



# Maternal glucose levels during pregnancy and childhood adiposity in the Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study

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Received: 21 September 2018 / Accepted: 12 December 2018 / Published online: 15 January 2019  
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## Abstract

**Aims/hypothesis** Maternal type 2 diabetes during pregnancy and gestational diabetes are associated with childhood adiposity; however, associations of lower maternal glucose levels during pregnancy with childhood adiposity, independent of maternal BMI, remain less clear. The objective was to examine associations of maternal glucose levels during pregnancy with childhood adiposity in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) cohort.

**Methods** The HAPO Study was an observational epidemiological international multi-ethnic investigation that established strong associations of glucose levels during pregnancy with multiple adverse perinatal outcomes. The HAPO Follow-up Study (HAPO FUS) included 4832 children from ten HAPO centres whose mothers had a 75 g OGTT at ~28 weeks gestation 10–14 years earlier, with glucose values blinded to participants and clinical caregivers. The primary outcome was child adiposity, including: (1) being overweight/obese according to sex- and age-specific cut-offs based on the International Obesity Task Force (IOTF) criteria; (2) IOTF-defined obesity only; and (3) measurements >85th percentile for sum of skinfolds, waist circumference and per cent body fat. Primary predictors were maternal OGTT and HbA<sub>1c</sub> values during pregnancy.

**Results** Fully adjusted models that included maternal BMI at pregnancy OGTT indicated positive associations between maternal glucose predictors and child adiposity outcomes. For one SD difference in pregnancy glucose and HbA<sub>1c</sub> measures, ORs for each child adiposity outcome were in the range of 1.05–1.16 for maternal fasting glucose, 1.11–1.19 for 1 h glucose, 1.09–1.21 for 2 h glucose and 1.12–1.21 for HbA<sub>1c</sub>. Associations were significant, except for associations of maternal fasting glucose with offspring being overweight/obese or having waist circumference >85th percentile. Linearity was confirmed in all adjusted models. Exploratory sex-specific analyses indicated generally consistent associations for boys and girls.

**Conclusions/interpretation** Exposure to higher levels of glucose in utero is independently associated with childhood adiposity, including being overweight/obese, obesity, skinfold thickness, per cent body fat and waist circumference. Glucose levels less than those diagnostic of diabetes are associated with greater childhood adiposity; this may have implications for long-term metabolic health.

**Keywords** Adiposity · Childhood obesity · Glucose · Pregnancy

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Members of the HAPO Follow-up Study Cooperative Research Group are listed in the Appendix at the end of the manuscript.

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s00125-018-4809-6>) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

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## Abbreviations

GDM	Gestational diabetes mellitus
HAPO	Hyperglycemia and Adverse Pregnancy Outcome Study
HAPO FUS	HAPO Follow-up Study
IADPSG	International Association of Diabetes in Pregnancy Study Groups
IOTF	International Obesity Task Force

## Research in context

### What is already known about this subject?

- Diabetes during pregnancy and GDM are associated with childhood adiposity
- Associations of maternal glucose with childhood adiposity are often complicated by maternal adiposity and have generally been attenuated after adjusting for maternal BMI

### What is the key question?

- Are maternal glucose levels during pregnancy across a continuum of glucose levels, including lower levels than those diagnostic of GDM, associated with measures of childhood adiposity independent of maternal BMI?

### What are the new findings?

- Maternal glucose levels across a continuum at ~28 weeks of gestation were associated with childhood obesity and per cent body fat and sum of skinfolds >85th percentile, after adjustment for maternal BMI
- Maternal fasting, 1 h and 2 h glucose levels and HbA<sub>1c</sub> at ~28 weeks of gestation were positively associated with per cent fat, waist circumference and sum of skinfolds in children after adjustment for maternal BMI; the only exception was the lack of association of maternal fasting glucose with child waist circumference
- Most of the above associations were consistent between boys and girls

### How might this impact on clinical practice in the foreseeable future?

- These findings could have implications for glucose treatment targets in mothers with pre-existing diabetes or GDM and could inform approaches to the monitoring of glucose levels during pregnancy in mothers with other risk factors for offspring adiposity (e.g. obesity)

## Introduction

The intrauterine environment affects fetal development with maternal glucose and adiposity having independent associations with newborn adiposity [1–5]. Although both type 2 diabetes mellitus during pregnancy and gestational diabetes mellitus (GDM) are associated with childhood adiposity, women with these conditions are more likely to be overweight or obese. Thus, the independent relationship between maternal hyperglycaemia and childhood adiposity is less clear. Previous studies of maternal glucose levels during pregnancy and childhood obesity have generally focused on women with pre-existing diabetes (type 1 or type 2 diabetes) or GDM and were often confounded by, or did not account for, diabetes treatment or maternal BMI [6–13]. Studies of the association of maternal glucose across a spectrum of glucose values with childhood adiposity outcomes have not been reported.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study recruited a large, multinational, racially and ethnically diverse cohort of women and showed that glucose levels during pregnancy, below those diagnostic of diabetes, were associated with adverse newborn outcomes and that these associations were continuous across increasing levels of glucose [4]. The HAPO Follow-up Study (HAPO FUS) offered a unique opportunity to examine associations of maternal glucose levels during pregnancy with childhood adiposity, not

confounded by treatment of maternal hyperglycaemia. We recently reported that, while GDM based on International Association of Diabetes in Pregnancy Study Groups (IADPSG) criteria [14, 15] was not associated with an increase in being overweight/obese in childhood, it was associated with a higher risk of obesity and other measures of adiposity, including sum of skinfolds, per cent body fat and waist circumference >85th percentile, in children aged 10–14 years from the HAPO FUS cohort [16]. The objective of the analyses reported herein was to assess whether in utero exposure to levels of maternal glucose across the continuous spectrum of glucose values, including values less than those diagnostic of GDM based on IADPSG criteria, is also associated with adiposity, including being overweight/obese, obesity and other anthropometric measures in children from the HAPO FUS cohort.

## Methods

HAPO Study methods have been described [4, 17, 18]. Briefly, eligible women underwent a 75 g OGTT at 24–32 weeks' gestation. Fasting, 1 h, and 2 h plasma glucose, and HbA<sub>1c</sub> were measured. Maternal height, weight and blood pressure were measured at the time of the pregnancy OGTT using standard procedures and calibrated equipment. Demographic data including race/ethnicity were collected via questionnaire and

parity by medical record abstraction. OGTT results remained blinded to caregivers and participants unless fasting glucose was  $>5.8$  mmol/l and/or 2 h glucose was  $>11.1$  mmol/l or if either measure was  $<2.5$  mmol/l [4, 17, 18]. Data from unblinded women were not included in HAPO analyses.

## Participants

HAPO FUS participants were recruited during 2013–2016 from ten of 15 original HAPO field centres that demonstrated feasibility for this study. Eligibility criteria included the following: having remained blinded to OGTT results during HAPO; gestational age at delivery  $\geq 37$  weeks and no major neonatal malformations or fetal/neonatal death. This yielded 15,812 eligible mother–child pairs (electronic supplementary material [ESM] Table 1). A target sample size of 7000 was specified, with 300 mother–child pairs to be recruited at Chicago and Cleveland and 800 at each of the other eight field centres [16].

