajectory interaction was also examined. The relationship between birthweight as a continuous variable and HOMA-IR was examined using linear mixed modeling.

Results are presented as percentages, means with standard deviations or medians with upper and lower quartiles. Stata v17.0 (Stata Corp., College Station, Texas, USA) was used for all statistical analyses with 2-sided significance at $p<0.05$.

RESULTS

General characteristics of the Gen2 adults at 20, 22 and 27-years and their mothers (Gen1) during pregnancy are shown in Table-1. Ninety percent of Gen2 adults were Caucasians. Males had a higher BMI, waist circumference and WHtR compared to females at all three ages. The highest proportion of central adiposity (identified by WHtR ≥ 0.5) was in females at 22-years and in males at 27-years. Median HOMA-IR values tended to be higher in females compared to males at 20 and 22-years. Alcohol was consumed by approximately 70-85% of participants at the three ages. The frequency of smoking was approximately 16% at 20-years and 21-24% at 27-years. Physical activity in both males and females was higher at 20-years than at 22 and 27-years. Female hormonal contraceptive use was 60% at 20-years and 49% at 27-years. Mean

birthweight of the participants was between 3.30-3.42 kg. The distribution of Gen2 with prediabetes or diabetes was uniform across AC, FL and HC trajectory groups at 20, 22 and 27-years (Supplementary Tables 1-3) (new ref 21). *Type 2* diabetes was diagnosed in one person at 20-years and five each at 22- and 27-years.

In relation to maternal characteristics (Gen1), up to 6% reported preterm deliveries, 3.5% gestational diabetes, 27.7% uncomplicated-HTN and 3.3% complicated-HTN (Table-1). Up to 25% of Gen1 mothers smoked and 60% consumed alcohol during pregnancy. About 32-38% of Gen1 families had an annual income <$24 000 (AUS) at the time of pregnancy.

Growth trajectories and Gen2 HOMA-IR

(i) Relationship of AC trajectories with HOMA-IR

Participants in Group-1 (low-falling) had 26% higher HOMA-IR (β=1.26, P=0.005), compared with the reference group (Group-3), after adjusting for age, sex, hormonal contraceptive use, ethnicity, SES, BMI and alcohol intake (Model-1: Table-2, Figure-2 and Supplementary Table-4) (new ref 21). The association remained significant with further adjustment for maternal covariates (Model-2: Table-2 and Supplementary Table-4) (new ref 21). Maternal alcohol drinking in pregnancy (Model-2) was found to be independently associated with HOMA-IR (P=0.004).

A sex-trajectory interaction was detected (P=0.025) and in sex-specific analysis, males in Group-7 (high-rising) had 22% lower (β= 0.78, P=0.008) HOMA-IR (adjusted for age, BMI, ethnicity and SES) while females in Group-1 (low-falling) had 56% higher (β= 1.56, P<0.001) HOMA-IR (adjusted for age, contraceptive use, BMI, ethnicity and SES) (Model-1: Supplementary Table-5) (new ref 21). These associations remained significant with additional adjustment for maternal covariates (Model-2: Supplementary Table-5) (new ref 21).

Using WHtR to adjust for adult adiposity instead of BMI, Group-1 participants associated with 23% higher HOMA-IR (P=0.008) while Group-7 participants associated with 11% lower HOMA-IR (P=0.040), compared to the reference group (Model-1: Table-2 and Model-1: Supplementary Table-6) (new ref 21).

(ii) Relationship of FL trajectories with HOMA-IR

Compared with reference Group-4, participants in Group-5 (high-stable) associated with 12% lower HOMA-IR (β= 0.88, P=0.002) (Model-1: Table-2, Figure-2 and Supplementary Table-7) (new ref 21). This association persisted with adjustment for maternal covariates (Model-2: Table-2 and Supplementary Table-7) (new ref 21) and showed maternal alcohol drinking was independently associated with HOMA-IR (P=0.002). There was no sex-trajectory interaction (P=0.812). Using WHtR instead of BMI produced similar β coefficients for Group-5 (Supplementary Table-8) (new ref 21).

(iii) Relationship of HC trajectories with HOMA-IR

Participants in Group-1 (low-stable) and Group-2 (average-falling) associated with 20% (β= 1.20, P=0.006) and 8% (β= 1.08, P=0.021) higher HOMA-IR respectively, compared to reference Group-4 (average-stable) (Model-1: Table-2, Figure-2 and Supplementary Table-9) (new ref 21). In the same model, participants in Group-3 (low-rising) associated with 9% (β= 0.91, P=0.021) lower HOMA-IR compared to the reference group. Adjustment for maternal covariates (Model-2) resulted in similar coefficients, with maternal alcohol drinking independently associated with HOMA-IR (P=0.002). There was no sex-trajectory interaction (P=0.639).

Replacing BMI with WHtR for adiposity as a covariate resulted in similar coefficients for Groups-1, -2 and -3 (Table-2 and Supplementary Table-10) (new ref 21). Additionally, with

WHtR as a covariate, Group-5 (high-stable) participants associated with 9% (β= 0.91, P=0.042) lower HOMA-IR compared to the reference group (Model-1: Table 2 and Model-1: Supplementary Table-10) (new ref 21).

In all analyses examining associations between AC, FL and HC trajectories and HOMA-IR, family history of diabetes was not statistically significant in the final model and did not significantly change the coefficients.

