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ORIGINAL RESEARCH

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Gestational diabetes exposure and adiposity outcomes in childhood and adolescence: An analysis of effect modification by breastfeeding, diet quality, and physical activity in the EPOCH study

Katherine A. Sauder[1,2,3] | Traci A. Bekelman[1,3] | Kylie K. Harrall[3] | Deborah H. Glueck[1,3] | Dana Dabelea[1,2,3]

[1] Department of Pediatrics, School of Medicine, University of Colorado, Aurora, CO, USA

[2] Department of Epidemiology, Colorado School of Public Health, University of Colorado, Aurora, CO, USA

[3] Lifecourse Epidemiology of Adiposity and Diabetes (LEAD) Center, University of Colorado, Aurora, CO, USA

Correspondence
K Sauder, LEAD Center, University of Colorado, Mail Stop F426, 12474 E 19th Ave, Aurora, CO 80045, USA.
Email: katherine.sauder@ucdenver.edu

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Summary

Background: Intrauterine exposure to gestational diabetes (GDM) is associated with increased adiposity; however, not all offspring exposed to GDM exhibit excess adiposity.

Objectives: Examine whether optimal diet and activity behaviours in infancy, childhood, and adolescence modify the association between GDM exposure and adiposity.

Methods: In 564 offspring (84 exposed to GDM), we assessed breastfeeding (maternal recall), dietary intake (food frequency questionnaire), physical activity (3-day recall), and adiposity (BMI, waist-to-height ratio, visceral and subcutaneous adipose tissue, and subscapular-to-triceps skinfold ratio) at 10.4 (SD, 1.5) and 16.7 (SD, 1.2) years. Optimal behaviours were defined as ≥6 breastmilk months, Healthy Eating Index score ≥60, and daily vigorous activity >1 hour. Linear mixed models assessed the association between GDM exposure and adiposity among those with optimal versus suboptimal health behaviours, adjusting for sex, race/ethnicity, age, and pubertal status.

Results: GDM exposure was associated with increased skinfold ratio, visceral and subcutaneous adipose tissue among those with <6 breastmilk months (all *P*s < .05), but only associated with increased skinfold ratio among those with ≥6 breastmilk months ($P = .01$). GDM exposure was associated with increases in all adiposity measures among those with Healthy Eating Index scores <60 ($P < .01$), but not those with scores ≥60 ($P > .10$). GDM exposure was associated with increased BMI and subcutaneous adipose tissue among those with >1 hour of vigorous activity ($P < .05$) but not among those with <1 hour of vigorous activity ($P > .30$).

Conclusions: The association of GDM exposure with excess adiposity is attenuated in offspring with more optimal diet and activity behaviours in infancy, childhood, and adolescence.

KEYWORDS

activity, adiposity, breastfeeding, diet

1 | INTRODUCTION

Offspring exposed to maternal diabetes (type 1, type 2, or gestational) in pregnancy are at increased risk of excess body size and adiposity during childhood, adolescence, and adulthood.[1-4] However, not every child who is exposed to diabetes in utero becomes obese, indicating that additional factors are involved in the development of obesity. Health factors or behaviours during other critical periods in early life, such as infancy and puberty, may ameliorate the effect of intrauterine exposures on offspring health. For example, breastfeeding has been associated with a reduced risk of obesity among offspring exposed to any type of maternal diabetes.[5-8] We and others have previously reported that 6 months or more of exclusive breastfeeding among offspring exposed to gestational diabetes (GDM) is associated with a normalization of body size and adiposity at 2 to 12 years relative to offspring not exposed.[9,10] Less is known about the potential of other health behaviours in childhood to attenuate the obesity risks of this intrauterine exposure. One study of Chinese children exposed to GDM reported that those who did not watch television daily were less than half as likely to be obese compared with those who watched ≥1 hour daily.[11] However, there was no difference in obesity risk according to physical activity, and diet was not assessed. Another study of Canadian children reported that those who were exposed to GDM and consumed a healthy diet were four times more likely to be overweight/obese than children who were exposed but did not consume a healthy diet.[12] Given the increasing number of individuals who are exposed to maternal diabetes in utero each year,[13] a better understanding how early life health behaviours may mitigate the adverse effects of this exposure is needed to guide the development of targeted prevention efforts for children at highest risk of obesity.

