Maternal blood glucose level and offspring glucose–insulin homeostasis: what is the role of offspring adiposity?

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Abstract
Aims/hypothesis The aim of this work was to investigate the association of maternal HbA1c during mid-pregnancy with biomarkers of glucose–insulin homeostasis during early childhood (4–7 years of age) and to assess whether and how offspring adiposity at birth and at age 4–7 years mediates this relationship among 345 mother–child pairs in the Healthy Start Study.

Methods The exposure was maternal HbA1c (mmol/mol) measured at 20–34 gestational weeks and categorised into tertiles. The outcomes were offspring fasting glucose, 1/insulin, HOMA2-IR, and HOMA2-B at age 4–7 years. The mediators were per cent fat mass (%FM) at birth, %FM at age 4–7 years, and the sum of the two as a metric of cumulative adiposity. Mediation analyses were conducted via a counterfactual-based approach. All models accounted for maternal race/ethnicity, offspring age and sex.

Results There was a significant total effect of maternal HbA1c on offspring glucose and 1/insulin. Specifically, we observed a positive trend across tertiles of HbA1c and offspring glucose (p trend < 0.001), and an inverse trend across tertiles of HbA1c and offspring 1/insulin (p trend = 0.04). For instance, compared with offspring of women in the lowest tertile of HbA1c, whose mothers were in the second and third tertiles had 0.04 mmol/l (95% CI –0.05, 0.13) and 0.17 mmol/l (95% CI 0.08, 0.26) higher fasting glucose concentrations at age 4–7 years, respectively. Adjustment for pre-pregnancy BMI did not appreciably change the results. We found no evidence of mediation by offspring adiposity at any life stage.

Conclusions/interpretation Offspring of women with higher HbA1c during pregnancy had higher fasting glucose and lower insulin sensitivity by early childhood. These relationships were largely unaffected by the child’s own adiposity.

Keywords Childhood glucose metabolism • Lifecourse epidemiology • Maternal glycaemic control • Pregnancy

Abbreviations
ADP Air displacement plethysmography
FFM Fat-free mass
%FM Per cent fat mass

GDM Gestational diabetes mellitus
HAPO-FUS Hyperglycemia and Adverse Pregnancy Outcomes Follow-up Study

Introduction
Several studies show a dose–response relationship between maternal blood glucose levels (even below gestational diabetes mellitus [GDM] diagnostic criteria) and offspring adiposity starting at birth [1, 2] and biomarkers of glucose–insulin homeostasis as early as 7 years of age [3, 4]. Given the co-occurrence of excess adiposity and alterations in glucose–insulin homeostasis, it is challenging to disentangle how blood glucose levels during pregnancy influence offspring metabolism independent of adiposity. Further, the extent to which the relationship between maternal blood glucose and offspring metabolism is mediated by adiposity at a specific life
stage (e.g. infancy vs childhood) or cumulatively over time remains ambiguous.

Two recent studies from the Hyperglycemia and Adverse Pregnancy Outcomes [5] Follow-up Study (HAPO-FUS) investigated associations between maternal blood glucose and offspring metabolic biomarkers independent of adiposity [3, 6]. In both analyses, the association between maternal blood glucose and offspring biomarkers at 7–14 years of age was robust to adjustment for offspring BMI or sum of skinfolds, notwithstanding some slight attenuation in the estimate of interest, suggesting minimal mediation by offspring adiposity in late childhood and adolescence. Given that development of metabolic risk likely transpires from chronic excess adiposity, the dynamic changes in fat accrual across infancy and early childhood, and that these life stages are sensitive periods for development of obesity-related diseases, it is important to assess the role of adiposity during multiple life stages and consider the impact of cumulative adiposity over time.

In the present study, we close gaps in current literature by investigating the association of maternal HbA1c during mid-to-late pregnancy with fasting biomarkers of glucose–insulin homeostasis during early childhood (age 4–7 years). Use of HbA1c provides an assessment of blood glucose control over the prior 3–4 months, which is likely more relevant to offspring metabolism than acute assessments of maternal blood glucose levels. In the current study, HbA1c was assessed at 27 gestational weeks to capture early- to mid-pregnancy maternal glucose metabolism, which may be a sensitive gestational period for metabolic programming given that divergences in fetal growth trajectories become apparent at around 20 weeks [7] and that the maternal metabolic milieu during the first and second trimester is more strongly associated with offspring adiposity and metabolic risk than later in pregnancy [8].

In addition, we are interested in assessing whether offspring adiposity at birth and at 4–7 years of age may mediate the association of interest by way of two lifecourse epidemiological conceptual models: sensitive periods and accumulation of risk [9]. The conceptual model for testing these lifecourse models is depicted in Fig. 1. We hypothesised that higher maternal HbA1c is positively associated with glucose concentrations in offspring during early childhood (age 4–7 years) and that this relationship is mediated to the largest extent by cumulative adiposity.