Relationship of growth trajectories with Insulin and Glucose

Associations between growth trajectories and insulin were similar to HOMA-IR (Supplementary Table-11) (new ref 21). However, the two falling AC trajectory groups: Group-1 (low-falling) and Group-6 (high-falling) had higher fasting glucose (β= 0.10, P=0.014 and β= 0.09, P=0.047 respectively), compared to the reference Group-3. No association was found for FL and HC trajectories and glucose (Supplementary Table-11) (new ref 21).

Relationship of birthweight and adult HOMA-IR and WHtR

Birthweight (kg), adjusted for gestational age, was inversely associated with HOMA-IR (β= 0.86, P<0.001), representing 14% lower HOMA-IR for every 1kg increase in birthweight, in models adjusted for age, sex, female contraceptive use, ethnicity, SES, BMI and alcohol intake (Model-1: Supplementary Table-12) (new ref 21). This association remained significant with adjustment for maternal covariates (Model-2).

DISCUSSION

This study has shown significant relationships between *in utero* fetal growth trajectories from early in pregnancy and measures of insulin resistance in the offspring during adulthood. In

particular, trajectories reflecting lower-than-average head and abdominal circumference, representing restricted fetal growth, associated with higher adult HOMA-IR, while the trajectory reflecting above-average and rising abdominal growth associated with lower HOMA-IR. Similarly, above-average growth in femur length and head circumference, and accelerated growth in head circumference, associated with lower HOMA-IR. The associations were independent of maternal and adult lifestyle factors and showed some differences between the sexes. For example, the relation between the restricted abdominal growth patterns and HOMA-IR was substantially greater in females than males. The results complement our previous findings of relationships between fetal growth patterns and markers of adult risk factors for cardiometabolic diseases including blood pressure, BMI, waist circumference and hs-CRP (14,15). The associations between HOMA-IR and growth trajectories in this study were mainly driven by serum insulin. Use of waist-to-height ratio instead of BMI as a covariate for the relationship between trajectories and HOMA-IR showed similar results although in some instances, strengthened the coefficients, which highlight the value of WHtR as a measure for assessing cardiometabolic risk (21,22).

Fetal growth is determined by many interactions including those between genetics, environmental factors, placental nutrition, and oxygen, and is an identified risk factor for the development of several diseases in adulthood including *type 2* diabetes (6,10,23,24). Poor maternal nutrition during gestation and consequent placental insufficiency can cause lower-than-average growth of fetal head circumference, reflecting diminished brain size and poor development (25). The development of the hypothalamic-pituitary-adrenal (HPA) axis, responsible for neuroendocrine regulation of insulin metabolism and immune responses, begins in early fetal life. One could speculate that reduced head size and related *in utero* environmental stressors during critical periods of growth can alter normal neuropeptide synthesis, thereby

disrupting proper functioning of the HPA axis and leading to a dysregulation of glucose-insulin homeostasis (26). Abdominal circumference, on the other hand, approximates growth of fetal liver and abdominal subcutaneous fat. Restricted fetal abdominal growth could cause reduced beta cell mass with reduced secretory capacity in the pancreas, reduced glucose uptake and increased gluconeogenesis in the liver, increased lipid oxidation in the muscles and decreased insulin inhibition of lipolysis in the adipocytes, all cumulatively leading to glucose intolerance (27). While these adaptive mechanisms help in fetal survival, many persist into postnatal life and may increase the propensity of future abdominal obesity, insulin resistance and T2DM. Preterm birth, exposure to antenatal corticosteroids in growth restricted fetuses and rapid catch-up growth in infancy can also contribute to the risk of visceral adiposity and insulin resistance in later life (28,29). The role of insulin in mediating normal growth in healthy individuals and promoting adiposity during hyperinsulinemia through maintenance of the insulin-growth hormone (GH)- insulin-like growth factor 1 (IGF-1) axis is well recognized (30). However, the Raine Study does not have measures of insulin, GH or IGF-1 of the mothers during pregnancy and GH or IGF-1 of the offspring during childhood, adolescence and adulthood.

Lifestyle maternal characteristics during pregnancy have been identified as determinants of the long-term health of the offspring (31). As reported previously, mothers with a fetus in a restricted growth trajectory in this study cohort were more likely to experience a preterm delivery. Similarly, mothers of a fetus with restricted abdominal growth had a higher BMI at 16-weeks of gestation, while those with a fetus with restricted head growth were more likely to smoke during pregnancy (14). Our findings reinforce the importance of public health strategies targeting lifestyle interventions like maternal obesity and smoking to ameliorate the future risk of diabetes in the offspring.

Fetal growth during pregnancy has largely been assessed using birthweight and less commonly using ultrasound based *in utero* anthropometric growth markers (13). Systematic reviews and meta-analyses have shown an inverse relationship between birthweight and measures of insulin resistance and/or T2DM during adolescence and adulthood (32-35). In our analysis, HOMA-IR in adulthood was 14% lower for every 1kg increase in birthweight, after adjusting for adult lifestyle and maternal factors. As we have previously shown, birthweight may not provide an accurate measure of different patterns of fetal development *in utero* (14). Use of growth trajectories as a measure of fetal growth therefore provides a more complete picture of the dynamics of the intrauterine environment which may be contributing to programming of adult diseases (24,36).