We examined the association of intrauterine exposure to GDM with body size and adiposity in childhood and adolescence (6-19 y) among offspring with optimal versus suboptimal diet and physical activity behaviours. We hypothesized that exposure to GDM would be associated with greater body size and adiposity among youth with suboptimal health behaviours, but not among youth with optimal health behaviours.

2 | METHODS

The Exploring Perinatal Outcomes among Children (EPOCH) study is a historical prospective cohort study based in Denver, Colorado. From 2005 to 2010, we recruited children born to women who were members of the Kaiser Permanente of Colorado health plan and resided in Colorado. We enrolled children exposed to maternal diabetes in utero and a random sample of children not exposed to maternal diabetes. The first in-person research visit (visit 1) was completed by 604 offspring (n = 90 exposed to GDM, n = 9 exposed to type 1 diabetes, and n = 505 not exposed) aged 6 to 12 years (mean, 10.4; SD, 1.5) in 2005 to 2010. The second in-person research visit (visit 2) was completed by 417 offspring (n = 70 exposed to GDM, n = 7 exposed to type 1 diabetes, and n = 340 not exposed) aged 12 to 19 years (mean, 16.7; SD, 1.2) in 2010 to 2015. All study activities occurred at the University of Colorado Anschutz Medical Campus, with approval from the Colorado Multiple Institutional Review Board. Mothers provided written informed consent, and offspring provided written assent.

2.1 | GDM exposure assessment

Maternal diabetes in pregnancy was obtained from Kaiser Permanente of Colorado medical records. Pregnant women at Kaiser Permanente of Colorado were routinely screened for GDM at 24 to 28 weeks using the two-step standard protocol.[14] GDM was diagnosed if glucose values exceeded two or more thresholds set by the National Diabetes Data Group on the 3-hour 100-g oral glucose tolerance test.[15]

2.2 | Offspring diet and physical activity assessment

Offspring diet during infancy was assessed at the first research visit via maternal recall of breastfeeding and formula feeding, which has been shown to correlate well with prospective collection of infant feeding data.[16,17] These data were used to calculate breastmilk months, a measure that reflects both duration and exclusivity of breastfeeding.[9] For exclusively breastfed infants, breastmilk months is equivalent to the duration of breastfeeding (eg, 8 mo of breastfeeding = 8 breastmilk months). For infants fed both breastmilk and formula, breastmilk months is the duration of exclusive breastfeeding plus the weighted duration of mixed feeding (eg, 4 mo of exclusive breastfeeding + 2 mo of 50% breastmilk and 50% formula = 5 breastmilk months. For infants fed formula exclusively, breastmilk month is 0.

Offspring diet in childhood and adolescence was assessed at both research visits with the Block Kids Food Frequency Questionnaire. This semi-quantitative questionnaire was developed and validated for children ≥8 years[18,19] It queries intake, frequency, and average portion size of 85 foods and beverages over the last week. These data were used to calculate Healthy Eating Index 2010,[20] a diet quality index that compares usual intake to the Dietary Guidelines for Americans. Intake is classified according to 10 food groups (total vegetables, greens and beans, total fruit, whole fruit, whole grains, dairy, total protein foods, seafood and plant protein, refined grains, and empty calories) and two nutrients (sodium and fatty acid ratio). The empty calories component is standardized to total energy intake, and all other components except the fatty acid ratio are standardized to daily intake of 1000 kcal. The scores for all 12 components are used to derive an overall Healthy Eating Index score, which ranges from 1 to 100, and higher scores indicate better diet quality. For this analysis, two modifications to the standard scoring were necessary because of the nature of the available data. First, the whole fruit component score included whole fruits and fruit juice, instead of just whole fruits. Second, the empty calories component included solid fats, added sugars, and oils, instead of solid fats, added sugars, and alcohol

(alcohol is not assessed with the Block Kids Food Frequency Questionnaire).