**Methods**

**Study population** Study participants were from the Healthy Start Study, a prospective longitudinal cohort of 1410 racially/ethnically diverse pregnant women who were enrolled at ≤24 gestational weeks from prenatal clinics at the University of Colorado Hospital between 2009 and 2014 [10, 11]. In brief, women completed in-person research visits during pregnancy. Following delivery, air displacement plethysmography (ADP) and anthropometric measurements were taken on neonates prior to discharge. When offspring were 4–7 years of age, they returned for an in-person visit during which an assessment of body composition via ADP, anthropometry and a fasting blood sample were obtained. All mothers provided written informed consent and children 7 years of age or older provided written
assent. The study protocol and procedures were approved by the Colorado Multiple Institutional Review Board.

Of the offspring of the 1410 women enrolled in the study, 778 attended an in-person child visit at age 4–7 years. We excluded 77 women who did not have data on HbA1c during pregnancy and 87 offspring who did not have per cent fat mass (%FM) measurements at birth. We further excluded 263 mother–child pairs without data on offspring adiposity and metabolic biomarkers at age 4–7 years, followed by six children who had %FM values less than 4.5% and whose study record indicated movement during ADP measurement, yielding an analytic sample of 345 mother–child pairs (Fig. 2). We compared the maternal and offspring characteristics of those included vs excluded. The two samples were generally similar, except women in the analytical sample were ~1.1 years older than women excluded, and offspring were ~76.2 g heavier at birth and had ~1.2% higher fat mass at 4–7 years of age.

Exposure: maternal blood glucose levels during pregnancy At median 17 (range 11–20) and 27 (range 20–34) gestational weeks, fasting blood was drawn from the women. Our primary exposure of interest was HbA1c, assayed from blood collected at 27 weeks, measured using a potassium ferricyanide assay by DCA Vantage Analyzer (Siemens, USA). Our secondary exposure was glucose concentrations measured at both time points using manufacturer pre-packaged enzymatic kits and the AU400e Chemistry Analyzer (Olympus America), and insulin was measured using an RIA by Millipore Corporation (USA). We calculated 1/(fasting insulin) as a measure of insulin sensitivity [12] and calculated an updated HOMA (HOMA2-IR and HOMA2-B) [13].

Mediators: neonatal and early childhood adiposity Neonatal body composition, including fat mass and fat-free mass (FFM), was measured by PEA POD (Life Measurement, USA) using densitometric techniques based on ADP [14]. This technology assesses %FM via the direct measurement of a participant’s mass and volume. Mass is measured on an electronic scale. A chamber is used to measure volume by applying laws of gas to pressure changes in the volume of air in the enclosed chamber prior to and after the participant enters. Body density is computed from participants’ mass and volume and inserted into a standard formula [15] for estimating %FM [14]. Measurements for each participant were taken in triplicate and the average of the two closest measures was used for analyses. At the visit at age 4–7 years, fat mass and FFM were measured using whole-body air plethysmography (BodPod; Life Measurement) with the Pediatric Option [16]. For this analysis, we focused on %FM as the adiposity measure of interest because it provides an estimate of fat mass relative to total mass. In addition to assessing %FM at birth and at age 4–7 years, we took the sum across both time points to capture cumulative adiposity from birth through early childhood.

Outcomes: biomarkers of offspring glucose–insulin homeostasis Fasting glucose was measured using manufacturer pre-packaged enzymatic kits and the AU400e Chemistry Analyzer (Olympus America, USA).

Covariates and background characteristics We calculated maternal pre-pregnancy BMI (kg/m²) based on pre-pregnancy weight obtained from medical records (89%) or
self-report (11%) and height measured at the first research visit. GDM status was determined based on medical record review. Maternal race/ethnicity, educational attainment, parity and smoking status during pregnancy were self-reported via questionnaire.

Among all offspring in the analytic sample, gestational age at birth was abstracted from medical records and offspring’s weight and skinfold thickness were measured by trained nurses. Gestational age-specific birthweight z scores were derived using US natality data as reference [17]. Triceps, subscapular and mid-thigh skinfolds were measured in triplicate and the two closest measurements were averaged. Skinfolds were summed (sum of skinfolds) as a measure of subcutaneous adiposity. At the visit at age 4–7 years, a child’s age was calculated as the difference between date of the research visit and delivery date.

**Data analysis** Prior to formal analysis, we examined bivariate associations of maternal and offspring characteristics across tertiles of HbA1c. This step in conjunction with our prior knowledge informed selection of covariates, selection of potential confounders of the mediator–outcome relationship, and confounders of the mediator–outcome relationship that could be affected by exposure [18]. In the main analysis, we assessed HbA1c continuously as well as in tertiles to allow for potential non-linear associations. We tested for a linear trend by introducing the three-level variable as a continuous indicator, with each level set to the median value of each tertile [19]. Due to multiple participants with the same HbA1c value, the number of participants within each HbA1c tertile was unequal, with 151 participants in tertile 1, 98 in tertile 2 and 96 in tertile 3. For this reason, we focus our interpretation on associations with respect to tertiles of HbA1c.

