The Role of Maternal Height in Pregnancy Outcomes and Complications

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Abstract

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Background: Adult height reflects not only an individual's genetic make-up but also their early life environmental exposures, socioeconomic status, infectious disease history, nutrition, and growth and development. Increasing evidence suggests an inverse association of height with the risk of type 2 diabetes and cardiovascular disease among men and non-pregnant women. Studies of the association of maternal height with pregnancy complications and outcomes have shown inconsistent results. Further, understanding the role of maternal height in pregnancy outcomes and complications, independent of pre-pregnancy weight, represents a major gap in the literature.

Objectives: The specific aims of this dissertation were to 1) examine overall and infant-sex specific associations of maternal height, independent of maternal pre-pregnancy weight, with

infant birth size (birth weight [BW], birth length [BL], and head circumference [HC]); 2) examine associations of maternal height, independent of maternal pre-pregnancy weight, with pregnancy complications (gestational diabetes [GDM], preeclampsia, and preterm birth); 3) examine the joint association of maternal height and GDM with neonatal outcomes: BW, BL, HC, and infant macrosomia; and 4) examine the causal effect of maternal height, independent of pre-pregnancy weight, on glucose tolerance during pregnancy using a Mendelian randomization approach.

Methods: The specific aims were addressed using data collected as part of three prospective cohort studies of pregnant women: Omega (Aims 1–3), Hyperglycemia and Adverse Pregnancy Outcome (HAPO) (Aims 1–4) and Growing Up in Singapore Towards healthy Outcomes (GUSTO) (Aim 1). Socio-demographic and historical data for the participants were collected using a questionnaire at approximately 15 weeks (Omega) or 28 weeks (HAPO and GUSTO) of gestation whereas information on pregnancy outcomes, infant birth size, and other relevant information was abstracted from medical records. We defined cohort-specific percentiles of height (cm) using self-reported height (Omega) or the measured height collected during the oral glucose tolerance test visit (HAPO and GUSTO). We categorized height as short, average, or tall based on the $<20^{th}$, 20^{th}–80^{th}, and $\geq 80^{th}$ percentile values, respectively. We estimated the average difference in the mean of the infant birth size (BW, BL, HC) or the relative risk (RR) of the pregnancy complications (GDM, preterm birth, preeclampsia) and the corresponding 95% confidence interval (CI) using unadjusted and adjusted linear regression models or Poisson regression models (with robust standard errors), respectively. We repeated the analysis for associations of each height category (short, average, and tall) with infant birth size, including

macrosomia (≥ 4000 g). We evaluated the p-value of the cross-product term between overall height and 1) GDM or 2) infant sex to determine whether maternal height-infant birth size association varied by GDM or infant sex, respectively. Using height-related single nucleotide polymorphisms (SNPs) (N = 36) and genotype data, we calculated two weighted genetic risk scores (GRS) for maternal height for each individual in HAPO—one using the effect size estimates (the increase in height Z-score per one additional risk allele) from a previous GWAS (external weight) and another from similar estimates derived from our analytical cohort (internal weight). We determined whether genetically determined height was associated with the risk of GDM using the Mendelian randomization approach.

Results: Mean height and mean pre-pregnancy weight of the participants were 168 (Standard Deviation [SD]: 7.67) cm and 65.9 (SD: 13.6) kg in Omega, 161 (SD: 7.51) cm and 64.8 (13.6) kg in HAPO, and 158 (SD: 5.64) cm and 56.6 (11.3) kg in GUSTO, respectively. A 5 cm greater height of the mother was associated with an average of 23.82 g to 46.26 g greater birth weight in the three cohorts, and 1% and 18% lower the risk of gestational diabetes in Omega and HAPO, respectively. We found associations of maternal height (continuous as well as short and tall categories) with birth weight, birth length, and gestational diabetes, but not head circumference. We did not find any evidence of a non-linear relationship between maternal height and infant birth size. We observed evidence of infant sex-specific association of maternal height with BW in one cohort (GUSTO) such that associations for short height were significant only among female infants. There was a significant positive association between maternal height and preterm birth and a significant inverse association with preeclampsia in the Omega study, although the association with preeclampsia was not seen in HAPO. Results from the Omega study showed no

significant association of gestational diabetes with birth weight, birth length, head circumference, and macrosomia within categories of short, average, or tall height women. In HAPO, gestational diabetes was associated with a significantly increased risk of macrosomia as well as a greater birth length in infants among tall height mothers or short height mothers, but not mothers of average height. There was no significant interaction between gestational diabetes and maternal height on birth weight, birth length, head circumference, or macrosomia in either cohort studied (interaction $p > 0.05$). The internal and external weighted height GRS were strongly associated with maternal height. Variants that predicted adult height were inversely associated with fasting, one-hour, and two-hour OGTT glucose levels. We did not find statistically significant associations between the externally weighted or internally weighted height GRS and gestational diabetes.

Conclusion: We found that maternal height was associated with infant BW, BL, and HC, and short women, compared to average-height women, were more likely to deliver babies with lower BW and BL. Our findings indicate that the association of maternal height on infant BW varies by infant sex and the association of GDM on infant BL and macrosomia may vary by maternal height. Our results showed that maternal height is causally related with blood glucose levels. Future studies should include replicating the findings from this study and explore the effect of maternal height on other maternal health outcomes and long-term health in the post-natal period. Such studies can provide additional evidence for risk stratification based on maternal height to improve infant growth and pregnancy outcomes across generations.

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INTRODUCTION

Adult height reflects genetic susceptibility (80-90% heritability) factors and environmental factors (including exposures during early life and adolescence such as nutrition, infection, other diseases, and socioeconomic conditions) that are linked across generations (1). Increasing evidence suggests an inverse association of height with the risk of type 2 diabetes and cardiovascular disease among men and non-pregnant women (2–7). Adult height of the mother is determined by genetics and early life nutritional and environmental factors such as intrauterine exposures, childhood nutrition, disease, infection, and parent's socioeconomic condition, through various biological (8,9), genetic (10) and epigenetic pathways (11,12). As such, maternal height reflects alterations in the structure and or functions of other organs that may lead to pregnancy complications and outcomes including gestational diabetes (GDM), preeclampsia, preterm birth, and impaired infant birth measures (see Figure 0.1).

While pregnancy complications and infant birth size have been consistently shown to be associated with later-life maternal and infant morbidity and mortality from cardiovascular and metabolic diseases (13), investigations of the association of height of pregnant women with pregnancy complications and outcomes, however, are limited and show inconsistent results (14–20). Among pregnant women, studies suggest inverse associations of short maternal height with a greater risk of gestational diabetes (15,16,20,21), preeclampsia (17–19,22), and preterm birth (20,23). Previous studies also suggest inverse associations of short maternal height with birth weight (20,24–27), birth length (25,28,29), and head circumference (25,28,29) but the findings are not consistent (30–32). Considering growing evidence that there is a sex difference in fetal growth and complex interaction between the placenta and maternal physiology or pathophysiology (33),

studies have not examined whether the association of maternal height with infant birth size differs by infant sex. In addition, the independent association of maternal height and pregnancy outcomes such as GDM, preterm birth, and preeclampsia, not affected by maternal pre-pregnancy weight, has not been examined.

Despite the associations of maternal height with gestational diabetes (15,16,20,21) and neonatal birth measures (20,24–27), the joint association of gestational diabetes and maternal height on neonatal birth outcomes has not been widely studied. Existing evidence (34,35) suggests a significant interaction between maternal height and gestational diabetes on infant birth weight (35) such that tall women with gestational diabetes, compared to tall women without gestational diabetes, were reported to be more likely to deliver larger babies (34). This association, however, was not observed among short women (34).

The specific aims of this dissertation were to 1) examine overall and infant-sex specific associations of maternal height, independent of maternal pre-pregnancy weight, with infant birth size (birth weight, birth length, and head circumference); 2) examine associations of maternal height, independent of maternal pre-pregnancy weight, with pregnancy complications (gestational diabetes, preeclampsia, and preterm birth); 3) examine the joint association of maternal height and gestational diabetes with neonatal outcomes: birth weight, birth length, head circumferences, and infant macrosomia; and 4) examine the causal effect of maternal height, independent of pre-pregnancy weight, on glucose intolerance (including gestational diabetes risk) using a Mendelian randomization approach. The specific aims were addressed using the data collected as part of three prospective cohort studies of pregnant women: Omega (Aims 1–3), Hyperglycemia and Adverse Pregnancy Outcome (HAPO) (Aims 1–4) and Growing Up in Singapore Towards healthy Outcomes (GUSTO) (Aim 1). A detailed description of these three studies and methods, results,

and discussion of the findings of the studies included in this dissertation are discussed in the following chapters: Chapter 1 describes the overall and infant-sex specific associations of maternal height with infant birth size (birth weight, birth length, and head circumference), Chapter 2 describes the associations of maternal height with pregnancy complications (gestational diabetes, preeclampsia, and preterm birth), Chapter 3 describes the joint association of maternal height and gestational diabetes with neonatal outcomes: birth weight, birth length, head circumferences, and infant macrosomia, and Chapter 4 describes the causal association between maternal height and glucose intolerance (including gestational diabetes) using a Mendelian randomization approach. Lastly, a summary of the main findings along with the implication of the findings and direction for future research are presented at the end.

