Associations of Maternal Glycemia in the First Half of Pregnancy With Alterations in Cardiac Structure and Function in Childhood

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OBJECTIVE

Gestational diabetes mellitus has been associated with offspring cardiac congenital malformations, ventricular hypertrophy, and diastolic dysfunction in large observational cohort studies and experimental animal models. We assessed the associations of maternal random glucose concentrations across the full range with childhood cardiac ventricular structure and function.

RESEARCH DESIGN AND METHODS

In a population-based prospective cohort among 1,959 women and their offspring, maternal random glucose concentrations were measured at a median 13.1 weeks' gestation (95% range 10.5–16.8 weeks). We obtained offspring cardiac outcomes, relative to body size, through cardiac MRI at 10 years.

RESULTS

The mean maternal random glucose concentration was 4.4 mmol/L (SD 0.8). The highest quintile of maternal glucose concentrations, compared with the lowest quintile, was associated with a lower childhood left ventricular mass (−0.19 SD score [SDS]; 95% CI −0.31, −0.07) and left ventricular end-diastolic volume (−0.17 SDS; 95% −0.28, −0.05). Also, higher maternal glucose concentrations across the full range per 1 mmol/L increase were associated with a lower childhood left ventricular mass and left ventricular end-diastolic volume (*P* values ≤0.05). Adjustment for maternal prepregnancy BMI, gestational age, and weight at birth or childhood BMI and blood pressure did not influence the effect estimates. Maternal glucose concentrations were not significantly associated with childhood right ventricular end-diastolic volume or left and right ventricular ejection fraction.

CONCLUSIONS

Higher maternal random glucose concentrations in the first half of pregnancy are associated with a lower childhood left ventricular mass and left ventricular end-diastolic volume, with the strongest associations for childhood left ventricular mass. These associations were not explained by maternal, birth, or childhood characteristics. Further studies are needed to replicate these findings using repeated maternal glucose measurements throughout pregnancy and offspring cardiac outcomes throughout childhood and adulthood.

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Diabetes in pregnancy is an important risk factor for congenital heart disease (1). Children exposed to both maternal pregestational and gestational diabetes mellitus have increased risks of defects in cardiogenesis, including septal defects and hypoplastic left heart syndrome (2). Several studies have reported that pregestational and gestational diabetes mellitus are also associated with subclinical cardiac changes in fetal and infant life, including a higher ventricular mass and lower ventricular diastolic function (3–5). Studies among pregnant women without diabetes observed that offspring exposed to higher gestational glucose concentrations, but below diagnostic thresholds of gestational diabetes mellitus, had an increased risk of cardiac structural defects (6,7). These observations, together with findings from studies among diabetic and nondiabetic animals, suggest that maternal hyperglycemia may have a direct effect on fetal cardiac development (8–10). The human heart is the first functional organ to develop, and development already starts in the early embryonic stage. Already from early pregnancy onward, higher maternal glucose concentrations may influence growth and proliferation of fetal cardiomyocytes and subsequently affect myocardial structure and function (5,10–13). Thus far, it remains unknown whether these cardiac alterations in early life, in response to higher maternal gestational glucose concentrations, also have consequences for offspring cardiac development in later life.

We hypothesized that higher maternal glucose concentrations from early pregnancy onward are associated with persistent offspring cardiac adaptations, including altered left and right ventricular dimensions and a lower ventricular function in childhood. We especially expected the right ventricle, as the dominant ventricle in fetal life, to be affected. We examined, in a population-based prospective cohort study among 1,959 mothers and their children, the associations of maternal random glucose concentrations in the first half of pregnancy with childhood left and right ventricular structure and function measured by cardiac MRI at 10 years.

RESEARCH DESIGN AND METHODS

Study Design and Subjects

This study was embedded in the Generation R Study, a population-based prospective cohort study in Rotterdam, the Netherlands (14). Approval was obtained from the local Medical Ethical Committee (Erasmus University Medical Center, Rotterdam, the Netherlands). Written consent was obtained from participants' parents. The study enrolled 7,145 pregnant women <18 weeks' gestation, of whom 6,099 had singleton pregnancies and glucose measurements available, of which 3,811 had offspring with follow-up visits at 10 years (Supplementary Fig. 1). As a result of later implementation of MRI scans within follow-up visits, a subgroup of 2,294 children was scanned, of which 1,965 had good-quality cardiac MRI measurements. After exclusion of children with cardiac abnormalities in their medical history ($n = 6$), our population for analysis consisted of 1,959 mothers and children.

