Effects of a low–glycemic index diet during pregnancy on offspring growth, body composition, and vascular health: a pilot randomized controlled trial[1]

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ABSTRACT

Background: Elevated maternal blood glucose concentrations may contribute to macrosomia, adiposity, and poorer vascular health in the offspring.

Objective: The aim was to explore the effect of a low–glycemic index (low-GI) diet during pregnancy on offspring growth, adiposity, and arterial wall thickness during infancy.

Design: This was a longitudinal follow-up study in a self-selected subgroup of mother-infant pairs (n = 59) participating in a larger randomized trial comparing the effects on perinatal outcomes of a low-GI diet and a conventional high-fiber (HF) diet during pregnancy. Infant anthropometric measurements were taken every month for 6 mo and then at 9 and 12 mo of age. Adiposity was assessed at birth and at 3 mo by air-displacement plethysmography by using the Pea Pod system (Cosmed) and at 6 and 12 mo by bioimpedance analysis (Bodystat). Aortic intima-media thickness was assessed at 12 mo by high-resolution ultrasound (Philips).

Results: Maternal dietary GI was lower in the low-GI group than in the HF group (51 ± 1 compared with 57 ± 1; $P < 0.001$). No differences in neonatal outcomes were observed in the main trial. In the self-selected subsample, birth weight and length z scores were lower in the low-GI group than in the HF group (birth weight z score: 0.2 ± 0.2 compared with 0.7 ± 0.2, respectively; P = 0.04; birth length z score: 0.3 ± 0.2 compared with 0.9 ± 0.2, respectively; P = 0.04), but adiposity from birth to 12 mo of age and growth trajectories from 1 to 12 mo of age were similar. Aortic intima-media thickness was lower in the low-GI group than in the HF group (657 ±12 compared with 696 ± 12 μm, respectively; P = 0.02), which was partly mediated by differences in birth weight.

Conclusion: In women at risk of gestational diabetes mellitus, a low-GI diet influences offspring birth weight, birth length, and arterial wall thickness in early childhood, but not adiposity or growth trajectory during the first year of life. This trial was registered at anzctr.org.au as ACTRN12610000681055. *Am J Clin Nutr* 2016;103:1073–82.

Keywords: body composition, gestational diabetes mellitus, glycemic index, infant, intima-media thickness

INTRODUCTION

High birth weight, adiposity, and rapid weight gain in infancy have been identified as early predictors for obesity, metabolic disorders, and atherosclerotic vascular disease in adult life (1–3). Evidence in humans and animals supports the hypothesis that elevated maternal blood glucose concentrations may link these indicators of excessive early-life growth with metabolic disorders and poor vascular health in the offspring (4–6). Pregnancy is characterized by a state of physiologic insulin resistance, enabling sufficient substrate delivery to the fetus. Intrauterine overnutrition through maternal impaired glucose metabolism has been shown to increase fetal and childhood adiposity (7, 8). Excessive fetal and infant growth has further been associated with structural manifestations of atherosclerosis in early childhood and across the life span (3, 6, 9, 10). Importantly, the consequences of maternal glucose concentrations on fetal growth do not occur at definite thresholds but rather across a continuum (11).

Interventions that lower elevated maternal blood glucose concentrations have been shown to improve perinatal outcomes (12). Maternal diet, particularly the type and amount of carbohydrate, influences maternal postprandial blood glucose concentrations and, hence, potentially affects fetal overnutrition and adiposity (7, 13). Low–glycemic index (low-GI)[11] foods produce lower postprandial increases in blood glucose and reduce diurnal

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[11] Abbreviations used: FM, fat mass; GDM, gestational diabetes mellitus; GI, glycemic index; HF, high fiber; IMT, intima-media thickness; LAZ, length-for-age z score; RCT, randomized controlled trial; WAZ, weight-for age z score.

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postprandial glucose and insulin responses compared with high-GI foods (14–16). Because glucose is the principal substrate for fetal growth, low-GI diets might be of particular relevance during pregnancy. Nonetheless, results of randomized controlled trials (RCTs) are mixed with regard to whether a low-GI diet during pregnancy affects birth weight (13, 17–20).

The effects of a low-GI diet during pregnancy on offspring growth and vascular health beyond the immediate postnatal period have not been studied in the context of a RCT. The aim of this study was therefore to determine the potential longer-term effects of a low-GI diet compared with a conventional moderate-GI, high-fiber (HF) diet on infant growth, body composition, and aortic intima-media thickness (IMT). We focused on mothers identified clinically as being at risk of developing gestational diabetes mellitus (GDM), because this group is more likely to show elevated blood glucose concentrations than other pregnant women. We hypothesized that infants born to mothers at high risk of developing GDM randomly assigned to receive the low-GI diet would have lower adiposity and growth velocity from birth to 12 mo and reduced aortic IMT at 1 y of age.

