Citation for published version:
Zhao, P, Liu, E, Qiao, Y, Katzmarzyk, PT, Chaput, J-P, Fogelholm, M, Johnson, WD, Kuriyan, R, Kurpad, A, Lambert, EV, Maher, C, Maia, JAR, Matsudo, V, Olds, T, Onywera, V, Sarmiento, OL, Standage, M, Tremblay, MS, Tudor-Locke, C, Hu, G 2016, 'Maternal gestational diabetes and childhood obesity at age 9-11: results of a multinational study', Diabetologia, vol. 59, no. 11, pp. 2339–2348. https://doi.org/10.1007/s00125-016-4062-9

DOI:
10.1007/s00125-016-4062-9

Publication date:
2016

Document Version
Peer reviewed version

Link to publication

The final publication is available at Springer via 10.1007/s00125-016-4062-9

Revised manuscript: Diab-16-0448

Maternal gestational diabetes and childhood obesity at age 9-11 years in 12 countries

Pei Zhao[1], Enqing Liu[1], Yijuan Qiao[1,2], Peter T. Katzmarzyk[2], Jean-Philippe Chaput[3], Mikael Fogelholm[4], William D. Johnson[2], Rebecca Kuriyan[5], Anura Kurpad[5], Estelle V. Lambert[6], Carol Maher[7], José A.R. Maia[8], Victor Matsudo[9], Timothy Olds[7], Vincent Onywera[10], Olga L. Sarmiento[11], Martyn Standage[12], Mark S. Tremblay[3], Catrine Tudor-Locke[2,13], Gang Hu[2]; for the ISCOLE Research Group

[1]Tianjin Women's and Children's Health Center, Tianjin, China; [2]Pennington Biomedical Research Center, Baton Rouge, United States; [3]Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada; [4]Department of Food and Environmental Sciences, University of Helsinki, Helsinki, Finland; [5]St. Johns Research Institute, Bangalore, India; [6]Division of Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, South Africa; [7]Alliance for Research In Exercise Nutrition and Activity (ARENA), School of Health Sciences, University of South Australia, Adelaide, Australia; [8]CIFI^{2}D, Faculdade de Desporto, University of Porto, Porto, Portugal; [9]Centro de Estudos do Laboratório de Aptidão Física de São Caetano do Sul, Sao Paulo, Brazil; [10]Department of Recreation Management and Exercise Science, Kenyatta University, Nairobi, Kenya; [11]School of Medicine Universidad de los Andes, Bogota, Colombia; [12]Department for Health, University of Bath, Bath, United Kingdom; [13]Department of Kinesiology, University of Massachusetts Amherst, Amherst, United States

Address for correspondence: Gang Hu, PhD, Chronic Disease Epidemiology Laboratory, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808, Tel: 225-763-3053, Fax: 225-763-3009, Email: gang.hu@pbrc.edu

Word count of the abstract: 242

Word count of the main text: 3382

Abstract

Aims: To examine the association between maternal gestational diabetes mellitus (GDM) and childhood obesity at age 9-11 years in 12 countries around the world.

Methods: A multinational cross-sectional study of 4740 children aged 9-11 years was conducted. Maternal GDM was diagnosed according to the American Diabetes Association (ADA) or World Health Organization (WHO) criteria. Height and waist circumference were measured using standardized methods. Weight and body fat were measured using a portable Tanita SC-240 Body Composition Analyzer. Multi-level modeling was used to account for the nested nature of the data.

Results: The prevalence of reported maternal GDM was 4.3%. The overall prevalence of childhood obesity, central obesity and high body fat were 12.3%, 9.9%, and 8.1%, respectively. The multivariable-adjusted (maternal age at delivery, education, infant feeding mode, gestational age, number of younger siblings, child unhealthy diet pattern scores, moderate-to-vigorous physical activity, sleeping time, sedentary time, sex, and birth weight) odd ratios among children of GDM mothers compared with children of non-GDM mothers were 1.53 (95% CI: 1.03-2.27) for obesity, 1.73 (95% CI: 1.14-2.62) for central obesity, and 1.42 (95% CI: 0.90-2.26) for high body fat, respectively. The positive association was still significant for central obesity after additional adjustment for current maternal body mass index but was no longer significant for obesity and high body fat.

Conclusions: Maternal GDM was associated with increased odds of childhood obesity at 9-11 years old but this association was not fully independent of maternal body mass index.

Keywords Children, gestational diabetes, obesity

Abbreviations

GDM	Gestational diabetes mellitus
ADA	The American Diabetes Association
WHO	World Health Organization
BMI	Body Mass Index
ISCOLE	The International Study of Childhood Obesity, Lifestyle and the Environment
FFQ	Food frequency questionnaire
OGTT	Oral Glucose Tolerance
NHANES	National Health and Nutrition Examination Survey

Introduction

Childhood obesity has increased dramatically in both developed and developing countries [1]. It has been suggested that prenatal, perinatal, and postnatal environmental factors impact childhood obesity [2]. Some studies have found that intrauterine exposure to maternal gestational diabetes mellitus (GDM) places offspring at increased risk for long-term adverse outcomes including obesity [3-12]. GDM, defined as any degree of glucose intolerance with onset or first recognition during pregnancy [3], is a common pregnancy outcome affecting about 1-28% of pregnancies in a survey of 173 countries, which was based on the uniform criteria for the diagnosis of GDM [4].

Early research from the Pima Indian Study and the Diabetes in Pregnancy Study at Northwestern University in the United States provided initial evidence of the association between maternal GDM and the risk of childhood obesity [5, 6]. However, other studies did not find a clear association between maternal GDM and offspring's obesity [7-12]. A recent review has indicated that this difference may be due to the high type 2 diabetes mellitus risk in the unique Pima Indian population and a specialized pregnancy clinical population in Chicago [2]. Furthermore, most previous studies are from high income countries, and very few studies are from low to middle income countries, thus studies including children from multiple regions of the world are needed.

It has also been shown that indicators of central obesity, such as waist circumference, may be a better predictor of cardiovascular disease than adiposity measured by BMI [13]. However, limited data exist on the association between maternal GDM and different indicators of childhood obesity. The aim of the present study was to examine the association between self-reported maternal GDM and three indicators of childhood obesity (BMI, waist circumference, and body fat) among children aged 9-11 years from 12 countries around the world.

Methods

Study design

The International Study of Childhood Obesity, Lifestyle and the Environment (ISCOLE) is a multi-national cross-sectional study conducted at urban and suburban sites in 12 countries (Australia, Brazil, Canada, China, Colombia, Finland, India, Kenya, Portugal, South Africa, United Kingdom and the United States) [14]. These countries are classified as low to high income countries according to the World Bank Classification (Table 1). More details on the study design and methods can be found elsewhere [14]. The Institutional Review Board at the Pennington Biomedical Research Center (coordinating center) approved the overarching protocol, and the Institutional/Ethical Review Boards at each participating institution also approved the local protocol. Written informed consent was obtained from parents or legal guardians, and child assent was also obtained as required by local Institutional/Ethical Review Boards before participation in the study.