Maternal Random Glucose and Insulin Concentrations

Nonfasting random venous blood samples were collected once at 13.1 weeks' gestation (95% range 10.5–16.8) by research nurses and briefly stored at room temperature and subsequent temporarily stored on ice. Blood samples were obtained after at least 30 min of fasting, because of which we considered the samples as random nonfasting samples. Blood was collected in EDTA tubes, and processing was aimed to finish within a maximum of 3 h after sampling. Glucose (mmol/L) was measured with c702 module on the Cobas 8000 analyzer. Insulin (pmol/L) was measured with electrochemiluminescence immunoassay on the Cobas e411 analyzer. We considered maternal glucose concentrations as our main exposure. As a secondary exposure, we used maternal insulin concentrations as another marker of maternal glucose metabolism and for its potential additional effect on offspring cardiac development through other alterations in maternal metabolism as a consequence of insulin insensitivity and altered placental development (15,16).

Cardiac Measurements

At 10 years, we performed childhood cardiac MRI using a wide-bore GE Discovery MR 750 3T scanner (General Electric, Milwaukee, MI) (17). We included left ventricular mass, left and right ventricular end-diastolic volume, and left and right ventricular ejection fraction as outcomes, based on our hypothesis that higher maternal glucose concentrations directly affect embryonic and fetal cardiomyocyte development and proliferation leading to alterations in right and left ventricular structure and function in later life (9). Histograms of outcomes are shown in Supplementary Materials 1. Because cardiac outcomes are strongly dependent on childhood size, we corrected all cardiac outcomes measures for body surface area (BSA), leading to normally distributed BSA-corrected outcomes (18). To further enable comparison of effect sizes for associations of maternal glucose metabolism with childhood left and right ventricular outcomes, we constructed SD scores (SDS) of outcomes (details in Supplementary Materials 1). As a secondary outcome and as a potential mediator, we measured childhood blood pressure at 10 years.

Covariates

Information on maternal age, ethnicity, educational level, parity, prepregnancy weight, folic acid supplement use, alcohol consumption, smoking, total caloric intake, nausea and vomiting, and diagnosis of type 1 or 2 diabetes before pregnancy was obtained through participants' questionnaires (14). Maternal height was measured at intake without shoes. BMI was calculated. Information on diagnosis of gestational diabetes mellitus, gestational hypertensive disorders, and the child's sex, gestational age, and weight at birth was obtained from medical records (14). Gestational diabetes mellitus was diagnosed by a community midwife or an obstetrician according to Dutch midwifery and obstetric guidelines using the following criteria: a random glucose level >11.0 mmol/L, a fasting glucose ≥7.0 mmol/L, or a fasting glucose between 6.1 and 6.9 mmol/L with a subsequent abnormal glucose tolerance test result. In clinical practice and for this study sample, an abnormal glucose tolerance test result was defined as 1-h postprandial glucose concentration >7.8 mmol/L after an oral glucose load of 75 g. Screening for gestational diabetes mellitus was conducted in women with one or more of the following risk factors according to Dutch midwifery and obstetric guidelines: gestational diabetes mellitus in a previous pregnancy, BMI >30 kg/m^2 at the first prenatal visit, macrosomia or large-for-gestational-age infant in a previous pregnancy, first-degree relative

with diabetes, high-risk ethnicities, unexplained intrauterine death in a previous pregnancy, or polycystic ovarian syndrome. We further refer to pregestational and gestational diabetes mellitus as (pre)gestational diabetes mellitus. At 10 years, we measured the child's BMI (14). This measurement preceded the cardiac MRI by a median of 1.1 month (95% range 0.0–2.2).

Statistical Analyses

First, we performed a nonresponse analysis to compare characteristics of mothers and children with cardiac MRI measurements to those without. Second, we assessed associations of maternal random glucose concentrations with childhood cardiac outcomes. Based on previous studies showing linear associations of higher maternal glucose concentrations with perinatal complications, childhood BMI, and glucose metabolism, we hypothesized a linear tendency for associations of maternal glucose concentrations with offspring cardiac outcomes (19–22). We first categorized maternal glucose concentrations into quintiles, based on the distribution of maternal glucose concentrations, to assess whether associations were restricted to women with relatively high glucose concentrations and to explore linearity. We plotted unadjusted means of childhood cardiac outcomes per maternal glucose concentration quintile and examined the associations of the higher maternal glucose concentrations quintiles with childhood cardiac outcomes, compared with the lowest quintile, using multiple linear regression models. Next, we assessed the associations of maternal glucose concentrations continuously per 1 mmol/L increase with childhood cardiac outcomes to explore the continuous associations across the full range of maternal glucose concentrations, which is not fully captured by the quintile analyses. We assessed linearity by visualizing the data by categorizing maternal glucose concentrations into deciles and by testing for quadratic terms for maternal glucose concentrations within our models. We also estimated cubic spline models, with additional boundary knots at the 5th and 95th percentile, and assessed whether this significantly improved model fit. These analyses showed the linear model was the best fit for the data. Linear regression model assumptions were fulfilled.