METHODS

The GI Baby 4 Study was a pilot prospective follow-up study exploring the growth velocity and body composition of the infants born to mothers enrolled in the GI Baby 3 Study, a 2-arm RCT assessing the effects of a low-GI diet compared with a conventional HF diet during pregnancy on perinatal outcomes (20). For the GI Baby 3 Study, singleton pregnant women (week 12–20 of gestation) were recruited from the antenatal clinic at the Royal Prince Alfred Hospital, Sydney, Australia. They were eligible if they had at least one of the following risk factors: prepregnancy BMI (in kg/m^2) $\geq$30, age $\geq$35 y, polycystic ovary syndrome, previous history of GDM or glucose intolerance, history of a previous newborn weighing $>$4000 g, family history of type 2 diabetes (first-degree relative), or belonging to an ethnic group with a high prevalence of GDM (Aboriginal, Torres Strait Islander, Polynesian, Middle Eastern, Indian, or Asian). Women with special dietary requirements (gluten-intolerant, celiac disease) or pre-existing diabetes were excluded. For the GI Baby 4 Study, eligible participants were infants ($\geq$36 wk of gestation) with no congenital defects or metabolic disturbances influencing growth. Recruitment for the GI Baby 4 Study spanned the period June 2011 to February 2013, and data collection ended in March 2014. The study was in accordance with the ethical standards of the Human Research Ethics Committee of the Sydney South West Area Health Service (RPAH Zone, reference no. HREC/11/RPAH/190). Parental informed written consent was obtained, and participation was voluntary.

Maternal demographic characteristics, perinatal outcomes, and dietary intake during pregnancy were collected as part of the GI Baby 3 Study, as previously described (20). Glucose, lipids, and fructosamine were measured by using standard enzymatic techniques (Roche Cobas C702). Insulin was measured by immunoassay (Abbott Architect i2000SR). Adiponectin was measured by radioimmunoassay (Millipore HADP-61K). GDM diagnosis was based on modified 1998 Australasian Diabetes in Pregnancy Society Australian criteria, as follows: fasting blood glucose concentrations $\geq$5.5 mmol/L, 1-h blood glucose concentration of $\geq$10.0 mmol/L, or 2-h blood glucose concentration of $\geq$8.0 mmol/L (21). HOMA-IR was calculated as follows (22): [fasting insulin (mU/mL)] $\times$ [fasting glucose (mmol/L)]/22.5. The maternal insulin sensitivity index was calculated according to the Matsuda and DeFronzo formula (23). Maternal BMI was calculated by dividing self-reported prepregnancy weight by measured height squared. Gestational weight gain was computed as the difference between measured weight at week 34–36 of gestation and self-reported prepregnancy weight and categorized according to the 2009 Institute of Medicine recommendations on weight gain during pregnancy (24). Dietary data (2 weekdays and 1 weekend day) were collected by using estimated 3-d food records at baseline (12–20 wk of gestation) and at the end of the intervention (34–36 wk of gestation). Dietary GI values were assigned to carbohydrate food items with the use of published sources (25) and the University of Sydney GI Research Service database. Dietary data were analyzed with the software FoodWorks 7 Professional (Xyris Software), based on the Australian food-composition database AUSNUT2007.

Infant anthropometric and body-composition measurements

Birth weight, length, and head circumference were obtained from medical records. Gestational age was estimated from the date of last menstrual period and early pregnancy ultrasound. Infant anthropometric measurements were taken every month for the first 6 mo and then at 9 and 12 mo of age. Measurements were taken at the Human Nutrition Unit of the University of Sydney. A nude weight was obtained to the nearest 0.01 kg by using an electronic scale (Tanita BD-590 pediatric scale). Recumbent length was measured heel to crown to the nearest 0.1 cm by using an infant length board (Seca 416 infantometer). Head circumference and abdominal girth were measured to the nearest 0.1 cm by using a flexible nonstretchable measuring tape (Seca 212 measuring tape). Measures were taken in duplicate and averaged. A third measurement was performed if results differed by $>$1.0 cm, and the average of the 2 nearest measurements was used. In unsettled infants, these measurements were taken once only.

Weight-for-age z score (WAZ), length-for-age z score (LAZ), weight-for-length z score, and BMI-for-age z score were calculated by using a sex-specific reference database from the WHO (Anthro 3.0.1 software) (26). Ponderal index was calculated as birth weight (g)/length (cm)^3 $\times$ 100. Birth weight centile was calculated by using a macro program from Microsoft Excel (available from http://www.gestation.net) and was used to categorize infants as small-for-gestational-age (birth weight $<$10th centile) or large-for-gestational-age (birth weight $>$90th centile). Body composition was assessed within 48 h after birth and at 3 mo of age by using Pea Pod (Cosmed), an air-displacement plethysmography device previously validated in infants (27).

At 6 and 12 mo of age, body composition was assessed by multifrequency bioimpedance (Quadscan 4000 Bodystat), a noninvasive technique that derives a 2-compartment model of body composition by measuring the body impedance to a multifrequency electric current (5, 50, 100, and 200 kHz) that passes through the body. Infants were lightly dressed and lay in the supine position on a mattress. Skin sites were first cleaned with alcohol wipes. Two pairs of self-adhesive electrodes (Skintact

Easitabs RT14; Leonhard Lang GmbH) were placed on the infant. One pair was placed on the dorsal surface of the right hand, one on the distal metacarpal joints, and one between the right radius and ulna. The second pair of electrodes was placed on the dorsal surface of the right foot, one at the distal metatarsal joints and one between the lateral malleoli. Infant percentage fat mass (FM) was obtained by using the 50-kHz raw data fitted by using the Cole fitting method. Infant adiposity is also expressed as FM index, calculated as FM (kg)/length $(m)^2$ (28).