In the multivariable linear regression models, maternal HbA1c (tertiles and per 1 mmol/mol) was the exposure and offspring glucose, 1/insulin, HOMA2-IR and HOMA2-B were assessed as separate outcomes. Model 1 adjusted for maternal race/ethnicity and offspring sex, age and number of days between birth and neonatal ADP assessment to account for potential changes in body composition following delivery. Model 2 further accounted for maternal pre-pregnancy BMI as a sensitivity analysis given the overlap in developmental pathways linking higher BMI and blood glucose level during pregnancy to offspring outcome [20].

We conducted mediation analysis using a counterfactual-based approach [18], which allows for exposure–mediator interactions, though we did not observe such interactions in our data. The Directed Acyclic Graphs for the analysis are shown in Fig. 3. We estimated the total effect (i.e. overall effect) of the exposure–outcome association (path C in Fig. 3), the exposure–mediator association (path A in Fig. 3), and the mediator–outcome association (path B in Fig. 3). When the mediator is included as a covariate (%FM at birth, age 4–7 years, or cumulative %FM), the exposure–outcome association is referred to as the natural direct effect (path C’ in Fig. 3). Here, we interpret the natural direct effect as the effect of HbA1c on offspring biomarkers that does not operate through offspring %FM. The magnitude of mediation
was determined by taking the difference between the total effect (path C in Fig. 3) and the natural direct effect (path C′ in Fig. 3) [18].

We tested two lifecourse epidemiological models to evaluate the role of %FM as a mediator: the sensitive-period model, wherein exposure to risk factors during a specific life stage has long-term effects on disease risk; and the accumulation-of-risk model wherein risk factors for disease accumulate across the lifecourse and have additive effects on disease risk. To assess whether %FM mediates the above associations via a sensitive-period or an accumulation-of-risk framework, we compared the natural direct effects between models that included %FM at birth, at age 4–7 years, or the sum of %FM across the two life stages as a metric of cumulative adiposity (Fig. 1). We hypothesised that if %FM followed a sensitive-period model, then the magnitude of mediation would be greater at a specific life stage. Alternatively, if %FM followed an accumulation-of-risk model, then inclusion of cumulative %FM would result in greater mediation than inclusion of either life stage by itself. For all models, we tested for an interaction with maternal race/ethnicity and offspring sex and considered stratified analyses if \( p \) for interaction was <0.05.

We performed sensitivity analyses to examine the robustness of our findings. First, rather than %FM, we used offspring BMI as the indicator of adiposity [21] and assessed this variable as a mediator using the same steps described above for %FM. Second, because maternal fasting glucose is a more commonly used metric of maternal blood glucose, we examined Pearson’s correlations among HbA1c with fasting glucose at 17 weeks (range 11–20) and at 27 weeks (range 20–34) and assessed whether the associations of interest differed when maternal fasting glucose at either time point was the exposure. Third, we excluded cases of preterm delivery (<37 gestational weeks), pre-eclampsia (\( n = 12 \)) and overt GDM (\( n = 14 \)) to assess the impact of these complications on results. All models met assumptions of multivariate normality. We considered two-sided \( p \) values <0.05 to be statistically significant. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

**Results**

**Characteristics** The mean ± SD age of the women at enrolment was 28.7 ± 6.0 years, most were non-Hispanic white (58.6%) and the median (range) of maternal HbA1c was 96.8 mmol/mol (59.5–134.1) (5.0% [3.7–6.1]). At the 4–7 years visit, the children were 4.8 ± 0.7 years of age and approximately half (46.7%) were female. As expected, we observed differences in membership of HbA1c tertiles by maternal race/ethnicity. For example, 70.9% of non-Hispanic white women were in the lowest tertile of HbA1c, as compared with 16.6% of Hispanic women and 9.9% of non-Hispanic black women (\( p \) for difference across all race/ethnic groups <0.001). We also observed an
inversely related to education level (p difference < 0.001) and a positive association for pre-pregnancy BMI (p trend < 0.001) with HbA1c. In terms of offspring characteristics, maternal HbA1c was positively correlated with indicators of adiposity at birth and during early childhood (age 4–7 years), with more prominent associations in early childhood. Higher maternal HbA1c corresponded with higher fasting glucose (p trend = 0.03), HOMA2-IR (p trend < 0.0001) and 1/(fasting insulin) (p trend = 0.01) during early childhood. Maternal HbA1c was not related to HOMA2-B. Additional participant characteristics are shown in Table 1.

**Total effect of maternal HbA1c and early childhood biomarkers of glucose–insulin homeostasis** Table 2 shows total effects of maternal HbA1c on the metabolic biomarkers in offspring. In Model 1, which accounted for maternal race/ethnicity and child’s age and sex, we observed a positive linear trend across tertiles of HbA1c in relation to offspring fasting glucose (p trend < 0.001). Specifically, offspring of women in the second and third tertiles of HbA1c had glucose concentrations that were 0.04 mmol/l (95% CI –0.05, 0.13) and 0.17 mmol/l (95% CI 0.08, 0.26), respectively, higher than those of women in the lowest tertile. We also found an inverse association for HbA1c tertiles and offspring 1/(fasting insulin) (p trend = 0.04). Adjustment for pre-pregnancy BMI in Model 2 did not change these results, although the upper confidence limit for 1/(fasting insulin) crossed the null.