Participants

A total of 7372 children aged 9-11 years participated in ISCOLE, of whom 4740 remained in the present study after excluding participants who did not have valid data/information on accelerometer (N=1 214), maternal history of GDM (N=359), body mass index (BMI) (N=5), waist circumference (N=4), percentage of body fat (N=58), birth weight (N=383), gestational age (N=101), diet scores (N=82), maternal age at child's birth (N=134), maternal current BMI (N=216) and other information (maternal education, and infant breast feeding) (N=76). Participants who were excluded in the present analysis did not differ in age or BMI z-score, but there were higher proportion of boys than those who were included in the analysis. Data were collected from September 2011 through December 2013.

Measurements

Demographics and family health history

Maternal education, current maternal body weight and height, maternal age at child's birth, child age, child sex, birth weight, infant feeding mode, gestational age, and number of young siblings were collected from parents or guardians by a demographic and family health history questionnaire. Maternal education was classified into three categories: did not complete high school, completed high school or college, and completed bachelor or post-graduate degree. The child's parents were asked whether the child was fed breast milk or not, age when completely stopped being fed breast milk, age when first fed formula and age when completely stopped drinking formula. These responses were classified into four categories: exclusive breast feeding, mixed feeding, weaned from breast feeding, and exclusive formula feeding.

Maternal history of GDM

Maternal history of GDM was recalled by parents or guardians and reported on the questionnaire. Maternal history of GDM was diagnosed between July, 1999 and July, 2004, which was inferred by the participant's date of birth. Diagnostic criteria of GDM during this period were checked from local maternity hospitals by each study site. Maternal GDM was diagnosed by the World Health Organization (WHO) or modified WHO criteria based on a 2-hour 75 g oral glucose tolerance test (OGTT), or the American Diabetes Association (ADA) or modified ADA criteria based on 3-hour 100 g OGTT add references. WHO criteria for GDM require one plasma glucose ⩾7.0mmol/l (fasting) or ⩾7.8mmol/l (2h) [15]. ADA criteria require two plasma glucose values from ⩾5.3 mmol/l (fasting), ⩾10.0 mmol/l (1h), ⩾8.6 mmol/l (2h) and ⩾ 7.8mmol/l (3h) [16].

Dietary pattern

A food frequency questionnaire (FFQ) that was adapted from the Health Behavior in School-aged Children Survey (HBSC) and validated [17-19] was administered to all ISCOLE student participants. The FFQ asked the participants about their "usual" consumption of 23 food categories, with response categories including *never, less than once per week, once per week, 2-4 days per week, 5-6 days per week, once a day every day, and more than once a day*. Two diet pattern scores which represented an "unhealthy diet pattern" (with positive loadings for fast food, hamburgers, soft drinks, sweets, fried food, etc.) and a "healthy diet pattern" (with positive loadings for vegetables, fruit, whole grains, low-fat milk, etc.) were obtained using principal components analyses [18, 19].

Anthropometric measurements

A battery of anthropometric measurements was taken according to standardized procedures across all study sites. Height was measured without shoes using a Seca 213 portable stadiometer (Hamburg, Germany), with the participant's head in the Frankfurt Plane. Waist circumference was measured at the end of normal expiration with a non-elastic tape held midway between the lower rib margin and the iliac crest. Each measurement was repeated, and the average was used for analysis (a third measurement was obtained if the first two measurements were greater than 0.5 cm apart, and the average of the two closest measurements was used in analyses) [14].

The participant's weight and percentage of body fat were measured using a portable Tanita SC-240 Body Composition Analyzer (Arlington Heights, IL) after all outer clothing, heavy pocket items and shoes and socks were removed. Two measurements were obtained, and the average was used in the analysis (a third measurement was obtained if the first two measurements were more than 0.5 kg or 2.0% apart, for weight and percentage of body fat, respectively and the closest two were averaged for the analysis)[14].

Maternal and childhood BMI were calculated by dividing weight in kilograms by the square of height in meters. Childhood BMI z-scores were computed using age- and sex-specific reference data from the WHO. Waist circumference z-scores were computed using age-and sex-specific reference data from the National Health and Nutrition Examination Survey from 1988-1994 (NHANES III) [20]. Body fat z-scores were computed using the National Health and Nutrition Examination Survey from 1999-2004 (NHANES IV) [21]. Child obesity was defined as BMI z-scores > +2 SD. Central obesity was defined as waist circumference ≥ 90th percentile of NHANES III reference [22]. High body fat was defined as body fat ≥ 90th percentile of NHANES IV reference [21]. Maternal overweight was defined as BMI greater than or equal to 25 kg/m^2, based on the self-reported maternal current height and weight.

Accelerometry

An ActiGraph GT3X+ accelerometer (ActiGraph, LLC, Pensacola, FL, USA) was used to objectively measure moderate-to-vigorous physical activity, sedentary behavior and sleeping time. The accelerometer was worn at the waist on an elasticized belt on the right mid-axillary line. Participants were encouraged to wear the accelerometer 24 hours per day (removing only for water-related activities) for at least 7 days (plus an initial familiarization day and the morning of the final day), including 2 weekend days [14]. Nocturnal sleep duration was estimated from the accelerometer data using a fully automated algorithm for 24-h waist-worn accelerometers, which was recently validated for ISCOLE [23]. The weekly total sleep time averages were calculated using only days where valid sleep was accumulated (total sleep period time ⩾ 160 min) and only for participants with at least 3 nights of valid sleep, including one weekend day [24]. After exclusion of total sleep time and awake non-wear time (any sequence of ⩾20 consecutive minutes of zero activity counts), moderate-to-vigorous physical activity was defined as all activity ≥574 counts per 15 s and total SED as all movement ≤25 counts per 15 s, consistent with the widely used Evenson cutoffs [25].

Statistical analyses

Variables were compared using a t-test for means and a chi-squared test for proportions between women with and without GDM. Multilevel linear regression models were used to estimate the association between maternal GDM and z-scores of childhood BMI, waist circumference, and body fat. Multilevel logistic regression models were used to estimate the association between maternal GDM and the odds of childhood obesity, central obesity and high body fat. We defined child as level 1, school as level 2, and study site as level 3 for the multi-level analyses. Study site and school were considered to have random effects. The analyses were adjusted for maternal age at delivery (continuous variable) , maternal current BMI (continuous variable), maternal education (categorical variable), infant feeding mode (categorical variable), birth weight (continuous variable), gestational age (continuous variable), number of younger siblings (continuous variable), child unhealthy diet pattern scores (continuous variable), moderate-to-vigorous physical activity (continuous variable), sleeping time (continuous variable), sedentary time (continuous variable), age (continuous variable) and sex (categorical variable). The criterion for statistical significance was $p<0.05$. All statistical analyses were performed with SPSS for Windows, version 21.0 (Statistics 21, SPSS, IBM, USA) or SAS for Windows, version 9.4 (SAS Institute, Cary, NC).