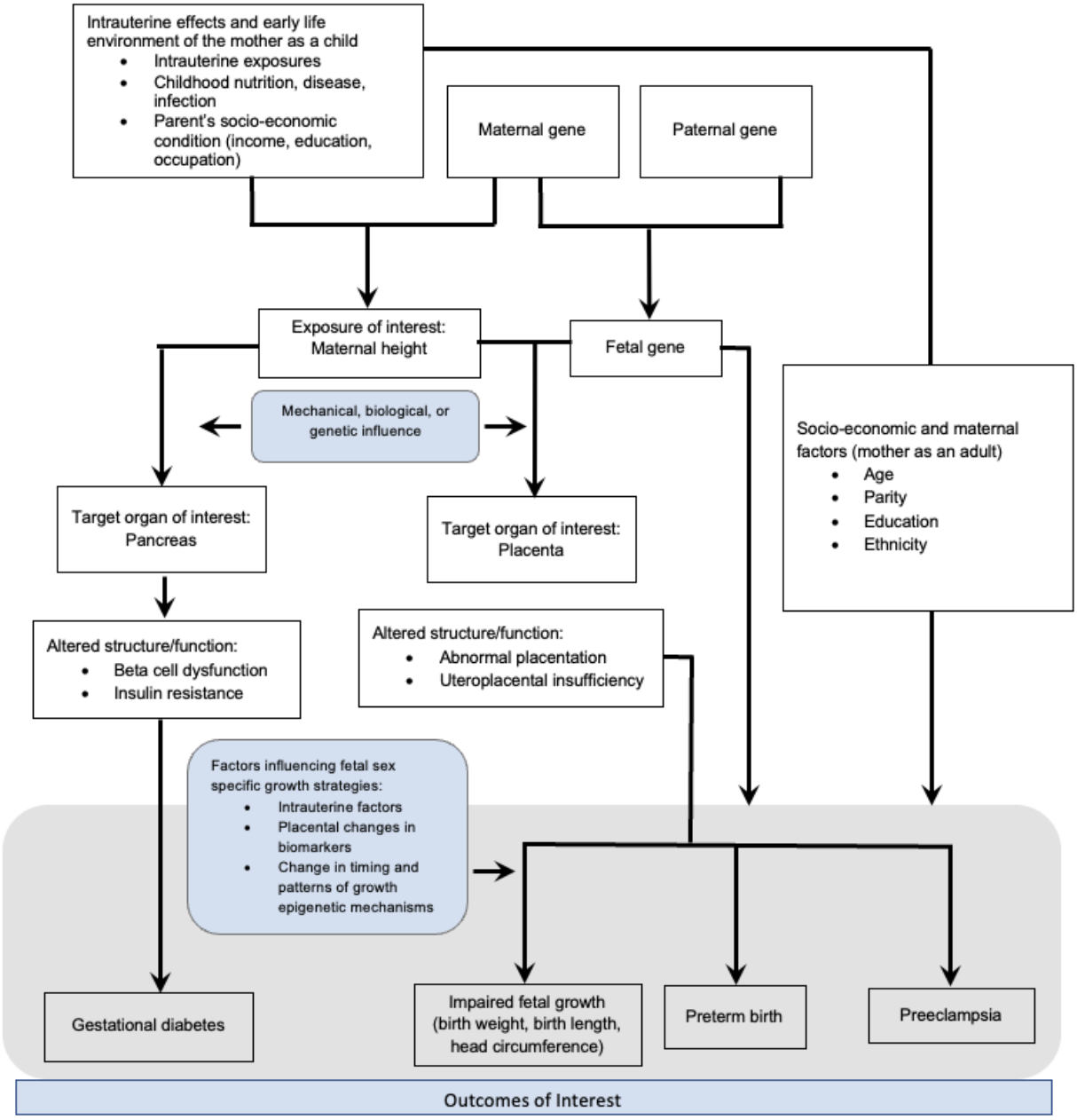

Figure 0.1 Conceptual model of the effect of height on selected pregnancy complications and outcomes

Chapter 1. ASSOCIATION OF MATERNAL HEIGHT WITH INFANT BIRTH SIZE

1.1 ABSTRACT

Background: Previous studies suggest inverse associations of short maternal height with birth weight, birth length, and head circumference but the findings are inconsistent and not independent of maternal pre-pregnancy weight (30–32). In addition, the infant sex specific association of maternal height on the outcomes has not yet been examined. The objective of the current study was to examine overall and infant sex-specific associations of maternal height on infant birth size, independent of maternal pre-pregnancy weight.

Methods: We used data from three prospective cohort studies of pregnant women: Omega, Hyperglycemia, and Adverse Pregnancy Outcome (HAPO), and Growing Up in Singapore Towards healthy Outcomes (GUSTO) studies. We categorized the height of participants as short (< 20^{th}), average (20^{th}–80^{th}), or tall (≥ 80^{th}) based on the percentile values of height for each population. Information on outcomes, birth weight (g), birth length (cm), and head circumference (cm), were abstracted from newborn medical records. Using unadjusted, partially adjusted, and fully adjusted linear regression models, we estimated the average difference in mean and 95% confidence intervals (CI) of outcomes associated with 1) a 5 cm change in maternal height, and 2) tall height and short height, compared to average height. We used the likelihood ratio test (LRT) to test the non-linearity of height-birth size associations (restricted cubic spline with 5 knots located at 5^{th}, 25^{th}, 50^{th}, 75^{th}, and 95^{th} percentiles of height) along with the test of effect modification of the height-birth size associations by infant sex.

Results: Mean height and mean pre-pregnancy weight of the participants were 168 (standard deviation [SD]: 7.67) cm and 65.9 (SD: 13.6) kg in Omega, 161 (SD: 7.51) cm and 64.8 (13.6) kg

in the HAPO, and 158 (SD: 5.64) cm and 56.6 (11.3) kg in GUSTO, respectively. A 5 cm greater height of the mother was associated with an average of 23.82 g (95% CI: 2.44, 44.81; $p < 0.001$ in GUSTO) to 46.26 g (95% CI: 34.69, 57.84; $p < 0.001$ in HAPO) greater birth weight in the three cohorts. We found associations of both short maternal height and tall maternal height (compared to average height), with infant birth weight and birth length, but not head circumference. Infants born to short women had 70.83 g (95% CI: -111.87, -29.78; $p < 0.001$ in HAPO) to 98.03 g (95% CI: -134.84, -61.23; $p < 0.001$ in Omega) lower birth weight and infants born to tall women had 0.40 cm (95% CI: 0.16, 0.64, $p < 0.05$ in Omega) to 0.53 cm (95% CI: 0.36, 0.69; $p < 0.05$ in HAPO) greater birth length. We did not find any evidence of a non-linear relationship between maternal height and outcomes. We observed evidence of infant sex-specific association of maternal height with birth weight in one cohort (GUSTO) such that male infants had a greater birth weight than female infants among mothers of similar height (by 139.37 g, $p < 0.05$ among short women and 93.41 g, $p = 0.07$ among tall women).

Conclusion: We found that maternal height was associated with infant weight, length, and head circumference, and short women, compared to average-height women, were more likely to deliver babies with lower birth weight and birth length. Infant sex modified maternal height-infant birth size associations. Further research to replicate the study findings, particularly infant-sex specific associations is needed.

1.2 BACKGROUND

Adult height reflects an individual's genetic make-up, intrauterine experience, postnatal exposures (e.g., environmental, socioeconomic status, infection, and nutrition) and growth and development, and their complex interplay (36,37). A growing body of literature among the general population of men and non-pregnant women has identified that short adult height is associated with the risk of diabetes and higher morbidity and mortality from cardiovascular diseases (2–7). Similarly, among pregnant women, studies have reported an inverse association of maternal height with pregnancy outcomes, although these studies were limited in number, and the findings were inconsistent (24,38).

Infant birth size reflected by birth weight, birth length, and head circumference has been associated with perinatal morbidity and mortality and adult adverse health outcomes (38–40). For instance, birth weight has been inversely associated with the risk of diabetes, hypertension, cardiovascular disease, and neurological disorders in later life with varying shape of associations (41,42). Birth length is an important predictor of both adult height (43,44) and adult weight (44) that are associated with health problems, particularly cardiovascular diseases (43,45–48). Head circumference is a measure of brain growth (49) that has been associated with neurological development and cognitive function in childhood (50). Previous studies suggest inverse associations of short maternal height with birth weight (20,24–27), birth length (25,28,29), and head circumference (25,28,29); however, the findings are not consistent (30–32). In addition, the independent association of maternal height, not affected by maternal pre-pregnancy weight, has not been examined.

The difference in fetal growth pattern and birth weight between male and female infants is well documented (33,51,52). Recent studies have highlighted difference in associations between

various maternal exposures and infant size at birth (53,54) by infant sex. Despite increasing evidence of sex difference in anthropometry from the very early stage of gestation, studies have not yet examined the potential difference in the association of maternal height with infant birth size by infant sex.

Hence, our primary aim was to determine if mothers who have short height, independent of their pre-pregnancy body weight, are at a higher risk of delivering babies with low birth weight, birth length, and head circumferences. In this multi-cohort study, we also sought to assess if the impact of height on the infant birth size was modified by infant sex and maternal characteristics – age, parity, and race/ethnicity– that influence adverse outcomes during birth.

1.3 METHODS

1.3.1 *Study Settings and Study Populations*

We conducted the study using data collected as part of three prospective pregnancy cohort studies: 1) Omega; 2) Hyperglycemia, and Adverse Pregnancy Outcome (HAPO); and 3) Growing Up in Singapore Towards healthy Outcomes (GUSTO). Details on the study objectives, study designs, inclusion and exclusion criteria, and data collection have been reported elsewhere (55–59). A brief overview is presented here.

Omega participants were recruited from among pregnant women attending prenatal care clinics affiliated with Swedish Medical Center and Tacoma General Hospital in Seattle and Tacoma, Washington State, respectively, between 1996 and 2008. Women were eligible if they were 18 years of age or older, were able to speak and read English, initiated prenatal care before 16 weeks of gestation, and planned to carry the pregnancy to term and deliver at one of the two study hospitals. The primary goal of the Omega study was to examine dietary and metabolic risk factors of pregnancy complications (15). Out of 5,063 eligible women, 4,602 (91%) provided

informed consent and were enrolled in the cohort. The study was approved by the institutional review boards of Swedish Medical Center and Tacoma General Hospital.