**Assessment of offspring adiposity as mediator** Estimates of total effects and natural direct effects after inclusion of %FM at birth, at age 4–7 years and cumulatively across both life stages can be found in Table 3. Maternal HbA1c was positively associated with offspring %FM at both life stages individually and cumulatively (electronic supplementary material [ESM] Table 1), and all three metrics of %FM were associated with 1/(fasting insulin), HOMA-IR and HOMA-B, but not fasting glucose (ESM Table 2). Adjusting for offspring %FM at any time point did not appreciably attenuate the association of HbA1c with offspring biomarkers. After exploring different indicators of %FM, there was no indication that offspring %FM played a mediating role that followed the sensitive-period model or the accumulation-of-risk model.

To illustrate this, when comparing the total effect of the third tertile vs first tertile of HbA1c in relation to offspring glucose (0.17 mmol/l [95% CI 0.08, 0.26]), we observed minimal differences between this estimate and the natural direct effect after including %FM at birth (0.17 mmol/l [0.08, 0.27]; 0% change), % FM at 4–7 years (0.16 mmol/l [0.07, 0.26]; 6% decrease), and cumulative %FM (0.17 mmol/l [0.08, 0.26]; 0% change). Similarly, there were minimal differences between the natural direct effects and total direct effect for 1/(fasting insulin).

In all models, we noted similar but largely non-significant associations when continuous maternal HbA1c was the exposure of interest. This is likely due to the fact that, despite having a relatively normal distribution and meeting assumptions of multivariate normality, several women in our sample had a similar HbA1c (n = 98 [28.4%] with HbA1c = 96.8 mmol/mol [5.1%] or 99.7 mmol/mol [5.0%]), thereby reducing variability in the explanatory variable.

**Sensitivity analyses** In sensitivity analyses, we observed similar findings when using offspring BMI as a mediator and when maternal fasting glucose at 17 or 27 weeks was the exposure (ESM Table 3), which aligns with the finding that HbA1c was significantly positively correlated to maternal fasting glucose (ESM Table 4). We noted a statistical interaction between HbA1c and race/ethnicity for some of the offspring biomarkers but did not observe different associations in stratified models. Therefore, final models are among all race/ethnic groups. The magnitude and direction of associations were unchanged after excluding individuals experiencing preterm delivery, pre-eclampsia and GDM; thus we included these individuals in the study sample.

**Discussion**

In this prospective study of 345 racially/ethnically diverse US mother–offspring pairs, higher maternal early- to mid-pregnancy HbA1c, even below diagnostic levels for diabetes, corresponded with higher offspring fasting glucose levels and lower insulin sensitivity (1/(fasting insulin)) by 4–7 years of age, even after accounting for maternal pre-pregnancy BMI. Offspring adiposity at birth or at age 4–7 years, or cumulatively across the two time points, did not play a substantial role in mediating the effect of maternal HbA1c on metabolic biomarkers in offspring. These findings suggest the existence of alternative pathways through which maternal blood glucose levels may impact offspring glucose–insulin homeostasis.

**Maternal HbA1c is associated with biomarkers of glucose–insulin homeostasis in offspring** The total effect of maternal HbA1c on metabolic biomarkers in offspring was most evident for fasting glucose and 1/(fasting insulin), a biomarker of insulin sensitivity. This was consistent with findings from a small historical cohort of 89 mother–child dyads [22], a sample of 514 mother–offspring pairs in India [23], and an analysis among 4160 HAPO-FUS participants [24]. However, these previous studies focused on in utero exposure to overt maternal diabetes [23] or GDM [22, 24], whereas we were able to detect effects of maternal blood glucose levels on offspring metabolic biomarkers in a cohort of predominantly GDM-free women. The positive association between maternal HbA1c and offspring glucose, in conjunction with the inverse association with 1/(fasting insulin), could indicate diminished capacity to maintain glucose–insulin homeostasis among...
Table 1  Bivariate associations of maternal and offspring characteristics with maternal HbA1c