Multiple attempts were made to contact all eligible participants through various means approved by local institutional review boards. Screening questionnaires were completed by 9322 eligible mothers over the telephone to ascertain willingness to participate and confirm eligibility. From these, 4834 children completed all or part of the HAPO FUS visit, which represented 69.1% of the recruitment goal of 7000 mother–child pairs (Fig. 1). Data from two children were excluded, one due to inadequate fasting and one because of inability to complete the protocol due to autism spectrum disorder, leaving 4832 children for analyses. Of these, 4821 had at least one physical measurement, while 4775 had BMI measurements and were analysed for overweight/obesity outcomes.

The HAPO FUS Protocol was approved by each centre's institutional review board. All mothers gave written informed consent for their child's participation and children provided assent where required. The study was overseen by an external Observational Study Monitoring Board.

## Study visit

During the HAPO FUS visit, height was measured twice (with the participant's shoes removed) to the nearest 0.5 cm with a stadiometer and was measured for a third time if results differed by  $>1.0$  cm. Weight was measured twice on a calibrated scale to the nearest 0.1 kg and was measured for a third time if results differed by  $>0.5$  kg. Waist circumference was measured twice at the iliac crest to the nearest 0.1 cm and was measured for a third time if results differed by  $>1.0$  cm. Skinfolds were measured (triceps, subscapular, suprailiac) twice with calibrated calipers (Harpenden, London, UK) to the nearest 0.1 mm and were measured for a third time if

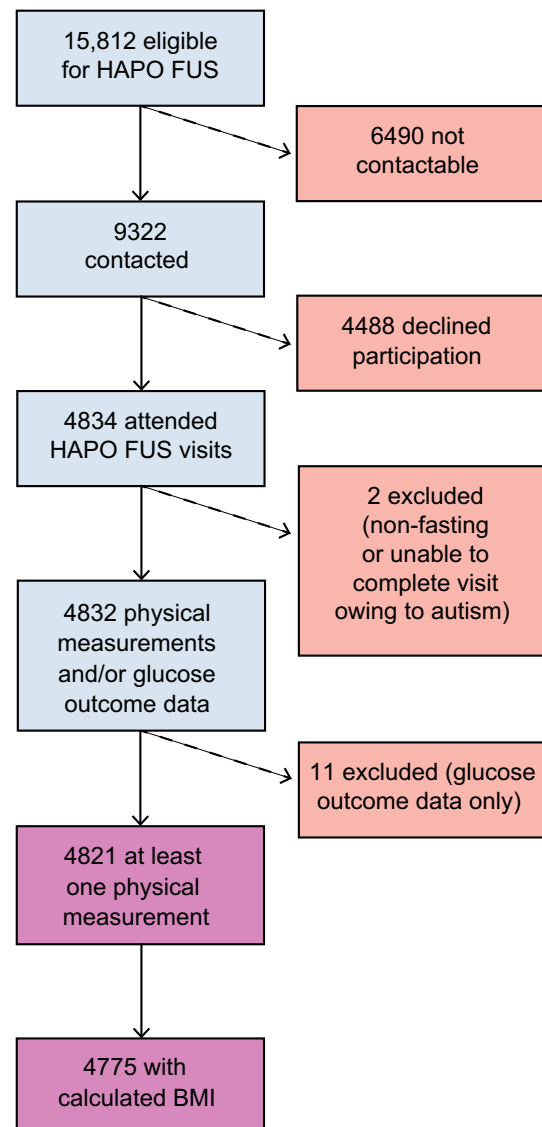


Fig. 1 Flowchart illustrating enrolment for HAPO FUS

results differed by  $>1.0$  mm. Means of the two measurements, or the two closest measurements if three measurements were made, were used for analysis. Per cent fat was measured by air displacement plethysmography using a BOD POD (Cosmed, Rome, Italy). Tanner staging was performed by trained individuals using breast/areolar development for girls and testicular volume (Prader orchidometer) for boys. Mothers provided girls' menstrual status via questionnaire.

## Outcomes

Child adiposity was the primary outcome and included the following: (1) children who were overweight/obese according to age- and sex-specific cut-offs based on International Obesity Task Force (IOTF) criteria (Asian-specific cut-offs were used for self-reported Asian children and international cut-offs were used for all other children [19]); (2) IOTF-

defined obesity only; and (3) measurements of per cent body fat (BOD POD), waist circumference and sum of skinfolds >85th percentile according to quantile regression adjusted for sex, age and field centre. BMI, BMI *z* score [19], per cent body fat, waist circumference and sum of skinfolds were also assessed as continuous outcomes.

## Predictors

The primary predictors were continuous values of fasting, 1 h and 2 h glucose and HbA<sub>1c</sub> from the original HAPO OGTT during pregnancy. Continuous predictors were scaled by their SDs as estimated in original HAPO data.

Additionally, to confirm graded associations, these continuous variables were divided into discrete categorical variables with five categories for each measure. The fifth and highest category for each measure corresponded to IADPSG diagnostic thresholds for GDM. The lowest three categories for fasting, 1 h and 2 h glucose were the same as those used for analyses of glucose levels during the original HAPO Study. The fourth category included values between the third and fifth categories. For the HbA<sub>1c</sub> values, the lowest three categories were used during the original HAPO Study and the fourth and fifth categories combined smaller categories used for original analyses of HbA<sub>1c</sub> in HAPO. Categories were defined as follows: fasting glucose  $\leq 4.2$ , 4.2–4.4, 4.5–4.7, 4.8–5.0,  $\geq 5.1$  mmol/l; 1 h glucose  $\leq 5.8$ , 5.9–7.3, 7.4–8.6, 8.7–9.9,  $\geq 10.0$  mmol/l; 2 h glucose  $\leq 5.0$ , 5.1–6.0, 6.1–6.9, 7.0–8.4,  $\geq 8.5$  mmol/l; HbA<sub>1c</sub>  $\leq 25$ , 26–28, 29–31, 32–36,  $\geq 37$  mmol/mol ( $\leq 4.4$ , 4.5–4.7, 4.8–5.0, 5.1–5.4,  $\geq 5.5\%$ ).

## Statistical analyses

HAPO FUS data were summarised using frequencies and counts for categorical variables and means and SDs for continuous variables. Summary statistics from pregnancy were also compared for eligible children who did and did not participate in HAPO FUS, including field-centre summaries weighted by the proportion of the total eligible at each field centre. Histograms and boxplots were examined to determine the shape of distributions and to identify potential outlying observations. Multiple logistic regression was used for dichotomous outcomes; results are reported as ORs with 95% CIs. Multiple linear regression was used for continuous outcomes; results are reported as regression coefficients ( $\beta$  estimates) with 95% CIs. Multiple models were considered for all outcomes, with variables identified according to study design, known potential confounders and adjustments used in HAPO analyses [4, 16]. Covariate adjustments were examined as follows: Model 1: field centre, sex, child's age at follow-up. Since IOTF definitions are sex- and age-specific, Model 1 for IOTF outcomes included field centre adjustment only.