Infant aortic IMT

At 12 mo of age, aortic IMT was measured in a straight, nonbranched longitudinal segment of the proximal abdominal aorta by high-resolution ultrasound (Philips iE33; Philips), as previously described (29, 30). The aortic IMT (the distance from the lumen-intima interface to the media-adventitia interface) was quantified by using semiautomated and validated offline software (Carotid Analyzer; Medical Imaging Applications) in a 0.5- to 1-cm-long segment of the dorsal aortic wall, from 2 loops of ≥40 frames each. Both the sonographer (MRS) and reader (YK) were blinded to participant identity, characteristics, and study group. These methods for the measurement and analysis of the IMT have been used previously by our research team (30, 31) and have been shown to be highly reproducible (30). Aortic IMT assessed by high-resolution ultrasound is currently considered to be the most sensitive noninvasive measure of structural changes to the arterial vasculature consistent with the earliest physical manifestations of atherosclerosis (29). This technique enables the identification of putative risk factors in infants, with findings thus far being consistent with those derived from direct histologic examination in postmortem studies (9, 30, 32).

Infant feeding practice

Information on the duration of breastfeeding and solid food introduction was collected at each visit by questionnaire. Mothers were asked, "How old was your baby when [child] completely stopped breastfeeding?" Possible answers were "still breastfeeding," "child's age (days/weeks/months) when stopped breastfeeding," and "never breastfed." Mothers were also asked, "How old was your baby when [child] first regularly had solid food?" Possible answers were "child's age (days/weeks/months) when solid food was started" and "never given solid food." This variable was treated as a categorical variable, such as exclusively breastfed, breastfed, weaned, or never breastfed. The term "exclusive breastfeeding" referred to infants who received only breast milk and no other liquids or solid foods, with the exception of medicines. The duration of exclusive breastfeeding was defined as the time from birth until introduction of

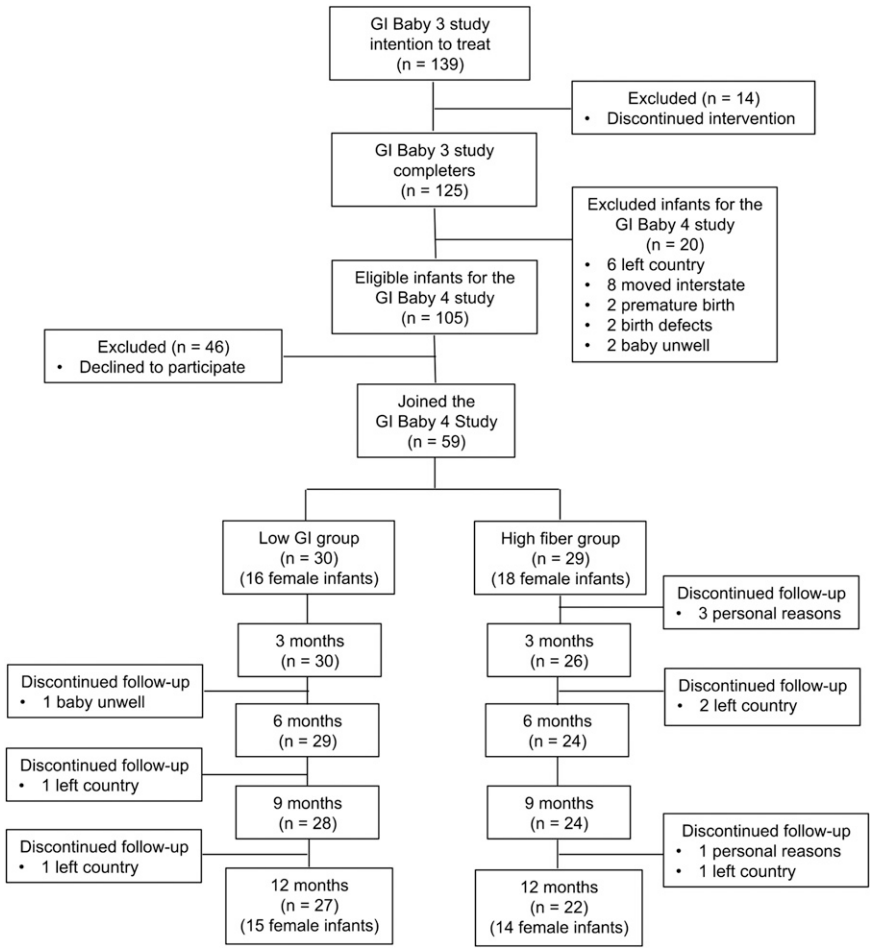

FIGURE 1 Participant flow diagram. GI, glycemic index.

TABLE 1
Maternal characteristics and pregnancy outcomes[1]