Results

The prevalence and diagnosis criteria of maternal GDM at 1999-2004 in 12 study sites are presented in Table 1. The overall prevalence of self-reported maternal GDM was 4.3%, ranging from 1.9% in the United Kingdom and China to 8.8% in Portugal. Characteristics of study participants by maternal GDM status are presented in Table 2. GDM mothers had significantly older age at delivery than non-GDM mothers (29.9 years vs 28.3 years). Children of GDM mothers had significantly higher mean birth weight (3415 g vs 3274 g), and significantly higher prevalence of obesity (18.4% vs 12.0%), central obesity (16.0% vs 9.6%) and high body fat (12.1% vs 7.9%) than children of non-GDM mothers.

After adjustment for maternal age at delivery and education, infant feeding mode, gestational age, number of younger siblings, child unhealthy diet pattern scores, moderate-to-vigorous physical activity, sleeping time, sedentary time, sex, and birth weight, children of GDM mothers had significantly higher mean values for BMI z-score (0.71 vs 0.54), waist circumference z-score (0.06 vs -0.02), and body fat z-score (0.17 vs 0.02) than children of non-GDM mothers (Table 3). These significant associations disappeared after additional adjustment for maternal current BMI.

Table 4 presents associations of maternal GDM with the odds of childhood obesity, central obesity and high body fat by all GDM mothers or by GDM mothers with normal weight or overweight. The multivariable-adjusted (maternal age at delivery and education, infant feeding mode, gestational age, number of younger siblings, child unhealthy diet pattern scores, moderate-to-vigorous physical activity, sleeping time, sedentary time, sex, and birth weight) odd ratios among children of GDM mothers compared with children of non-GDM mothers were 1.53 (95% CI: 1.03-2.27) for obesity, 1.73 (95% CI: 1.14-2.62) for central obesity, and 1.42 (95% CI: 0.90-2.26) for high body fat, respectively (Table 4). The positive association was still significant for central obesity after additional adjustment for current maternal BMI but was no longer significant for obesity and high body fat. In the multivariable-adjusted analyses, the positive associations of maternal GDM with the odds of childhood obesity and central obesity were present among GDM mothers with overweight but not among GDM mothers with normal weight.

When stratified by maternal GDM diagnosis criteria, childhood sex, and different levels of childhood moderate-to-vigorous physical activity, unhealthy diet scores, sleep time, breastfeeding status, and children from different income countries, the positive association of maternal GDM with the odds of central obesity was only present in girls, and in children of mothers whose GDM was diagnosed by ADA criteria (Table 5). There were no significant interactions between maternal GDM and sex of children, maternal GDM diagnosis criteria, child moderate-to vigorous physical activity, child unhealthy diet pattern scores, child sleep time, child breastfeeding status, or children from different income countries with the risks of childhood obesity, central obesity and high body fat (all p values for interactions are >0.05).

Discussion

In this multinational cross-sectional study, we found that maternal GDM was associated with increased odds of obesity and central obesity in 9-11 years old children in 12 countries, and these associations were not fully independent of maternal BMI.

Early research in the Pima Indian Study has demonstrated that the offspring of Pima Indian women with diabetes prior to pregnancy and GDM were heavier at birth, and had much higher rates of obesity at age 5-19 years than the offspring of pre-diabetic or non-diabetic women [5, 26]. In the Northwestern Diabetes in Pregnancy Study, diabetes during pregnancy, including both GDM and insulin-treated diabetes prior to pregnancy, was associated with increased BMI of the offspring at birth and after the age of 5 years [27]. However, other studies did not find a clear association between maternal GDM and obesity in offspring of more than 5 years old [7-11]. One study found that prenatal exposure to the metabolic effects of mild, diet-treated GDM did not increase the risk of childhood obesity [7]. Another study also found little association between maternal glucose during pregnancy and obesity in the offspring at 2 years [10]. A systematic review of 12 studies reported that the crude odds ratios for the relationship between maternal GDM and childhood overweight and obesity ranged from 0.7 to 6.3 and the association was not statistically significant in 8 studies [28]. Most of studies were from high income countries, and only one from a middle income country [29]. Thus, one large study using uniform methods to assess maternal GDM and childhood obesity across various populations was needed to evaluate the generalizability of this question. Our study is the first to evaluate the association between maternal GDM and childhood obesity using such widespread, multinational data, and found that maternal GDM was associated with an increased odd of childhood obesity among children aged 9-11 years from 12 countries. Moreover, we also indicated that the positive association between maternal GDM and the risk of childhood obesity was significant among children from low to middle income countries but this association was no longer significant after additional adjustment for current maternal BMI. The positive association between maternal GDM and the risk of childhood central obesity was significant among children from high income countries and became no longer significant after adjustment for current maternal BMI (Table 5).

Several prenatal and perinatal factors including maternal pre-pregnancy BMI, gestational weight gain, maternal GDM, and child birth weight have been found to be associated with an increased risk of obesity in offspring [2, 30, 31]. Several studies have also found that the significant association between maternal GDM and an increased risk of childhood obesity was either independent [32] or dependent [33] of maternal pre-pregnancy BMI. Since maternal pre-pregnancy obesity is a risk factor for maternal GDM [34], adjustment for maternal pre-pregnancy BMI as a confounding factor or as a proxy for genetic predisposition in the analysis of maternal GDM and childhood obesity may be over-adjusted. The present study found that the positive association between maternal GDM and childhood obesity risk was only slightly attenuated by birth weight but was not fully independent of current maternal BMI. We used current maternal BMI (postpartum BMI at about 10 years) but not maternal pre-pregnancy BMI in the multivariable-model due to three reasons: first, data on maternal pre-pregnancy BMI, and gestational weight gain were not available in the present study; second, we found the stronger correlation (0.827) between maternal pre-pregnancy BMI and current BMI in another study which has both variables [35]; third, although current maternal BMI represents shared post-natal environmental factors, we still included current maternal BMI in the last multivariable-adjusted model (Model 4) which can partially control for the maternal pre-pregnancy BMI effect.