For per cent body fat, waist circumference and sum of skinfolds >85th percentiles, logistic regression Model 1 was unadjusted since 85th percentiles included age, sex and field centre in their definition. Model 2 was as for Model 1 plus adjustment for child's pubertal status (Tanner stage 1, 2/3, 4/5) with sex-by-Tanner stage interaction. Model 3 was as for Model 2 plus adjustment for maternal variables at pregnancy OGTT (age, height, family history of diabetes in first-degree relatives, mean arterial pressure, parity [0, 1+], smoking (yes/no), alcohol (yes/no), gestational age). Model 4 was as for Model 3 plus adjustment for maternal BMI at pregnancy OGTT. Exploratory analyses were also conducted to evaluate differences in associations according to sex and race/ethnicity, using field centre as a proxy for race/ethnicity. Statistical interaction terms between continuous maternal glucose and HbA<sub>1c</sub> with sex and field centre were reviewed, and group-specific model variable estimates were compared. Multiple imputation under a 'missing at random' assumption [20, 21] using the *mice* R package [22] was used for imputation of all missing data, with Tanner stage being the primary source of missingness, and incorporated sex steroid measurements (ESM Methods). Logistic regression model fit was measured by *C* statistics and confirmed by Hosmer–Lemeshow goodness-of-fit tests [23]. Linear regression model fit was assessed by scatterplots of residuals vs fitted values, histograms and qqplots of residuals, and DFBeta statistics. Adjusted *R*<sup>2</sup> values were used to gauge variability explained in linear models. Quadratic terms and restricted cubic splines estimated with the *rms* R package [24] were used to assess linearity between the continuous predictor and the log odds of the outcome for logistic regression models and continuous outcomes for linear regression models. All analyses were conducted in R (3.4.1) [25].

## Results

### Participants

Characteristics of participating children during HAPO FUS and their mothers during HAPO are shown in Table 1. The mean age of the children at follow-up was 11.4 years. The mean age at the time of the HAPO OGTT and frequency of GDM according to IADPSG criteria [14] among mothers of offspring who did not participate (unable to contact or declined) was 29.1 years and 16.9%, respectively, compared with 30.0 years and 14.9% among mothers of offspring who participated (ESM Table 1). Mean maternal BMI, HbA<sub>1c</sub> and fasting, 1 h and 2 h glucose during the HAPO OGTT and race/ethnicity were similar between groups who did and did



not participate (summaries weighted to reflect full eligible population, ESM Table 1).

### Model diagnostics

Hosmer–Lemeshow  $p$  values for logistic regression models with continuous maternal glucose and HbA<sub>1c</sub> predictors were in the range 0.06–0.99 for all outcomes, indicating reasonable model fit.  $C$  statistics for logistic regression models with continuous maternal glucose and HbA<sub>1c</sub> predictors were in the range 0.54–0.77 and  $R^2$  values were in the range 0.04–0.35 for continuous maternal glucose and HbA<sub>1c</sub> predictors with continuous outcomes. Both  $C$  statistics and  $R^2$  values increased across Models 1–4, suggesting improved fit for additional covariate adjustments (Tables 2 and 3). Co-linearity was not a concern with pairwise correlations in the range 0–0.20 for model covariates. Visual inspection of residual plots confirmed linear modelling assumptions and DFBeta statistics indicated no observations of undue influence. Quadratic terms and restricted cubic spline modelling indicated no significant departure from linearity for all analyses of continuous maternal glucose and HbA<sub>1c</sub> predictors with  $p$  values in the range 0.29–0.98.

### Continuous measures of maternal glucose level and childhood adiposity

Initial analyses examined the association of maternal glucose across the continuum with dichotomous child adiposity outcomes. ORs for each dichotomous child adiposity outcome were estimated for one SD difference in maternal fasting, 1 h and 2 h glucose, and HbA<sub>1c</sub> during pregnancy (Table 2). In Models 1–3, positive associations for each child adiposity outcome were observed for higher levels of each glucose measure and HbA<sub>1c</sub>. ORs were attenuated after adjusting for maternal BMI during pregnancy (Model 4). However, for one SD difference in pregnancy glucose and HbA<sub>1c</sub> measures, ORs for each child adiposity outcome were in the range of 1.05–1.16 for maternal fasting glucose, 1.11–1.19 for 1 h glucose, 1.09–1.21 for 2 h glucose and 1.12–1.21 for HbA<sub>1c</sub> (Table 2). All of these results were significant except for the associations of maternal fasting glucose with offspring being overweight/obese or having waist circumference >85th percentile. Linearity for the continuous maternal glucose and HbA<sub>1c</sub> predictors was confirmed as described above.

Linear associations of continuous child BMI  $z$  score, per cent fat, waist circumference and sum of skinfolds with maternal fasting, 1 h and 2 h glucose and HbA<sub>1c</sub> during pregnancy were also evaluated (Table 3). In Models 1–3, positive associations for each continuous child adiposity outcome were observed for one SD differences in each maternal glucose measure and HbA<sub>1c</sub>. Associations were again attenuated after adjusting for maternal BMI during pregnancy (Model 4). For child BMI  $z$  score, associations with maternal fasting, 1 h and

**Table 1** Characteristics of mothers during HAPO pregnancy OGTT and their children at follow-up

Characteristic	$N = 4832$ Mean (SD)
<b>Mothers during HAPO pregnancy</b>	
Age at OGTT, years	29.9 (5.7)
Gestational age at OGTT, weeks	27.7 (1.7)
Height, cm	161.8 (6.8)
Weight, kg	72.0 (14.2)
BMI, kg/m <sup>2</sup>	27.5 (4.9)
Mean arterial pressure, mmHg	80.5 (8.0)
Fasting glucose, mmol/l	4.5 (0.4)
1 h glucose, mmol/l	7.4 (1.7)
2 h glucose, mmol/l	6.1 (1.3)
HbA <sub>1c</sub> , mmol/l	29.0 (4.5)
HbA <sub>1c</sub> , %	4.8 (0.4)
<b>Race/Ethnicity</b>	
White, non-Hispanic, $n$ (%)	2287 (47.3)
Hispanic, $n$ (%)	507 (10.5)
Black, non-Hispanic, $n$ (%)	775 (16.0)
Asian, $n$ (%)	1176 (24.3)
Other, $n$ (%)	87 (1.8)
Any prenatal smoking, $n$ (%)	245 (5.1)
Any prenatal alcohol use, $n$ (%)	406 (8.4)
Parity (any prior delivery $\geq 20$ weeks), $n$ (%)	2485 (51.4)
Family history of diabetes, $n$ (%)	1077 (22.3)
<b>Children at follow-up</b>	
Age, years	11.4 (1.2)
Height, cm	148.6 (10.2)
Weight, kg	43.2 (13.3)
Sex, female, $n$ (%)	2367 (49.0)
<b>Tanner stage, girls, <math>n</math> (%)</b>	
1	381 (19.0)
2/3	853 (42.5)
4/5	774 (38.5)
<b>Tanner stage, boys, <math>n</math> (%)</b>	
1	565 (36.0)
2/3	726 (46.2)
4/5	279 (17.8)

Data are shown as means (SD) or  $n$  (%)

2 h glucose were not significant after adjustment for maternal BMI during pregnancy. Associations between child per cent fat and maternal HbA<sub>1c</sub> and child waist circumference and maternal fasting glucose were also not significant in the fully adjusted Model 4. However, all other associations between continuous maternal glucose levels and HbA<sub>1c</sub> and continuous child adiposity outcomes were positive and statistically significant. As described above, linearity of all observed associations was confirmed.