Offspring physical activity in childhood and adolescence was assessed at both research visits with the 3-day Physical Activity Recall.[21] Participants recalled prior day activities in 30-minute blocks, along with intensity level (light, moderate, hard, and very hard) as appropriate. We calculated the average daily number of 30-minute blocks of physical activities with metabolic equivalents (METs) of 6 or greater, in accordance with the 2018 Physical Activity Guidelines for Americans.[22]

2.3 | Offspring obesity outcomes assessment

At both research visits, offspring height (via stadiometer) and weight (via calibrated electronic scale) were measured in duplicate in light clothing without shoes. Waist circumference was measured in duplicate against the skin, midway between the lowest rib margin and the right iliac crest, using a nontension tape. Subscapular and triceps skinfold thicknesses were measured in triplicate using Holtaine calipers. Visceral and subcutaneous adipose tissue were measured with a 3T imager (General Electric, Waukesha, Wisconsin). A series of T1-weighted coronal images were taken at the L4/L5 plane while the participant was supine, with subcutaneous and visceral adipose tissue area (cm^2) measured by a blinded, single reader from a single axial 10-mm image at the umbilicus or L4/L5 vertebra. The above data were used to calculate three indices of adiposity: body mass index (BMI, kg/m^2), waist-to-height ratio, and subscapular-to-triceps skinfold ratio.

2.4 | Covariate assessment

Demographic information (age, sex, and race/ethnicity) was collected via self-report. Race/ethnicity was classified as non-Hispanic White or all other race/ethnicities. Pubertal development was self-reported by the offspring using diagrammatic representations of Tanner staging adapted from Marshall and Tanner,[23] with staging classified as prepubertal or pubertal according to pubic hair in males and breast development in females.

2.5 | Statistical analyses

EPOCH participants were eligible for the present analysis if they had data on at least one adiposity outcome and complete data on breastfeeding, diet quality, physical activity, and all covariates at one or both research visits. We excluded offspring who were exposed to maternal type 1 diabetes in pregnancy. All analyses were conducted in SAS 9.4 (SAS Institute, Cary, North Carolina).

Thresholds defining optimal or suboptimal diet and physical activity behaviours were determined by considering both relevant recommendations and distribution of the behaviours among EPOCH participants. Infant diet was dichotomized as $\geq$6 breastmilk months (optimal) versus <6 breastmilk months (suboptimal), in accordance with the American Academy of Pediatrics' recommendation for 6 months of exclusive breastfeeding.[24] Childhood and adolescent diet quality were dichotomized as Healthy Eating Index $\geq$60 (optimal) versus <60 (suboptimal). While this is below the recommended score of 80 for the prevention of chronic disease,[25] which was met by only 1% of our participants, it approximates the 75th percentile of scores in both our EPOCH sample and a nationally representative sample of US children and adolescents.[26] Child and adolescent physical activities were dichotomized as daily vigorous activity >1 hour versus $\leq$1 hour. Again, this approximates the 75th percentile of vigorous activity in our EPOCH cohort and aligns with the US Department of Health and Human Services' recommendation for children to engage in 1 hour or more of physical activity daily, with at least 3 d/wk including of vigorous activity.[22]

We used linear mixed models (PROC MIXED) with an unstructured covariance matrix to assess the association of intrauterine exposure to GDM with adiposity outcomes among participants with optimal versus suboptimal health behaviours across both research visits. Five identical models were constructed so that each adiposity outcome could be analysed separately. We did not adjust for multiple testing because the separate outcomes were specified a priori. For each of the five models, the predictors included maternal GDM, breastfeeding category at each visit, Healthy Eating Index category at each visit, physical activity category at each visit, and the interaction terms for each health behaviour category with GDM (eg, breastfeeding category × GDM). We planned a priori to examine the effect of GDM exposure within each health behaviour category even if the *P* value for the interaction term was not statistically significant (two-sided $P > .05$). We included all three health behaviour categories in each model to ensure that effects of one behaviour were independent of the other behaviours. For each of the five models, the covariates included offspring race/ethnicity, sex, age at each visit, pubertal status at each visit, and an Age × pubertal status interaction term, as in previous analyses from this cohort.[1] Because we had repeated measurements of the health behaviour exposures and adiposity outcomes, we also entered time as a repeated effect to account for the correlation between measures within each participant. All adiposity outcomes required natural log transformation prior to analysis to ensure model assumptions were met. The resulting beta estimates and confidence intervals (CI) were back-transformed for presentation.

3 | RESULTS

Of the 604 child participants who completed visit 1 and the 417 child participants who completed visit 2, we excluded data from 41 observations at visit 1 (nine who were exposed to type 1 diabetes and 32 who were missing data for breastfeeding, diet, and/or activity) and 42 observations at visit 2 (seven who were exposed to type 1 diabetes and 35 who were missing data for breastfeeding, diet, and/or activity). Complete data were available for 564 (n = 84 exposed to GDM exposed) and 375 (n = 63 exposed to GDM) child participants at visits 1 and 2, respectively, resulting in 939 repeated observations (n = 147

exposed to GDM) that were included in this analysis. There were no notable differences between participants whose observations were excluded versus included (data not shown). Maternal and child characteristics of the final sample are presented in Table 1, stratified by visit and GDM exposure.