In addition, inconsistent associations were found in some studies which targeted different ages of children. The Diabetes in Pregnancy Study at Northwestern University reported that the relative weight in children of GDM mothers increased dramatically after 5 years of age, and half of the children of GDM mothers had a weight >90^{th} percentile by age 8 [6]. One study in China found that maternal GDM increased the offspring's cardio-metabolic risk in early childhood at 8 years of age, but not at 15 years of age [36]. Our study found that the children of GDM mothers had 1.42-1.73 times higher odds of developing obesity than children of non-GDM mothers at 9-11 years old. A prospective pregnancy cohort from the United Kingdom reported that the odds ratio of obesity among children of GDM mothers at 9-11 years old was 1.51 (0.76-2.98), which was similar to our study [37].

BMI, waist circumference, and body fat are three main indicators used to evaluate obesity. In the United States, the National Institutes of Health clinical guidelines for the identification and treatment of overweight and obesity among adults recognized the importance of including measurements of both obesity and central obesity, which were assessed by BMI and waist circumference [38]. Some studies have established that central obesity predicts obesity-related health risk [39]. However, the most common measure was BMI in the majority of available studies, and few studies included waist circumference and body fat at the same time [11, 37, 40]. Our study demonstrated a positive association of maternal GDM with the odds of childhood obesity and central obesity, however, this association was still significant only for central obesity but not for obesity after additional adjustment for current maternal BMI. Thus more studies with data on maternal GDM with the risks of childhood obesity and central obesity are needed.

The mechanisms by which exposure to diabetes in utero increases the risk of offspring obesity are not fully understood. Exposure to maternal diabetes is associated with excess fetal growth in utero, possibly mainly due to an increase in fetal fat mass and alterations of fetal hormones [2]. In addition, exposure to maternal diabetes results in offspring's elevated hyperglycemia hyperinsulinemia, and elevated leptin synthesis [2]. Maternal prenatal GDM may also influence the fetal epigenome, thereby influencing the expression of genes that direct the accumulation of body fat or related metabolism [2].

There were several strengths of our study including the recruitment of a large multi-national sample of children from low to high income countries across several regions of the world, the highly standardized measurement protocol, the use of direct measurements whenever possible, and the rigorous quality control program. In addition, body weight, waist circumference and body fat were directly measured by standardized methods. One limitation of the study is that it is a cross-sectional study. Thus we could not make cause-and-effect inferences. Second, since data on maternal pre-pregnancy BMI and gestational weight gain were not available in the present study, we were not able to assess the effect of these variables on the association of GDM with the risk of childhood obesity. Third, the information on maternal GDM status, current maternal body weight and height, infant feeding mode, gestational age, and children's birth weight was recalled from parents by a self-reported questionnaire, which may introduce recall bias. Although no specific assessment of validity of self-reporting of these variables has been carried out in the present study, similar questionnaires have been used in a large number of epidemiological studies. Finally, maternal GDM was diagnosed by different criteria among different sites, which may bias the results.

In conclusion, GDM was associated with the increased odds of obesity among children aged 9-11 years and this association was not fully independent of maternal BMI. This study also provided evidence for a long-term association with maternal GDM on offspring's obesity odds by different GDM diagnosis criteria.

Acknowledgements

We wish to thank the ISCOLE External Advisory Board and the ISCOLE participants and their families who made this study possible. The ISCOLE Research Group includes: **Coordinating Center, Pennington Biomedical Research Center**: Peter T. Katzmarzyk, PhD (Co-PI), Timothy S. Church, MD, PhD (Co-PI), Denise G. Lambert, RN (Project Manager), Tiago Barreira, PhD, Stephanie Broyles, PhD, Ben Butitta, BS, Catherine Champagne, PhD, RD, Shannon Cocreham, MBA, Kara D. Denstel, MPH, Katy Drazba, MPH, Deirdre Harrington, PhD, William Johnson, PhD, Dione Milauskas, MS, Emily Mire, MS, Allison Tohme, MPH, Ruben Rodarte MS, MBA; **Data Management Center, Wake Forest University:** Bobby Amoroso, BS, John Luopa, BS, Rebecca Neiberg, MS, Scott Rushing, BS**; Australia, University of South Australia:** Timothy Olds, PhD (Site Co-PI), Carol Maher, PhD (Site Co-PI)**,** Lucy Lewis, PhD, Katia Ferrar, B Physio (Hon), Effie Georgiadis, BPsych, Rebecca Stanley, BAppSc (OT) Hon**; Brazil, Centro de Estudos do Laboratório de Aptidão Física de São Caetano do Sul (CELAFISCS):** Victor Keihan Rodrigues Matsudo, MD, PhD (Site PI), Sandra Matsudo, MD, PhD, Timoteo Araujo, MSc, Luis Carlos de Oliveira, MSc, Luis Fabiano, BSc, Diogo Bezerra, BSc, Gerson Ferrari, MSc**; Canada, Children's Hospital of Eastern Ontario Research Institute:** Mark S. Tremblay, PhD (Site Co-PI), Jean-Philippe Chaput, PhD (Site Co-PI), Priscilla Bélanger, MA, Mike Borghese, MSc, Charles Boyer, MA, Allana LeBlanc, MSc, Claire Francis, M.Sc.,Geneviève Leduc, PhD**; China, Tianjin Women's and Children's Health Center:** Pei Zhao, MD (Site Co-PI), Gang Hu, MD, PhD (Site Co-PI), Chengming Diao, MD, Wei Li, MD, Weiqin Li, MSc, Enqing Liu, MD, Gongshu Liu, MD, Hongyan Liu, MD, Jian Ma, MD, Yijuan Qiao, MD, Huiguang Tian, PhD, Yue Wang, MD, Tao Zhang, MSc, Fuxia Zhang, MD**; Colombia, Universidad de los Andes:** Olga Sarmiento, MD, PhD (Site PI), Julio Acosta, Yalta Alvira, BS, Maria Paula Diaz, Rocio Gamez, BS, Maria Paula Garcia, Luis Guillermo Gómez, Lisseth Gonzalez, Silvia Gonzalez, RD, Carlos Grijalba, MD, Leidys Gutierrez, David Leal, Nicolas Lemus, Etelvina Mahecha, BS, Maria Paula Mahecha, Rosalba Mahecha, BS, Andrea Ramirez, MD, Paola Rios, MD, Andres Suarez, Camilo Triana**; Finland, University of Helsinki:** Mikael Fogelholm, ScD (Site-PI), Elli Hovi, BS, Jemina Kivelä, Sari Räsänen, BS, Sanna Roito, BS, Taru Saloheimo, MS, Leena Valta**; India**, **St. Johns Research Institute:** Anura Kurpad, MD, PhD (Site Co-PI), Rebecca Kuriyan, PhD (Site Co-PI), Deepa P. Lokesh, BSc, Michelle Stephanie D'Almeida, BSc, Annie Mattilda R, MSc, Lygia Correa, BSc, Vijay D, BSc**; Kenya, Kenyatta University:** Vincent Onywera, PhD (Site Co-PI), Mark S. Tremblay, PhD (Site Co-PI), Lucy-Joy Wachira, PhD, Stella Muthuri, PhD**; Portugal, University of Porto:** Jose Maia, PhD (Site PI), Alessandra da Silva Borges, BA, Sofia Oliveira Sá Cachada, Msc, Raquel Nichele de Chaves, MSc, Thayse Natacha Queiroz Ferreira Gomes, PhD, MSc, Sara Isabel Sampaio Pereira, BA, Daniel Monteiro de Vilhena e Santos, PhD, Fernanda Karina dos Santos, MSc, Pedro Gil Rodrigues da Silva, BA, Michele Caroline de Souza, MSc; **South Africa, University of Cape Town:** Vicki Lambert, PhD (Site PI), Matthew April, BSc (Hons), Monika Uys, BSc (Hons), Nirmala Naidoo, MSc, Nandi Synyanya, Madelaine Carstens, BSc(Hons); **United Kingdom, University of Bath:** Martyn Standage, PhD (Site PI), Sean Cumming, PhD, Clemens Drenowatz, PhD, Lydia Emm, MSc, Fiona Gillison, PhD, Julia Zakrzewski, PhD; **United States, Pennington Biomedical Research Center:** Catrine Tudor-Locke, PhD (Site-PI), Ashley Braud, Sheletta Donatto, MS, LDN, RD, Corbin Lemon, BS, Ana Jackson, BA, Ashunti Pearson, MS, Gina Pennington, BS, LDN, RD, Daniel Ragus, BS, Ryan Roubion, John Schuna, Jr., PhD; Derek Wiltz**. The ISCOLE External Advisory Board includes** Alan Batterham, PhD, Teesside University, Jacqueline Kerr, PhD, University of California, San Diego; Michael Pratt, MD, Centers for Disease Control and Prevention, Angelo Pietrobelli, MD, Verona University Medical School.