**Table 2** Associations of continuous measures of maternal glucose and HbA<sub>1c</sub> during pregnancy with dichotomous adiposity outcomes among children at follow-up

Predictor	Model 1 <sup>a</sup>			Model 2 <sup>b</sup>			Model 3 <sup>c</sup>			Model 4 <sup>d</sup>		
	OR (95% CI)	p value	C statistic	OR (95% CI)	p value	C statistic	OR (95% CI)	p value	C statistic	OR (95% CI)	p value	C statistic
<b>IOTF overweight/obese</b>												
Fasting glucose	1.27 (1.19, 1.36)	<0.001***	0.64	1.26 (1.18, 1.35)	<0.001***	0.67	1.22 (1.13, 1.31)	<0.001***	0.70	1.05 (0.98, 1.14)	0.19	0.74
1 h glucose	1.22 (1.14, 1.30)	<0.001***	0.64	1.21 (1.13, 1.29)	<0.001***	0.67	1.18 (1.10, 1.27)	<0.001***	0.69	1.11 (1.03, 1.19)	0.006**	0.74
2 h glucose	1.17 (1.10, 1.25)	<0.001***	0.64	1.18 (1.10, 1.26)	<0.001***	0.67	1.15 (1.07, 1.23)	<0.001***	0.69	1.09 (1.01, 1.17)	0.019*	0.74
HbA <sub>1c</sub>	1.23 (1.15, 1.33)	<0.001***	0.64	1.25 (1.16, 1.35)	<0.001***	0.67	1.24 (1.15, 1.34)	<0.001***	0.69	1.12 (1.04, 1.22)	0.004**	0.74
<b>IOTF obesity</b>												
Fasting glucose	1.40 (1.28, 1.54)	<0.001***	0.69	1.40 (1.27, 1.53)	<0.001***	0.71	1.34 (1.21, 1.48)	<0.001***	0.74	1.16 (1.05, 1.29)	0.005**	0.77
1 h glucose	1.24 (1.13, 1.36)	<0.001***	0.68	1.23 (1.12, 1.35)	<0.001***	0.70	1.20 (1.08, 1.32)	<0.001***	0.73	1.13 (1.01, 1.25)	0.025*	0.77
2 h glucose	1.28 (1.17, 1.40)	<0.001***	0.68	1.29 (1.18, 1.41)	<0.001***	0.71	1.25 (1.14, 1.38)	<0.001***	0.71	1.21 (1.09, 1.34)	<0.001***	0.78
HbA <sub>1c</sub>	1.37 (1.23, 1.52)	<0.001***	0.69	1.37 (1.23, 1.52)	<0.001***	0.71	1.36 (1.22, 1.52)	<0.001***	0.74	1.21 (1.08, 1.35)	<0.001***	0.77
<b>BOD POD % fat &gt;85th percentile<sup>e</sup></b>												
Fasting glucose	1.35 (1.25, 1.47)	<0.001***	0.54	1.34 (1.24, 1.46)	<0.001***	0.62	1.29 (1.18, 1.41)	<0.001***	0.65	1.15 (1.05, 1.26)	0.002**	0.68
1 h glucose	1.27 (1.17, 1.38)	<0.001***	0.55	1.25 (1.15, 1.36)	<0.001***	0.62	1.23 (1.13, 1.34)	<0.001***	0.65	1.18 (1.08, 1.29)	<0.001***	0.69
2 h glucose	1.20 (1.10, 1.29)	<0.001***	0.54	1.20 (1.11, 1.30)	<0.001***	0.61	1.19 (1.09, 1.29)	<0.001***	0.64	1.15 (1.06, 1.26)	0.001**	0.69
HbA <sub>1c</sub>	1.25 (1.14, 1.36)	<0.001***	0.52	1.25 (1.14, 1.37)	<0.001***	0.61	1.23 (1.12, 1.35)	<0.001***	0.64	1.14 (1.03, 1.25)	0.009**	0.68
<b>Waist circumference &gt;85th percentile<sup>e</sup></b>												
Fasting glucose	1.34 (1.23, 1.45)	<0.001***	0.54	1.31 (1.21, 1.42)	<0.001***	0.61	1.25 (1.14, 1.36)	<0.001***	0.65	1.09 (0.99, 1.19)	0.067	0.69
1 h glucose	1.22 (1.13, 1.32)	<0.001***	0.55	1.22 (1.12, 1.32)	<0.001***	0.60	1.21 (1.11, 1.32)	<0.001***	0.64	1.15 (1.05, 1.26)	0.002**	0.69
2 h glucose	1.20 (1.10, 1.29)	<0.001***	0.53	1.21 (1.12, 1.31)	<0.001***	0.60	1.20 (1.11, 1.31)	<0.001***	0.64	1.17 (1.07, 1.27)	0.003**	0.69
HbA <sub>1c</sub>	1.23 (1.13, 1.34)	<0.001***	0.52	1.27 (1.16, 1.38)	<0.001***	0.60	1.26 (1.15, 1.38)	<0.001***	0.65	1.15 (1.05, 1.27)	0.004**	0.69
<b>Sum of skinfolds &gt;85th percentile<sup>e</sup></b>												
Fasting glucose	1.36 (1.25, 1.47)	<0.001***	0.54	1.34 (1.23, 1.45)	<0.001***	0.61	1.30 (1.19, 1.41)	<0.001***	0.64	1.16 (1.06, 1.27)	0.001**	0.67
1 h glucose	1.25 (1.16, 1.36)	<0.001***	0.55	1.26 (1.16, 1.37)	<0.001***	0.60	1.24 (1.14, 1.35)	<0.001***	0.64	1.19 (1.09, 1.30)	<0.001***	0.68
2 h glucose	1.23 (1.14, 1.33)	<0.001***	0.54	1.25 (1.15, 1.36)	<0.001***	0.60	1.24 (1.14, 1.35)	<0.001***	0.63	1.21 (1.11, 1.31)	<0.001***	0.68
HbA <sub>1c</sub>	1.25 (1.15, 1.37)	<0.001***	0.52	1.26 (1.15, 1.38)	<0.001***	0.59	1.24 (1.13, 1.36)	<0.001***	0.63	1.15 (1.05, 1.26)	0.004**	0.67

ORs for the dichotomous outcomes are for the continuous predictors higher by one SD estimated in the original HAPO data: fasting glucose 0.4 mmol/l; 1 h glucose 1.7 mmol/l; 2 h glucose 1.3 mmol/l; HbA<sub>1c</sub> 5.0 mmol/mol (0.45%)

p values are from logistic regression model; \* p < 0.05, \*\* p < 0.01 and \*\*\* p < 0.001