The association of GDM exposure with adiposity outcomes among offspring with optimal versus suboptimal health behaviours is presented in Table 2. For all health behaviours, we found that exposure to GDM was associated with statistically and clinically significant increases in multiple measures of adiposity when offspring health behaviours were suboptimal. However, when offspring health behaviours were optimal, the adverse effect of GDM exposure on adiposity was attenuated to nonsignificance.

3.1 | Infant breastmilk months

Among offspring with <6 breastmilk months, GDM exposure was associated with statistically significant increases in visceral adipose tissue (unexposed mean = 23.2 cm^2 [95% CI, 20.7-25.9], exposed = 28.3 cm^2 [23.0-34.8], P = .05), subcutaneous adipose tissue (unexposed = 121.8 cm^2 [107.0-138.6], exposed = 160.1 cm^2 [125.4-204.3], P = .03), and skinfold ratio (unexposed = 0.81 [0.77-0.86] vs exposed = 0.95 [0.85-1.06], P = .01) and with nonstatistically significant increases in BMI (unexposed = 20.6 kg/m^2 [19.9-21.2], exposed = 21.8 kg/m^2 [20.4-23.3], P = .08) and waist-to-height ratio (unexposed = 0.47 [0.45-0.48], exposed = 0.49 [0.46-0.51], P = .10). In contrast, among offspring with ≥6 breastmilk months, GDM exposure was associated with a statistically significant increase only for skinfold ratio (unexposed = 0.81 [0.76-0.86], exposed = 0.92 [0.83-1.03], P = .01). The interaction term between breastmilk months category and GDM exposure, however, was not statistically significant for any of the adiposity outcomes.

3.2 | Child/adolescent Healthy Eating Index

Among offspring with a Healthy Eating Index <60, exposure to GDM was associated with significant increases in BMI (unexposed = 20.2 kg/m^2 [19.7-20.7], exposed = 21.6 kg/m^2 [20.6-22.7],

TABLE 1 Maternal and offspring characteristics at each visit, stratified by gestational diabetes exposure status

	Visit 1		Visit 2	
	Nonexposed n = 480	Exposed n = 84	Nonexposed n = 312	Exposed n = 63
Maternal characteristics				
Age at delivery, y	30.1 (5.7)	33.3 (5.5)	30.6 (5.6)	33.7 (5.4)
Prepregnant BMI, kg/m^2	25.4 (5.8)	27.8 (6.3)	25.5 (6.1)	27.4 (5.9)
Education				
Less than high school degree	16 (3%)	4 (5%)	8 (3%)	2 (3%)
High school graduate	91 (19%)	14 (17%)	48 (15%)	10 (16%)
Some college, 2-y degree	153 (32%)	30 (36%)	102 (33%)	22 (35%)
Bachelor's degree	157 (33%)	25 (30%)	103 (33%)	20 (32%)
Graduate degree	63 (13%)	11 (13%)	51 (16%)	9 (14%)
Offspring characteristics				
Female (n)	250 (52%)	40 (48%)	163 (52%)	26 (41%)
Non-Hispanic white (n)	213 (44%)	53 (63%)	151 (48%)	40 (63%)
Prepubertal (n)	204 (43%)	53 (63%)	0 (0%)	0 (0%)
Age, y	10.6 (1.4)	9.5 (1.7)	16.8 (1.2)	15.8 (1.0)
Breastmilk months	7.0 (7.4)	6.4 (6.8)	7.7 (7.8)	6.2 (5.5)
Healthy Eating Index	49 (10)	50 (9)	59 (11)	56 (10)
Vigorous physical activity (30-min blocks)	1.6 (1.7)	1.3 (1.8)	1.6 (2.1)	1.9 (2.3)
BMI, kg/m^2	19.0 (4.6)	19.0 (4.7)	23.6 (5.8)	23.4 (4.9)
Waist-to-height ratio	0.45 (0.07)	0.47 (0.07)	0.48 (0.08)	0.48 (0.07)
Visceral adipose tissue, cm^2	22.2 (16.1)	24.4 (18.4)	33.3 (23.0)	32.2 (19.1)
Subcutaneous adipose tissue, cm^2	121.1 (109.5)	128.4 (110.0)	199.0 (153.6)	197.4 (136.4)
Visceral to subcutaneous ratio	0.24 (0.12)	0.24 (0.14)	0.21 (0.12)	0.19 (0.08)
Subscapular to triceps skinfold ratio	0.76 (0.22)	0.81 (0.22)	1.38 (0.99)	1.48 (1.02)

Note. Data are mean (SD) or n (%).