Funding: ISCOLE was funded by The Coca-Cola Company. Dr. Hu was supported by grant from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number R01DK100790. The funder had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript.

Duality of interest

MF has received a research grant from Fazer Finland and has received an honorarium for speaking for Merck. AK has been a member of the Advisory Boards of Dupont and McCain Foods. RK has received a research grant from Abbott Nutrition Research and Development. VM is a member of the Scientific Advisory Board of Actigraph and has received an honorarium for speaking for The Coca-Cola Company. TO has received an honorarium for speaking for The Coca-Cola Company. The authors reported no other potential conflicts of interest.

Contribution statement

PZ., YQ. and GH. drafted the manuscript, EL., PK., JC., MF., WJ., RK, AK., EL., CM., JM., VM., TO., VO., OS, MS., MT., and CT. reviewed/edited the manuscript. GH is responsible for the integrity of the work as a whole.

References

[1] Wu JF (2013) Childhood obesity: a growing global health hazard extending to adulthood. Pediatrics and neonatology 54: 71-72

[2] Dabelea D (2007) The predisposition to obesity and diabetes in offspring of diabetic mothers. Diabetes care 30: S169-S174

[3] Consultation W Definition, diagnosis and classification of diabetes mellitus and its complications

[4] Jiwani A, Marseille E, Lohse N, Damm P, Hod M, Kahn JG (2012) Gestational diabetes mellitus: results from a survey of country prevalence and practices. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 25: 600-610

[5] Pettitt DJ, Nelson RG, Saad MF, Bennett PH, Knowler WC (1993) Diabetes and obesity in the offspring of Pima Indian women with diabetes during pregnancy. Diabetes Care 16: 310-314

[6] Silverman BL, Rizzo T, Green OC, et al. (1991) Long-term prospective evaluation of offspring of diabetic mothers. Diabetes 40: 121-125

[7] Whitaker RC, Pepe MS, Seidel KD, Wright JA, Knopp RH (1998) Gestational diabetes and the risk of offspring obesity. Pediatrics 101: E9

[8] Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA (2003) Maternal gestational diabetes, birth weight, and adolescent obesity. Pediatrics 111: e221-226

[9] Tam WH, Ma RC, Yang X, et al. (2008) Glucose intolerance and cardiometabolic risk in children exposed to maternal gestational diabetes mellitus in utero. Pediatrics 122: 1229-1234

[10] Pettitt DJ, McKenna S, McLaughlin C, Patterson CC, Hadden DR, McCance DR (2010) Maternal Glucose at 28 Weeks of Gestation Is Not Associated With Obesity in 2-Year-Old Offspring: The Belfast Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Family Study. Diabetes care 33: 1219-1223

[11] Patel S, Fraser A, Davey Smith G, et al. (2012) Associations of gestational diabetes, existing diabetes, and glycosuria with offspring obesity and cardiometabolic outcomes. Diabetes Care 35: 63-71

[12] Regnault N, Gillman MW, Rifas-Shiman SL, Eggleston E, Oken E (2013) Sex-specific associations of gestational glucose tolerance with childhood body composition. Diabetes care: DC_130333

[13] Klein S, Allison DB, Heymsfield SB, et al. (2007) Waist circumference and cardiometabolic risk: a consensus statement from shaping America's health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. Obesity 15: 1061-1067

[14] Katzmarzyk PT, Barreira TV, Broyles ST, et al. (2013) The International Study of Childhood Obesity, Lifestyle and the Environment (ISCOLE): design and methods. BMC Public Health 13: 900

[15] Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 15: 539-553

[16] Association AD (2000) Gestational diabetes mellitus. Diabetes care 23: S77

[17] Currie C, Gabhainn SN, Godeau E, et al. (eds) (2008) Inequalities in Children's Health: HBSC International Report from the 2005/2006 Survey World Health Organization, Geneva

[18] V Mikkilä HV, T Saloheimo, SA Gonzalez, JD Meisel, G Hu, (2015) An international comparison of dietary patterns in 9–11-year-old children. International Journal of Obesity Supplements 5: S17-21

[19] T Saloheimo SG, M Erkkola, DM Milauskas, JD Meisel (2015) The reliability and validity of a short food frequency questionnaire among 9–11-year olds: a multinational study on three middle-income and high-income countries. International Journal of Obesity Supplements 5: S22-28

[20] McDowell MA, Fryar CD, Ogden CL (2009) Anthropometric reference data for children and adults: United States, 1988-1994. Vital and health statistics Series 11, Data from the national health survey: 1-68

[21] Laurson KR, Eisenmann JC, Welk GJ (2011) Body fat percentile curves for U.S. children and adolescents. American journal of preventive medicine 41: S87-92