	Low-GI group		HF group		
	n	Value	*n*	Value	*P*
Age at study entry, y	30	34.9 ± 0.8	29	35.5 ± 0.7	0.587
Prepregnancy BMI, kg/m^2	30	25.8 ± 1.0	29	25.9 ± 1.0	0.988
Ethnicity, %	30		29		0.359
Asian		20		14	
White		63		80	
Others		17		7	
Employment, %	30		29		0.370
Full-time		67		66	
Part-time		17		28	
Unemployed		17		7	
Education, %	30		29		0.357
Secondary		13		14	
Tertiary		53		55	
Postgraduate		23		31	
Parity (≥1), %	30	50	29	62	0.502
Gestational weight gain, kg	30	10.6 ± 1.0	29	10.7 ± 1.0	0.949
IOM weight gain range, %	30		29		0.293
Below		50		31	
Within		23		38	
Above		27		31	
Delivery, %	30		29		0.348
Vaginal		70		69	
Elective cesarean		17		7	
Emergency cesarean		13		24	
GDM, %	30	27	29	31	0.711
Insulin use, %	30	20	29	14	0.747
Adiponectin,[2] μmol/L	30	13.6 ± 1.3	28	13.8 ± 1.2	0.881
Fructosamine,[2] μmol/L	17	188.6 ± 4.6	14	196.2 ± 4.1	0.236
Total cholesterol,[2] mmol/L	30	5.2 ± 0.2	28	5.5 ± 0.2	0.242
Triglycerides	30	1.2 ± 0.1	28	1.3 ± 0.1	0.437
HDL cholesterol	30	2.0 ± 0.1	29	2.1 ± 0.1	0.451
LDL cholesterol	30	2.7 ± 0.1	29	2.7 ± 0.2	0.910
HbA1c[2]					
%	30	5.0 ± 0.7	28	5.0 ± 0.6	0.865
mmol/L	30	31.0 ± 7.7	28	31.0 ± 6.6	
Glucose,[2] mmol/L					
Fasting	30	4.4 ± 0.1	29	4.4 ± 0.1	0.886
30 min	26	7.0 ± 0.3	24	7.3 ± 0.2	0.423
60 min	30	6.8 ± 0.3	29	7.2 ± 0.3	0.413
120 min	30	6.0 ± 0.3	29	6.2 ± 0.3	0.722
Insulin,[2] pmol/L					
Fasting	30	36 ± 3	25	42 ± 4	0.214
30 min	26	290 ± 23	24	359 ± 41	0.136
60 min	29	257 ± 23	24	408 ± 55	0.009
120 min	29	203 ± 22	24	351 ± 58	0.023
HOMA-IR[2]	30	1.0 ± 0.1	25	1.2 ± 0.1	0.329
ISI[2]	29	11.2 ± 1.0	24	8.0 ± 1.0	0.017
GDM risk factors, %					
Age >35 y	30	53.3	29	65.5	0.341
Family history of T2D	30	63.3	29	37.9	0.051
Previous newborn >4000 g	30	6.7	29	10.3	0.612
Ethnicity[3]	30	23.3	29	17.2	0.561
BMI >30 kg/m^2	30	20.0	29	10.3	0.302
Previous GDM	30	13.3	29	10.3	0.723
PCOS	27	0	29	7.1	0.157

[1]Values are means ± SEMs for continuous variables and percentages for categorical variables. *P* values were derived by 2-sample *t* test or chi-square test. GDM, gestational diabetes mellitus; GI, glycemic index; HbA1c, glycated hemoglobin; HF, high fiber; IOM, Institute of Medicine; ISI, insulin sensitivity index; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes.
[2]Measured at baseline (12–20 wk of gestation).
[3]High-risk ethnicities include Aboriginal or Torres Strait Islander, Polynesian, Middle Eastern, Indian, and Asian.

non–breast milk or any solid. The term "breastfeeding" referred to infants who received breast milk, in combination with other liquids.

Statistical analysis

Descriptive data are presented as means ± SEMs for continuous variable and numbers (*n*) and percentages for frequency variables unless otherwise stated. Data were assessed for normality. Differences between dietary groups were determined by using an independent-samples *t* test for continuous variables and chi-square test for categorical variables. Associations between dietary groups and infant anthropometric and body-composition measurements at birth were investigated by using linear regression, adjusting for maternal prepregnancy BMI, gestational weight gain, and GDM unless otherwise stated. Associations between dietary groups and infant body composition at 3, 6, and 12 mo of age were investigated by using linear regression. The model was adjusted for maternal prepregnancy BMI, gestational weight gain, gestational age, GDM, sex, and infant feeding practice. Linear mixed models were used to assess differences in growth velocity between the 2 diet groups. This approach allows for intrasubject correlation of repeated measures on subjects and accounts for an unbalanced design in the number of observations and the age (time) at which they were collected. Models were fitted for the infancy period from birth to 12 mo of age, with birth and 3-, 6-, 9-, and 12-mo growth measurements included in the model. Models were adjusted for maternal prepregnancy BMI, gestational weight gain, GDM, and infant feeding practice. As a pilot study, it was not powered to detect significant differences in the primary outcome (body composition at 12 mo) but rather to explore the feasibility of carrying out an RCT examining the efficacy of a low-GI diet on offspring growth, metabolism, and vascular health. Statistical analysis was undertaken with the use of IBM SPSS Statistics (version 21; IBM Corporation), and significance was inferred at a 2-sided P value <0.05.

RESULTS

A total of 125 subjects completed the GI Baby 3 Study and 105 infants met the inclusion criteria for the GI Baby 4 Study. Of these, 59 mother-infant pairs agreed to join the GI Baby 4 Study: 30 from the low-GI group and 29 from the HF group (**Figure 1**). Mothers who participated in the follow-up study were more likely to be white (71% compared with 45.5%; $P = 0.01$), have a lower dietary GI at baseline (55 ± 5 compared with 58 ± 6; $P = 0.007$), have higher fiber intakes at the end of the intervention (28.4 ± 7.6 compared with 25.3 ± 8.5 g; $P = 0.04$), and deliver infants who were heavier (3.5 ± 0.5 compared with 3.3 ± 0.4 kg; $P = 0.05$) and longer at birth (50.5 ± 1.9 compared with 49.7 ± 1.8 cm; $P = 0.01$) compared with those who declined to participate in the follow-up study. Of the 59 mother-infant pairs who participated in the follow-up study, 49 infants completed the 12-mo assessment. Baseline characteristics are presented in **Table 1**. There were no significant differences in maternal characteristics, including risk factors for GDM, fasting and postchallenge glucose concentrations, fasting insulin, and HOMA-IR between those randomly assigned to the low-GI compared with the HF intervention. However, women in the HF group had a significantly lower insulin sensitivity index, indicative of a lower composite hepatic and peripheral insulin sensitivity, and higher post–glucose load insulin concentrations at baseline.