HAPO study participants were recruited among pregnant women less than 31 weeks of gestation from 15 field centers located in Asia, Australia, Europe, North America, and the Middle East, between July 2000 and April 2006. Women were eligible if they were 18 years of age or older, planned delivery at participating health centers, were able to complete the oral glucose tolerance test (OGTT) by 32 weeks' gestation, and were either certain of the date of last menstrual period or ultrasound estimation from 6 to 24 weeks of gestational age was available. Women with multiple pregnancy, conception using gonadotropin ovulation induction or by in vitro fertilization, glucose testing before recruitment or gestational diabetes diagnosis prior to enrollment in the HAPO study, history of overt diabetes, pre-existing diabetes requiring treatment with medication, known to be HIV positive or to have hepatitis B or C, or inability to converse in the languages used in field center forms without the aid of an interpreter were excluded. If glucose measurements were made outside of HAPO after initial enrollment, the participant was excluded from further participation. All participants provided written informed consent. The objective of the HAPO study was to clarify unanswered questions on associations of maternal glycemia that was below the threshold for diagnosis of overt diabetes mellitus with risks of adverse pregnancy outcomes particularly increased birth weight, increased cord-blood serum C-peptide, and primary cesarean delivery (57). Of 53,295 eligible women (all centers), 28,562 (53.59%) agreed to participate and among those, 25,505 (89.29%) completed an OGTT. However, we had access to publicly available phenotype data on only 4,994 genotyped mother/infant pairs which we downloaded from the Database of Genotypes and Phenotypes (dbGaP) website, under phs000096.v4.p1. The study was approved by the institutional review boards at all 15 field centers.

GUSTO study participants were recruited among pregnant women less than 14 weeks of gestation, attending their first trimester antenatal dating ultrasound scan clinic at Singapore's two major public maternity units, namely the National University Hospital and KK Women's and Children's Hospital, between June 2009 and September 2010. Women were enrolled if they were between 18 and 50 years of age, intended to live in Singapore for 5 years following delivery, planned to deliver in one of the study centers, were willing to donate blood tissues at delivery, had homogeneous ethnicity of the parents and spouse's parents; and provided written informed consent. Mothers receiving chemotherapy, psychotropic drugs or who had type 1 diabetes mellitus were excluded. The primary objective of the GUSTO cohort study was to evaluate the role of factors operating during early development, affecting pathways to metabolic compromise, and altered body composition in the offspring (59). Of 2,034 eligible women, 1,445 (71.04%) women participated in the study. The study was approved by the National Healthcare Group Domain Specific Review Board and the SingHealth Centralized Institutional Review Board.

For the current study, participants were excluded if they had one or more of the following conditions 1) individuals with missing values for height (N = 333 Omega, N = 21 HAPO, N = 248 GUSTO), infant birth weight (N = 12 Omega, N = 26 HAPO, N = 50 GUSTO), birth length (N = 69 Omega, N = 7 HAPO, N = 2 GUSTO) or head circumference (N = 58 in Omega, N = 0 HAPO, N = 1 GUSTO); 2) height less than 140 cm or greater than 200 cm (N = 5 Omega, N = 6 HAPO, N = 0 GUSTO); or 3) pre-existing diabetes or hypertension and other pregnancy complications (e.g., placental abnormities, chorioamnionitis, and congenital anomalies) that can influence infant birth size (N = 236 Omega, N = 121 HAPO, N = 25 GUSTO). After exclusion, the final analytical sample included 3,889 mother-newborn pairs for the Omega study, 4,813 for the HAPO study and 1,119 for the GUSTO study.

1.3.2 *Data Collection*

In the Omega study, information on maternal socio-demographic and medical characteristics, family and medical history, height, and pre-pregnancy weight, smoking and alcohol drinking habits was collected through interviewer-administered questionnaire at an average of 15 weeks of gestation. Information on gestational age at delivery, maternal health during the pregnancy and at the time of delivery, and pregnancy outcomes (including newborn health) were abstracted from hospital labor and delivery medical records and clinic records by trained study personnel after the estimated delivery date (15).

The participants in the HAPO study underwent 75 g OGTT as close to 28 weeks' gestation as possible (maximal range 24–32 weeks' gestation). At the OGTT visit, height, weight, and blood pressure were measured while other prenatal information, including socio-demographic characteristics and participant's report of pre-pregnancy weight, was collected using questionnaires. Following OGTT, routine pregnancy care was continued at the field centers. Neonatal anthropometric measures were taken after delivery, and follow-up data were collected at 4-6 weeks after delivery.

In the GUSTO study, detailed interviewer-administered interviews were conducted to collect socio-demographic and historical data, including participant's report of pre-pregnancy weight, in the clinic at recruitment. Maternal height and weight were measured at the OGTT visit at 26–28 weeks' gestation. Within the first 24 hours after delivery, neonatal anthropometric measures were taken, and other relevant information was abstracted from medical records.

In all three study cohorts, we used self-reported pre-pregnancy weight for our analyses. For each study population, we defined quintiles of height (centimeter) using the self-reported (Omega) or measured height (HAPO and GUSTO). There are limited studies regarding the best way to

classify maternal height. Similar to a previous study (20), based on the quintiles, we further categorized height as short height if the maternal height was less than 20th percentile in that cohort, average height if the height was in between 20th and 80th percentile and tall if the height was greater than or equal to the 80th percentile value. To address the potential non-linear relationship of maternal height with infant birth size, we used restricted cubic splines with 5 knots located at 5th, 25th, 50th, 75th, and 95th percentiles of height. The use of 5 knots or fewer has been sufficient in the use of restricted cubic splines in practice and knot position doesn't impact the results (60).

Information on birth weight (g), birth length (cm) and head circumference (cm) were abstracted from newborn medical records. To ensure robustness of our findings, we defined birth weight as low birth weight if the weight was less than 2500 g. We further calculated cohort-specific Z-scores for birth weight, birth length, and head circumference separately for male and female infants.

1.3.3 *Statistical Analysis*

For each study population, we examined the socio-demographic, pregnancy, and infant-related characteristics of the participants overall and by the quintiles of height. We calculated mean and standard deviation (SD) for continuous variables and the percent of total for categorical variables.

To estimate the associations between height and outcomes, we fit unadjusted, partially adjusted, and fully adjusted regression models. In unadjusted models, the crude association between maternal height and outcomes (continuous measures of birth weight, birth length, and head circumference, including Z-scores) was estimated using linear regression models. We estimated the average difference in mean of the outcome measures and the corresponding 95% confidence intervals (CI) associated with 1) a 5 cm change in maternal height (linear height), 2) tall height and short height, compared to average height (categorical height), and 3) a unit change

in maternal height within each spline windows (cubic spline height). Similarly, for the binary outcome of low birth weight, we estimated relative risks (RR) and 95% CI using modified Poisson regression models with robust standard errors (61). To test the non-linearity of height-birth size associations, we used p-value from likelihood ratio tests comparing the fully adjusted model with linear height as a predictor to the fully adjusted linear model with the restricted cubic spline for height.

To estimate the adjusted associations between maternal height and the outcomes, the following covariates were identified a *priori* and added to the unadjusted regression models, either as confounder or precision variables: Maternal age (years), pre-pregnancy weight (kg), and gestational age at delivery were included as continuous variables. Post-high school education married marital status, nulliparity, smoking during pregnancy, alcohol use during pregnancy, pregnancy complications (defined as the presence of gestational diabetes or preeclampsia), and male infant were included as binary variables. Of note, information on marital status was available only in the Omega study. We modeled maternal race/ethnicity as an indicator variable in the adjusted models. Maternal race/ethnicity was categorized as White/African-American/Asian/Hispanic in the Omega and HAPO studies and Chinese/Malay/Indian in the GUSTO study. Diagnosis of gestational diabetes was made post hoc in HAPO data based on the current International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (62). Using blood glucose values from 75-gram OGTT done in the fasting state at 24–28 weeks of gestation, we applied the diagnosis of gestational diabetes mellitus if any of the following cut-offs was met 1) ≥ 92 mg/dl (≥ 5.2 mmol/l) or 2) one-hour ≥ 180 mg/dl (≥ 10 mmol/l) or 3) two-hour ≥ 153mg/dl (≥ 8.5 mmol/l). We additionally included study sites as a grouped categorical variable in all adjusted models for the HAPO study population. Partially adjusted regression models

included all covariates listed above except pregnancy complications while the fully adjusted models included all covariates. We fitted partially adjusted models to examine whether the observed associations were sensitive to potential confounding by pregnancy complications.

To examine potential effect modification, we re-ran the fully adjusted regression models for categorical height stratified by the potential effect modifiers: infant sex (male/female), parity (nulliparous/multiparous), age group (≥ 35 years, <35), and race/ethnicity (categorized as above). Next, we included interaction terms between maternal height and each effect modifier in the fully adjusted regression models. We used the likelihood ratio test to test the null hypothesis of no effect modification of the association between maternal height and infant birth size.

In all analyses, the p-value was two-sided and statistical significance was calculated at $\alpha = 0.05$. All calculations and analyses were done in a cohort-specific manner. Analyses were conducted using R studio software (R Version 4.1.1 [2021-08-10]).