We constructed five different models, based on a directed acyclic graph analysis (Supplementary Materials 2):

1. basic model adjusted for gestational age at blood sampling, child's age and sex, and time difference between the BSA and MRI measurement;
2. confounder model, as main model: basic model additionally adjusted for maternal ethnicity, educational level, folic acid supplement use, alcohol consumption, smoking, and gestational hypertensive disorders;
3. maternal BMI model: confounder model additionally adjusted for maternal prepregnancy BMI;
4. birth model: maternal BMI model additionally adjusted for the child's gestational age and weight at birth; and
5. child model: birth model additionally adjusted for childhood concurrent BMI and blood pressure.

We tested statistical interaction terms for maternal prepregnancy BMI, fetal sex, and child's concurrent BMI, but none were significant. Additionally, we repeated all analyses using maternal random insulin concentrations as exposure. To enable comparison of effect sizes for the associations of different measures of maternal glucose metabolism with childhood cardiac outcomes, these analyses were performed using maternal random glucose and insulin concentrations in SDS. We log-transformed maternal insulin concentrations before the construction of the SDS given its skewed distribution.

To assess robustness of findings, we performed several sensitivity analyses: *1*) excluding women with (pre)gestational diabetes mellitus to assess the associations of maternal glucose concentrations within a population without diabetes; *2*) excluding women with the diagnosis of gestational hypertensive disorders; and *3*) excluding women with glucose concentrations sampled at >14 weeks' gestation to assess the associations of first trimester maternal glucose concentrations with offspring cardiac development. Multiple imputations of covariates (pooled results of five imputed data sets) were performed. All analyses were performed using SPSS 24.0 for Windows software (IBM, Armonk, NY), except for spline analyses, which were conducted in R 3.6.3 software with the splines package.

RESULTS

Subject Characteristics

Table 1 reports that the mean maternal random glucose concentration was 4.4 mmol/L (SD 0.8). The glucose concentration in 0.3% of women was ≥7.8 mmol/L. Population characteristics according to quintiles of maternal glucose concentrations are provided in Supplementary Table 1. Nonresponse analysis showed that mothers of children with cardiac MRI measurements at 10 years, compared with those without, had slightly higher glucose concentrations (Supplementary Table 2).

Maternal Glycemia and Childhood Cardiac Function and Structure

Figure 1 shows that the unadjusted means of childhood left ventricular mass and that the left and right ventricular end-diastolic volumes were lowest in the highest maternal glucose concentrations quintile. In the confounder models, compared with children from mothers with glucose concentrations in the lowest quintile, children from mothers with glucose concentrations in the highest quintile had a lower left ventricular mass (−0.19 SDS; 95% CI −0.31, −0.07) and a lower left ventricular end-diastolic volume (−0.17 SDS; 95% CI −0.28, −0.05). A similar nonsignificant tendency was present for childhood right ventricular end-diastolic volume. No consistent associations of maternal glucose concentrations quintiles with left and right ventricular ejection fraction were present.

In the basic models, higher maternal glucose concentrations across the full range were associated with a lower childhood left ventricular mass, left ventricular end-diastolic volume, and right ventricular end-diastolic volume (all *P* values ≤0.05) (Table 2). In the confounder models, higher maternal glucose concentrations were associated with a lower childhood left ventricular mass and lower left ventricular end-diastolic volume only (−0.06 SDS [95% CI −0.10, −0.01] and −0.04 SDS [95% CI −0.09, 0.00], per 1 mmol/L increase in maternal glucose concentration, respectively). Adjustment for maternal prepregnancy BMI and child's gestational age and weight at birth and