[22] Fernandez JR, Redden DT, Pietrobelli A, Allison DB (2004) Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. The Journal of pediatrics 145: 439-444

[23] Barreira TV, Schuna Jr JM, Mire EF, et al. (2015) Identifying Children's Nocturnal Sleep Using 24-h Waist Accelerometry. Medicine and science in sports and exercise 47: 937-943

[24] Tudor-Locke C, Barreira TV, Schuna JM, Jr., Mire EF, Katzmarzyk PT (2014) Fully automated waist-worn accelerometer algorithm for detecting children's sleep-period time separate from 24-h physical activity or sedentary behaviors. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 39: 53-57

[25] Evenson KR, Catellier DJ, Gill K, Ondrak KS, McMurray RG (2008) Calibration of two objective measures of physical activity for children. Journal of sports sciences 26: 1557-1565

[26] Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC (1983) Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. New England Journal of Medicine 308: 242-245

[27] Silverman BL, Rizzo TA, Cho NH, Metzger BE (1998) Long-term effects of the intrauterine environment. The Northwestern University Diabetes in Pregnancy Center. Diabetes care 21: B142-149

[28] Kim SY, England JL, Sharma JA, Njoroge T (2011) Gestational Diabetes Mellitus and Risk of Childhood Overweight and Obesity in Offspring: A Systematic Review. Experimental diabetes research 2011: 541308

[29] Zhang S, Liu H, Zhang C, et al. (2015) Maternal Glucose during Pregnancy and after Delivery in Women with Gestational Diabetes Mellitus on Overweight Status of Their Children. BioMed research international 2015: 543038

[30] Qiao Y, Ma J, Wang Y, et al. (2015) Birth weight and childhood obesity: a 12-country study. International journal of obesity supplements 5: S74-79

[31] Li N, Liu E, Guo J, et al. (2013) Maternal prepregnancy body mass index and gestational weight gain on offspring overweight in early infancy. PLoS One 8: e77809

[32] Deierlein AL, Siega-Riz AM, Chantala K, Herring AH (2011) The association between maternal glucose concentration and child BMI at age 3 years. Diabetes Care 34: 480-484

[33] Philipps LH, Santhakumaran S, Gale C, et al. (2011) The diabetic pregnancy and offspring BMI in childhood: a systematic review and meta-analysis. Diabetologia 54: 1957-1966

[34] Li N, Liu E, Guo J, et al. (2013) Maternal prepregnancy body mass index and gestational weight gain on pregnancy outcomes. PLoS One 8: e82310

[35] Hu G, Tian H, Zhang F, et al. (2012) Tianjin Gestational Diabetes Mellitus Prevention Program : Study design, methods, and 1-year interim report on the feasibility of lifestyle intervention program. Diabetes Research & Clinical Practice 98: 508-517

[36] Tam WH (2012) The long term effect of maternal gestational diabetes to both the mothers and their offspring. In. The Chinese University of Hong Kong

[37] Lawlor DA, Fraser A, Lindsay RS, et al. (2010) Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort. Diabetologia 53: 89-97

[38] Panel NOEIE (1998) Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults

[39] Janssen I, Katzmarzyk PT, Ross R (2004) Waist circumference and not body mass index explains obesity-related health risk. The American journal of clinical nutrition 79: 379-384

[40] Crume T, Ogden L, West N, et al. (2011) Association of exposure to diabetes in utero with adiposity and fat distribution in a multiethnic population of youth: the Exploring Perinatal Outcomes among Children (EPOCH) Study. Diabetologia 54: 87-92

Table 1. Prevalence and diagnosis criteria of gestational diabetes (GDM) at 1999-2004 in 12 study sites

Country(Site)	World bank classification	Diagnostic criteria for GDM	No. of participants	GDM	
				No. of cases	Prevalence (%)
Australia (Adelaide)	High Income	Modified WHO	386	20	5.2
Canada (Ottawa)	High Income	ADA	443	14	3.2
Finland (Helsinki, Espoo & Vantaa)	High Income	WHO	401	22	5.5
Portugal (Porto)	High Income	Modified ADA	533	47	8.8
United Kingdom (Bath & NE Somerset)	High Income	WHO	324	6	1.9
United States (Baton Rouge)	High Income	ADA	363	21	5.8
Brazil (São Paulo)	Upper-Middle Income	WHO	354	11	3.1
China (Tianjin)	Upper-Middle Income	WHO	413	8	1.9
Colombia (Bogotá)	Upper-Middle Income	ADA	700	23	3.3
South Africa (Cape Town)	Upper-Middle Income	WHO	120	6	5.0
India (Bangalore)	Lower-Middle Income	Modified ADA	414	20	4.8
Kenya (Nairobi)	Low Income	WHO	289	8	2.8
All Sites			4740	206	4.3

WHO, World Health Organization; ADA, American Diabetes Association.

Table 2. Characteristics of study participant by maternal gestational diabetes (GDM) status

Characteristic	Non-GDM (N = 4534)	GDM (N = 206)	P Value
Maternal characteristics			
Age at delivery (years)	28.3 (5.7)	29.9 (5.8)	<0.001
Current body mass index (kg/m^2)	25.6 (4.9)	27.5 (5.0)	<0.001
Current overweight status, N (%)	2083 (45.9)	130 (63.1)	<0.001
Education, N (%)			0.54
Did not complete high school	997 (22.0)	52 (25.2)	
Completed high school/some college	2064 (45.5)	89 (43.2)	
Bachelor's degree or postgraduate degree	1473 (32.5)	65 (31.6)	
Offspring characteristics at birth or first year			
Boys, N (%)	2091 (46.1)	95 (46.1)	1.00
Birth weight (g)	3274 (576)	3415 (623)	0.001
Gestational age (weeks)	38.6 (2.2)	38.3 (2.1)	0.035
Infant breast feeding, N (%)			0.158
Exclusive breast feeding	1722 (38.0)	63 (30.6)	
Mixed feeding	2137 (47.1)	105 (51.0)	
Weaned from breast feeding	47 (1.0)	3 (1.5)	
Exclusive formula feeding	628 (13.9)	35 (17.0)	
Offspring characteristics at age 9-11 years			
Age (years)	10.4 (0.6)	10.4 (0.5)	0.764
Number of younger siblings	0.60 (0.8)	0.55 (0.7)	0.391
Body mass index (kg/m^2)	18.4 (3.4)	19.1 (3.6)	0.002
Waist circumference (cm)	64.2 (8.8)	66.3 (9.5)	0.001
Body fat (%)	20.8 (7.6)	22.4 (7.6)	0.002
Unhealthy diet pattern score	-0.15 (0.85)	-0.13 (0.93)	0.694
Moderate-to-vigorous physical activity (minutes/day)	59.6 (24.7)	59.0 (24.1)	0.708

Sedentary time (minutes/day)	518 (68)	520 (64)	0.634
Duration of night sleep (minutes/day)	528 (53)	521 (56)	0.051
General obesity, N (%) [a]	546 (12.0)	38 (18.4)	0.006
Central obesity, N (%) [b]	437 (9.6)	33 (16.0)	0.003
High body fat, N (%) [c]	359 (7.9)	25 (12.1)	0.030

Data are means (SD) or number (%).