1.4 RESULTS

Pregnant women in the Omega study had a mean age of 32.8 (SD: 4.47) years, a mean body mass index (BMI) of 23.4 (SD:4.53) kg/m^2, a mean pre-pregnancy body weight of 65.9 (SD: 13.6) kg and a mean height of 168 (SD: 7.67) cm (Table 1.1, Table 1.2 and Figure 1.1). These women were predominantly White (85.3%), unmarried (91.3%), had completed post-high school education (90.8%) and had no previous pregnancies (61.6%). The majority of the participants in the HAPO study were White (30.0%) or African-American (26.8%), nulliparous during enrollment (68.0%), and younger, with a mean age of 28.4 (SD: 5.88) years (Table 1.3). The mean BMI, pre-pregnancy body weight and height of HAPO participants were 25.2 (SD: 4.91) kg/m^2, 64.8 (SD: 13.6) kg, and 161 (7.51) cm, respectively (Table 1.1, Table 1.3 and Figure 1.2). More than half of the pregnant women participating in the GUSTO study were Chinese (57.0%), followed by Malay

(24.8%) (Table 1.4). GUSTO participants were on average 30.6 (SD: 5.06) years old. They were generally shorter (mean height: 158 cm, SD: 5.64 cm) and had lower pre-pregnancy body weight (mean: 56.6 kg, SD: 11.3 kg) and lower BMI (mean: 22.6 kg/m^2, SD: 4.34 kg/m^2) than women in other two cohorts (Table 1.1, Table 1.4 and Figure 1.3). The averages of infant birth size for each study are presented in Table 1.1. Mean birth weight of infants born to women in the Omega cohort was 3,430 (SD: 561) g, birth length was 50.60 (SD: 3.43) cm and head circumference was 34.70 cm (SD: 2.23). The corresponding values in HAPO and GUSTO were 3,290 (SD: 470) g, 50.00 (SD: 2.17) cm, 34.20 (SD: 1.45) cm and 3,080 (SD: 448) g, 48.60 (SD: 2.33) cm, 33.3 (SD: 1.45) cm, respectively.

Selected characteristics of pregnant women in each study population are presented by height quintiles in Tables 1.2, 1.3, and 1.4. In general, shorter women (i.e., women in the first quintile of height), compared to taller women (in other quintiles), tended to be less educated and had lighter pre-pregnancy body weight, higher pre-pregnancy BMI, and a greater likelihood of being diagnosed with gestational diabetes. Based on the quintile values of height in the Omega, HAPO, and GUSTO studies, women were considered short if their height was less than 161.40 cm, 154.05 cm or 153.53 cm (corresponding to first quintile value) and tall if their height was greater than or equal to 174.02 cm, 167.0 cm, or 163.00 cm (corresponding to last quintile value), respectively.

Table 1.5 through Table 1.11 presents the mean estimates or risk estimates (for low birth weight) obtained from unadjusted, partially adjusted, and fully adjusted multivariable regression models for the various measures of infant birth size considered in relation to maternal height in the three study populations.

Results from regression models that included a linear term for maternal height showed a strong positive association of maternal height with birth weight, birth length and head

circumference in the unadjusted models for all three study cohorts (all p-value<0.01) (Table 1.5 to Table 1.7). After partial adjustment of confounders, the associations were attenuated but remained significant for all outcomes, except head circumference in the GUSTO study. After additional adjustment for pregnancy complications (fully adjusted models), the associations of linear height with birth weight, birth length, and head circumference did not change, as compared to the partially adjusted models. In the fully adjusted model, a 5 cm greater height of the mother was associated with an average of 34.93 gram (95% CI: 25.17, 44.69; $p < 0.001$) greater birth weight, 0.23 cm (95% CI: 0.16, 0.30; $p < 0.001$) greater birth length and 0.05 cm (95% CI: 0.01, 0.10; $p = 0.03$) greater head circumference of the infant in the Omega study; 46.26 gram (95% CI: 34.69, 57.84; $p < 0.001$) greater birth weight, 0.26 cm (95% CI: 0.20, 0.31; $p < 0.001$) greater birth length and 0.06 cm (95% CI: 0.02, 0.09; $p < 0.01$) greater head circumference of the infant in the HAPO study, and 23.82 gram (95% CI: 2.44, 44.81; $p < 0.001$) greater birth weight, 0.17 cm (95% CI: 0.06, 0.29; $p < 0.001$) greater birth length and 0.03 cm (95% CI: -0.05, 0.10; $p = 0.49$) greater head circumference of the infant in the GUSTO study.

Results from fully adjusted regression models that included three categories of maternal height (indicator variable) showed that women with short height, compared to women with average height, in the Omega study, gave birth to infants with significantly lower birth weight (-98.03 g, 95% CI: -134.84, -61.23; $p < 0.001$) and lower birth length (-0.44 cm, 95% CI: -0.69, -0.19; $p < 0.001$) (Tables 1.5 and 1.6). We observed similar results for HAPO participants (birth weight: -70.83 g, 95% CI: -111.87, -29.78; $p < 0.001$ and birth length: 0.44 cm, 95% CI: -0.63, -0.24; $p < 0.001$). However, we did not observe any association of short height with birth weight and birth length among GUSTO participants (birth weight: -54.89 g, 95% CI: -111.49, 1.70; $p = 0.060$ and birth length: 0.44 cm, 95% CI: -0.53, 0.08; $p = 0.15$). Similarly, tall height of the mother was

associated with greater birth weight in Omega (55.15 g, 95% CI: 20.00, 90.30; $p < 0.01$) and HAPO cohorts (99.27 g, 95% CI: 64.65, 133. 88; $p < 0.001$) and greater birth length of infants in all cohorts (Omega: 0.40 cm, 95% CI: 0.16, 0.64; HAPO: 0.53 cm, 95% CI: 0.36, 0.69; GUSTO: 0.43 cm, 95% CI: 0.12, 0.74; all $p < 0.05$). We did not observe any associations of short height or tall height with head circumference in either cohort (all p-values > 0.05). One exception was for HAPO study where, head circumference of infants born to tall women was larger compared to infants born to average height women (0.15 cm, 95% CI: 0.04, 0.27; $p = 0.01$). The above associations were similar in magnitude and significance in models that did not adjust for pregnancy complications. Findings from analyses using sex-specific Z-scores for birth size measures were similar to those reported above and are presented in Tables 1.8 to 1.10. Further, we did not observe associations of maternal height (linear and categorical) with low birth weight after complete adjustments in any of the cohorts (Table 1.11). In addition, results from restricted cubic spline models did not show any evidence of a non-linear relationship between height and infant birth size measure. (Likelihood ratio test $p > 0.05$ for all birth size measures in all cohorts).

We report the results of analyses stratified by infant sex, age group ≥ 35 years, parity, and race/ethnicity in Table 1.12. Adjusted mean change in birth weight of infants born to short height mothers, compared to average height mothers, was -86.48 g (95% CI: -138.66, -34.29; $p < 0.05$) for male and -107.33 g (-159.32, -55.33; $p < 0.05$) for female in the Omega study; -70.43 (95% CI: -129.65, -11.22; $p = 0.01$) for male and -76.92 (95% CI: -133.91, -19.92; $p = 0.02$) for female in the HAPO study; -23.80 (95% CI: -106.30, 58.70; $p = 0.57$) for male and -77.4 (95% CI: -154.20, -0.57; $p = 0.05$) for female in the GUSTO study. However, the p-value from the likelihood ratio test comparing the fully adjusted model to the model with an interaction term between height categories and sex was significant for GUSTO ($p < 0.001$) but not Omega ($p = 0.67$) and HAPO

($p = 0.48$). Our results indicate that male infants exceeded females by an average of 152.36 g ($p < 0.05$), 88.21 g ($p < 0.001$), and 139.37 g ($p < 0.05$) among short women and 183.03 g ($p < 0.05$), 135.48 g ($p < 0.01$), and 93.41 g ($p = 0.07$) among tall women in Omega, HAPO, and GUSTO studies, respectively. Results of height-infant birth size associations were generally similar in age group-stratified and parity-stratified models for all cohorts, except that the difference in birth length of infants between short, average, or tall women varied significantly between older age group (≥ 35 years) and younger (< 35 years) women in the Omega study ($p = 0.04$), and nulliparous and primi/multiparous women in the Omega ($p = 0.03$) and GUSTO ($p = 0.03$) studies. Race/ethnicity modified the height-birth size associations for all measures in GUSTO but not HAPO and Omega studies. Among Indian women in the GUSTO study, short height, compared to average height, was associated with 11.6 g lower birth weight (-11.6, 95% CI: -157.55, 134.34; $p = 0.88$), 0.26 cm higher birth length (0.26, 95% CI: -0.48, 1.00; $p = 0.49$), and 0.16 cm lower head circumference (-0.16, 95% CI: -0.66, 0.35; $p = 0.54$). The corresponding mean change among Chinese women was -49.08 (95% CI:-124.90, 26.74; $p = 0.21$), -0.09 (95% CI:-0.48, 0.30; $p = 0.30$), and -0.04 (95% CI:-0.31, 0.23; $p = 0.79$) and among Malay women was -89.21 (95% CI:-199.43, 21.01; $p = 0.11$), -0.31 (95% CI:-0.85, 0.23; $p = 0.26$), and -0.09 (95% CI:-0.48, 0.30; $p = 0.66$).

1.5 DISCUSSION

In this secondary data analysis of three prospective cohort studies of pregnant women, we observed a strong positive linear relationship between maternal height and infant birth size in each of the three cohorts after adjusting for maternal age, maternal race/ethnicity, pre-pregnancy weight, gestational age at delivery, post-high school education, married marital status, nulliparity at enrollment, smoking during pregnancy, alcohol use during pregnancy, pregnancy complications,

male infant, and study sites. A 5 cm greater height of the mother was associated with an average of 23.82 g to 46.26 g greater birth weight in the three cohorts. We found associations of both short maternal height and tall maternal height (compared to average height), with infant birth weight and birth length, but not head circumference. Infants born to short women had 70.83 g to 98.03 g lower birth weight and infants born to tall women had 0.40 cm to 0.53 cm greater birth length. We did not find any evidence of a non-linear relationship between maternal height and outcomes. We observed evidence of infant sex-specific association of maternal height with infant birth weight in one cohort such that associations for short height were significant only among female infants. Additionally, we found some differences in maternal height-birth size associations by parity, maternal age ≥ 35 years, and race/ethnicity, although the associations varied depending upon the birth size measure and study cohort.