Table 1—Characteristics of the study population

	Total group (N = 1,959)
Maternal characteristics	
Age at enrollment, mean (SD), years	30.9 (4.6)
Gestational age at intake, median (95% range), weeks	13.1 (10.5–16.8)
Prepregnancy BMI, median (95% range), kg/m^2	22.5 (18.7–31.6)
Gestational weight gain, mean (SD), kg	15.1 (5.8)
Parity, *n* nulliparous (%)	1,190 (60.7)
Ethnicity, *n* Dutch or European (%)*	1,306 (66.7)
Education level, *n* high (%)	1,011 (51.6)
Income, *n* high (%)	1,374 (70.1)
Smoking during pregnancy, *n* (%)	418 (21.3)
Alcohol consumption during pregnancy, *n* (%)	1,063 (54.3)
Folic acid supplement use, *n* (%)	1,262 (64.4)
Glucose, mean (SD), mmol/L	4.4 (0.8)
First quintile, mean (SD), mmol/L	3.4 (0.4)
Second quintile, mean (SD), mmol/L	4 (0.1)
Third quintile, mean (SD), mmol/L	4.3 (0.1)
Fourth quintile, mean (SD), mmol/L	4.8 (0.1)
Fifth quintile, mean (SD), mmol/L	5.7 (0.6)
Insulin, median (95% range), pmol/L	113.0 (24.4–502.8)
First quintile, median (95% range), pmol/L	31.8 (16.4–44.4)
Second quintile, median (95% range), pmol/L	64.4 (47.8–82.9)
Third quintile, median (95% range), pmol/L	113.1 (86.7–145.0)
Fourth quintile, median (95% range), pmol/L	195.9 (152.0–251.4)
Fifth quintile, median (95% range), pmol/L	373.1 (266.9–887.6)
(Pre)Gestational diabetes mellitus, *n* (%)	11 (0.6)
Gestational hypertensive disorders, *n* (%)	131 (6.7)
Birth characteristics	
Sex, *n* female (%)	1,028 (52.5)
Birth weight, mean (SD), g	3,448 (546)
Gestational age at birth, median (95% range), weeks	40.3 (37.1–42.1)
Child characteristics at 10 years	
Age, median (95% range), years	9.9 (9.5–11.6)
Height, mean (SD), cm	141.6 (6.7)
Weight, median (95% range), kg	33.8 (26.4–48.8)
BMI, median (95% range), kg/m^2	16.9 (14.4–22.9)
Body surface area, median (95% range), m^2	1.1 (1.0–1.4)
Blood pressure	
Systolic, mean (SD), mmHg	103.1 (7.9)
Diastolic, mean (SD), mmHg	58.5 (6.4)
Cardiac MRI measures	
Left ventricular mass, median (95% range), g	47.5 (34.5–67.9)
Left ventricular end-diastolic volume, median (95% range), mL	98.7 (73.7–132.7)
Left ventricular ejection fraction, mean (SD), %	58.4 (4.6)
Right ventricular end-diastolic volume, median (95% range), mL	98.2 (71.3–134.8)
Right ventricular ejection fraction, mean (SD), %	58.2 (4.9)

For normally distributed data, the mean with SD is stated. For nonnormally distributed data, the median with the 95% range is stated. Number of missings per covariate: maternal ethnicity, n = 24 (1.2%); maternal educational level, n = 82 (4.2%); folic acid supplement use during pregnancy, n = 432 (22.1%); alcohol consumption, n = 216 (11.0%); smoking during pregnancy, n = 197 (10.1%); gestational hypertensive disorders, n = 33 (1.7%). *Maternal ethnicities within the study population included Dutch, n = 1,148 (58.6%); European, n = 158 (8.1%); Surinamese, n = 154 (7.9%); Turkish, n = 102 (5.2%); Moroccan, n = 85 (4.3%); Cape Verdeans, n = 84 (4.3%); Indonesian, n = 70 (3.6%); Asian, n = 41 (2.1%); Dutch Antilleans, n = 35 (1.8%); American, n = 24 (1.2%); and other ethnicities (all <1% per ethnicity).

childhood BMI and blood pressure did not materially change these effect estimates. There was a nonsignificant tendency for an association of higher maternal glucose concentrations with a lower childhood right ventricular ejection fraction. Higher maternal glucose concentrations were not associated with childhood blood pressure, which we considered as a potential mediator of the associations of maternal glucose concentrations with childhood cardiac outcomes (Supplementary Table 3).

Additional Analyses

Higher maternal insulin concentrations were associated with lower childhood left and right ventricular end-diastolic volume (all P values ≤0.05), but not with left ventricular mass or left and right ventricular ejection fraction (Supplementary Table 4). Strength of these associations was comparable to maternal glucose concentrations. Excluding mothers with (pre)gestational diabetes mellitus or gestational hypertensive disorders had no effect on the associations (Supplementary Table 5). When we repeated the analyses among women with glucose concentrations <14 weeks' gestation available, effect estimates for the association with childhood left ventricular mass were similar but borderline significant, effect estimates for the association with childhood left ventricular end-diastolic volume were in similar direction but attenuated toward nonsignificant, and effect estimates for the association with childhood right ventricular ejection fraction were in similar direction and slightly stronger (Supplementary Table 5).

CONCLUSIONS

In a population without diabetes, higher maternal random glucose concentrations in the first half of pregnancy, especially maternal glucose concentrations within the highest quintile, were associated with a lower childhood left ventricular mass and left ventricular end-diastolic volume. The strongest association was present for childhood left ventricular mass. These associations were not explained by maternal, birth, and childhood characteristics.