Abbreviation: BMI, body mass index.

TABLE 2 Association of gestational diabetes exposure and adiposity outcomes at 6 to 19 years, stratified by optimal versus suboptimal health behaviours

	Unexposed			Exposed				Unexposed			Exposed				
	n	Mean	(95% CI)	n	Mean	(95% CI)	*P* Value	n	Mean	(95% CI)	n	Mean	(95% CI)	*P* Value	Interaction *P* value[a]
	Breastmilk months < 6							Breastmilk months ≥ 6							
BMI, kg/m^2	399	20.6	(19.9-21.2)	76	21.8	(20.4-23.3)	.08	391	19.7	(19.0-20.3)	70	20.6	(19.3-22.1)	.18	.82
Waist-to-height ratio	400	0.47	(0.45-0.48)	75	0.49	(0.46-0.51)	.10	392	0.45	(0.44-0.46)	71	0.46	(0.44-0.49)	.25	.71
Visceral adipose tissue, cm^2	375	23.2	(20.7-25.9)	71	28.3	(23.0-34.8)	.05	369	21.1	(18.8-23.6)	69	23.5	(19.1-28.9)	.28	.50
Subcutaneous adipose tissue, cm^2	375	121.8	(107.0-138.6)	71	160.1	(125.4-204.3)	.03	369	106.7	(93.5-121.8)	69	132.4	(103.6-169.1)	.08	.73
Skinfold ratio	396	0.81	(0.77-0.86)	75	0.95	(0.85-1.06)	.01	390	0.81	(0.76-0.86)	70	0.92	(0.83-1.03)	.01	.68
	Healthy Eating Index < 60							Healthy Eating Index ≥ 60							
BMI, kg/m^2	572	20.2	(19.7-20.7)	112	21.6	(20.6-22.7)	.006	218	20.1	(19.4-20.7)	34	20.8	(19.5-22.2)	.25	.24
Waist-to-height ratio	574	0.46	(0.45-0.47)	111	0.49	(0.47-0.50)	.0006	218	0.46	(0.45-0.47)	35	0.46	(0.44-0.49)	.73	.02
Visceral adipose tissue, cm^2	538	22.3	(20.2-24.5)	107	27.5	(23.4-32.4)	.004	206	22.0	(19.5-24.7)	33	24.2	(19.6-29.8)	.35	.22
Subcutaneous adipose tissue, cm^2	538	114.2	(102.2-127.5)	107	155.5	(128.7-187.9)	.001	206	113.9	(100.0-129.6)	33	136.3	(108.4-171.3)	.11	.18
Skinfold ratio	569	0.80	(0.76-0.84)	111	0.96	(0.89-1.04)	.0001	217	0.82	(0.77-0.88)	34	0.91	(0.78-1.05)	.21	.24
	Vigorous activity ≤ 1 h/d							Vigorous activity > 1 h/d							
BMI, kg/m^2	584	20.2	(19.7-20.8)	106	21.4	(20.3-22.6)	.03	206	20.0	(19.4-20.6)	40	21.0	(19.8-22.3)	.12	.74
Waist-to-height ratio	586	0.46	(0.45-0.47)	106	0.48	(0.46-0.50)	.08	206	0.45	(0.44-0.46)	40	0.47	(0.45-0.49)	.13	.83
Visceral adipose tissue, cm^2	547	23.1	(20.9-25.6)	103	26.7	(22.6-31.7)	.06	197	21.1	(18.9-23.7)	37	24.9	(20.2-30.6)	.12	.87
Subcutaneous adipose tissue, cm^2	547	118.1	(105.3, 132.5)	103	159.1	(130.9-193.3)	.001	197	110.1	(97.1-124.8)	37	133.2	(106.1-167.2)	.10	.30
Skinfold ratio	581	0.84	(0.79-0.88)	105	0.89	(0.81-0.98)	.17	205	0.78	(0.73-0.83)	40	0.98	(0.86-1.11)	.001	.01

Note. Data are means and standard error from linear mixed models with repeated adiposity measurements, adjusted for sex, race/ethnicity, age, pubertal status, and Age × Pubertal status.