Our findings of a linear association between maternal height and birth weight were consistent with results from previous reports (28,38,63,64). A study conducted among the participants of the German Perinatal Survey found a linear relationship between maternal height and birth weight (38). In that study, a 1 cm greater maternal height was associated with an average 17 g greater infant birth weight. In a meta-analysis of findings from birth cohorts of three countries (Finland, Denmark, and Norway), Zhang et al. (28) reported that 1 cm greater maternal height was associated with 9.46 g higher birth weight (meta-analysis p-value $2.19 * 10^{-15}$) and 0.05 cm higher birth length (meta-analysis p-value $6.31 * 10^{-9}$). Our results demonstrate a similar change in birth weight (5.45 g in Omega, 9.25 g in HAPO, and 4.72 g in GUSTO) and birth length (0.05 cm in Omega and HAPO and 0.03 cm in GUSTO) for a 1cm change in maternal height. The finding that maternal height is associated with head circumference in HAPO and Omega studies is consistent with a previous report from India where a 5 cm greater maternal height was associated with a 0.09 SD

increase in head circumference at birth ($p = 0.046$), after adjustment for maternal age, parity, socioeconomic status, religion and household smokers (63). In our study, we found that a 5 cm greater maternal height is associated with a 0.02 SD increase in head circumference in Omega ($p = 0.02$) and a 0.04 SD increase in HAPO ($p < 0.001$). Another study conducted in Austria found that maternal height was associated with fetal growth parameters, including head circumference (64). In that study, the fetal growth parameters were obtained from ultrasound in the third trimester and the association was independent of maternal age, nicotine consumption, and fetal sex.

In HAPO and Omega, we also observed that short women were more likely to give birth to lower birth weight and lower birth length infants. The lack of relationship of short height with birth weight and birth length in GUSTO as opposed to that in the Omega and HAPO studies may be due to generally shorter stature of the women in the GUSTO study (mean height in Omega = 168 cm, HAPO = 161 cm, GUSTO = 158 cm). Furthermore, the first quartile and third quartile values of maternal height in GUSTO for each ethnic group were 152.53 cm, 152.60 cm, and 154.45 cm and 158.65 cm, 158.00 cm, 160.40 cm for Indian, Malay, and Chinese, respectively. We used overall quartile values of height instead of racial/ethnic-specific values to define the short and tall height. Thus, it is possible that the results in the GUSTO study are not consistent due to misclassification resulting from variation in height between racial/ethnic groups. Another possible explanation may be that the three study cohorts differed greatly in terms of the racial/ethnic composition of the participants and parity status. GUSTO included predominantly Chinese women and primi/multiparous women while HAPO and Omega enrolled mostly White women and nulliparous women. The associations of height and birth size in GUSTO may be outweighed by other factors that may be different between Chinese and White women or nulliparous and primi/multiparous women (e.g., lower uteroplacental perfusion in primipara).

Similarly, our results showed that infants had a 55.15 g (Omega) to 99.27 g (HAPO) greater birth weight and 0.40 cm (Omega) to 0.53 cm (HAPO) greater birth length from tall maternal height. This is consistent with findings from previous investigators who have reported that the mean birth weight and birth length were higher in tall mothers than the reference group (65).

Although we found an association of maternal height with birth weight and birth length, the associations with low birth weight were not significant. Our finding that maternal height is not associated with low birth weight is consistent with some (30,31) but not all (32) previous studies. Of note, the definitions of short stature and tall stature varied greatly between these studies. A recent systematic review and meta-analysis reported that short women had a greater risk of delivering low birth weight babies compared to the reference category (crude RR 1.81, 95% CI: 1.47, 2.23, 8 studies) while the risk was halved in tall women (crude RR 0.56, 95% CI: 0.46, 0.69, 4 studies) (66). However, the estimates in the meta-analysis were crude estimates; thus, there is a possibility of confounding of these findings by factors such as socioeconomic status and smoking. Fully adjusted models in our study showed that the risk of delivering low birth weight babies was the same for short, tall, or average height women in each of the three study cohorts.

We observed infant sex-specific associations of maternal height with infant birth size in the GUSTO study. For male infants, mother's short height was associated with 86.48 g lower birth weight (Omega, $p < 0.05$), and tall height was associated with 106.91 g greater birth weight (HAPO, $p < 0.05$). For female infants, mother's short height was associated with 77.40 g lower birth weight (GUSTO, $p < 0.05$), and tall height was associated with 89.93 g greater birth weight (HAPO, $p < 0.05$. This was consistent with findings from a study in Chile (51) that reported that male infants were more sensitive to change in maternal height than female infants. The study by Lampl et al. reported that male infants were on an average 150 g heavier than female infants among

short and heavy weight mothers and 191 g among tall and light weight mothers (both $p < 0.001$). Studies examining the infant sex-specific effect of maternal height on infant birth size are limited. However, several potential biological (8,9), genetic (10) and epigenetic mechanisms (11,12) have been proposed that can explain the sex-specific associations.

Our study provides suggestive evidence of a difference in the effect of maternal height on infant birth weight and birth length when the mother was Chinese, Malay, or Indian (GUSTO) and on birth length when the mother was older vs younger (Omega) or nulliparous vs primi/multiparous (Omega, GUSTO). To our knowledge, this study was the first to examine the effect modification of the association of height with birth size by infant sex and maternal age, parity, and race/ethnicity. More research is needed to establish if the associations of height with birth size differ by age group, parity, and race/ethnicity in other populations.

One major strength of this study is the use of three large, prospective, racially/ethnically diverse, multi-country study cohorts. This enabled us to compare the findings across the studies and provide evidence for the generalizability of the findings to other study populations with similar characteristics as the three cohorts. All three study cohorts provided access to a wide range of confounders which were collected/retrieved by trained health personnel using validated measurement techniques. Most previous studies have adjusted for pre-pregnancy BMI and have failed to assess the independent effect of height because height itself is a component of the BMI. We assessed the independent contribution of maternal height on outcomes by adjusting for pre-pregnancy weight instead of pre-pregnancy BMI. Height was measured in HAPO and GUSTO increasing the validity of the findings. Measurement of height additionally allows measuring height with increased precision, particularly for women of average height who may tend to report

height with less granularity. We explored sex-specific associations along with examining the potential non-linear relationship between maternal height and outcomes.

Several limitations of our study deserve mention. There was high missingness for the pre-pregnancy weight variable in HAPO. However, excluding this covariate from the regression models did not change the statistical significance of our findings. Height was self-reported in the Omega and self-reported height tends to be overestimated (36). For all analyses, some misclassification due to overreporting or underreporting of reported measures (such as pre-pregnancy weight) is a possibility. This may have resulted in non-differential misclassification of the height-birth size associations and hence underestimation of the effect size. Residual confounding due to incomplete adjustment of confounders and unmeasured confounding in the findings of an observational study such as ours is another limitation. Type I error due to multiple tests might be an issue because of the many statistical tests we conducted. The findings from this study are not generalizable to the groups of women that were excluded from the analysis (e.g., women with pre-existing diabetes or hypertension).

In conclusion, we found that maternal height was associated with infant weight, length, and head circumference, and short women, compared to average-height women, were more likely to deliver babies with lower birth weight and birth length. Infant sex modified maternal height-birth weight associations such that male infants had a greater birth weight than female infants among mothers of similar height. Our findings can improve our understanding of the role of maternal height in infant birth size. Through better risk categorization based on maternal height, women at risk of lower infant birth size can be identified and monitoring approaches and prevention strategies, including for beyond the pregnancy period, can be implemented. Findings from these analyses have important public health implications as they highlight life-course risk development

and the need for interventions aimed at determinants of women's height that are in play largely during her early life. Further research to establish if maternal height is associated differently with infant birth size depending on age group, race/ethnicity, or parity is needed.

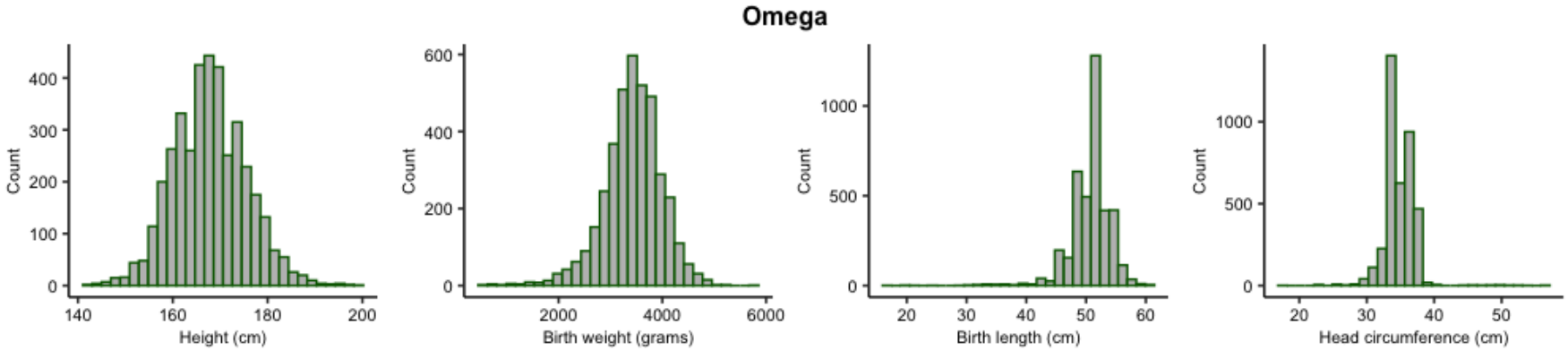

Figure 1.1 Histogram showing distribution of key variables - height, birth weight, birth length and head circumference in the **Omega** study