Interpretation of Main Findings

Maternal hyperglycemia during pregnancy seems associated with an altered fetal cardiac development. (Pre)gestational diabetes mellitus is associated with congenital heart defects and with alterations in fetal cardiac structure and function within the normal range of cardiac development (1–7,12,23). Studies among women with diabetes measuring fetal ventricular mass, ventricular filling velocities (early [E]-to-late [A] ratio), and isovolumetric relaxation time, showed a higher left ventricular mass and lower left and right ventricular diastolic function in fetuses of mothers with poor glycemic control compared with mothers with

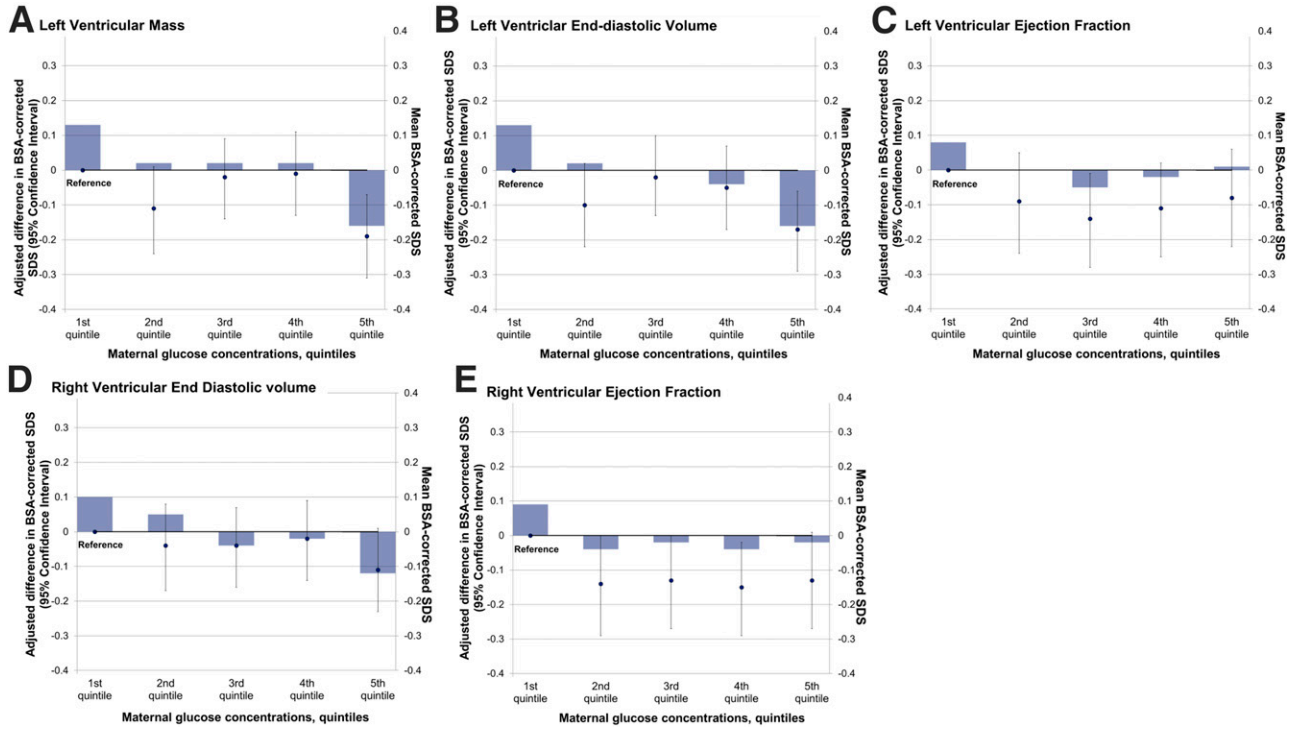

Figure 1—Maternal random glucose concentrations and childhood cardiac outcomes at the age of 10 years. Adjusted difference in left ventricular mass (*A*), left ventricular end-diastolic volume (*B*), left ventricular ejection fraction (*C*), right ventricular end-diastolic volume (*D*), and right ventricular ejection fraction (*E*). Black circles represent regression coefficients (95% CI) from linear regression models that reflect differences in childhood cardiac outcomes in SDS for maternal glucose concentrations in quintiles compared with the lowest quintile (left *y*-axis). Regression models were adjusted for gestational age at enrollment, child's age and sex at follow-up measurements and time difference between measurement of child's BSA and cardiac MRI, maternal ethnicity, educational level, folic acid supplement use during pregnancy, alcohol consumption and smoking during pregnancy, and gestational hypertensive disorders. Bars represent the unadjusted means of BSA-corrected SDS of childhood cardiac outcomes (right *y*-axis). *N* per quintile of maternal glucose concentrations are 433 for quintile 1, 327 for quintile 2, 432 for quintile 3, 389 for quintile 4 and 378 for quintile 5. Mean (SD) per quintile of maternal glucose concentrations in mmol/L are 3.4 (0.4) for quintile 1, 4.0 (0.1) for quintile 2, 4.3 (0.1) for quintile 3, 4.8 (0.1) for quintile 4, and 5.7 (0.6) for quintile 5. Median (95% range) per quintile of maternal glucose concentrations in mmol/L are 3.6 (2.6–3.8) for quintile 1, 4.0 (3.9–4.1) for quintile 2, 4.3 (4.2–4.5) for quintile 3, 4.8 (4.6–5.0) for quintile 4, and 5.5 (5.1–6.8) for quintile 5.

good glycemic control (3,23). Studies among newborns of mothers with diabetes showed similar results (4,24). One small study suggested that pathologic ventricular hypertrophy in newborns of mothers with diabetes normalized within the first 6 months of life (25). Associations may not be limited to populations with diabetes only. A study showed that in 277 pregnant women without diabetes, offspring exposed to higher random glucose concentrations in midpregnancy had a higher risk of tetralogy of Fallot but not of transposition of the great arteries (7). Similarly, a study among 19,171 pregnant women without diabetes showed that higher maternal glucose concentrations and higher postprandial glucose concentrations after an oral glucose tolerance test were associated with increased risks of any offspring congenital heart defect (6).