Maternal dietary intake during pregnancy

At baseline (12–20 wk of gestation), no significant differences were observed between the 2 groups in total energy intake and macronutrient distribution (**Table 2**). At the end of the intervention (34–36 wk of gestation), as per protocol, dietary GI was significantly lower in the low-GI group than in the HF group (low-GI compared with HF group: 51 ± 1 compared with 57 ± 1; $P < 0.001$). The overall ratio of carbohydrates, protein, and fats

TABLE 2
Maternal diet at baseline and at the end of the intervention[1]

	Baseline			End of intervention			P^3	
	Low-GI group	HF group	P^2	Low-GI group	HF group	P^2	Low-GI group	HF group
n	30	29		28	26	—	—	—
Energy, kJ	8900 ± 270	8890 ± 325	0.976	8480 ± 290	8390 ± 260	0.816	0.171	0.181
Protein, g	98 ± 4	96 ± 4	0.719	98 ± 4	94 ± 4	0.516	0.891	0.804
Total fat, g	78 ± 4	83 ± 4	0.400	78 ± 4	78 ± 4	0.918	0.923	0.231
Saturated fat, g	30 ± 2	32 ± 2	0.555	27 ± 2	30 ± 2	0.175	0.144	0.247
Total available carbohydrate, g	245 ± 9	235 ± 10	0.454	219 ± 9	218 ± 10	0.987	0.010	0.192
Sugars, g	105 ± 6	96 ± 6	0.288	91 ± 6	97 ± 7	0.554	0.107	0.977
Starch, g	137 ± 7	138 ± 7	0.979	126 ± 5	120 ± 6	0.445	0.053	0.030
Fiber, g	27 ± 2	27 ± 2	0.805	30 ± 2	27 ± 1	0.075	0.179	0.728
GI	55 ± 1	56 ± 1	0.330	51 ± 1	57 ± 1	<0.001	0.002	0.253
Glycemic load	126 ± 6	123 ± 6	0.659	105 ± 5	117 ± 6	0.115	<0.001	0.523
Protein, % of energy	19 ± 1	19 ± 1	0.739	20 ± 1	19 ± 1	0.623	0.441	0.315
Total fat, % of energy	32 ± 1	34 ± 1	0.126	34 ± 1	34 ± 1	0.652	0.287	0.563
Saturated fat, % of energy	12 ± 1	13 ± 1	0.351	11 ± 1	13 ± 1	0.029	0.289	0.708
Carbohydrate, % of energy	45 ± 1	44 ± 1	0.245	43 ± 1	43 ± 1	0.942	0.075	0.787

[1]Values are means ± SEMs unless otherwise indicated. GI, glycemic index; HF, high fiber.
[2]Obtained by 2-sample *t* test to test differences between groups.
[3]Obtained by paired-sample *t* test to test for differences compared with baseline.

was similar, but the percentage of energy from saturated fat was significantly lower in the low-GI group (low-GI compared with HF group: 11% ± 1% compared with 13% ± 1%; $P = 0.03$). From baseline to the end of the intervention, there was a significant decrease in starch intake in the HF group and a significant decrease in dietary GI and glycemic load in the low-GI group (Table 2).

Maternal dietary GI in pregnancy and infant growth and arterial wall thickness

Infant anthropometric measurements at birth and body composition assessed at birth and 3, 6, and 12 mo of age are presented in **Table 3**. A sensitivity analysis revealed 2 outliers (1 male infant with a birth weight <2.5 kg and 1 female infant with an LAZ >3 SDs from the mean). Results are therefore presented for 57 infants: 28 in the low-GI group and 29 in the HF group. Gestational age was similar in both groups. Infant birth weight, birth length, WAZ, and LAZ were significantly higher in the HF group. In the model that adjusted for maternal prepregnancy BMI, gestational weight gain, and GDM, WAZ and LAZ remained significantly different between the 2 groups. When the 2 outlier infants were included in the analysis, only mean WAZ remained significantly different between the 2 groups (low-GI compared with HF group: 0.1 ± 0.2 compared with 0.7 ± 0.2; $P = 0.03$).

After birth, infant growth trajectories did not differ between the 2 groups (**Figure 2**). Head circumference and abdominal girth growth velocities did not differ between the 2 groups (data not shown). Data on infant feeding practice showed that, at 3 mo of age, 84% of the infants were exclusively breastfed, which decreased to 17% at 6 mo of age. At 12 mo of age, 78% of the infants were still breastfed.

TABLE 3
Neonatal anthropometric measurements and infant body composition in the first year of life[1]