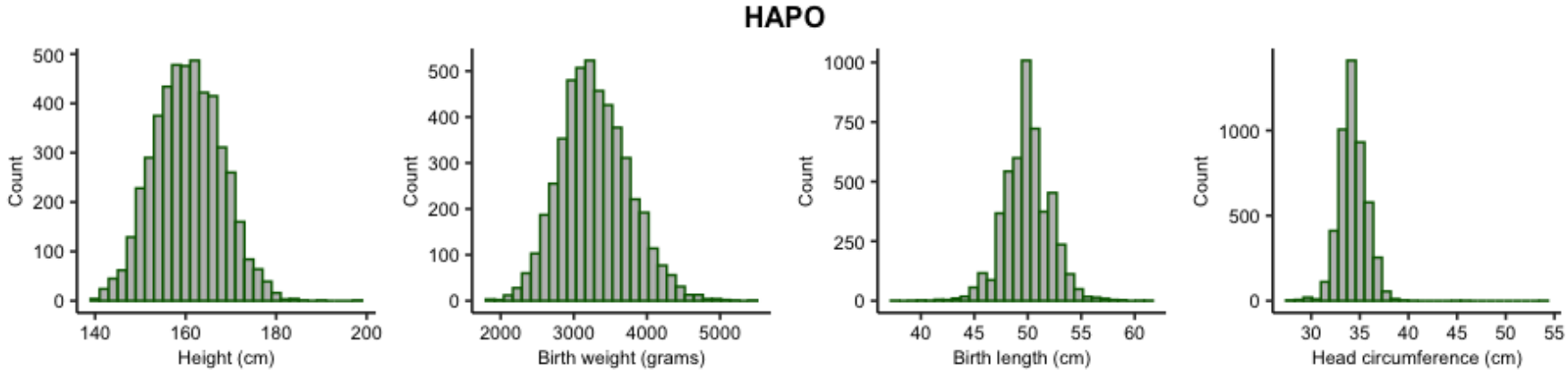

Figure 1.2 Histogram showing distribution of key variables - height, birth weight, birth length and head circumference in the **HAPO** study

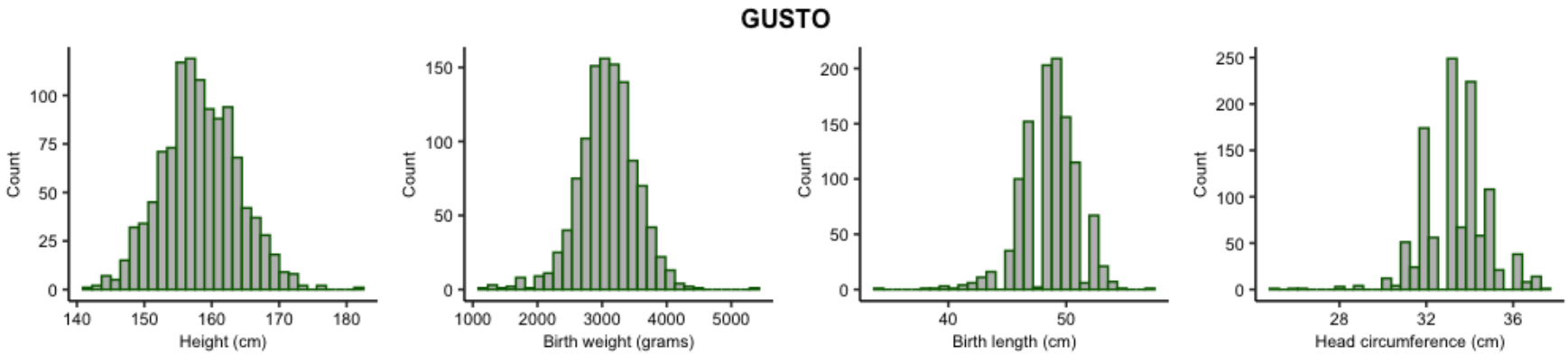

Figure 1.3 Histogram showing distribution of key variables - height, birth weight, birth length and head circumference in the **GUSTO** study

Table 1.1 Distribution of key variables - height, birth weight, birth length and head circumference in the **Omega, HAPO and GUSTO** studies.

Study population	N	Height (cm)			Birth weight (g)			Birth length (cm)			Head circumference (cm)		
		Mean	SD[a]	Median (Min, Max)	Mean	SD[a]	Median (Min, Max)	Mean	SD[a]	Median (Min, Max)	Mean	SD[a]	Median (Min, Max)
Omega	3,889	168	7.67	168 (142, 199)	3,430	561	3450 (578. 5810)	50.60	3.43	51.0 (16.0, 60.0)	34.70	2.23	35.0 (17.0, 56.0)
HAPO [b]	4,813	161	7.51	160 (140, 198)	3,290	470	3260 (1820, 5410)	50.00	2.17	50.10 (37.3, 61.0)	34.20	1.45	34.0 (28.0, 54.10)
GUSTO [c]	1,119	158	5.64	158 (142, 182)	3,080	448	3090 (1230, 5430)	48.60	2.33	49.0 (34.0, 57.0)	33.30	1.45	33.0 (25.0, 37.5)

[a] SD: Standard Deviation
[b] HAPO: Hyperglycemia, and Adverse Pregnancy Outcome
[c] GUSTO: Growing Up in Singapore Towards healthy Outcomes

Table 1.2 Selected characteristics of **Omega** study participants enrolled at Swedish Medical Center and Tacoma General Hospital in Washington State between1996 and 2008 by height quintiles

Characteristics [a]	First quintile[b] (N=778)	Second quintile[c] (N=778)	Third quintile[d] (N=777)	Fourth quintile[e] (N=778)	Last quintile[f] (N=778)	Overall (N=3889)
Mother						
Race/ethnicity						
White	545 (70.1%)	658 (84.6%)	688 (88.5%)	697 (89.6%)	731 (94.0%)	3319 (85.3%)
African-American	18 (2.3%)	14 (1.8%)	10 (1.3%)	17 (2.2%)	10 (1.3%)	69 (1.8%)
Asian	153 (19.7%)	66 (8.5%)	43 (5.5%)	24 (3.1%)	14 (1.8%)	300 (7.7%)
Hispanic	62 (8.0%)	40 (5.1%)	36 (4.6%)	40 (5.1%)	23 (3.0%)	201 (5.2%)
Age (years)	32.1 (4.77)	32.7 (4.52)	33.0 (4.34)	33.0 (4.36)	33.0 (4.32)	32.8 (4.47)
Age ≥ 35 years	249 (32.0%)	269 (34.6%)	280 (36.0%)	286 (36.8%)	281 (36.1%)	1365 (35.1%)
Married	81 (10.4%)	64 (8.2%)	63 (8.1%)	62 (8.0%)	69 (8.9%)	339 (8.7%)
Nulliparous [g]	465 (59.8%)	468 (60.2%)	496 (63.8%)	484 (62.2%)	481 (61.8%)	2394 (61.6%)
Post high school education[h]	665 (85.5%)	690 (88.7%)	721 (92.8%)	723 (92.9%)	734 (94.3%)	3533 (90.8%)
Smoked during pregnancy[i]	117 (15.0%)	173 (22.2%)	152 (19.6%)	147 (18.9%)	185 (23.8%)	774 (19.9%)
Intake of any alcohol during pregnancy[j]	68 (8.7%)	66 (8.5%)	79 (10.2%)	81 (10.4%)	65 (8.4%)	359 (9.2%)
Pre-pregnancy weight (kg)	59.4 (12.0)	63.7 (12.4)	65.2 (12.0)	68.2 (13.4)	73.3 (14.2)	65.9 (13.6)
Pre-pregnancy body mass index (kg/m^2)	24.0 (4.88)	23.8 (4.64)	23.2 (4.26)	23.2 (4.55)	22.9 (4.23)	23.4 (4.53)
Pre-pregnancy body mass index category (kg/m^2)						
Underweight (<18.5)	26 (3.3%)	28 (3.6%)	30 (3.9%)	40 (5.1%)	44 (5.7%)	168 (4.3%)
Normal (18.5–24.9)	551 (70.8%)	553 (71.1%)	560 (72.1%)	558 (71.7%)	555 (71.3%)	2777 (71.4%)
Overweight (25–29.9)	116 (14.9%)	130 (16.7%)	132 (17.0%)	126 (16.2%)	142 (18.3%)	646 (16.6%)
Obesity (≥ 30)	85 (10.9%)	67 (8.6%)	55 (7.1%)	54 (6.9%)	37 (4.8%)	298 (7.7%)
Gestational age at delivery (weeks) [k]	38.7 (2.68)	38.7 (1.96)	38.9 (1.68)	38.8 (1.99)	39.0 (1.97)	38.8 (2.09)
Gestational diabetes[l]	72 (9.3%)	35 (4.5%)	28 (3.6%)	33 (4.2%)	27 (3.5%)	195 (5.0%)
Pre-eclampsia[m]	14 (1.8%)	24 (3.1%)	12 (1.5%)	16 (2.1%)	14 (1.8%)	80 (2.1%)
Newborn						
Male infant [n]	409 (52.6%)	396 (50.9%)	378 (48.6%)	408 (52.4%)	402 (51.7%)	1993 (51.2%)
Preterm (<37 weeks)	91 (11.7%)	88 (11.3%)	60 (7.7%)	67 (8.6%)	55 (7.1%)	361 (9.3%)

Low birth weight	56 (7.2%)	57 (7.3%)	33 (4.3%)	32 (4.1%)	32 (4.1%)	210 (5.4%)