These findings, together with those from animal studies, suggest that maternal gestational glucose concentrations are an important factor influencing cardiogenesis (11). It is likely that women who develop gestational diabetes mellitus or hyperglycemia later in pregnancy already have a suboptimal glucose metabolism in the first half of pregnancy (26). As embryonic and fetal cardiac development starts in the 1st weeks after conception, this may be a critical period for potential adverse effects of a suboptimal maternal glucose metabolism on embryonic and fetal cardiac development (11). We observed that higher maternal random glucose concentrations, especially those within the highest quintile, were associated with a lower childhood left ventricular mass and left ventricular end-diastolic volume. These findings were already observed in a population of relatively lean women with random glucose concentrations largely within the normal range.

The association of higher maternal glucose concentrations with a lower childhood left ventricular end-diastolic volume is in line with studies among populations with diabetes focused on fetal cardiac adaptations. Ventricular end-diastolic volume defines the ventricular ability to fill during the diastolic phase. Filling during the diastolic phase could be affected by increased stiffness and decreased relaxation of the ventricles caused by structural changes in the myocardium (27,28). Animal studies have shown a decreased number of cardiomyocytes and transient hypertrophy after exposure to higher maternal glucose concentrations. Ventricular end-diastolic volume is one of the main determinants of stroke volume, and to maintain an adequate stroke volume, a lower ventricular end-diastolic volume may need to be compensated in the systolic phase, leading to an altered systolic function in the long-term (28). Nonsignificant tendencies were found for associations of higher maternal glucose concentrations with lower childhood ventricular ejection fraction, a measure of ventricular systolic function. Associations with ejection fraction may

Table 2—Maternal random glucose concentrations across the full range and childhood cardiac outcomes at 10 years of age

Model	Left ventricular mass (SDS)	*P* value	Left ventricular end-diastolic volume (SDS)	*P* value	Left ventricular ejection fraction (SDS)	*P* value	Right ventricular end-diastolic volume (SDS)	*P* value	Right ventricular ejection fraction (SDS)	*P* value
Maternal glucose (mmol/L)										
Basic model*	−0.06 (−0.11, −0.02)	0.01	−0.06 (−0.10, −0.01)	0.02	−0.04 (−0.09, 0.02)	0.16	−0.05 (−0.09, 0.00)	0.05	−0.05 (−0.10, 0.01)	0.09
Confounder model†	−0.06 (−0.10, −0.01)	0.02	−0.05 (−0.09, 0.00)	0.05	−0.05 (−0.10, 0.01)	0.15	−0.04 (−0.08, 0.01)	0.13	−0.05 (−0.10, 0.01)	0.10
Maternal BMI model‡	−0.05 (−0.10, −0.01)	0.03	−0.04 (−0.09, 0.00)	0.07	−0.05 (−0.10, 0.01)	0.08	−0.03 (−0.08, 0.02)	0.19	−0.06 (−0.11, 0.00)	0.04
Birth model§	−0.05 (−0.10, −0.01)	0.02	−0.05 (−0.09, 0.00)	0.04	−0.05 (−0.10, 0.01)	0.09	−0.04 (−0.08, 0.01)	0.12	−0.05 (−0.11, 0.00)	0.05
Child model‖	−0.05 (−0.10, 0.00)	0.04	−0.04 (−0.09, 0.00)	0.06	−0.04 (−0.10, 0.01)	0.12	−0.03 (−0.08, 0.02)	0.19	−0.05 (−0.11, 0.00)	0.05