| Characteristic                              | Overall (n = 345) | HbA1c | Tertile 1 | Tertile 2 | Tertile 3 | p value |
|---------------------------------------------|-------------------|-------|-----------|-----------|-----------|---------|
| HbA1c, mmol/mol, median (range)             | 96.8 (59.5–134.1) | 89.4 (59.5–93.9) | 98.2 (96.8–99.7) | 107.5 (102.5–134.1) |          |         |
| HbA1c, %, median (range)                    | 5.0 (3.7–6.1)     | 4.8 (3.7–4.9)     | 5.1 (5.0–5.1)     | 5.3 (5.2–6.1)     | <0.001   |         |
| GA at HbA1c measurement, weeks              | 27 ± 2.4          | 26 ± 2.2          | 27 ± 2.4          | 27.8 ± 2.3         | <0.001   |         |
| Age at the first pregnancy visit, years     | 28.7 ± 6.0        | 28.5 ± 5.9        | 29.4 ± 6          | 28.2 ± 6.2         | 0.76     |         |
| Race/ethnicity                              |                   |                   |                       |                       | <0.001   |         |
| Non-Hispanic white                          | 202 (58.6)        | 107 (70.9)        | 60 (61.2)          | 35 (36.5)          |         |         |
| Non-Hispanic black                          | 52 (15.1)         | 15 (9.9)          | 15 (15.3)          | 22 (22.9)          |         |         |
| Hispanic                                    | 74 (21.5)         | 25 (16.6)         | 20 (20.4)          | 29 (30.2)          |         |         |
| Other                                       | 17 (4.9)          | 4 (2.6)           | 3 (3.1)            | 10 (10.4)          |         |         |
| Education                                   |                   |                   |                       |                       | <0.001   |         |
| High school or less                         | 94 (27.2)         | 32 (21.2)         | 24 (24.5)          | 38 (39.6)          |         |         |
| Some college/associates degree              | 79 (22.9)         | 28 (18.5)         | 26 (26.5)          | 25 (26.0)          |         |         |
| College graduate                            | 79 (22.9)         | 40 (26.5)         | 24 (24.5)          | 15 (15.6)          |         |         |
| Graduate degree                             | 93 (27.0)         | 51 (33.8)         | 24 (24.5)          | 18 (18.8)          |         |         |
| Nulliparous                                 | 160 (46.4)        | 74 (49.0)         | 55 (56.1)          | 56 (58.3)          | 0.13     |         |
| Smoked during pregnancy                     | 25 (7.2)          | 9 (5.9)           | 6 (6.2)            | 10 (10.4)          | 0.21     |         |
| Pre-pregnancy BMI, kg/m²                    | 25.9 ± 6.1        | 24.7 ± 5          | 26.5 ± 7.3         | 27.2 ± 6.0         | <0.001   |         |
| Gestational weight gainab                   |                   |                   |                       |                       | 0.09     |         |
| Insufficient                                | 56 (16.4)         | 21 (14.1)         | 10 (10.2)          | 25 (26.3)          |         |         |
| Adequate                                    | 47 (13.7)         | 23 (15.4)         | 14 (14.3)          | 10 (10.5)          |         |         |
| Excessive                                   | 239 (69.9)        | 105 (70.5)        | 74 (75.5)          | 60 (63.2)          |         |         |
| Offspring characteristics                    |                   |                   |                       |                       | <0.001   |         |
| Female sex                                  | 161 (46.7)        | 79 (52.3)         | 39 (40.2)          | 39 (44.3)          | 0.12     |         |
| Race/ethnicity                              |                   |                   |                       |                       | <0.001   |         |
| Non-Hispanic white                          | 185 (53.6)        | 95 (62.9)         | 54 (55.1)          | 36 (37.5)          |         |         |
| Non-Hispanic black                          | 43 (12.5)         | 14 (9.3)          | 9 (9.2)            | 20 (20.8)          |         |         |
| Hispanic                                    | 76 (22.0)         | 26 (17.2)         | 21 (21.4)          | 29 (30.2)          |         |         |
| Other                                       | 41 (11.9)         | 16 (10.6)         | 14 (14.3)          | 11 (11.5)          |         |         |
| Neonatal                                    |                   |                   |                       |                       |         |         |
| GA at delivery, weeks                       | 39.5 ± 1.2        | 39.6 ± 1.2        | 39.5 ± 1.2         | 39.4 ± 1.4         | 0.18     |         |
| Birthweight, g                              | 3166 ± 426        | 3147 ± 388        | 3158 ± 413         | 3205 ± 491         | 0.30     |         |
| Birthweight-for-gestational age z scorebc   | −0.6 ± 0.9        | −0.6 ± 0.8        | −0.6 ± 0.9         | −0.4 ± 0.9         | 0.06     |         |
| Fat mass, kg                                | 0.3 ± 0.1         | 0.3 ± 0.1         | 0.3 ± 0.1          | 0.3 ± 0.2          | 0.06     |         |
| %FM                                        | 9.5 ± 3.8         | 9.2 ± 3.6         | 9.4 ± 3.9          | 10.0 ± 4.0         | 0.11     |         |
| Sum of skinfolds, mm                        | 15.3 ± 3.7        | 15.3 ± 3.3        | 15.1 ± 3.8         | 15.5 ± 4.1         | 0.73     |         |
| Early childhood                             |                   |                   |                       |                       |         |         |
| Age, years                                  | 4.8 ± 0.7         | 4.7 ± 0.6         | 4.8 ± 0.8          | 4.9 ± 0.7          | 0.06     |         |
| BMI, kg/m²                                  | 15.6 ± 1.5        | 15.4 ± 1.4        | 15.6 ± 1.3         | 15.8 ± 1.7         | 0.04     |         |
| BMI-for-age z scored                       | 0.2 ± 1.0         | 0.1 ± 0.9         | 0.2 ± 0.9          | 0.3 ± 1.1          | 0.08     |         |
| Fat mass, kg                                | 3.8 ± 1.5         | 3.5 ± 1.3         | 3.8 ± 1.3          | 4.1 ± 1.7          | <0.001   |         |
| %FM                                        | 20.4 ± 6.1        | 19.9 ± 6.1        | 20.3 ± 6           | 21.1 ± 6.2         | 0.15     |         |
| Sum of skinfolds, mm                        | 32.5 ± 9.5        | 31.2 ± 8.8        | 31.1 ± 9.4         | 33.8 ± 10.5        | 0.03     |         |
| Glucose, mmol/l                             | 4.6 ± 0.4         | 4.5 ± 0.4         | 4.6 ± 0.3          | 4.7 ± 0.4          | 0.03     |         |
| HOMA2-IRd                                   | 0.8 ± 0.4         | 0.75 ± 0.37       | 0.81 ± 0.41        | 0.89 ± 0.39        | <0.001   |         |
| HOMA2-BEc                                   | 96.9 ± 27.0       | 95.2 ± 27.4       | 97.1 ± 26.9        | 98.5 ± 26.6        | 0.43     |         |
| 1/(fasting insulin), pmol/lf                | 0.03 ± 0.02       | 0.03 ± 0.01       | 0.03 ± 0.02        | 0.03 ± 0.01        | 0.01     |         |