Our analyses have also accounted for maternal factors influencing fetal growth such as maternal drinking, maternal BMI, and hypertension in pregnancy, as well as family history of diabetes. In particular, maternal alcohol drinking was found to be independently associated with HOMA-IR. Several animal studies have reported strong evidence of linkage between prenatal alcohol exposure and T2DM through alteration of insulin expression and insulin-like growth factor signaling leading to metabolic dysregulation in the offspring (37,38). However, establishing causality in humans is an ethical challenge and alcohol consumption during pregnancy continues to be major health concern with an estimated global prevalence of about 10% (39). About 58% mothers in the Raine Study consumed alcohol in pregnancy, possibly due to lack of awareness about the detrimental effects of fetal alcohol exposure during 1989-91. The HAPO study on associations with maternal BMI showed that higher maternal BMI is strongly associated with excess fetal growth and adiposity (40). We have previously shown strong associations of maternal BMI with offspring adiposity (15) in the Raine cohort. In the present study, although maternal BMI was significantly associated ($P<0.001$) with offspring

HOMA-IR in the univariate analysis, no significant association was found in the final multivariate analysis, most likely as the latter was adjusted for offspring adiposity.

In this study, we showed significant relationships between fetal growth patterns and HOMA-IR, adjusting for either BMI or WHtR as a measure of adult central adiposity. Both BMI and WHtR were found to be independent significant predictors of diabetes risk in adulthood. Jayedi et al have recently shown significant associations between different anthropometry measures and the risk of T2DM in the general population (41). An increase in WHtR by 0.01 units, BMI by one unit and waist circumference by 1 cm associates with a 7.3%, 14.4% and 6.1%, respectively, higher risk of T2DM (41). A meta-analysis by Ashwell et al provides robust evidence from studies involving >300 000 adults from several ethnic groups, showing that WHtR is a better measure than BMI and waist-circumference in predicting cardiometabolic risk (22). WHtR has also been recognized as a more reliable measure to distinguish differences in body fat distribution, thereby allowing more accurate interpretations of visceral adiposity both in men and women (42). Use of WHtR in the present analysis strengthens our previous findings that showed significant associations between trajectories and adult BMI and waist circumference and builds strong evidence of association between early fetal growth and risk factors for T2DM in adulthood.

Strengths of this study include the application of serial ultrasound measures to identify unique fetal growth patterns and longitudinal analysis of adult measures across three ages from 20 to 27 years. The Raine Study cohort is a well characterized homogenous population, primarily Caucasians of above-average socioeconomic status. The cohort is representative of the contemporary Western Australian population both at the time of recruitment and at subsequent follow-ups, even allowing for attrition (16,43,44). Information related to pregnancy, birth and

follow-up visits has been carefully documented through medical records and online databases, eliminating any concerns for recall bias. Longitudinal analysis using mixed modeling made efficient use of the available data and allowed us to examine relationships independent of a number of adult and maternal factors. Study limitations include the relatively small sample for some trajectories restricting the use of multiple comparisons to explore sex-trajectory interactions and limiting our statistical ability to detect more subtle relationships in sub-group analyses. Non-availability of sibling rank data was another limitation, but we did account for mother's parity during trajectory modelling. Low rates of gestational diabetes in this cohort, could be due to lack of routine testing in late pregnancy and lower rates of maternal obesity in the 1990s. Allocation of hypertensive pregnancies was performed by mid-wives based on the retrieval of medical records which could have led to an overestimation of the proportion of pregnancies with Uncomplicated-HTN. Additionally, Gen1 mothers were recruited from King Edward Memorial Hospital, Perth which historically associated with a higher proportion of pregnancies with complications (38.6% compared to 30% in the contemporary Western Australian obstetric population) (43). However, follow-up studies have shown that those who attended subsequent follow-ups were more representative of the contemporary population. Importantly, we adjusted for uncomplicated-HTN in our analysis. Whilst analyses accounted for several antenatal, postnatal, current lifestyle and socioeconomic factors, we cannot exclude the contribution of unmeasured residual confounding factors including a possible genetic influence on the relationship between in utero growth trajectories and adult insulin sensitivity. Lastly, assumptions about causality need a cautious approach due to the observational nature of the study.

To our knowledge, this is the first study to investigate the relationship between fetal growth trajectories based on serial ultrasound and markers of insulin resistance in adulthood using novel modeling techniques. While the Raine Study cohort is relatively young with a low

incidence of diabetes, follow-up is ongoing and will provide more evidence as the cohort matures. A global increase in the rates of obesity in the 30-year period since the Raine Study was initiated is likely to further amplify the metabolic risk shown in our study. Together with our previous results, these findings provide further insight to our understanding of early gestational determinants of adult diabetes. Early identification of fetuses with future risk based on ultrasound-based growth assessment could play an important role in long-term risk-prevention of diabetes and related cardiometabolic diseases.

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Author Contributions

Conceptualization: TAM, LJB; Funding acquisition: TAM, LJB; Study design: AY, TAM, LJB, RCH; Data acquisition: TAM, AY; Formal analysis: AY; Data interpretation: AY, TAM, LJB, RCH; Writing- original draft: AY; Writing- review & editing: AY, TAM, LJB, RCH, JPN, SWW. All authors provided critical feedback and helped shape the research, analysis and paper. All authors gave final approval for this version to be published.