Values represent regression coefficients (95% CI) from linear regression models that reflect differences in childhood cardiac outcomes in SDS per 1 mmol/L increase in maternal random glucose concentrations. *Basic model is adjusted for gestational age at enrollment, child's age and sex at follow-up measurements, and time difference between measurement of child's body surface area and cardiac MRI. †Confounder model is the basic model additionally adjusted for maternal ethnicity, maternal educational level, folic acid supplement use during pregnancy, alcohol consumption and smoking during pregnancy, and gestational hypertensive disorders. ‡Maternal BMI model is the confounder model additionally adjusted for maternal prepregnancy BMI. §Birth model is the maternal BMI model additionally adjusted for gestational age and weight at birth. ‖Child model is the birth model additionally adjusted for child's BMI and blood pressure at 10 years of age.

become more apparent at older ages. Thus, our findings suggest that higher maternal random glucose concentrations, already within the normal range, are associated with childhood ventricular diastolic function and filling capacity.

In contrast to findings of studies in fetal and infant life, we observed that higher maternal random glucose concentrations, especially those within the highest quintile, were associated with a lower childhood left ventricular mass. Effect estimates were consistent among all sensitivity analyses, but became borderline significant among women with first trimester glucose concentrations available. This is most likely due to smaller sample size. These findings are in line with observations in experimental animal models which show that the influence of maternal glycemia on cardiac development may be different in childhood and adulthood than in fetal life and infancy (8,10). Higher fetal glucose and insulin concentrations, in response to maternal glycemia, may decrease the number of cardiomyocytes but simultaneously accelerate individual cardiomyocyte growth (8–10). This may result in ventricular hypertrophy in fetal and early postnatal life, due to accelerated growth of individual cardiomyocytes, but a decreased ventricular mass in later life resulting from the reduction in cardiomyocyte number (10). When our results are compared with those from previous studies, differences in study design and populations should be considered, because most previous studies were conducted in pregnant women with diabetes and focused on offspring left ventricular mass during fetal and early postnatal life (3,4). Thus, our study shows for the first time that in a population without diabetes, higher maternal glucose concentrations within the normal range are associated with a lower childhood left ventricular mass.

Contrary to our prior hypothesis that the right ventricle might be more affected by intrauterine exposure to higher maternal glucose concentrations, we mainly observed associations with offspring left cardiac outcomes. We observed a tendency for associations of higher maternal glucose concentrations with a lower childhood right ventricular ejection fraction, which were slightly stronger in the sensitivity analysis with maternal glucose concentrations $<$14 weeks' gestation available. This could suggest that maternal glucose metabolism impacts embryonic right ventricular development. During fetal transition to extrauterine life, major adaptations in the cardiovascular system occur, and the afterload for the left ventricle increases strongly compared with the right ventricle. As a result of the higher workload of the left ventricle during postnatal life, alterations in the left ventricle in response to a suboptimal maternal glucose metabolism may be more pronounced in childhood. We observed the strongest association with childhood left ventricular mass. Similarly, the associations of higher maternal glucose concentrations might be stronger with offspring right ventricular mass than with right ventricular end-diastolic volume or ejection fraction. At 10 years, right ventricular mass cannot be measured accurately with MRI because the right ventricular wall is too thin and is prone to measurement error (29). Studies among offspring at older ages should evaluate whether maternal glycemia is associated with right ventricular mass and should compare the strength of associations of maternal glycemia with right and left ventricular outcomes. Furthermore, studies using detailed measurements of embryonic and fetal cardiac development, including advanced ultrasound techniques, can be used to provide insight into critical periods of maternal glucose metabolism on right and left embryonic and fetal cardiac development.

We used maternal insulin concentrations as an additional measure of maternal glucose metabolism. We observed that higher maternal insulin concentrations were also associated with a lower childhood left ventricular end-diastolic volume, with a similar strength as maternal glucose concentrations but not with childhood left ventricular mass. Higher maternal insulin concentrations were also associated with lower childhood right ventricular end-diastolic volume. On the basis of experimental animal models, it seems that primarily maternal glucose concentrations would directly affect embryonic and fetal cardiomyocyte development (3). Maternal insulin does not cross the placenta but does affect maternal metabolism and placental development, which may also indirectly influence offspring cardiac development through, for example, alterations in fetal-placental blood flow patterns (15,16). Experimental studies need to distinguish whether maternal insulin concentrations have a potential indirect effect, in addition to the effect of maternal glucose concentrations, on embryonic and fetal cardiac development.