[a] Values are N (%) or mean (Standard Deviation)
[b] First quintile, height <161.40 cm.
[c] Second quintile, height ≥ 161.40 cm to <165.48 cm.
[d] Third quintile, height ≥ 165.48 cm to <169.61 cm.
[e] Fourth quintile, height ≥ 169.61 cm to >174.02 cm.
[f] Fifth quintile, height ≥ 174.02 cm
[g] Information on parity missing for 1 subject. For each quintile: 1 (quintile 1) was missing.
[h] Educational status missing for 234 subjects. For each quintile: 83 (quintile 1), 61 (quintile 2), 33 (quintile 3), 38 (quintile 4), 19 (quintile 5)
[i] Smoking status missing for 250 subjects. For each quintile: 86 (quintile 1), 65 (quintile 2), 37 (quintile 3), 41 (quintile 4), 21 (quintile 5)
[j] Alcohol intake missing for 56 subjects. For each quintile: 14 (quintile 1), 15 (quintile 2), 9 (quintile 3), 4 (quintile 4), 14 (quintile 5)
[k] Gestational age at delivery missing for 2 subjects. For each quintile: 1 (quintile 3), 1 (quintile 4)
[l] Gestational diabetes missing for 2 subjects. For each quintile: 2 (quintile 4)
[m] Preeclampsia missing for 1 subject. For each quintile: 1 (quintile 4)
[n] Infant sex missing for 2 subjects. For each quintile: 1 (quintile 1), 1 (quintile 5)

Table 1.3 Selected characteristics of **HAPO** study participants enrolled at field centers between July 2000 and April 2006 by height quintiles

Characteristics [a]	First quintile [b] (N=928)	Second quintile [c] (N=984)	Third quintile [d] (N=909)	Fourth quintile [e] (N=936)	Last quintile [f] (N=1056)	Overall (N=4813)
Mother						
Race/ethnicity						
White	74 (8.0%)	215 (21.8%)	282 (31.0%)	374 (40.0%)	499 (47.3%)	1444 (30.0%)
African-American	91 (9.8%)	188 (19.1%)	261 (28.7%)	300 (32.1%)	448 (42.4%)	1288 (26.8%)
Hispanic	152 (16.4%)	188 (19.1%)	229 (25.2%)	206 (22.0%)	96 (9.1%)	871 (18.1%)
Asian	611 (65.8%)	393 (39.9%)	137 (15.1%)	56 (6.0%)	13 (1.2%)	1210 (25.1%)
Age (years)	28.3 (5.64)	28.1 (5.68)	28.4 (5.92)	28.5 (5.90)	28.7 (6.20)	28.4 (5.88)
Age ≥ 35 years	121 (13.0%)	124 (12.6%)	128 (14.1%)	139 (14.9%)	188 (17.8%)	700 (14.5%)
Nulliparous [g]	497 (53.6%)	610 (62.0%)	623 (68.5%)	702 (75.0%)	841 (79.6%)	3273 (68.0%)
Post high school education [h]	256 (27.6%)	435 (44.2%)	480 (52.8%)	533 (56.9%)	655 (62.0%)	2359 (49.0%)
Smoking habits						
Smoking during pregnancy	13 (1.4%)	39 (4.0%)	47 (5.2%)	59 (6.3%)	61 (5.8%)	219 (4.6%)
Number of cigarettes/days during pregnancy	1.02 (0.163)	1.05 (0.254)	1.07 (0.306)	1.08 (0.319)	1.07 (0.304)	1.06 (0.277)
Alcohol drinking habits						
Alcohol during pregnancy	22 (2.4%)	55 (5.6%)	68 (7.5%)	84 (9.0%)	119 (11.3%)	348 (7.2%)
Number of alcoholic drinks/days during pregnancy						
<1 per day	19 (2.0%)	55 (5.6%)	67 (7.4%)	84 (9.0%)	116 (11.0%)	341 (7.1%)
1–2 per day	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	3 (0.3%)	4 (0.1%)
Illicit drug use in pregnancy	0 (0%)	3 (0.3%)	5 (0.6%)	7 (0.7%)	8 (0.8%)	23 (0.5%)
Pre-pregnancy weight (kg) [i]	58.7 (9.64)	62.5 (11.4)	64.6 (12.7)	67.4 (14.0)	70.9 (15.9)	64.8 (13.6)
Pre-pregnancy body mass index (kg/m^2) [i]	26.1 (4.18)	25.6 (4.66)	25.1 (4.97)	24.9 (5.17)	24.3 (5.32)	25.2 (4.91)
Pre-pregnancy body mass index category (kg/m^2)						

Underweight (<18.5)	10 (1.1%)	17 (1.7%)	35 (3.9%)	36 (3.8%)	82 (7.8%)	180 (3.7%)
Normal (18.5–24.9)	391 (42.1%)	437 (44.4%)	413 (45.4%)	442 (47.2%)	479 (45.4%)	2162 (44.9%)
Overweight (25–29.9)	354 (38.1%)	299 (30.4%)	249 (27.4%)	214 (22.9%)	202 (19.1%)	1318 (27.4%)
Obesity (≥ 30)	128 (13.8%)	126 (12.8%)	106 (11.7%)	120 (12.8%)	102 (9.7%)	582 (12.1%)
Gestational age at delivery (weeks)	39.5 (1.23)	39.6 (1.22)	39.7 (1.18)	39.8 (1.24)	39.9 (1.22)	39.7 (1.23)
Blood glucose level at OGTT (mg/dl)						
Fasting	81.0 (7.39)	81.1 (6.89)	81.9 (7.51)	81.9 (7.41)	81.4 (7.15)	81.5 (7.27)
One hour	145 (32.9)	137 (31.9)	133 (31.1)	131 (30.7)	127 (28.8)	134 (31.6)
Two hour	119 (25.7)	115 (23.8)	110 (22.5)	110 (22.3)	106 (21.3)	112 (23.5)
Gestational diabetes[j]	204 (22.0%)	163 (16.6%)	129 (14.2%)	122 (13.0%)	101 (9.6%)	719 (14.9%)
Pre-eclampsia[k]	15 (1.6%)	27 (2.7%)	40 (4.4%)	37 (4.0%)	39 (3.7%)	158 (3.3%)
Newborn						
Male infant	457 (49.2%)	494 (50.2%)	453 (49.8%)	476 (50.9%)	548 (51.9%)	2428 (50.4%)
Preterm (<37 weeks)	0 (0%)	0 (0%)	1 (0.1%)	2 (0.2%)	3 (0.3%)	6 (0.1%)
Low birth weight	39 (4.2%)	38 (3.9%)	31 (3.4%)	21 (2.2%)	29 (2.7%)	158 (3.3%)

[a] Values are N (%) or mean (Standard Deviation)
[b] First quintile, height <154.05 cm.
[c] Second quintile, height ≥ 154.05 cm to <158.75 cm.
[d] Third quintile, height ≥ 158.75 cm to <162.56 cm.
[e] Fourth quintile, height ≥ 162.56 cm to <167.00 cm.
[f] Fifth quintile, height ≥ 167.0 cm
[g] Information on parity missing for 577 subjects. For each quintile: 258 (quintile 1), 169 (quintile 2), 80 (quintile 3), 45 (quintile 4), 25 (quintile 5)
[h] Educational status missing for 235 subjects. For each quintile: 89 (quintile 1), 42 (quintile 2), 37 (quintile 3), 36 (quintile 4), 31 (quintile 5)
[i] Pre-pregnancy weight and BMI missing for 571 subjects. For each quintile: 45 (quintile 1), 105 (quintile 2), 106 (quintile 3), 124 (quintile 4), 191 (quintile 5)
[j] Diagnosis of gestational diabetes was made post hoc based on IADPSG criteria (1 or more values exceeding the thresholds: fasting ≥92 mg/dl, one-hour ≥180 mg/dl, and two-hour ≥153 mg/dl)
[k] Preeclampsia includes cases of both preeclampsia and severe preeclampsia.

Table 1.4 Selected characteristics of **GUSTO** study participants enrolled at National University Hospital and KK Women's and Children's Hospital in Singapore between 2009 and 2011 by height quintiles