TAM is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, Pavkov ME, Ramachandaran A, Wild SH, James S, Herman WH, Zhang P, Bommer C, Kuo S, Boyko EJ, Magliano DJ. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Research and Clinical Practice*. 2022;183:109119.
2. Health AIo, Welfare. Diabetes. Canberra: AIHW; 2020.
3. Abarca-Gómez L, Abdeen ZA, Hamid ZA, Abu-Rmeileh NM, Acosta-Cazares B, Acuin C, Adams RJ, Aekplakorn W, Afsana K, Aguilar-Salinas CA. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128· 9 million children, adolescents, and adults. *The lancet*. 2017;390(10113):2627-2642.
4. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature reviews endocrinology*. 2018;14(2):88-98.
5. Knop MR, Geng TT, Gorny AW, Ding R, Li C, Ley SH, Huang T. Birth weight and risk of type 2 diabetes mellitus, cardiovascular disease, and hypertension in adults: a meta-analysis of 7 646 267 participants from 135 studies. *Journal of the American Heart Association*. 2018;7(23):e008870.
6. Tian M, Reichetzeder C, Li J, Hocher B. Low birth weight, a risk factor for diseases in later life, is a surrogate of insulin resistance at birth. *Journal of hypertension*. 2019;37(11):2123-2134.
7. Bakhtiani P, Geffner ME. Early anthropometric indicators of type 2 diabetes mellitus. *Current Opinion in Endocrinology & Diabetes and Obesity*. 2022;29(1):52-56.
8. Kivimäki M, Virtanen M, Kawachi I, Nyberg ST, Alfredsson L, Batty GD, Bjorner JB, Borritz M, Brunner EJ, Burr H. Long working hours, socioeconomic status, and the risk of incident type 2 diabetes: a meta-analysis of published and unpublished data from 222 120 individuals. *The lancet Diabetes & endocrinology*. 2015;3(1):27-34.
9. Organization WH. Consideration of the evidence on childhood obesity for the Commission on Ending Childhood Obesity: report of the ad hoc working group on science and evidence for ending childhood obesity, Geneva, Switzerland. 2016.
10. Hattersley AT, Tooke JE. The fetal insulin hypothesis: an alternative explanation of the association of low bir thweight with diabetes and vascular disease. *The Lancet*. 1999;353(9166):1789-1792.
11. Gluckman PD, Hanson MA, Morton SM, Pinal CS. Life-long echoes–a critical analysis of the developmental origins of adult disease model. *Neonatology*. 2005;87(2):127-139.
12. Barker DJP. Adult consequences of fetal growth restriction. *Clinical obstetrics and gynecology*. 2006;49(2):270-283.
13. Jornayvaz FR, Vollenweider P, Bochud M, Mooser V, Waeber G, Marques-Vidal P. Low birth weight leads to obesity, diabetes and increased leptin levels in adults: the CoLaus study. *Cardiovascular diabetology*. 2016;15(1):1-10.
14. Yadav A, Beilin LJ, Huang R-C, Vlaskovsky P, Newnham JP, White SW, Mori TA. The relationship between intrauterine foetal growth trajectories and blood pressure in young adults. *Journal of Hypertension*. 2022;40(3):478-489.
15. Yadav A, Beilin LJ, Huang R-C, Vlaskovsky P, Newnham JP, White SW, Mori TA. Relationships between intrauterine fetal growth trajectories and markers of adiposity and inflammation in young adults. *International Journal of Obesity*. 2022:1-11.
16. Newnham JP, Evans SF, Michael CA, Stanley FJ, Landau LI. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. *Lancet*. 1993;342(8876):887-891.

17. Davis EF, Lewandowski AJ, Aye C, Williamson W, Boardman H, Huang RC, Mori TA, Newnham J, Beilin LJ, Leeson P. Clinical cardiovascular risk during young adulthood in offspring of hypertensive pregnancies: insights from a 20-year prospective follow-up birth cohort. *BMJ Open*. 2015;5(6):e008136.
18. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M. 2020 International Society of Hypertension global hypertension practice guidelines. *Hypertension*. 2020;75(6):1334-1357.
19. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF. International physical activity questionnaire: 12-country reliability and validity. *Medicine & science in sports & exercise*. 2003;35(8):1381-1395.
20. Association AD. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. *Diabetes Care*. 2020;44(Supplement_1):S15-S33.
21. Ashwell M, Gibson S. Waist-to-height ratio as an indicator of 'early health risk': simpler and more predictive than using a 'matrix'based on BMI and waist circumference. *BMJ open*. 2016;6(3):e010159.
22. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obesity reviews*. 2012;13(3):275-286.
23. Nobile S, Di Sipio Morgia C, Vento G. Perinatal Origins of Adult Disease and Opportunities for Health Promotion: A Narrative Review. *Journal of Personalized Medicine*. 2022;12(2):157.
24. Fernandez-Twinn DS, Hjort L, Novakovic B, Ozanne SE, Saffery R. Intrauterine programming of obesity and type 2 diabetes. *Diabetologia*. 2019;62(10):1789-1801.
25. Hoffman DJ, Powell TL, Barrett ES, Hardy DB. Developmental origins of metabolic diseases. *Physiological Reviews*. 2021;101(3):739-795.
26. Sheng JA, Bales NJ, Myers SA, Bautista AI, Roueinfar M, Hale TM, Handa RJ. The Hypothalamic-Pituitary-Adrenal Axis: Development, Programming Actions of Hormones, and Maternal-Fetal Interactions. *Frontiers in Behavioral Neuroscience*. 2021;14.
27. Kanaka-Gantenbein C. Fetal origins of adult diabetes. *Annals of the New York Academy of Sciences*. 2010;1205(1):99-105.
28. Kajantie E, Strang-Karlsson S, Hovi P, Wehkalampi K, Lahti J, Kaseva N, Järvenpää A-L, Räikkönen K, Eriksson JG, Andersson S. Insulin sensitivity and secretory response in adults born preterm: the Helsinki Study of Very Low Birth Weight Adults. *The Journal of Clinical Endocrinology & Metabolism*. 2015;100(1):244-250.
29. Ong YY, Sadananthan SA, Aris IM, Tint MT, Yuan WL, Huang JY, Chan YH, Ng S, Loy SL, Velan SS. Mismatch between poor fetal growth and rapid postnatal weight gain in the first 2 years of life is associated with higher blood pressure and insulin resistance without increased adiposity in childhood: the GUSTO cohort study. *International journal of epidemiology*. 2020;49(5):1591-1603.
30. Janssen JAMJL. Hyperinsulinemia and Its Pivotal Role in Aging, Obesity, Type 2 Diabetes, Cardiovascular Disease and Cancer. *International Journal of Molecular Sciences*. 2021;22(15):7797.
31. Gaillard R, Wright J, Jaddoe VW. Lifestyle intervention strategies in early life to improve pregnancy outcomes and long-term health of offspring: a narrative review. *Journal of developmental origins of health and disease*. 2019;10(3):314-321.
32. Zhao H, Song A, Zhang Y, Zhen Y, Song G, Ma H. The association between birth weight and the risk of type 2 diabetes mellitus: a systematic review and meta-analysis. *Endocrine Journal*. 2018:EJ18-0072.