<sup>a</sup>Model 1: adjusted for field centre for being overweight/obese and obesity outcomes; unadjusted for BOD POD % fat, waist circumference and sum of skinfolds >85th percentile outcomes

<sup>b</sup>Model 2: Model 1 + child pubertal status (Tanner stage 1, 2/3, 4/5, sex × Tanner stage interaction)

<sup>c</sup>Model 3: Model 2 + maternal variables during pregnancy OGTT (age, height, any family history of diabetes, mean arterial pressure, parity [0, 1+], smoking [yes/no], alcohol [yes/no], gestational age)

<sup>d</sup>Model 4: Model 3 + maternal BMI during pregnancy

<sup>e</sup>85th percentiles were determined using quantile regression adjusted for age, sex and field centre

**Table 3** Associations of continuous measures of maternal glucose and HbA<sub>1c</sub> during pregnancy with continuous adiposity outcomes among children at follow-up

Predictor	Model 1 <sup>a</sup>			Model 2 <sup>b</sup>			Model 3 <sup>c</sup>			Model 4 <sup>d</sup>		
	$\beta$ (95% CI)	<i>p</i> value	Adjusted <i>R</i> <sup>2</sup>	$\beta$ (95% CI)	<i>p</i> value	Adjusted <i>R</i> <sup>2</sup>	$\beta$ (95% CI)	<i>p</i> value	Adjusted <i>R</i> <sup>2</sup>	$\beta$ (95% CI)	<i>p</i> value	Adjusted <i>R</i> <sup>2</sup>
<b>BMI z score</b>												
Fasting glucose	0.14 (0.10, 0.18)	<0.001***	0.07	0.13 (0.09, 0.16)	<0.001***	0.13	0.10 (0.06, 0.14)	<0.001***	0.15	0.001 (-0.04, 0.04)	0.96	0.22
1 h glucose	0.10 (0.06, 0.14)	<0.001***	0.07	0.09 (0.06, 0.12)	<0.001***	0.14	0.07 (0.03, 0.10)	<0.001***	0.14	0.02 (-0.01, 0.05)	0.26	0.22
2 h glucose	0.08 (0.04, 0.11)	<0.001***	0.07	0.08 (0.04, 0.11)	<0.001***	0.12	0.05 (0.02, 0.09)	0.003**	0.14	0.02 (-0.02, 0.05)	0.38	0.22
HbA <sub>1c</sub>	0.13 (0.09, 0.16)	<0.001***	0.07	0.14 (0.10, 0.18)	<0.001***	0.21	0.13 (0.09, 0.16)	<0.001***	0.22	0.06 (0.02, 0.10)	0.001**	0.29
<b>BOD POD % fat</b>												
Fasting glucose	1.35 (1.04, 1.66)	<0.001***	0.08	1.29 (0.99, 1.59)	<0.001***	0.13	1.09 (0.78, 1.40)	<0.001***	0.14	0.46 (0.14, 0.77)	0.004**	0.18
1 h glucose	1.11 (0.81, 1.41)	<0.001***	0.08	1.05 (0.75, 1.34)	<0.001***	0.12	0.93 (0.63, 1.24)	<0.001***	0.14	0.62 (0.32, 0.92)	<0.001***	0.18
2 h glucose	0.87 (0.57, 1.17)	<0.001***	0.08	0.86 (0.57, 1.16)	<0.001***	0.12	0.75 (0.45, 1.05)	<0.001***	0.14	0.50 (0.20, 0.80)	<0.001***	0.18
HbA <sub>1c</sub>	0.66 (0.34, 0.99)	<0.001***	0.08	0.81 (0.49, 1.13)	<0.001***	0.19	0.68 (0.36, 1.01)	<0.001***	0.21	0.25 (0.07, 0.58)	0.13	0.25
<b>Waist circumference, cm</b>												
Fasting glucose	1.50 (1.15, 1.85)	<0.001***	0.10	1.35 (1.02, 1.67)	<0.001***	0.21	1.09 (0.75, 1.43)	<0.001***	0.22	0.24 (0.09, 0.28)	0.16	0.28
1 h glucose	1.07 (0.73, 1.41)	<0.001***	0.09	0.99 (0.68, 1.31)	<0.001***	0.20	0.86 (0.53, 1.19)	<0.001***	0.22	0.45 (0.13, 0.76)	0.006**	0.28
2 h glucose	0.98 (0.64, 1.32)	<0.001***	0.09	0.91 (0.59, 1.22)	<0.001***	0.20	0.78 (0.46, 1.11)	<0.001***	0.22	0.46 (0.14, 0.77)	0.005**	0.28
HbA <sub>1c</sub>	0.51 (0.15, 0.88)	0.005**	0.09	1.07 (0.73, 1.41)	<0.001***	0.28	0.96 (0.61, 1.31)	<0.001***	0.30	0.39 (0.05, 0.74)	0.025*	0.35
<b>Sum of skinfolds, mm</b>												
Fasting glucose	2.71 (2.05, 3.35)	<0.001***	0.05	2.70 (2.06, 3.34)	<0.001***	0.09	2.32 (1.67, 2.99)	<0.001***	0.10	0.98 (0.31, 1.65)	0.004**	0.14
1 h glucose	1.89 (1.26, 2.52)	<0.001***	0.04	1.91 (1.29, 2.53)	<0.001***	0.08	1.62 (0.97, 2.26)	<0.001***	0.10	0.95 (0.31, 1.58)	0.003**	0.15
2 h glucose	1.66 (1.03, 2.29)	<0.001***	0.04	1.76 (1.14, 2.38)	<0.001***	0.08	1.48 (0.84, 2.13)	<0.001***	0.10	0.95 (0.32, 1.58)	0.003**	0.15
HbA <sub>1c</sub>	1.61 (0.94, 2.29)	<0.001***	0.04	1.96 (1.29, 2.64)	<0.001***	0.17	1.74 (1.04, 2.43)	<0.001***	0.18	0.83 (0.14, 1.51)	0.018*	0.22

$\beta$  estimates represent change in each continuous outcome for the continuous predictors higher by one SD estimated in the original HAPO data: fasting glucose 0.4 mmol/l; 1 h glucose 1.7 mmol/l; 2 h glucose 1.3 mmol/l; HbA<sub>1c</sub> 5.0 mmol/mol (0.45%)

*p* values are from linear regression model; \**p* < 0.05, \*\**p* < 0.01 and \*\*\**p* < 0.001

<sup>a</sup> Model 1: adjusted for field centre for being overweight/obese and obesity outcomes; unadjusted for BOD POD % fat, waist circumference and sum of skinfolds >85th percentile outcomes

<sup>b</sup> Model 2: Model 1 + child pubertal status (Tanner stage 1, 2/3, 4/5, sex × Tanner stage interaction)

<sup>c</sup> Model 3: Model 2 + maternal variables during pregnancy OGTT (age, height, any family history of diabetes, mean arterial pressure, parity [0, 1+], smoking [yes/no], alcohol [yes/no], gestational age)