	Low-GI group		HF group			
	n	Value	*n*	Value	*P*	*P*-adjusted[2]
Birth						
Female, *n* (%)	28	15 (54)	29	18 (62)	—	—
Gestational age, wk	28	39.4 ± 0.3	29	39.9 ± 0.2	0.141	0.113
Weight, kg	28	3.4 ± 0.1	29	3.6 ± 0.1	0.040	0.100[3]
Length, cm	28	50 ± 0.3	29	51 ± 0.3	0.019	0.068[3]
Head circumference, cm	27	34.3 ± 0.2	27	34.9 ± 0.3	0.067	0.144[3]
Ponderal index, kg/m^3	28	2.7 ± 0.0	29	2.7 ± 0.1	0.836	0.740[3]
Birth weight centile	28	40.1 ± 4.3	29	48.1 ± 5.0	0.230	NA
Small-for-gestational-age, *n* (%)	28	3 (10.7)	29	2 (6.9)	0.336	NA
Large-for-gestational-age, *n* (%)	28	0 (0.0)	29	2 (6.9)	—	—
Weight-for-age *z* score	28	0.2 ± 0.2	29	0.7 ± 0.2	0.035	0.037
Weight-for-length *z* score	28	0.1 ± 0.2	29	0.1 ± 0.2	0.992	0.993
Length-for-age *z* score	28	0.3 ± 0.2	29	0.9 ± 0.2	0.013	0.016
BMI-for-age *z* score	28	0.1 ± 0.2	29	0.3 ± 0.2	0.315	0.307
Fat mass,[4] %	24	9.8 ± 1.0	21	10.9 ± 0.7	0.393	0.503[3]
Fat mass index[4]	24	1.3 ± 0.1	21	1.4 ± 0.1	0.450	0.521[3]
3 mo						
Female, *n* (%)	28	15 (54)	26	17 (65)	—	—
Weight, kg	28	6.1 ± 0.1	26	6.2 ± 0.2	0.706	0.763[5]
Fat mass, %	28	25.2 ± 1	26	24.6 ± 0.9	0.681	0.451[5]
Fat mass index	28	7.0 ± 0.3	26	6.8 ± 0.3	0.489	0.428[5]
6 mo						
Female, *n* (%)	27	14 (51.9)	24	16 (66.7)	—	—
Weight, kg	27	7.8 ± 0.2	24	7.7 ± 0.2	0.785	0.963
Fat mass,[6] %	27	30.0 ± 0.8	23	31.1 ± 0.8	0.344	0.646[5]
Fat mass index[6]	27	5.4 ± 0.2	23	5.4 ± 0.2	0.922	0.892[5]
12 mo						
Female, *n* (%)	25	14 (56)	22	14 (63.6)	—	—
Weight, kg	25	9.7 ± 0.2	22	9.7 ± 0.2	0.955	0.862
Fat mass,[7] %	24	33.6 ± 0.7	20	34.4 ± 0.5	0.464	0.449[5]
Fat mass index[7]	24	5.9 ± 0.2	20	6.0 ± 0.2	0.671	0.655[5]

[1]Values are means ± SEMs for continuous variables and *n* (%) for categorical variables. Groups were compared by using independent-samples *t* test. GDM, gestational diabetes mellitus; GI, glycemic index; HF, high fiber; NA, not applicable as centile accounts for maternal height, weight, ethnicity, parity, infant sex, gestational age, and birth weight.
[2]*P* values adjusted for maternal prepregnancy BMI, gestational weight gain, and GDM unless otherwise indicated.
[3]Adjusted for maternal prepregnancy BMI, gestational weight gain, GDM, gestational age, and sex.
[4]Available data in 12 and 13 female infants in the low-GI and HF groups, respectively.
[5]Adjusted for maternal prepregnancy BMI, gestational weight gain, GDM, gestational age, sex, and feeding practice.
[6]Available data in 14 and 15 female infants in the low-GI and HF groups, respectively.
[7]Available data in 14 and 13 female infants in the low-GI and HF groups, respectively.