33. Xu Y, Chen S, Yang H, Gong F, Wang L, Jiang Y, Yan C, Zhu H, Pan H. Decreased insulin sensitivity and abnormal glucose metabolism start in preadolescence in low-birth-weight children—Meta-analysis and systematic review. *Primary Care Diabetes*. 2019;13(5):391-398.
34. de Mendonça ELSS, de Lima Macêna M, Bueno NB, de Oliveira ACM, Mello CS. Premature birth, low birth weight, small for gestational age and chronic non-communicable diseases in adult life: A systematic review with meta-analysis. *Early Human Development*. 2020;149:105154.
35. Martín-Calvo N, Goni L, Tur JA, Martínez JA. Low birth weight and small for gestational age are associated with complications of childhood and adolescence obesity: Systematic review and meta-analysis. *Obesity Reviews*. 2022;23:e13380.
36. Hughes AE, Hattersley AT, Flanagan SE, Freathy RM. Two decades since the fetal insulin hypothesis: what have we learned from genetics? *Diabetologia*. 2021;64(4):717-726.
37. Vaiserman AM. Early-Life Exposure to Substance Abuse and Risk of Type 2 Diabetes in Adulthood. *Current Diabetes Reports*. 2015;15(8):48.
38. Jiang X, Ma H, Wang Y, Liu Y. Early life factors and type 2 diabetes mellitus. *Journal of diabetes research*. 2013;2013.
39. Popova S, Lange S, Probst C, Gmel G, Rehm J. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. *The Lancet Global Health*. 2017;5(3):e290-e299.
40. Group HSCR. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2010;117(5):575-584.
41. Jayedi A, Soltani S, Motlagh SZ-t, Emadi A, Shahinfar H, Moosavi H, Shab-Bidar S. Anthropometric and adiposity indicators and risk of type 2 diabetes: systematic review and dose-response meta-analysis of cohort studies. *bmj*. 2022;376.
42. Swainson MG, Batterham AM, Tsakirides C, Rutherford ZH, Hind K. Prediction of whole-body fat percentage and visceral adipose tissue mass from five anthropometric variables. *PLOS ONE*. 2017;12(5):e0177175.
43. Straker L, Mountain J, Jacques A, White S, Smith A, Landau L, Stanley F, Newnham J, Pennell C, Eastwood P. Cohort Profile: The Western Australian Pregnancy Cohort (Raine) Study–Generation 2. *International journal of epidemiology*. 2017;46(5):1384-1385j.
44. White SW, Eastwood PR, Straker LM, Adams LA, Newnham JP, Lye SJ, Pennell CE. The Raine study had no evidence of significant perinatal selection bias after two decades of follow up: a longitudinal pregnancy cohort study. *BMC pregnancy and childbirth*. 2017;17(1):207.

Table-1: General characteristics of the participants (Gen2) at 20, 22 and 27 years and their mothers (Gen1) during pregnancy