Data are presented as mean ± SD or n (%) unless stated otherwise. Not all characteristics were observed within the 345 mother–offspring pairs; therefore, percentages represent the distribution among women or offspring with available data for the specific characteristic

a Other includes Asian, American Indian/Alaska natives, Hawaiian/Pacific Islanders and multiracial

b Gestational weight gain categories classified according to the Institute of Medicine 2009 guidelines [42]

c Birthweight z score specific to gestational age derived from US natality reference [17]

d BMI specific to age derived from WHO growth standards [43]

e Updated HOMA calculated using a computer program [13]

f A measure of insulin sensitivity [12]

p values represent type III main effects for categorical variables and are shown as p trend for ordinal variables test for significant differences across HbA1c tertiles based on generalised linear models

GA, gestational age
offspring exposed to higher maternal blood glucose levels in utero. While modest, the differences we detected are noteworthy given that decreases in insulin sensitivity and mild increases in fasting glucose are precursors to development of diabetes [25, 26]. Our data suggest that differences in glucose–insulin homeostasis are detectable as early as 4–7 years of age following exposure to a spectrum of HbA1c levels during gestation.

The effect of maternal HbA1c on offspring insulin–glucose metabolism is not mediated by adiposity. We did not find evidence for mediation by offspring adiposity at birth, at age 4–7 years, or cumulatively across both time points. While consistent with results of the aforementioned studies led by Scholtens et al [3] and Tam et al [6], these null findings are counter to our hypothesis, given that cumulative adiposity is a strong risk factor for dysregulated glucose–insulin homeostasis in children and adults [27, 28]. Regardless, adiposity tracks throughout the life course [29] and metabolic diseases transpire from chronic (as opposed to acute) exposures over time. Therefore, as offspring age, cumulative adiposity may become a more biologically relevant mediator. In studies assessing longitudinal effects of GDM on offspring insulin and glucose, differences in these biomarkers with respect to GDM exposure became greater as the children approached puberty [23, 30]. Thus, we suspect that differences in early childhood glucose–insulin homeostasis are likely to persist and become amplified later in life, with divergences in offspring metabolic trajectories proportional to the degree of maternal hyperglycaemia.

Potential mechanisms There are a few mechanisms that might link maternal hyperglycaemia to offspring glucose–insulin metabolism independent of offspring adiposity. Emerging data from human and animal studies suggest that chronic nutrient excess and beta cell overstimulation in early life lead to beta cell dysfunction, which later develops into hyperglycaemia [31]. Animal models also demonstrate that altered maternal insulin secretion and resistance directly alter fetal beta cell development, insulin secretion and insulin uptake by target tissues [32–34]. Additionally, we cannot rule out the effects of maternal adiposity on offspring metabolism, although in the present analysis, adjustment for maternal prepregnancy BMI did not change our findings. These mechanisms, either independently or jointly, may lead to unfavourable changes in development and function of key organs and tissues involved in glucose metabolism [34, 35].

Beyond fetal programming, the associations between higher maternal HbA1c and higher concentrations of glucose among offspring may simply represent shared genetic predisposition. However, studies in Pima Indians demonstrated that