[a] General obesity was defined as BMI z-score >+2 SD for age and gender specific distribution based on from the World Health Organization growth reference.

[b] Central obesity was defined as waist circumference ≥90th percentile for age and gender specific distribution using NHANES III reference.

[c] High body fat was defined as body fat ≥90th percentile for age and gender specific distribution using NHANES IV reference.

Table 3. Mean value of z-score for body mass index, waist circumference, and percentage body fat among offspring by maternal gestational diabetes (GDM) status

Outcome	Body mass index z-score			Waist circumference z-score			Body fat z-score		
	Non-GDM	GDM	P value	Non-GDM	GDM	P value	Non-GDM	GDM	P value
No. of participants	4534	206		4534	206		5434	206	
Model 1[a]	0.48 (0.08)	0.70 (0.12)	0.012	-0.04 (0.03)	0.06 (0.05)	0.006	-0.05 (0.09)	0.13 (0.12)	0.010
Model 2[b]	0.54 (0.08)	0.75 (0.11)	0.010	-0.03 (0.03)	0.07 (0.04)	0.006	0.02 (0.09)	0.20 (0.11)	0.009
Model 3[c]	0.54 (0.08)	0.71 (0.11)	0.045	-0.02 (0.03)	0.06 (0.04)	0.021	0.02 (0.09)	0.17 (0.11)	0.027
Model 4[d]	0.51 (0.08)	0.60 (0.11)	0.291	-0.04 (0.03)	0.01 (0.05)	0.144	-0.01 (0.09)	0.10 (0.11)	0.129

Data are mean (SE).

[a] Model 1 adjusted for child sex.

[b] Model 2 adjusted for maternal age at delivery and education, infant feeding mode, gestational age, number of younger siblings, child unhealthy diet pattern scores, moderate-to-vigorous physical activity, sleeping time, sedentary time, and sex.

[c] Model 3 adjusted for variables in model 2 and also for birth weight.

[d] Model 4 adjusted for variables in model 3 and also for current maternal BMI.

Table 4. Odds ratio of childhood obesity by maternal gestational diabetes (GDM) status at all or at different body mass index levels

Outcome	General obesity			Central obesity			High body fat		
	Non-GDM	GDM	P value	Non-GDM	GDM	P value	Non-GDM	GDM	P value
Total maternal sample									
No. of participants	4534	206		4534	206		5434	206	
No. of cases	546	38		437	33		359	25	
Model 1 [a]	1.00	1.65 (1.13, 2.41)	0.009	1.00	1.83 (1.23, 2.72)	0.003	1.00	1.55 (0.99, 2.42)	0.057
Model 2 [b]	1.00	1.62 (1.10, 2.40)	0.015	1.00	1.83 (1.21, 2.77)	0.004	1.00	1.51 (0.96, 2.40)	0.078
Model 3 [c]	1.00	1.53 (1.03, 2.27)	0.034	1.00	1.73 (1.14, 2.62)	0.010	1.00	1.42 (0.90, 2.26)	0.136
Model 4 [d]	1.00	1.37 (0.92, 2.04)	0.128	1.00	1.54 (1.01, 2.35)	0.046	1.00	1.30 (0.81, 2.06)	0.290
Maternal overweight									
No. of participants	2083	130		2083	130		2083	130	
No. of cases	338	34		284	28		251	23	
Model 1 [a]	1.00	1.77 (1.16, 2.70)	0.009	1.00	1.71 (1.09, 2.68)	0.019	1.00	1.54 (0.95, 2.51)	0.083
Model 2 [b]	1.00	1.75 (1.13, 2.73)	0.013	1.00	1.76 (1.10, 2.83)	0.019	1.00	1.53 (0.92, 2.55)	0.103
Model 3 [c]	1.00	1.60 (1.02, 2.51)	0.039	1.00	1.62 (1.00, 2.61)	0.048	1.00	1.42 (0.85, 2.39)	0.179
Maternal normal weight									

No. of participants	2451	76		2451	76		2451	76	
No. of cases	208	4		153	5		108	2	
Model 1 [a]	1.00	0.62 (0.22, 1.76)	0.369	1.00	1.22 (0.47, 3.15)	0.688	1.00	0.58 (0.14, 2.43)	0.456
Model 2 [b]	1.00	0.63 (0.22, 1.81)	0.388	1.00	1.26 (0.48, 3.34)	0.639	1.00	0.59 (0.14, 2.50)	0.473
Model 3 [c]	1.00	0.64 (0.22, 1.83)	0.402	1.00	1.27 (0.48, 3.35)	0.633	1.00	0.59 (0.14, 2.49)	0.468

[a] Model 1 adjusted for child age and sex.

[b] Model 2 adjusted for maternal age at delivery and education, infant feeding mode, gestational age, number of younger siblings, child unhealthy diet pattern scores, moderate-to-vigorous physical activity, sleeping time, sedentary time, age and sex.

[c] Model 3 adjusted for variables in model 2 and also for birth weight.

[d] Model 4 adjusted for variables in model 3 and also for current maternal BMI.

Table 5. Odds ratio of childhood obesity by maternal gestational diabetes (GDM) status of various subgroups

	General obesity			Central obesity			High body fat		
	Non-GDM	GDM	P value	Non-GDM	GDM	P value	Non-GDM	GDM	P value
Sex of children [a]									
Boys									
No. of participants	2091	95		2091	95		2091	95	
No. of cases	323	19		236	13		126	7	
Model 1[b]	1.00	1.31 (0.74, 2.30)	0.352	1.00	1.26 (0.65, 2.43)	0.496	1.00	1.21 (0.52, 2.82)	0.667
Model 2[c]	1.00	1.26 (0.72-2.19)	0.424	1.00	1.17 (0.61, 2.24)	0.639	1.00	1.15 (0.49, 2.67)	0.752
Girls									
No. of participants	2443	111		2443	111		2443	111	