Characteristics	Year 20 (n=414)		Year 22 (n=385)		Year27 (n=431)	
	Males n=204	Females n=210	Males n=198	Females n=187	Males n=215	Females n=216
Adult Participants (Gen2)						
Age (years) Mean (SD)	20.1 (0.5)	20.0 (0.5)	22.2 (0.6)	22.1 (0.6)	26.8 (0.4)	26.8 (0.4)
BMI (kg/m^2) Median (Q1, Q3)	23.4 (21.2,26.4)	23.0 (20.9,25.8)	24.1 (22.0,27.5)	23.8 (21.4,28.8)	24.7 (22.6,27.6)	23.7 (21.3,27.4)
Waist Circumference (cm) Median (Q1, Q3)	79.1 (75.0,86.9)	74.0 (68.0,81.8)	83.3 (77.0,91.2)	76.4 (70.5,90.3)	85.6 (79.8,94.3)	76.6 (70.8,85.8)
Waist-to-Height Ratio Median (Q1, Q3)	0.45 (0.42,0.49)	0.44 (0.41,0.49)	0.47 (0.43,0.51)	0.46 (0.42,0.54)	0.47 (0.44,0.52)	0.46 (0.42,0.52)
Waist Height Ratio ≥ 0.5 (%)	22.5	21.9	29.3	37.4	32.1	31.0
HOMA-IR Median (Q1, Q3)	0.48 (0.44,1.05)	0.57 (0.43,1.32)	1.50 (1.13,2.08)	1.75 (1.24,2.45)	1.13 (0.80,1.61)	1.12 (0.80,1.58)
Insulin (mIU/ml) Median (Q1, Q3)	2.0 (2.0,4.4)	2.7 (2.0,5.8)	6.6 (5.0,9.0)	8.1 (6.0,11.2)	5.0 (4.0,7.0)	5.5 (4.0,8.0)
Glucose (mmol/L) Mean (SD)	5.0 (0.4)	4.9 (0.4)	5.1 (0.4)	4.9 (0.4)	4.9 (0.4)	4.7 (0.6)
Alcohol drinkers (%)	74.5	70.5	84.3	79.7	75.4	69.9
Alcohol intake (g/wk ethanol) Median (Q1, Q3)	80.0 (0.0,200.0)	50.0 (0.0,110.0)	105.3 (36.8,238.0)	46.5 (11.1,106.7)	82.8 (10.0,203.3)	43.6 (0.0,120.7)
Smoking (% smokers)	15.7	15.7	14.7	16.0	23.7	20.8
Physical Activity (METmin /week) Median (Q1, Q3)	7386.0 (3672.0, 12834.0)	10441.5 (3291.0, 17280.0)	3822.0 (1866.0, 7164.0)	2079.0 (810.0, 4678.0)	2697.0 (1200.0, 5112.0)	1972.5 (495.0, 3582.0)
Socio-economic status (SEIFA score) Median (Q1, Q3)	1080.9 (1008.3, 1118.4)	1069.7 (1006.8, 1116.5)	1081.1 (1004.8, 1119.6)	1066.5 (1004.7, 1111.8)	1076.0 (997.1, 1115.2)	1072.2 (1004.7, 1117.8)
Educational status (%)						
Category-1	76.5	73.8	52.3	51.7	26.1	24.5
Category-2	18.1	17.6	25.6	19.2	36.3	31.5
Category-3	5.4	8.6	22.1	29.1	37.7	44.0
[#]Contraceptive use in females (%)	-	60.0	-	59.4	-	49.1
Ethnicity (% Caucasians)	86.7	90.0	88.9	89.8	90.7	91.2
Breastfed >6 months (%)	58.6	56.6	59.5	56.8	59.1	53.1
Birthweight (g) Mean (SD)	3386.4 (517.9)	3304.9 (491.4)	3366.3 (544.6)	3303.2 (528.1)	3413.7 (575.9)	3337.6 (531.2)
Maternal (Gen1)						
BMI at 16-weeks (kg/m^2) Median (Q1, Q3)	22.8 (20.8,24.7)	23.1 (21.1,25.8)	22.7 (20.7,24.4)	23.4 (21.1,26.2)	22.9 (21.1,25.3)	23.4 (21.1,25.9)
Preterm delivery (%)	4.4	5.2	5.1	5.4	6.1	4.2
GDM (%)	2.5	1.4	3.5	1.6	3.3	0
Maternal smoking (%)	20.6	23.3	18.2	24.1	16.7	25.5
Alcohol drinkers (%)	60.8	56.7	58.6	54.6	58.6	57.9
Uncomplicated HTN (%)	27.7	20.0	24.9	20.9	26.2	19.4
Complicated HTN (%)	3.0	2.9	2.5	1.1	3.3	2.3
Low income (%)	31.7	34.6	36.9	34.3	38.4	34.0

SD- Standard deviation, Q1- 1st quartile or 25th percentile, Q3- 3rd quartile or 75th percentile; BMI-body mass index; HOMA-IR- Homeostatic Model Assessment of insulin resistance; hs-CRP- high sensitivity C-reactive protein; SEIFA: Socio-economic indexes for areas; Educational status: Category-1 Those completing high school, Category-2 Those with apprenticeship or vocational training, Category-3 Those in university #Contraception refers to the female use of hormonal contraceptives; GDM- gestational diabetes mellitus; HTN-hypertension; Uncomplicated-HTN: History of HTN before pregnancy or HTN during pregnancy without proteinuria or preterm delivery. Complicated-HTN: HTN during pregnancy with proteinuria (>2+ on dipstix test) or 300mg on 24-hour urinary protein excretion or preterm delivery. Low income- family income in 1989-1991, low being annual income <$24 000 (AUS).