Abbreviation: BMI, body mass index.

[a]Interaction *P* value refers to the interaction of GDM exposure with each health behaviour (for example, Breastmilk months category × GDM exposure).

P = .006), waist-to-height ratio (unexposed = 0.46 [0.45-0.47], exposed = 0.49 [0.47-0.50], P < .001), visceral adipose tissue (unexposed = 22.3 cm^2 [20.3-24.5], exposed = 27.5 cm^2 [23.4-32.4], P = .004), subcutaneous adipose tissue (unexposed = 114.2 cm^2 [102.2-127.5], exposed = 155.5 cm^2 [128.7-187.9], P = .001), and skinfold ratio (unexposed = 0.80 [0.76-0.84], exposed = 0.96 [0.89-1.04], P < .001). In contrast, among offspring with a Healthy Eating Index ≥60, there was no difference across GDM exposure groups for any of the adiposity outcomes (all Ps > .05). The interaction term between Healthy Eating Index and GDM exposure was statistically significant only for waist-to-height ratio (P = .02).

3.3 | Child/adolescent physical activity

Among offspring with ≤1 h/d of vigorous activity, GDM exposure was associated with statistically significant increases in BMI (unexposed = 20.2 [19.7-20.8], exposed = 21.4 [20.3-22.6], P = .03) and subcutaneous adipose tissue (unexposed = 118.1 cm^2 [105.3-132.5], exposed = 159.1 cm^2 [130.9-193.3], P = .001) and with non-statistically significant increases in waist-to-height ratio (unexposed = 0.46 [0.45-0.47], exposed = 0.48 [0.46-0.50], P = .08), visceral adipose tissue (unexposed = 23.1 cm^2 [20.9-25.6], exposed = 26.7 cm^2 [22.6-31.7], P = .06), and skinfold ratio (unexposed = 0.84 [0.79-0.88], exposed = 0.89 [0.81-0.98], P = .17). Among offspring with >1 h/d of vigorous activity, GDM exposure was associated with a significant increase in skinfold ratio only (unexposed = 0.78 [0.73-0.83], exposed = 0.98 [0.86-1.11], P = .001). All other adiposity outcomes followed similar patterns as when vigorous activity was ≤1 h/d, but the differences between GDM exposure groups were attenuated and not statistically significant. The interaction term between vigorous activity and GDM exposure was statistically significant only for the skinfold ratio (P = .01).

4 | DISCUSSION

We found that the adverse association of GDM exposure with increased body size and adiposity was attenuated among offspring with optimal diet and activity behaviours in infancy, childhood, and adolescence. These differential results were clearest for optimal diet quality, while optimal breastfeeding and vigorous activity showed similar, though less consistent, results. Our study suggests that engaging in optimal early life health behaviours may be a potential strategy for mitigating the adverse effect of GDM exposure on offspring obesity risks.

Our novel findings regarding child and adolescent diet quality highlight the key role that postnatal nutrition may play in modifying the effect of fetal overnutrition resulting from exposure to GDM in utero. The fuel-mediated teratogenesis hypothesis suggests that elevations in maternal glucose and other nutrients during pregnancy trigger changes in fetal metabolism, cellular development, and growth that result in increased body size already evident at birth.[27] Prior studies report that this effect persists into childhood and adolescence even after adjustment for offspring daily energy intake[1,28,29] or data-derived dietary patterns.[30] However, those studies did not examine the potential for a healthy diet in childhood to attenuate the effect of GDM exposure. We observed a consistent protective effect of consuming a diet more aligned with the Dietary Guidelines for Americans across five different measures of adiposity for offspring exposed to GDM. This aligns with a recent Canadian study that reported a 75% reduced prevalence of overweight/obesity among offspring exposed to GDM who consumed a diet more aligned with the Canadian Food Guide.[12] These results suggest that fetal overnutrition does not definitively program offspring to exhibit increased adiposity, but rather increases vulnerability for developing greater adiposity in the presence of an obesogenic environment. We recognize that defining optimal diet quality as having a Healthy Eating Index score of 60 or more has its limitations, given that higher scores (≥80) have been recommended for prevention of chronic disease.[25] Yet the distribution of scores in our cohort is similar to the distribution in a nationally representative cohort[26] and thus reflects the typical intake of children and adolescents. Taken together, these results indicate that even incremental improvements in diet quality may benefit offspring at high risk of developing excess adiposity because of GDM exposure.