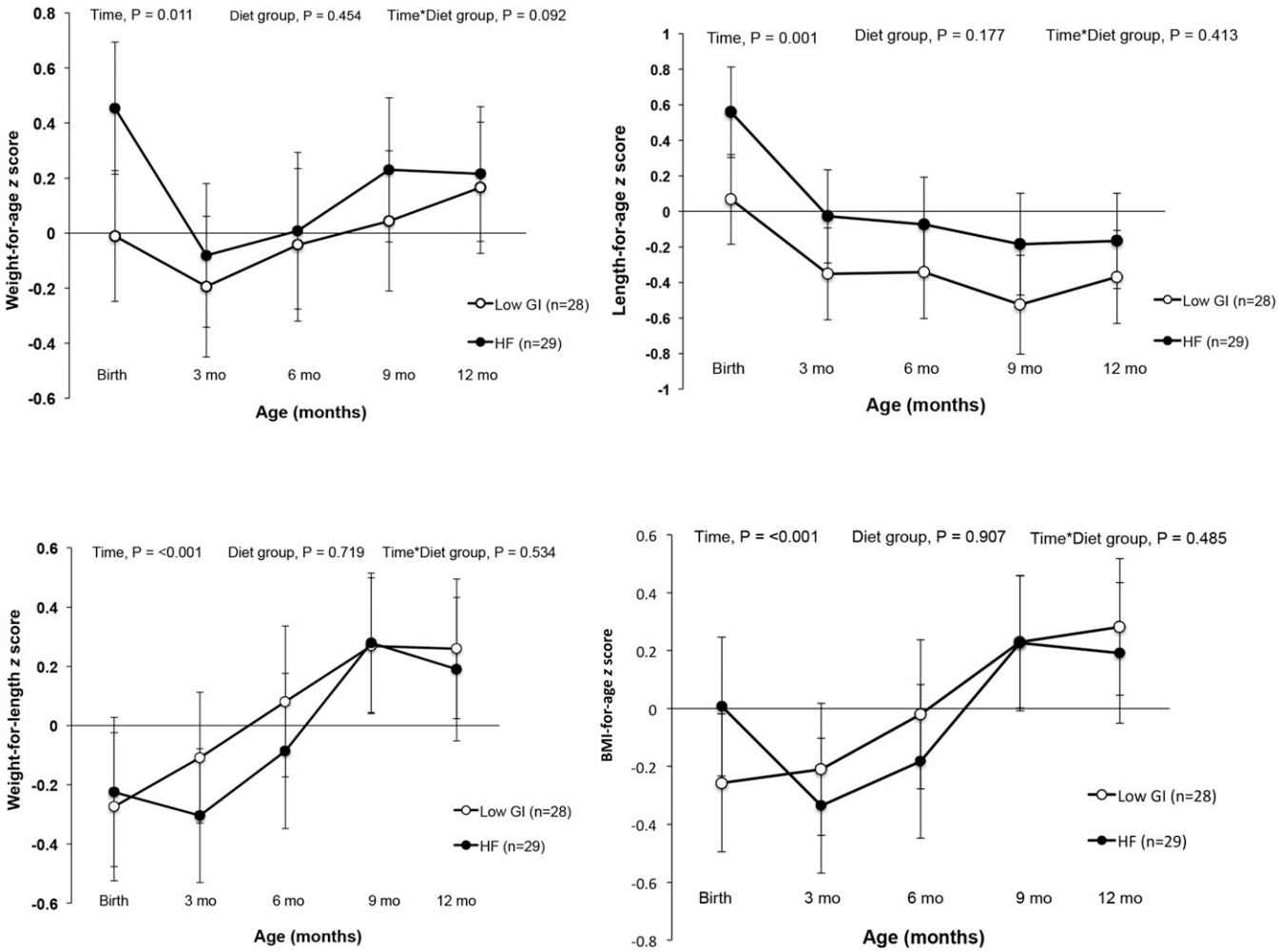

FIGURE 2 Effects of a low-GI compared with an HF diet during pregnancy on offspring postnatal growth trajectory from birth to 12 mo of age. Values are estimated marginal means ± SEMs obtained from linear mixed models for the low-GI and HF groups. Models adjusted for maternal prepregnancy BMI, gestational weight gain, GDM, and infant feeding practice. Missing values were extrapolated by the model (n = 57: 28 in the low-GI group and 29 in the HF group). (A) Weight-for-age z score trajectories from birth to 12 mo of age; (B) length-for-age z score trajectories from birth to 12 mo of age; (C) weight-for-length z score trajectories from birth to 12 mo of age; (D) BMI-for-age z score trajectories from birth to 12 mo of age. GI, glycemic index; HF, high-fiber.

Post hoc multivariable linear regression analysis showed no association of maternal GI at 36 wk of gestation with offspring aortic IMT at 12 mo (−1 μm; 95% CI: −5, 3 μm; P = 0.60); however, aortic IMT was significantly thinner in the low-GI group compared with the HF group (low-GI compared with HF group: 657 ± 12 compared with 696 ± 12 μm; P = 0.02) (**Figure 3**). Adjustment for birth weight marginally reduced the estimated effect size (low-GI compared with HF group: 661 ± 11 compared with 692 ± 11 μm; P = 0.07). Maximum aortic IMT showed greater variability per se, and the difference between groups was not significant (low-GI compared with HF group: 842 ± 17 compared with 882 ± 17 μm; P = 0.11).

DISCUSSION

To our knowledge, this is the first RCT to assess the effects of a low-GI diet during pregnancy on offspring growth and adiposity beyond birth. In women at risk of GDM, we found that, relative to a conventional healthy diet, a low-GI dietary intervention resulted in lower infant WAZ and LAZ at birth, thereby more closely resembling population norms (the 50th percentile). There was no evidence of differences in adiposity at birth or in postnatal growth trajectories from 1 to 12 mo of age. Hence, mothers randomly assigned to receive a lower-GI diet during pregnancy gave birth to smaller, but not leaner, infants. Nonetheless, the infants of mothers who consumed a lower-GI diet had thinner aortic walls at 12 mo of age than the offspring of mothers who consumed a conventional HF diet with a higher GI.

The smaller aortic IMT in the low-GI group provides proof-of-concept that a dietary intervention initiated during pregnancy may partially mitigate the vascular sequelae of maternal hyperglycemia, even within the normal range. The women recruited were considered "at risk" of developing GDM. There is good evidence that the children of these women are also likely, on average, to have thicker aortic IMT on the basis of a higher incidence of GDM and high birth weight (3, 6) and a greater prevalence of maternal obesity (31). Interestingly, others previously showed that the thicker aortic IMT in the macrosomic infants of mothers with GDM appears to be independent of their

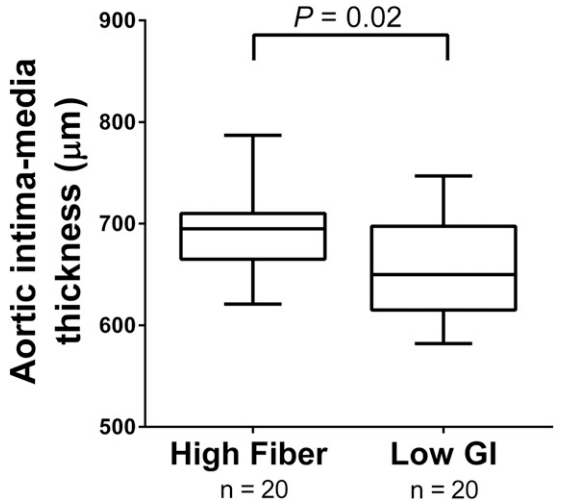

FIGURE 3 Effects of a low-GI compared with an HF diet during pregnancy on offspring aortic wall thickness at 12 mo of age. Error bars represent 10th and 90th percentiles, boxes represent 25th and 75th percentiles, and the line represents the 50th percentile (median) of mean aortic intima-media thickness (n = 40: 20 in the low-GI group and 20 in the HF group). GI, glycemic index; HF, high-fiber.

birth weight (6). Indeed, the observed difference in aortic IMT was predominantly independent of birth weight, suggesting that a maternal low-GI diet during pregnancy improves offspring vascular health via mechanisms that are not reflected by modification of birth weight. Putative mechanisms include epigenetic modifications or changes in the number and function of endothelial progenitor cells (33). Other dietary factors, such as saturated fat intake, may be implicated. Future studies should investigate maternal and infant markers that are closely associated with improvements in vascular health, including detailed analyses of maternal and infant dietary intake.