Table-2: Fetal growth trajectories and their association with HOMA-IR

Abdominal Circumference (AC)							
[#]Trajectories (Group membership)	Group1 Low-falling 4.9% (n=28)	Group2 Low-stable 13.0% (n=75)	Group4 Average-falling 21.2% (n=122)	Group5 Average-rising 13.0% (n=75)	Group6 High-falling 17.2% (n=99)	Group7 High-rising 5.6% (n=32)	Global P-value
HOMA-IR (using BMI) Exponentiated β coefficients							
Model 1	1.26**	1.01	1.03	0.96	1.06	0.88	0.011
Model 2	1.27**	1.01	1.03	0.96	1.07	0.90	0.014
HOMA-IR (using WHtR) Exponentiated β coefficients							
Model 1	1.23**	1.01	1.00	0.96	1.04	0.89*	0.010
Model 2	1.23**	1.01	1.00	0.96	1.05	0.91	0.015

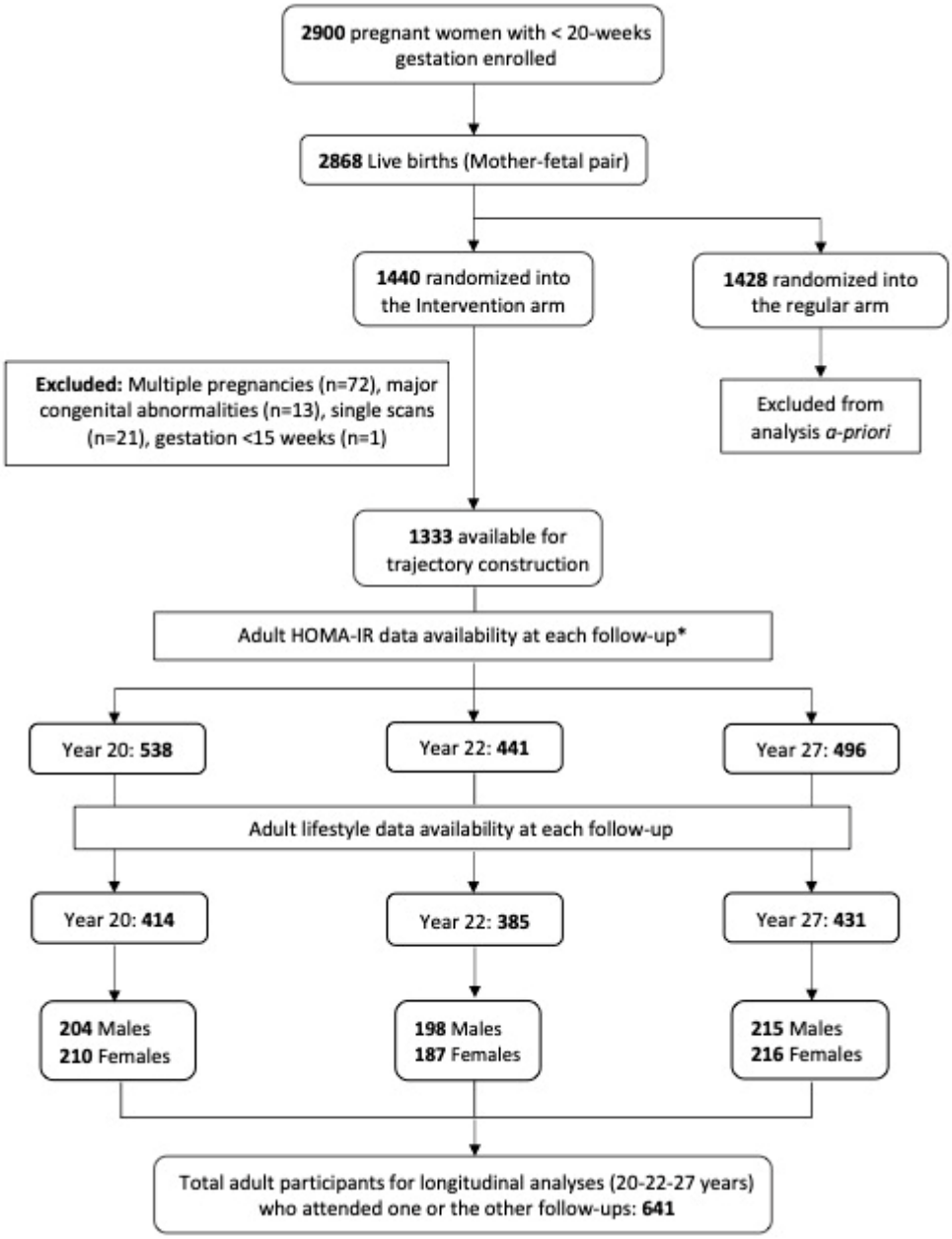
Femur Length (FL)					
[#]Trajectories (Group membership)	Group1 Low-falling 5.6% (n=32)	Group2 Very low-rising 8.0% (n=46)	Group3 Low-stable 30.8% (n=177)	Group5 High-stable 12.7% (n=73)	Global P-value
HOMA-IR (using BMI) Exponentiated β coefficients					
Model 1	0.99	0.94	0.98	0.88**	0.026
Model 2	0.99	0.94	0.98	0.87**	0.019
HOMA-IR (using WHtR) Exponentiated β coefficients					
Model 1	0.99	0.96	0.99	0.87***	0.005
Model 2	0.99	0.96	0.99	0.87***	0.005

Head Circumference (HC)					
[#]Trajectories (Group membership)	Group1 Low-stable 7.8% (n=45)	Group2 Average-falling 30.1% (n=173)	Group3 Low-rising 8.2% (n=47)	Group5 High-stable 12.2% (n=70)	Global P-value
HOMA-IR (using BMI) Exponentiated β coefficients					
Model 1	1.20**	1.08*	0.91**	0.92	<0.001
Model 2	1.20**	1.08*	0.90*	0.92	<0.001
HOMA-IR (using WHtR) Exponentiated β coefficients					
Model 1	1.17*	1.07*	0.90*	0.91*	<0.001
Model 2	1.17*	1.08*	0.90*	0.92	<0.001

Linear mixed modelling results displayed; HOMA-IR- Homeostatic Model Assessment for Insulin Resistance. WHtR- Waist-to-height Ratio. Significant P-values: *<0.05, **<0.01, ***<0.001.