| Biomarker | Model 1 | Model 2 |
|-----------|---------|---------|
|           | β (95% CI) | p value | β (95% CI) | p value |
| Glucose, mmol/l |         |         |         |         |
| HbA1c, T2 vs T1 | 0.04 (−0.05, 0.13) | 0.04 (−0.05, 0.13) |         |         |
| HbA1c, T3 vs T1 | 0.17 (0.08, 0.26)* | <0.001<sup>a</sup> | 0.16 (0.06, 0.25)<sup>a</sup> | <0.001<sup>a</sup> |
| HbA1c (per 1 mmol/mol) | 0.003 (−0.001, 0.008) | 0.14<sup>b</sup> | 0.003 (−0.002, 0.007) | 0.23<sup>b</sup> |
| 1/(fasting insulin), pmol/l |         |         |         |         |
| HbA1c, T2 vs T1 | −0.001 (−0.004, 0.003) | 0.000 (−0.004, 0.003) |         |         |
| HbA1c, T3 vs T1 | −0.004 (−0.008, −0.000)<sup>a</sup> | 0.04<sup>b</sup> | −0.004 (−0.008, 0.000) | 0.06<sup>a</sup> |
| HbA1c (per 1 mmol/mol) | −0.000 (−0.000, −0.000)<sup>a</sup> | 0.04<sup>b</sup> | −0.000 (−0.000, 0.000) | 0.07<sup>b</sup> |
| HOMA2-IR |         |         |         |         |
| HbA1c, T2 vs T1 | 0.05 (−0.05, 0.15) | 0.04 (−0.06, 0.14) |         |         |
| HbA1c, T3 vs T1 | 0.09 (−0.00, 0.20) | 0.08<sup>a</sup> | 0.08 (−0.02, 0.19) | 0.11<sup>a</sup> |
| HbA1c (per 1 mmol/mol) | 0.003 (−0.002, 0.008) | 0.21<sup>b</sup> | 0.002 (−0.002, 0.007) | 0.32<sup>b</sup> |
| HOMA2-B |         |         |         |         |
| HbA1c, T2 vs T1 | 1.10 (−5.65, 7.85) | 0.80 (−5.97, 7.58) |         |         |
| HbA1c, T3 vs T1 | 0.99 (−6.11, 8.08) | 0.78<sup>a</sup> | 0.62 (−6.52, 7.76) | 0.86<sup>a</sup> |
| HbA1c (per 1 mmol/mol) | 0.175 (−0.148, 0.498) | 0.29<sup>b</sup> | 0.156 (−0.170, 0.483) | 0.35<sup>b</sup> |

Model 1 adjusted for maternal race/ethnicity, child’s sex and age at assessment; Model 2 included the same adjustments as Model 1, and was additionally adjusted for prepregnancy BMI

* p trend
<sup>a</sup> p difference
<sup> Statistical significance at α = 0.05

T1, tertile 1; T2, tertile 2; T3, tertile 3
Table 3  Total and direct effects of maternal HbA1c on offspring biomarkers of glucose–insulin homeostasis at age 4–7 years and comparison of mediation by %FM at birth, during childhood (age 4–7 years) and cumulatively from birth to childhood

| Biomarker | Total effect | Natural direct effect |
|-----------|--------------|-----------------------|
|           | No adjustment for %FM | Adjusted for %FM at birth | Adjusted for %FM at age 4–7 years | Adjusted for cumulative %FM (at birth + age 4–7 years) |
|           | β (95% CI) | p value | β (95% CI) | p value | β (95% CI) | p value | β (95% CI) | p value |
| Glucose, mmol/l | | | | | | | | |
| HbA1c T2 vs T1 | 0.04 (−0.05, 0.13) | 0.05 (−0.04, 0.14) | 0.04 (−0.05, 0.13) | 0.05 (−0.04, 0.13) |
| HbA1c T3 vs T1 | 0.17 (0.08, 0.26)* | <0.001* | 0.17 (0.08, 0.27)* | <0.001* | 0.16 (0.07, 0.26)* | <0.001* | 0.17 (0.08, 0.26)* | <0.001* |
| HbA1c (per 1 mmol/mol) | 0.003 (−0.001, 0.008) | 0.14b | 0.004 (−0.001, 0.008) | 0.09b | 0.003 (−0.001, 0.008) | 0.15b | 0.003 (−0.001, 0.008) | 0.12b |
| 1/fasting insulin, pmol/l | | | | | | | | |
| HbA1c T2 vs T1 | −0.001 (−0.004, 0.003) | 0.04 (−0.004, 0.003) | −0.000 (−0.004, 0.003) | −0.000 (−0.004, 0.003) |
| HbA1c T3 vs T1 | −0.004 (−0.008, −0.000)* | 0.04* | −0.004 (−0.008, −0.000)* | 0.05* | −0.004 (−0.007, 0.000) | 0.08a | −0.003 (−0.007, 0.001) | 0.09a |
| HbA1c (per 1 mmol/mol) | −0.000 (−0.000, −0.000)* | 0.04* | −0.000 (−0.000, −0.000)* | 0.04* | −0.000 (−0.000, 0.000) | 0.06b | −0.000 (−0.000, 0.000) | 0.07b |
| HOMA2-IR | | | | | | | | |
| HbA1c T2 vs T1 | 0.05 (−0.05, 0.15) | 0.04 (−0.05, 0.14) | 0.04 (−0.06, 0.13) | 0.03 (−0.06, 0.13) |
| HbA1c T3 vs T1 | 0.09 (−0.00, 0.20) | 0.08a | 0.08 (−0.02, 0.19) | 0.11a | 0.07 (−0.03, 0.17) | 0.19a | 0.06 (−0.04, 0.16) | 0.23a |
| HbA1c (per 1 mmol/mol) | 0.003 (−0.002, 0.008) | 0.21b | 0.002 (−0.002, 0.007) | 0.31b | 0.002 (−0.002, 0.007) | 0.33b | 0.002 (−0.003, 0.006) | 0.51b |
| HOMA2-B | | | | | | | | |
| HbA1c T2 vs T1 | 1.10 (−5.65, 7.85) | 0.72 (−5.98, 7.43) | 0.44 (−6.14, 7.03) | 0.10 (−6.45, 6.65) |
| HbA1c T3 vs T1 | 0.99 (−6.11, 8.08) | 0.78a | −0.01 (−7.10, 7.09) | 0.99a | −0.74 (−7.70, 6.22) | 0.84a | −1.61 (−8.57, 5.35) | 0.71a |
| HbA1c (per 1 mmol/mol) | 0.175 (−0.148, 0.498) | 0.29b | 0.118 (−0.207, 0.443) | 0.48b | 0.130 (−0.186, 0.445) | 0.42b | 0.067 (−0.251, 0.385) | 0.68b |