<sup>d</sup> Model 4: Model 3 + maternal BMI during pregnancy

## Maternal glucose categories and childhood adiposity

To complement the above analyses, analyses of childhood adiposity across categories of maternal glucose levels during the HAPO OGTT and HbA<sub>1c</sub> at the time of the OGTT were also conducted. Frequencies of childhood adiposity outcomes, including being overweight/obese and obesity, and per cent fat, waist circumference and sum of skinfolds >85th percentiles, were higher across increasing categories of maternal glucose levels and HbA<sub>1c</sub> (ESM Fig. 1 and ESM Table 2). Adjusted associations of childhood adiposity outcomes across maternal glucose and HbA<sub>1c</sub> categories were examined next. Although adjustment for maternal BMI during pregnancy (Model 4) attenuated the associations, ORs for being overweight/obese and obesity, and per cent body fat, waist circumference and sum of skinfolds >85th percentiles, increased across higher categories of maternal glucose levels and HbA<sub>1c</sub> in all models (ESM Fig. 2 and ESM Tables 3–7). This confirmed higher risk of each outcome with increasing levels of maternal glucose and HbA<sub>1c</sub> (ESM Fig. 2 and ESM Tables 3–7).

To confirm a gradation of outcome means across maternal glucose categories, means of continuous childhood adiposity measures, including BMI *z* score, per cent fat, waist circumference and sum of skinfolds, by categories of maternal fasting, 1 h and 2 h glucose and HbA<sub>1c</sub> during pregnancy were also determined (ESM Fig. 3 and ESM Table 8). In general, means were greater for higher levels of maternal glucose. Adjusted mean differences for each child adiposity outcome across increasing categories of maternal glucose relative to the lowest category of maternal glucose were also determined (ESM Tables 9–12). In Models 1–3, adjusted mean differences for child BMI *z* score, per cent body fat, waist circumference and sum of skinfolds across categories of maternal fasting, 1 h and 2 h glucose and HbA<sub>1c</sub>, relative to the lowest category for each measure, confirmed higher means for each continuous child outcome across higher categories of maternal glucose and HbA<sub>1c</sub>. Adjustment for maternal BMI during pregnancy (Model 4) attenuated the adjusted mean differences of per cent fat, waist circumference and sum of skinfolds but the differences were still generally higher across categories of maternal glucose and HbA<sub>1c</sub> (ESM Tables 9–12). For child BMI *z* score, differences were no longer evident across categories of fasting, 1 h and 2 h glucose but were still present for categories of HbA<sub>1c</sub>.

## Analyses to explore sex- and field centre-specific associations

HAPO FUS was not intentionally powered to evaluate differences in associations according to subgroups, so exploratory analyses were performed to evaluate sex- and race/ethnicity-

specific associations using field centre as a proxy for race/ethnicity. Statistical interactions between sex and 2 h glucose yielded  $p < 0.05$  for per cent fat >85th percentile and per cent fat as a continuous outcome, which reflected stronger associations for these outcomes in boys than in girls (Tables 4 and 5). The statistical interaction between fasting glucose and sex was also significant for obesity, reflecting a higher OR estimate for girls than boys (Table 4). All other sex-specific analyses and statistical interaction terms confirmed generally consistent associations for boys and girls. No significant differences in associations across field centres were observed.

## Discussion

We recently reported that, while GDM based on IADPSG criteria was not associated with an increase in being overweight/obese, it was associated with a higher risk of obesity and measures of adiposity >85th percentile in children from the HAPO FUS cohort [16]. The present study now shows that the positive association between maternal glucose levels during pregnancy and measures of child adiposity in HAPO FUS children (aged 10–14 years) is present across the spectrum of maternal glucose levels during pregnancy. This was demonstrated in a number of ways. First, except for the association of being overweight/obese and waist circumference >85th percentile with fasting glucose, the risk for each of the child adiposity outcomes was significantly higher for each one SD difference in maternal fasting, 1 h or 2 h glucose levels as well as HbA<sub>1c</sub>. Second, other than the absence of an association between maternal glucose and child BMI *z* score, the continuous childhood adiposity outcomes were in general significantly higher for each one SD difference in continuous maternal glucose and HbA<sub>1c</sub> predictors, even after adjustment for maternal BMI during pregnancy. In addition, the linearity of the observed associations was confirmed. Finally, complementary studies examining the prevalence of child adiposity outcomes (being overweight/obese, obesity and sum of skinfolds, waist circumference and per cent body fat >85th percentiles) and means of continuous measures of child adiposity (BMI *z* score, per cent fat, sum of skinfolds and waist circumference) across increasing categories of maternal glucose generally confirmed the relationships described above. Thus, the present study demonstrates that the link between maternal glucose levels and child adiposity outcomes extends across the spectrum of maternal glucose levels, including glucose levels below the diagnostic threshold for GDM defined by IADPSG.

The original HAPO Study demonstrated continuous and graded associations between maternal glucose levels during pregnancy and newborn adiposity outcomes [4]. Recent smaller studies of children ages 5–10 years reported positive associations between maternal glucose levels during pregnancy and measures



**Table 4** Sex-specific fully adjusted associations of continuous measures of maternal glucose and HbA<sub>1c</sub> during pregnancy with dichotomous adiposity outcomes among children at follow-up

Predictor	Boys			Girls			Interaction term <i>p</i> value <sup>c</sup>
	OR (95% CI)	<i>p</i> value <sup>a</sup>	<i>C</i> statistic	OR (95% CI)	<i>p</i> value <sup>b</sup>	<i>C</i> statistic	
<b>IOTF overweight/obese</b>							
Fasting glucose	1.05 (0.96, 1.17)	0.33	0.73	1.04 (0.93, 1.16)	0.48	0.76	0.82
1 h glucose	1.10 (1.00, 1.22)	0.06	0.73	1.10 (0.99, 1.23)	0.08	0.76	0.98
2 h glucose	1.14 (1.03, 1.26)	0.01*	0.73	1.03 (0.93, 1.15)	0.55	0.76	0.12
HbA <sub>1c</sub>	1.10 (0.99, 1.23)	0.07	0.73	1.14 (1.02, 1.27)	0.03*	0.76	0.74
<b>IOTF obesity</b>							
Fasting glucose	1.07 (0.93, 1.24)	0.34	0.76	1.26 (1.08, 1.47)	0.003**	0.81	0.03*
1 h glucose	1.14 (0.99, 1.32)	0.06	0.76	1.12 (0.96, 1.30)	0.16	0.80	0.66
2 h glucose	1.31 (1.14, 1.50)	<0.001***	0.77	1.14 (0.98, 1.32)	0.10	0.80	0.08
HbA <sub>1c</sub>	1.21 (1.04, 1.42)	0.02*	0.77	1.18 (0.99, 1.40)	0.62	0.80	0.98
<b>BOD % fat &gt;85th percentile<sup>d</sup></b>							
Fasting glucose	1.12 (0.99, 1.28)	0.07	0.66	1.18 (1.03, 1.34)	0.01*	0.72	0.36
1 h glucose	1.18 (1.05, 1.33)	0.01*	0.67	1.19 (1.05, 1.36)	0.01*	0.72	0.77
2 h glucose	1.23 (1.09, 1.39)	<0.001***	0.67	1.08 (0.95, 1.22)	0.24	0.72	0.04*
HbA <sub>1c</sub>	1.22 (1.07, 1.39)	0.003**	0.67	1.03 (0.90, 1.19)	0.63	0.71	0.12
<b>Waist circumference &gt;85th percentile<sup>d</sup></b>							
Fasting glucose	1.08 (0.95, 1.22)	0.25	0.65	1.11 (0.97, 1.27)	0.13	0.73	0.39
1 h glucose	1.12 (0.99, 1.27)	0.06	0.66	1.20 (1.05, 1.36)	0.01*	0.74	0.79
2 h glucose	1.20 (1.06, 1.35)	0.003**	0.66	1.14 (1.00, 1.29)	0.04*	0.73	0.29
HbA <sub>1c</sub>	1.21 (1.06, 1.37)	0.005**	0.66	1.08 (0.94, 1.25)	0.27	0.73	0.24
<b>Sum of skinfolds &gt;85th percentile<sup>d</sup></b>							
Fasting glucose	1.07 (0.95, 1.22)	0.27	0.65	1.26 (1.11, 1.43)	<0.001***	0.70	0.07
1 h glucose	1.14 (1.01, 1.29)	0.03*	0.65	1.26 (1.11, 1.43)	<0.001***	0.70	0.41
2 h glucose	1.19 (1.06, 1.35)	0.004**	0.66	1.23 (1.09, 1.39)	0.001**	0.70	0.96
HbA <sub>1c</sub>	1.19 (1.04, 1.35)	0.009**	0.65	1.10 (0.96, 1.27)	0.17	0.69	0.63