[#]Trajectories based on 1333 participants; Reference group is Group-3 (Average-stable) with a membership of 25.0% (n=144) for abdominal circumference, Group-4 (Average-stable) with a membership of 43.0% (n=247) for femur length and Group-4 (Average-stable) with a membership of 41.7% (n=240) for head circumference. Sample size: Model 1 and 2: 1147 observations representing 575 participants who attended one or more follow up. Covariates: Model 1- age, sex, female contraceptive use, ethnicity, socioeconomic status, adult BMI & alcohol intake; Model 2- Model 1 plus maternal alcohol drinking.

Figure-1: Representation of the original cohort and subsequent follow ups



633 **Figure 2: Fetal growth trajectories highlighting the association with adult HOMA-IR**
634

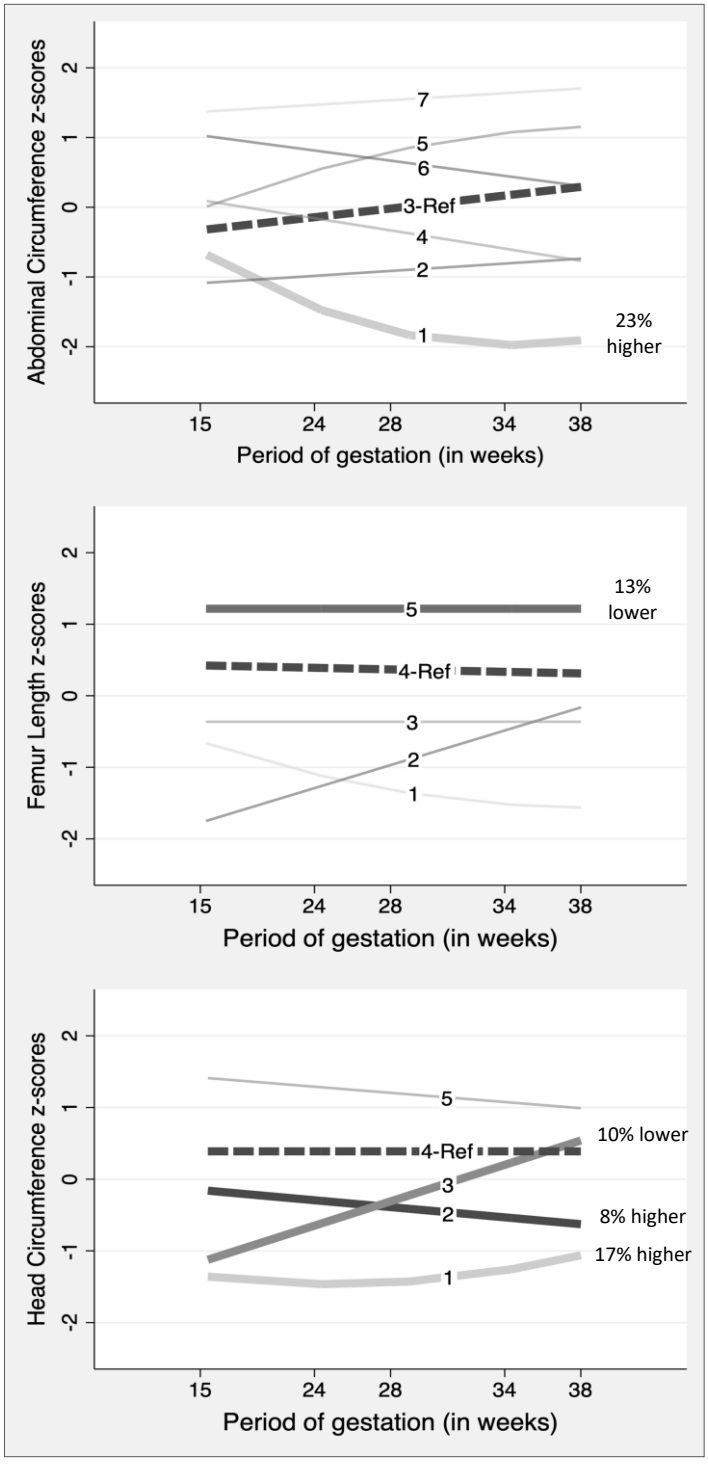


Figure Legends

Figure-1:

* HOMA-IR- Homeostatic Model Assessment of insulin resistance

Figure-2:

Y-axis: Standard deviation scores or z-scores for abdominal circumference (AC), femur length (FL) and head circumference (HC). X-axis: Gestational age in weeks.

Dashed lines (▬ ▬) represent the reference trajectory group while solid-bold lines (▬) represent those trajectory groups having a significant association with reference group. The percentages represent change in HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) values in the respective trajectory groups, compared to the HOMA-IR value in the reference group.

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