In terms of physical activity, we similarly observed that the increased adiposity risks for offspring exposed to GDM were diminished for children and adolescents who daily engaged in >1 hour of vigorous activity. While this finding was restricted to just two of the five adiposity measures, the point estimates for the remaining three adiposity outcomes follow a similar pattern. These results are in contrast to a large Chinese study, which observed no difference in obesity prevalence at 1 to 5 years of age for children exposed to GDM across higher or lower levels of indoor/outdoor physical activity.[11] However, that study did not include a control group of children not exposed to GDM and thus could not determine if increased physical activity can ameliorate the adverse effect of GDM exposure. The Chinese study also included a younger age group; it is possible that other factors in the early childhood period, such as diet, have a greater impact on obesity development than physical activity. We also note that our physical activity results are specific to daily vigorous activity, which is somewhat different from the national recommendation that children get at least 60 minutes of moderate-to-vigorous activity daily, including vigorous activity at least 3 d/wk.[22] When we classified participants according to daily moderate-vigorous activity, we observed no benefit of moderate-to-vigorous activity on obesity outcomes (data not shown). This suggests that more frequent engagement in higher intensity physical activity is needed in order to counteract the effect of GDM exposure on adiposity in childhood and adolescence. Importantly, these results were independent of the diet behaviours, indicating that increased vigorous activity may be beneficial even when diet is suboptimal.

We previously reported a beneficial effect of breastfeeding on adiposity measures in this cohort when offspring were 6 to 12 years of age.[9] We now report that this result persists to 12 to 19 years of age, although the beneficial effect of breastfeeding appears less strong in this analysis, suggesting that it may diminish with time. When adjusted for both diet quality and vigorous activity later in childhood,

we observed differential effects of GDM exposure by breastfeeding strata for only visceral and subcutaneous adipose tissue, while the skinfold ratio was similarly increased among exposed in both breastfeeding categories. Examination of the point estimates for the other adiposity measures suggests that the effect of GDM exposure is attenuated with greater breastfeeding, although not significantly so. Other studies that have similarly reported a protective effect of breastfeeding on body size and adiposity following intrauterine GDM exposure were restricted to children ≤8 years of age.[6,7,10] Even so, there is evidence that body size tracks from infancy through childhood and adolescence to adulthood,[31,32] highlighting the importance of early life breastmilk consumption in setting a trajectory toward obesity. Our data indicate that more proximal diet and activity exposures have a stronger effect on adiposity in childhood and adolescence than breastfeeding. Further, these data demonstrate that if mothers with a history of GDM are unwilling or unable to exclusively breastfeed for at least 6 months, optimal diet and activity behaviours beyond infancy present a plausible opportunity for reducing offspring obesity risks.

Among children with suboptimal behaviours, those exposed to GDM had an average BMI that was 1.2 to 1.4 kg/m^2 greater than children who were not exposed. This corresponds to a 0.30 unit change in BMI *z*-score for a 10-year-old male and a 0.50 unit change for a 16-year-old male. In studies of paediatric obesity treatment, a reduction of BMI *z*-score of 0.25 to 0.50 has been shown to improve insulin sensitivity,[33] suggesting that the difference we observed for offspring BMI is clinically significant. While the clinical significance of the other adiposity measures is not as clear, the results do indicate a shift to a more centralized fat distribution, which has been shown to track from childhood to young adulthood[34] and substantially increases risk of cardiovascular disease.[35] The increase in multiple adiposity measures among children exposed to GDM is likely due to a number of interrelated biological mechanisms. When excess maternal glucose crosses the placenta, the fetal pancreas responds by releasing insulin and insulin-like growth factor, resulting in excess fetal growth.[27] Excess maternal glucose may also alter the adipo-insular axis in offspring, which regulates leptin release from adipocytes and insulin release from pancreatic beta cells, contributing to fat mass.[36] There is some evidence from animal studies that elevations in insulin and leptin in utero can alter hypothalamic neuropeptidergic neurons in offspring, resulting in hyperphagia and overweight/obesity.[37] Lastly, maternal hyperglycaemia may alter offspring DNA methylation and subsequent expression of insulin-like growth factor 2.[38] While it is not understood exactly which mechanisms influence specific measures of adiposity, the current evidence is clear that fetal exposure to maternal hyperglycaemia has long-term consequences for obesity and cardiometabolic risks.