Effect estimates for the associations of maternal random glucose concentrations with a lower childhood left ventricular mass and left ventricular end-diastolic volume were small but important from a cardiovascular developmental perspective. Our findings add to evidence suggesting that maternal glucose metabolism during pregnancy may directly affect offspring cardiac development, because associations were not explained by maternal, birth, or childhood characteristics. Few studies have focused on how childhood cardiac development relates to adult cardiac structure and function and cardiovascular morbidity. Our findings are in line with previous studies showing associations of fetal growth restriction and small-size-for-gestational-age at birth with lower childhood left ventricular mass and left ventricular end-diastolic volume (17,30). Fetal growth restriction and small-size-for-gestational-age at birth are risk factors for cardiovascular diseases in adulthood, which may suggest that these childhood cardiac alterations may be related to adverse cardiac health outcomes in later life (31,32). Left ventricular mass tracks throughout childhood into adulthood, but whether left ventricular end-diastolic volume tracks into adulthood remains unknown (33,34). Studies among adult populations have shown that increased left ventricular mass is associated with a higher risk of cardiovascular morbidity, but whether a lower left ventricular mass is related to cardiovascular diseases is unclear (35). Among adult populations, both an increased and a reduced left ventricular end-diastolic volume are associated with a higher risk of cardiovascular morbidity, even with preserved ejection fraction, but these associations have not been assessed from childhood onward (36,37). Further studies need to replicate our findings and assess the long-term implications for offspring cardiac development. Intervention studies are needed to obtain further insight into the causality of these observed associations and the possibilities to improve offspring cardiovascular health by optimizing maternal glucose status during pregnancy.

Methodological Considerations

We had a prospective design with data collection from early pregnancy onward, including detailed measurements of childhood cardiac development using cardiac MRI scans. The number of cases of (pre)gestational diabetes mellitus and offspring cardiac abnormalities was relatively low. Women with pregestational diabetes mellitus may have been reluctant to participate, and children with cardiac abnormalities could be lost to follow-up, which may have led to selection bias. However, because we aimed to assess associations of maternal glycemia with offspring cardiac alterations within the normal range, it is unlikely that this biased results. We obtained information on the diagnosis of gestational diabetes mellitus from medical records. Glucose testing for the diagnosis of gestational diabetes mellitus was not performed in all women for study purposes, which may have led to misclassification. The nonresponse analysis, low number of cases, and relatively lean population suggests a selection to a relatively healthy population, which may affect the generalizability of our findings. Studies among higher-risk populations, such as obese women or women with a suboptimal glucose metabolism, need to replicate findings. We obtained random maternal glucose concentrations once during pregnancy at nonfixed times throughout the day. Owing to our study design, we were not able to collect repeated fasting blood samples.

Glucose concentrations throughout the day are influenced by multiple factors, such as dietary intake and exercise, and although blood samples were stored on ice for a maximum of 3 h, blood glucose concentrations may decline in EDTA tubes. These factors may have led to nondifferential misclassification, causing an underestimation of our associations. However, previous studies, including studies from our cohort, showed that random maternal gestational glucose concentrations are related to the risks of gestational diabetes mellitus, adverse birth outcomes, childhood obesity, and altered glucose metabolism (22,38–40). These associations were in a similar direction as those for maternal fasting and postprandial glucose concentrations with these adverse outcomes (19,20). Timing of sampling of maternal glucose concentrations in our study is relatively broad, but <18 weeks' gestation, covering the first half of pregnancy. This classification was aligned with the logistics of the study. Further studies need to replicate our findings using repeated maternal fasting and postprandial glucose measurements. These studies should already measure glucose before pregnancy, because maternal glycemia in the first half of pregnancy is likely to reflect maternal glucose before conception, and repeatedly throughout pregnancy from the first trimester onward, to identify critical periods of maternal glycemia for offspring cardiac development. Information on multiple maternal and childhood characteristics was available, but residual confounding may have influenced results.

Conclusion

Higher maternal random glucose concentrations in the first half of pregnancy, already within the normal range, were associated with a lower childhood left ventricular mass and lower left ventricular end-diastolic volume at 10 years. The strongest association was present for childhood left ventricular mass. Maternal, birth, and childhood characteristics did not explain these associations. Further studies are needed to replicate our findings and to assess the long-term associations of maternal glucose metabolism with offspring cardiac outcomes throughout childhood and adulthood.

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