No. of cases	223	19		201	20		233	18	
Model 1[b]	1.00	1.72 (0.99, 2.99)	0.055	1.00	2.06 (1.19, 3.56)	0.010	1.00	1.50 (0.85, 2.63)	0.162
Model 2[c]	1.00	1.53 (0.88, 2.68)	0.131	1.00	1.81 (1.05, 3.13)	0.033	1.00	1.35 (0.77, 2.37)	0.299
GDM diagnosis criteria [a]									
ADA criteria									
No. of participants	2328	125		2328	125		2328	125	
No. of cases	258	23		199	21		190	14	
Model 1[b]	1.00	1.41 (0.85, 2.32)	0.181	1.00	1.77 (1.04, 2.99)	0.034	1.00	1.09 (0.59, 2.01)	0.792
Model 2[c]	1.00	1.50 (0.91, 2.48)	0.113	1.00	1.91 (1.12, 3.24)	0.017	1.00	1.23 (0.67, 2.27)	0.506
WHO criteria									
No. of participants	2206	81		2206	81		2206	81	
No. of cases	288	15		238	12		169	11	
Model 1[b]	1.00	1.76 (0.91, 3.38)	0.091	1.00	1.76 (0.88, 3.52)	0.112	1.00	2.24 (1.08, 4.64)	0.029
Model 2[c]	1.00	1.23 (0.64, 2.36)	0.533	1.00	1.11 (0.61, 2.40)	0.598	1.00	1.52 (0.73, 3.14)	0.261
Moderate-to-vigorous physical activity [a]									
High level									

No. of participants	2273	101		2273	101		2273	101	
No. of cases	179	13		124	10		85	6	
Model 1[b]	1.00	1.57 (0.82, 3.01)	0.178	1.00	1.91 (0.93, 3.92)	0.079	1.00	1.44 (0.58, 3.60)	0.435
Model 2[c]	1.00	1.29 (0.65, 2.53)	0.465	1.00	1.52 (0.72, 3.21)	0.019	1.00	1.06 (0.41, 2.78)	0.901
Low level									
No. of participants	2261	105		2261	105		2261	105	
No. of cases	367	25		313	23		274	19	
Model 1[b]	1.00	1.52 (0.93, 2.48)	0.095	1.00	1.68 (1.02, 2.77)	0.044	1.00	1.43 (0.84, 2.43)	0.189
Model 2[c]	1.00	1.40 (0.85, 2.31)	0.191	1.00	1.54 (0.92, 2.59)	0.099	1.00	1.34 (0.78, 2.29)	0.292
Unhealthy diet scores [a]									
High level									
No. of participants	2267	103		2267	103		2267	103	
No. of cases	270	21		210	17		179	11	
Model 1[b]	1.00	1.67 (0.97, 2.88)	0.066	1.00	1.84 (1.03, 3.29)	0.041	1.00	1.78 (0.59, 2.34)	0.645
Model 2[c]	1.00	1.51 (0.87, 2.62)	0.144	1.00	1.69 (0.93, 3.05)	0.083	1.00	1.03 (0.51, 2.07)	0.936
Low level									
No. of participants	2267	103		2267	103		2267	103	

No. of cases	276	17		227	16		180	14	
Model 1[b]	1.00	1.46 (0.82, 2.60)	0.194	1.00	1.65 (0.90, 3.01)	0.103	1.00	1.81 (0.95, 3.44)	0.072
Model 2[c]	1.00	1.29 (0.71, 2.32)	0.403	1.00	1.45 (0.78, 2.70)	0.236	1.00	1.67 (0.87, 3.21)	0.123
Sleep time [a]									
High level									
No. of participants	2282	90		2282	90		2282	90	
No. of cases	207	13		170	12		147	8	
Model 1[b]	1.00	1.72 (0.90, 3.29)	0.102	1.00	2.04 (1.04, 4.02)	0.039	1.00	1.41 (0.64, 3.14)	0.395
Model 2[c]	1.00	1.56 (0.80, 2.98)	0.195	1.00	1.83 (0.92, 3.63)	0.084	1.00	1.28 (0.58, 2.84)	0.541
Low level									
No. of participants	2252	116		2252	116		2252	116	
No. of cases	339	25		267	21		212	17	
Model 1[b]	1.00	1.55 (0.94, 2.54)	0.084	1.00	1.69 (0.99, 2.88)	0.054	1.00	1.59 (0.89, 2.82)	0.115
Model 2[c]	1.00	1.39 (0.84, 2.30)	0.206	1.00	1.52 (0.88, 2.63)	0.131	1.00	1.45 (0.81, 2.60)	0.217
Region [a]									
High income countries									
No. of participants	2320	130		2320	130		2320	130	

No. of cases	255	20		175	20		166	15	
Model 1[b]	1.00	1.23 (0.72, 2.08)	0.436	1.00	1.85 (1.08, 3.18)	0.023	1.00	1.37 (0.74, 2.53)	0.322
Model 2[c]	1.00	1.14 (0.67, 1.93)	0.638	1.00	1.70 (0.98, 2.95)	0.059	1.00	1.28 (0.69, 2.38)	0.433
Low/middle income countries									
No. of participants	2214	76		2214	76		2214	76	
No. of cases	291	18		262	13		193	10	
Model 1[b]	1.00	1.93 (1.03, 3.62)	0.041	1.00	1.38 (0.70, 2.71)	0.356	1.00	1.43 (0.69, 3.00)	0.340
Model 2[c]	1.00	1.66 (0.87, 3.16)	0.125	1.00	1.19 (0.60, 2.38)	0.619	1.00	1.23 (0.58, 2.59)	0.596
Feeding mode [a]									
Exclusive breast feeding									
No. of participants	1722	63		1722	63		1722	63	
No. of cases	190	14		161	12		110	10	
Model 1[b]	1.00	2.12 (1.09, 4.14)	0.028	1.00	2.20 (1.09, 4.45)	0.028	1.00	2.34 (1.10, 4.98)	0.028
Model 2[c]	1.00	1.57(0.78, 3.14)	0.208	1.00	1.64 (0.79, 3.40)	0.185	1.00	1.69 (0.77, 3.72)	0.191
Not exclusive breast feeding									

No. of participants	2812	143		2812	143		2812	143	
No. of cases	356	24		276	21		249	15	
Model 1[b]	1.00	1.44 (0.89, 2.34)	0.142	1.00	1.66 (0.99, 2.78)	0.054	1.00	1.20 (0.67, 2.15)	0.551
Model 2[c]	1.00	1.37 (0.84, 2.25)	0.208	1.00	1.24 (0.95, 2.71)	0.076	1.00	1.16 (0.65, 2.10)	0.617

[a] All P-values for interactions are >0.05.

[b] Model 1 adjusted for maternal age at delivery and education, infant feeding mode, gestational age, number of younger siblings, child unhealthy diet pattern scores, moderate-to-vigorous physical activity, sleeping time, sedentary time, sex, and birth weight, other than the variable for stratification.

[c] Model 2 adjusted for variables in model 1 and also for current maternal BMI.