Our findings in relation to size at birth (i.e., significantly larger offspring in mothers randomly assigned to receive the HF diet) contrast with the findings in the entire GI Baby 3 cohort, in which no significant effects were evident (20). However, our results are consistent with other studies that reported lower birth weight among infants of women who consumed a low-GI diet during pregnancy (13, 17). We initially speculated that the mechanism through which a low-GI diet would result in normalization of offspring birth WAZ and LAZ may involve reduced maternal postprandial increases in glucose, lessening the availability of glucose to the fetus and thus normalizing fetal glycemia and insulin production (11, 34–36). However, the difference may also be attributable to the characteristics of the mothers who, after participating in the original trial, self-selected to participate in the follow-up study reported here. In general, women who were willing to continue participation beyond birth were highly educated and had a lower dietary GI and higher dietary fiber intake at the start and at the end of the intervention period. Both of these suggest a healthier diet at baseline and greater treatment fidelity during the intervention.

We hypothesized that infants born to mothers randomly assigned to the HF diet would show increased adiposity per se at birth, which would track throughout the first year of life. However, body fat at birth and through the follow-up was similar in both groups. There are several reasons that might account for this null finding. First, although significant, the difference in the dietary GI between the 2 groups was modest (51 $\pm$ 1 in the low-GI group compared with 57 $\pm$ 1 in the HF group), with the HF group consuming a diet that would usually be considered to be medium-GI rather than high-GI. Participants were highly educated and potentially had knowledge of dietary GI and on the importance of breastfeeding. In addition, normal neonatal body composition has been shown in women who achieve good glycemic control (37). In our sample, women in both groups, even those with a diagnosis of GDM, achieved good glycemic control (20). Last, it has been suggested that the effects of maternal hyperglycemia on offspring growth and adiposity differ depending on the age of the offspring. Differences have been shown at birth (11, 34) and in early and mid-childhood (8, 38) but not in infancy (39).

Finally, the ROLO study, an RCT of a low-GI diet in pregnancy to prevent the recurrence of macrosomia, reported significant positive effects of a modest lowering of dietary GI and glycemic load on maternal gestational weight gain and glucose tolerance (19). In the present study, we did not find a significant effect of a low-GI diet on these variables. However, women enrolled in the randomized controlled trial of a low glycemic index diet versus no dietary intervention to prevent recurrence of fetal macrosomia (ROLO) study had a higher BMI ($\sim$27 compared with $\sim$26) and had previously delivered a macrosomic infant ($>$4000 g), suggesting that a low-GI diet might be more beneficial for overweight and obese pregnant women (40).

The strengths and weaknesses of our study should be noted. A key component was the prospective cohort design and timely assessment of growth and body composition from birth to 12 mo of age, which provided unique information on the mechanisms underlying links between maternal diet, blood glucose concentrations, and subsequent infant growth and adiposity. The study had a low attrition rate (17%), which reduces bias and increases the generalizability of the findings. The primary limitations are those inherent to a self-selected group of volunteers, including selection bias and confounding. Individuals who participated in the follow-up study may differ in relevant ways from those initially randomly assigned to the study. In addition, other influences beyond the randomized diets may have influenced the outcome. Only 56% of the eligible women (n = 105) who completed the GI Baby 3 Study agreed to participate in the follow-up study, which did not provide sufficient power to detect some of the potentially important differences between the groups, such as adiposity. Although we aimed for a larger difference in GI between the 2 groups, the difference achieved was modest (6 units). Vascular health was assessed by using a single modality on a single occasion at 12 mo of age. Furthermore, for aortic IMT we prospectively anticipated an effect size of $\sim$25 μm, and therefore were underpowered in this pilot study. Finally, residual confounding or selection bias might have influenced the findings. Future larger trials are required to confirm whether these improvements in arterial wall thickness remain stable through childhood and into adulthood and to ascertain whether other aspects of vascular health, such as endothelial function and arterial stiffness, are also improved.

In conclusion, this study showed that, in pregnant women at risk of GDM, a low-GI diet resulted in lower offspring WAZ and

LAZ at birth but no difference in adiposity, weight gain, or growth trajectory during the first 12 mo after birth. At 12 mo of age, children whose mothers were randomly assigned to the low-GI diet had lower aortic wall thickness. These findings suggest a potential effect of dietary GI on fetal growth regulation and offspring vascular health, but not adiposity, in infancy.

The authors' responsibilities were as follows—NVK, SPG, JCB-M, and MRS: designed and conducted the study, interpreted the results, and wrote the manuscript; NVK, YK, and PP: analyzed and interpreted the data; LCW: analyzed the bioimpedance data; JCB-M: had primary responsibility for the final content; and all authors: contributed to the discussion and approved the final manuscript. JCB-M is the President of the Glycemic Index Foundation, Director of the University of Sydney Glycemic Index Research Service, and author of popular books about the glycemic index of foods. JCYL consults for the Glycemic Index Foundation. LCW consults for ImpediMed Ltd. The other authors did not report any conflicts of interest relevant to this article.

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