Model 1 adjusted for maternal race/ethnicity, child's sex and age at assessment

* a p trend
b p difference
* Statistical significance at α = 0.05

T1, tertile 1; T2, tertile 2; T3, tertile 3
among siblings discordant for exposure to GDM, the likelihood of later developing diabetes was greater among the sibling exposed to the hyperglycaemic uterine environment, suggesting additional specific programming effects [36].

**Strengths and limitations** This study has several strengths. We used a state-of-the-art methodology for assessing offspring fat mass, whereas most previous studies [4, 6, 23, 30] used BMI, which represents both fat and FFM, or skinfolds, which are prone to measurement error. In addition, our sample included mother–offspring pairs from a diverse racial/ethnic background, thereby enhancing the generalisability of our findings. To our knowledge, our study is the first to examine cumulative adiposity from birth to early childhood (age 4–7 years) as mediating pathways underlying the relationship between in utero exposure to maternal blood glucose and offspring glucose–insulin homeostasis.

The current study is not without limitations. First, the Healthy Start Study at present may not be an ideal population in which to test life course models, given the lack of temporal separation between adiposity assessment and the metabolic biomarkers during early childhood. Follow-up analyses with greater temporal separation between timing of adiposity measurement and assessment of the metabolic biomarkers are warranted. Second, maternal HbA1c may be a less-sensitive biomarker of blood glucose level than fasting glucose; however, HbA1c reflects glucose control over a longer period, so may be more relevant to in utero metabolic programming and long-term offspring outcomes. Third, given the low proportion of women with GDM in this analysis, it is possible that our null findings with respect to mediation by offspring adiposity could be due to a potential threshold effect, though previous studies among offspring exposed to more extreme levels of in utero hyperglycaemia also found that size at birth did not mediate offspring metabolic outcomes [37]. Fourth, as with all observational studies, we cannot exclude the possibility for residual confounding by unmeasured factors. However, we did not find large or concerning changes in the estimates of association, which is a typical sign that assumptions of mediation have been violated. Last, our study was conducted within a relatively small sample size. However, we do not think this hampered our ability to detect meaningful associations, given that findings from our study align with those from studies of over 4000 mother–offspring pairs [3, 6].

**Conclusions and future directions** Our primary finding was that children born to women in the highest vs lowest tertile of HbA1c during early- to mid-pregnancy had 0.17 mmol/l higher fasting glucose at age 4–7 years. While this effect size is modest, it is worth noting that the Bogalusa Heart Study found that small differences in glucose during early life track into adulthood and that this is a better predictor of future diabetes risk than BMI z score or change in BMI [38]. Further, among middle-aged non-diabetic adults, a 10 mg/dl (0.55 mmol/l) difference in fasting glucose at baseline (~43 years of age) was associated with overt type 2 diabetes 7–8 years later [39]. Although our estimate is roughly one-third of that found among adults, estimates in the current study are likely of clinical relevance given the young age of the offspring, and prior studies indicating that these biomarkers track across life and are independent predictors of chronic disease risk [38]. The fact that we did not observe mediation by offspring adiposity contributes to ongoing efforts to identify targets for primordial prevention of chronic metabolic diseases [28]. Obesity plays a pathophysiological role in insulin resistance and dysglycaemia and, therefore, understanding the extent to which adiposity during early life stages mediates the relationship between in utero exposures and cardiometabolic health is of great interest. However, our results suggest the existence of alternative mechanistic pathways that operate beyond offspring adiposity. Future studies are required to determine whether this continues to be the case as children age. Complementary to continued follow-up in prospective cohorts are mechanistic studies nested within human cohorts [40, 41], which have the potential to further explore biological pathways underlying observed epidemiological associations. These efforts will improve understanding of how maternal hyperglycaemia affects offspring glucose–insulin homeostasis, and whether there are critical time points during which interventions can reroute risk trajectories.

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**Data availability** The datasets analysed during the current study are available from the corresponding author on reasonable request.

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**Contribution statement** ECF, WP and DD conceived the research question. ECF conducted the analysis, wrote the initial draft of the paper and incorporated co-author comments. BMR curated the data, provided feedback on the analysis, and critically reviewed the manuscript. KAS, DD and WP contributed to data interpretation and reviewed the manuscript. All co-authors approved the final version of the paper. ECF and WP are the guarantors of this work and, as such, had full access to all the data in the study and take
responsibility for the integrity of the data and the accuracy of the data analysis.

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