ORs for the dichotomous outcomes are for the continuous predictors higher by one SD estimated in the original HAPO data: fasting glucose 0.4 mmol/l; 1 h glucose 1.7 mmol/l; 2 h glucose 1.3 mmol/l; HbA<sub>1c</sub> 5.0 mmol/mol (0.45%). Models are adjusted for field centre for being overweight/obesity and IOTF obesity outcomes, child pubertal status (Tanner Stage 1, 2/3, 4/5), maternal variables during pregnancy OGTT (age, height, any family history of diabetes, mean arterial pressure, parity [0, 1+], smoking [yes/no], alcohol [yes/no], gestational age, maternal BMI during pregnancy

<sup>a</sup> *p* value from regression model for boys only; \**p* < 0.05, \*\**p* < 0.01 and \*\*\* *p* < 0.001

<sup>b</sup> *p* value from regression model for girls only; \**p* < 0.05, \*\**p* < 0.01 and \*\*\* *p* < 0.001

<sup>c</sup> *p* value for sex × maternal predictor interaction term from regression model including boys and girls; \**p* < 0.05

<sup>d</sup> 85th percentiles were determined using quantile regression adjusted for age, sex and field centre

of adiposity [26, 27]. The HAPO FUS now demonstrates the novel finding that the continuous and graded association between maternal glucose levels and offspring adiposity is also observed in a multi-ethnic cohort during adolescence. Whether these relationships will continue into adulthood is yet to be determined; ongoing surveillance of this well-phenotyped at-risk population is required. However, previous studies have demonstrated associations of childhood obesity with higher risk for obesity as well as other cardiometabolic diseases as an adult [28–33], suggesting that children with greater childhood adiposity are at risk for poor metabolic outcomes as adults.

Previous studies that examined the association of maternal glucose levels during pregnancy with adiposity in childhood

typically compared offspring of mothers without vs with GDM [9, 10, 34–37]. In many cases, the associations were confounded by treatment for GDM. In contrast, HAPO mothers were not treated and remained blinded to their glucose levels during the pregnancy. Women with glucose levels during the HAPO pregnancy OGTT that exceeded levels for unblinding were treated according to local practice and were excluded from HAPO Study analyses. Thus, the present study was not confounded by treatment. Moreover, the relationships found in the present study, between glucose levels less than those diagnostic of GDM and childhood adiposity outcomes, demonstrated that the relationships between maternal glucose and measures of child adiposity were largely continuous without evidence for a threshold effect.

**Table 5** Sex-specific fully adjusted associations of continuous measures of maternal glucose and HbA<sub>1c</sub> during pregnancy with continuous adiposity outcomes among children at follow-up

Predictor	Boys			Girls			Interaction term <i>p</i> value <sup>c</sup>
	$\beta$ (95% CI)	<i>p</i> value <sup>a</sup>	Adjusted <i>R</i> <sup>2</sup>	$\beta$ (95% CI)	<i>p</i> value <sup>b</sup>	Adjusted <i>R</i> <sup>2</sup>	
<b>BMI <i>z</i> score</b>							
Fasting glucose	-0.005 (0.06, 0.05)	0.84	0.17	0.007 (-0.04, 0.06)	0.77	0.31	0.92
1 h glucose	0.02 (-0.03, 0.07)	0.46	0.17	0.01 (-0.03, 0.06)	0.56	0.31	0.46
2 h glucose	0.02 (-0.03, 0.07)	0.45	0.17	0.02 (-0.03, 0.06)	0.44	0.31	0.35
HbA <sub>1c</sub>	0.03 (-0.02, 0.09)	0.22	0.23	0.04 (-0.009, 0.09)	0.10	0.37	0.61
<b>BOD POD % fat</b>							
Fasting glucose	0.37 (-0.10, 0.83)	0.12	0.16	0.53 (0.11, 0.94)	0.01*	0.23	0.51
1 h glucose	0.73 (0.29, 1.17)	0.001**	0.16	0.49 (0.09, 0.89)	0.02**	0.23	0.08
2 h glucose	0.69 (0.25, 1.14)	0.002**	0.16	0.31 (-0.09, 0.70)	0.13	0.23	0.005**
HbA <sub>1c</sub>	0.33 (-0.15, 0.80)	0.18	0.23	0.15 (-0.28, 0.59)	0.49	0.29	0.52
<b>Waist circumference, cm</b>							
Fasting glucose	0.12 (-0.37, 0.60)	0.63	0.22	0.35 (-0.10, 0.81)	0.13	0.35	0.85
1 h glucose	0.43 (-0.03, 0.89)	0.07	0.23	0.44 (0.0002, 0.87)	0.05	0.35	0.28
2 h glucose	0.51 (0.04, 0.97)	0.03*	0.23	0.39 (-0.04, 0.82)	0.07	0.35	0.11
HbA <sub>1c</sub>	0.41 (-0.08, 0.90)	0.10	0.30	0.37 (-0.10, 0.85)	0.13	0.41	0.79
<b>Sum of skinfolds, mm</b>							
Fasting glucose	0.60 (-0.39, 1.59)	0.24	0.12	1.36 (0.48, 2.24)	0.002**	0.18	0.53
1 h glucose	0.89 (-0.05, 1.83)	0.06	0.12	0.97 (0.13, 1.81)	0.02*	0.18	0.34
2 h glucose	0.98 (0.03, 1.93)	0.04*	0.12	0.92 (0.09, 1.76)	0.03*	0.18	0.14
HbA <sub>1c</sub>	1.09 (0.09, 2.10)	0.03*	0.20	0.51 (-0.42, 1.43)	0.28	0.25	0.42