We note that most women who develop GDM also have prepregnancy obesity, and it can be difficult to distinguish between the effects of these two concurrent and interdependent exposures. Maternal obesity is a risk factor for GDM,[39] and rising mid-pregnancy glucose levels, even within the normal range, explain 21% of the relationship between prepregnancy BMI and neonatal adiposity in women without GDM.[40] However, offspring born to women with type 1 diabetes, who typically do not have prepregnancy obesity, do exhibit increased adiposity, therefore providing evidence of the independent effect of maternal glucose levels.[41-43] Other studies of offspring born to women with GDM report that the association of GDM with increased adiposity is attenuated for some measures after adjustment for maternal prepregnancy obesity, but remains statistically significant, suggesting that the specific effect of GDM is also independent of maternal obesity.[30,44,45] In our study, data on prepregnancy obesity were available for only a subset of participants (approximately 65%). We conducted an exploratory analysis that adjusted for prepregnancy obesity in this subset and similarly noted that some but not all associations were attenuated (data not shown). Collectively, these analyses indicate that there are independent contributions of both maternal GDM and maternal prepregnancy obesity to offspring adiposity, but the exact contribution of each exposure cannot be isolated because of the shared biological pathway. From a public health perspective, this also highlights the need to target the shared risk factors that precede the development of both maternal obesity and GDM (eg, excess caloric intake and sedentary lifestyles) in order to minimize the intergenerational transmission of diabetes and obesity.[46]

Strengths of our study include the diverse sample and longitudinal data collection. Our analyses revealed generally consistent results across multiple measures of adiposity, which increases the robustness of the findings. By including all three health behaviours in the same model, we were able to evaluate the independent effects of each optimal health behaviour and confirm that our results were not confounded by other behaviours that are often correlated. We acknowledge that our findings should be interpreted with caution, given that the Behaviour × GDM interaction term was statistically significant for only a few measures. We believe this is due to insufficient power driven by smaller sample sizes, particularly for the number of youth exposed to GDM with an optimal behaviours (n = 33-71, depending on the exact behaviour and outcome). Yet examination of the point estimates suggests that the difference between youth who were exposed versus unexposed was truly diminished when behaviours were optimal (for example, BMI of 20.2 and 21.6 for youth unexposed and exposed to GDM, respectively, when diet was suboptimal, versus BMI of 20.1 and 20.8 when diet was optimal). We were not powered to examine age- or sex-specific differences in adiposity outcomes; however, we did include adjustment for age and sex in the analyses. While our final model included few covariates, exploratory analyses indicated that the results did not change upon consideration of other potential confounders (household income, maternal smoking in pregnancy, maternal marital status, preeclampsia, hypertension in pregnancy, and excessive gestational weight gain). We were unable to explore the contribution of paternal BMI as data were not available. Reliance on maternal recall of breastfeeding is a limitation, although prior studies have demonstrated the validity of maternal recall of breastfeeding duration up to 17 years later.[16,17,47] We also note that the paediatric food frequency questionnaire we used was validated for children ≥8 years, but 25 participants (4.4%) were younger than 8 years at the first visit. Other limitations include use of self-reported offspring health behaviours, reliance on maternal recall of

breastfeeding after 6 to 12 years, use of a modified Healthy Eating Index calculation because of the nature of the available nutrition data, and no adjustment for testing multiple outcomes.

In conclusion, we have shown that engaging in optimal diet or activity behaviours in infancy, childhood, or adolescence is associated with a reduction or even elimination of the adverse effect of GDM exposure on multiple measures of offspring adiposity. While prevention of the initial GDM exposure is ideal for reducing offspring adiposity risks, studies of lifestyle interventions during pregnancy have shown that this is extremely difficult to accomplish.[48,49] For the 18 million offspring worldwide that are born to women with GDM each year, our study provides promising evidence that diet and activity behaviours in early life have potential to shift one's health trajectory away from excess adiposity even in the presence of adverse intrauterine exposures.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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ORCID

Katherine A. Sauder https://orcid.org/0000-0002-8473-8015
Traci A. Bekelman https://orcid.org/0000-0003-0840-1186

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