$\beta$  estimates represent change in each continuous outcome for the continuous predictors higher by one SD estimated in the original HAPO data: fasting glucose 0.4 mmol/l; 1 h glucose 1.7 mmol/l; 2 h glucose 1.3 mmol/l; HbA<sub>1c</sub> 5.0 mmol/mol (0.4%). Models are adjusted for field centre, child pubertal status (Tanner stage 1, 2/3, 4/5), maternal variables during pregnancy OGTT (age, height, any family history of diabetes, mean arterial pressure, parity [0, 1+], smoking [yes/no], alcohol [yes/no], gestational age, maternal BMI during pregnancy)

<sup>a</sup> *p* value from regression model for boys only; \* *p* < 0.05 and \*\* *p* < 0.01

<sup>b</sup> *p* value from regression model for girls only; \* *p* < 0.05 and \*\* *p* < 0.01

<sup>c</sup> *p* value for sex × maternal predictor interaction term from regression model including boys and girls; \*\* *p* < 0.01

These findings may have implications for target glucose levels in women with GDM, including in clinical trials designed to examine the effect of GDM treatment on childhood adiposity outcomes, and may also inform approaches to the monitoring of women with other independent risk factors for higher childhood adiposity (e.g. obesity).

In previous studies, associations between maternal glucose levels during pregnancy, typically in GDM, and measures of child adiposity were attenuated after adjustment for maternal BMI prior to or during pregnancy [9, 10, 35, 36]. In the present study, the associations of maternal glucose levels with risk for the five different child adiposity outcomes were also attenuated by adjustment for maternal BMI during pregnancy but remained significant, with the exception of the associations between maternal fasting glucose and risk for being overweight/obese and waist circumference >85th percentile. These data are consistent with an independent association of maternal glucose and measures of child adiposity. Whether this relationship is due solely to maternal glucose or to other metabolites related to maternal glucose has not been determined. While transplacental transfer of

glucose undoubtedly contributes to fetal growth, it has been suggested that lipids, including triacylglycerol and non-esterified fatty acids, are important contributors to excess fetal growth and fat accretion [38]. Indeed, in previous metabolomics studies performed in the HAPO cohort, we demonstrated associations of maternal 1 h glucose levels with maternal serum levels of triacylglycerol, non-esterified fatty acids,  $\beta$ -hydroxybutyrate and several amino acids [39]. This is consistent with the hypothesis proposed by Freinkel and colleagues that the association of GDM with newborn and childhood outcomes is mediated through the transplacental transfer of mixed nutrients [40].

Differences in adiposity in girls vs boys have been previously reported. At birth, per cent body fat is higher in girls than in boys [41], and sex-specific associations between maternal glucose levels and childhood adiposity have been described. In the present study, associations of maternal blood glucose levels with measures of child adiposity were generally consistent for boys and girls, although stronger associations of maternal 2 h glucose with per cent fat was observed in boys and the OR estimate for obesity with higher levels of maternal fasting glucose was higher

in girls. Other studies have also reported inconsistent associations. In one, GDM was associated with higher fat mass in boys but not girls at age ~8 years, while lesser degrees of maternal hyperglycaemia were associated with higher fat mass in girls only [42]. In an Indian cohort, at age ~9.5 years, higher adiposity was observed in girl but not boy offspring of mothers with GDM [43]. Similarly, among HAPO participants from Hong Kong, maternal glucose levels during the HAPO OGTT were associated with being overweight/obese and adiposity in girls but not boys [26]. Thus, consistent sex-specific effects of GDM and maternal blood glucose levels on measures of child adiposity have not been observed.

This study has several strengths. First, HAPO was a blinded observational study in which pregnant women and their clinical caregivers were not made aware of their glucose status. Thus, treatment is not a factor in this study of childhood outcomes. Second, the large number and racial/ethnic diversity of participants included in the HAPO FUS make the findings broadly applicable. Third, in addition to determining pubertal status of the children, this prospective study also used standardised procedures to characterise childhood adiposity via multiple methods, with generally consistent results across different measures. Finally, the HAPO FUS addressed limitations of previous studies that examined the association of GDM with childhood adiposity, including lack of complete data on glucose values in pregnancy, maternal BMI and child measures of age-adjusted BMI [6–13].

There are some limitations. The proportion of participants who met IADPSG GDM criteria and participated in the HAPO FUS (weighted estimate 14.9%) was lower than the frequency in all eligible participants (16.2%). In addition, we used maternal BMI at the pregnancy OGTT and not pre-gestational BMI, since objectively measured pre-pregnancy weight was not available in HAPO. The HAPO FUS also did not have detailed paternal data or data related to postnatal lifestyle variables which may affect childhood adiposity. By design, participants with fasting and/or 2 h OGTT glucose values during pregnancy that were above predefined thresholds were unblinded during the HAPO Study and were excluded from the HAPO FUS. This subgroup (1.8% of the HAPO cohort) is likely to have included children at highest risk of being overweight/obese and therefore the reported associations may be underestimates. Finally, the number of mother–child pairs recruited was 69.1% of the target, although the maternal characteristics during pregnancy for children who did and did not participate were similar.

In summary, the HAPO FUS provides new evidence for a continuous relationship between maternal glucose levels during pregnancy and childhood adiposity outcomes that is independent of maternal BMI. Since obese children are at high risk of obesity and related metabolic disorders as adults [28, 29], this has important public health implications and may have implications for treatment targets in mothers with pre-existing or gestational diabetes.

**Acknowledgements** The HAPO FUS investigators are grateful to all mothers and children who participated in the HAPO and HAPO Follow-up studies. Study data were collected and managed using REDCap electronic data capture tools hosted at Northwestern University Feinberg School of Medicine (FSM). REDCap is supported at FSM by the Northwestern University Clinical and Translational Science (NUCATS) Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

**Data availability** Data will be made available by the authors upon request.

**Funding** The HAPO Follow-up Study is funded by grant 1U01DK094830 from the National Institute of Diabetes and Digestive and Kidney Diseases and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Research reported in this publication was supported, in part, by the National Institutes of Health's National Center for Advancing Translational Sciences, grant UL1TR001422. BL (NIH) was a participating member of the study Steering Committee and the Writing Group for this manuscript because of the cooperative funding agreement. She was involved in the design of the study but not the conduct of the study; she was not involved in the collection, management and analysis of the data and she was involved in the preparation, review and approval of the manuscript and the decision to submit the manuscript for publication.

**Duality of interest** The authors declare that there is no duality of interest associated with this manuscript.

**Contribution statement** BEM, WLL, DMS, LPL, PMC, ARD, and BL contributed to the study concept and design. All authors contributed to the acquisition, analysis or interpretation of data. DMS, AK, MN and OT performed the statistical analyses. All authors critically revised the final paper for important intellectual content and approved the final version. BEM and DMS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## Appendix

### HAPO Follow-up Study Cooperative Research Group, field centre principal investigators and study staff

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**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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