Characteristics [a]	First quintile [b] (N=224)	Second quintile [c] (N=222)	Third quintile [d] (N=224)	Fourth quintile [e] (N=217)	Last quintile [f] (N=232)	Overall (N=1119)
Mother						
Race/ethnicity						
Chinese	109 (48.7%)	107 (48.2%)	134 (59.8%)	125 (57.6%)	163 (70.3%)	638 (57.0%)
Indian	47 (21.0%)	51 (23.0%)	35 (15.6%)	37 (17.1%)	34 (14.7%)	204 (18.2%)
Malay	68 (30.4%)	64 (28.8%)	55 (24.6%)	55 (25.3%)	35 (15.1%)	277 (24.8%)
Age (years)	30.4 (5.18)	30.5 (5.33)	31.0 (5.12)	30.5 (4.76)	30.5 (4.92)	30.6 (5.06)
Age ≥ 35 years	45 (20.1%)	44 (19.8%)	57 (25.4%)	34 (15.7%)	42 (18.1%)	222 (19.8%)
Nulliparous g	45 (20.1%)	44 (19.8%)	57 (25.4%)	34 (15.7%)	42 (18.1%)	222 (19.8%)
Post-secondary education [h]	117 (52.2%)	129 (58.1%)	129 (57.6%)	131 (60.4%)	165 (71.1%)	671 (60.0%)
Smoking during pregnancy [i]	12 (5.4%)	14 (6.3%)	6 (2.7%)	16 (7.4%)	9 (3.9%)	57 (5.1%)
Alcohol during pregnancy	4 (1.8%)	5 (2.3%)	4 (1.8%)	7 (3.2%)	4 (1.7%)	24 (2.1%)
Pre-pregnancy weight (kg) [j]	52.2 (10.6)	54.8 (10.3)	55.9 (10.3)	59.5 (12.2)	60.8 (11.0)	56.6 (11.3)
Pre-pregnancy body mass index (kg/m^2) j	23.0 (4.70)	22.7 (4.28)	22.4 (4.12)	22.9 (4.64)	22.0 (3.89)	22.6 (4.34)
Pre-pregnancy body mass index category (kg/m^2) [j]						
Underweight (<18.5)	21 (9.4%)	23 (10.4%)	26 (11.6%)	23 (10.6%)	26 (11.2%)	119 (10.6%)
Normal (18.5–24.9)	128 (57.1%)	131 (59.0%)	139 (62.1%)	128 (59.0%)	139 (59.9%)	665 (59.4%)
Overweight (25–29.9)	47 (21.0%)	42 (18.9%)	34 (15.2%)	33 (15.2%)	30 (12.9%)	186 (16.6%)
Obesity (≥ 30)	16 (7.1%)	14 (6.3%)	11 (4.9%)	19 (8.8%)	11 (4.7%)	71 (6.3%)
Pre-pregnancy body mass index category (kg/m^2) using Asia-Pacific criteria [k]						
Underweight (<18.5)	21 (9.4%)	23 (10.4%)	26 (11.6%)	23 (10.6%)	26 (11.2%)	119 (10.6%)
Normal (18.5-22.9)	106 (47.3%)	101 (45.5%)	109 (48.7%)	103 (47.5%)	114 (49.1%)	533 (47.6%)
Overweight (23-24.9)	22 (9.8%)	30 (13.5%)	30 (13.4%)	25 (11.5%)	25 (10.8%)	132 (11.8%)
Obesity (≥25)	63 (28.1%)	56 (25.2%)	45 (20.1%)	52 (24.0%)	41 (17.7%)	257 (23.0%)
Gestational age at delivery (weeks)	38.6 (1.59)	38.8 (1.32)	38.8 (1.25)	38.7 (1.55)	38.9 (1.43)	38.8 (1.44)
Gestational diabetes [l]	48 (21.4%)	39 (17.6%)	37 (16.5%)	35 (16.1%)	39 (16.8%)	198 (17.7%)
Pre-eclampsia [m]	8 (3.6%)	6 (2.7%)	5 (2.2%)	7 (3.2%)	7 (3.0%)	33 (2.9%)

Newborn						
Male infant	115 (51.3%)	127 (57.2%)	109 (48.7%)	116 (53.5%)	120 (51.7%)	587 (52.5%)
Preterm (<37 weeks)	20 (8.9%)	14 (6.3%)	15 (6.7%)	13 (6.0%)	19 (8.2%)	81 (7.2%)
Low birth weight	56 (7.2%)	57 (7.3%)	33 (4.3%)	32 (4.1%)	32 (4.1%)	210 (5.4%)

[a] Values are N (%) or mean (Standard Deviation)
[b] First quintile, height < 153.53 cm.
[c] Second quintile, height ≥ 153.53 cm to <156.55 cm.
[d] Third quintile, height ≥ 156.55 cm to <159.50 cm.
[e] Fourth quintile, height ≥ 159.50 cm to <163.00 cm.
[f] Fifth quintile, height ≥ 163.00 cm
[g] Information on parity missing for 63 subjects. For each quintile: 1 (quintile 2)
[h] Educational status missing for 1 subject. For each quintile: 3 (quintile 1), 3 (quintile 2), 1 (quintile 3), 5 (quintile 4), 2 (quintile 5)
[i] Smoking status missing for 39 subjects. For each quintile: 4 (quintile 1), 11 (quintile 2), 5 (quintile 3), 10 (quintile 4), 9 (quintile 5)
[j] Pre-pregnancy weight and BMI missing for 78 subjects. For each quintile: 12 (quintile 1), 12 (quintile 2), 14 (quintile 3), 14 (quintile 4), 26 (quintile 5)
[k] Using the Asia-Pacific cut offs Reference (67)
[l] Gestational diabetes status missing for 39 subjects. For each quintile: 4 (quintile 1), 11 (quintile 2), 5 (quintile 3), 10 (quintile 4), 9 (quintile 5)
[m] Preeclampsia includes cases of both preeclampsia and severe preeclampsia.

Table 1.5 Associations of maternal height with **infant birth weight** among Omega, HAPO and GUSTO study participants

	Unadjusted model [a]			Partially adjusted model [b]			Fully adjusted model [c]		
	ß	95% CI	p-value	ß	95% CI	p-value	ß	95% CI	p-value
Omega study									
Linear height (5 cm increase) [d]	64.49	(53.17, 75.81)	**<0.001**	34.82	(25.11, 44.53)	**<0.001**	34.93	(25.17, 44.69)	<**0.001**
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-155.80	(-200.77, -110.81)	**<0.001**	-97.71	(-134.36, -61.06)	**<0.001**	-98.03	(-134.84, -61.23)	**<0.001**
Tall height	125.10	(80.17, 170.13)	**<0.001**	54.99	(19.88, 90.10)	**<0.01**	55.15	(20.00, 90.30)	**<0.01**
Cubic spline [f]									0.60
Spline 1	16.02	(-21.53, 53.58)	0.40	-15.76	(-47.24, 15.72)	0.33	-15.81	(-47.29, 15.68)	0.33
Spline 2	-52.09	(-284.74, 180.57)	0.66	124.94	(-66.85, 316.74)	0.20	125.53	(-66.34, 317.40)	0.20
Spline 3	454.42	(-730.04, 1638.88)	0.45	-455.12	(-1412.87, 502.64)	0.35	-457.91	(-1416.00, 500.19)	0.35
Spline 4	-1306.39	(-3775.01, 1162.22)	0.30	369.85	(-1577.44, 2317.15)	0.71	373.86	(-1573.90, 2321.62)	0.71
Spline 5	1658.40	(-1310.68, 4627.49)	0.27	129.15	(-2168.98, 2427.29)	0.91	126.38	(-2172.13, 2424.89)	0.91
Spline 6	-1031.20	(-3113.70, 1051.30)	0.33	-282.59	(-1875.42, 1310.24)	0.73	-281.03	(-1874.10, 1312.04)	0.73
HAPO study									
Linear height (5 cm increase) [d]	81.97	(73.44, 90.5)	**<0.001**	43.65	(32.09, 55.22)	**<0.001**	46.26	(34.69, 57.84)	**<0.001**
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-176.38	(-210.3, -142.46)	**<0.001**	-176.38	(-210.3, -142.46)	**<0.001**	-70.83	(-111.87, -29.78)	**<0.001**
Tall height	158.43	(126.09, 190.76)	**<0.001**	158.43	(126.09, 190.76)	**<0.001**	99.27	(64.65, 133.88)	**<0.001**
Cubic spline [f]									0.61

Spline 1	11.85	(-19.49, 43.19)	0.46	-1.55	(-38.73, 35.64)	0.94	-1.7	(-38.77, 35.36)	0.93
Spline 2	84.59	(-344.54, 513.73)	0.7	161.93	(-333.4, 657.26)	0.52	176.92	(-316.81, 670.66)	0.48
Spline 3	-302.54	(-1792.08, 1187)	0.69	-714.17	(-2396.52, 968.18)	0.41	-770.95	(-2447.94, 906.03)	0.37
Spline 4	487.52	(-1813.15, 2788.19)	0.68	1500.46	(-1003.42, 4004.35)	0.24	1586.8	(-909.11, 4082.7)	0.21
Spline 5	-539.92	(-2691.76, 1611.93)	0.62	-1568.32	(-3830.52, 693.88)	0.17	-1642.08	(-3897.04, 612.89)	0.15
Spline 6	403.26	(-1004.9, 1811.43)	0.57	761.95	(-682.63, 2206.53)	0.3	811.34	(-628.64, 2251.31)	0.27
GUSTO study									
Linear height (5 cm increase) [d]	49.11	(26.00, 72.22)	**0.00**	22.35	(1.28, 43.42)	**0.04**	23.82	(2.44, 44.81)	**0.03**
Categorical height [e]									0.05
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-110.07	(-177.39, -42.75)	**0.00**	-51.70	(-108.04, 4.64)	0.07	-54.89	(-111.49, 1.70)	0.06
Tall height	64.72	(-1.73, 131.17)	**0.06**	31.59	(-26.17, 89.35)	0.28	32.24	(-25.52, 90.01)	0.27
Cubic spline [f]									0.25
Spline 1	0.28	(-80.62, 81.19)	0.99	-21.63	(-86.90, 43.64)	0.52	-22.66	(-87.95, 42.63)	0.50
Spline 2	-12.35	(-753.94, 729.24)	0.97	106.05	(-496.12, 708.22)	0.73	118.86	(-483.68, 721.41)	0.70
Spline 3	512.65	(-2103.71, 3129.02)	0.70	144.79	(-1990.36, 2279.93)	0.89	101.31	(-2035.05, 2237.66)	0.93
Spline 4	-2851.38	(-7874.97, 2172.20)	0.27	-2160.87	(-6298.39, 1976.64)	0.31	-2089	(-6228.12, 2050.11)	0.32
Spline 5	4612.35	(-922.17, 10146.86)	0.10	3823.54	(-769.43, 8416.52)	0.10	3747.88	(-846.65, 8342.41)	0.11
Spline 6	-3170.26	(-6567.61, 227.10)	0.07	-2863.02	(-5702.68, -23.36)	0.05	-2805.64	(-5646.89, 35.60)	0.05

[a] Unadjusted model included term (s) for height, measured in cm and birth weight, measured in grams.

[b] Partially adjusted models adjust for continuous variables -maternal age (years), pre-pregnancy weight (kg), gestational age (weeks) and binary variables- post-high school education married marital status, nulliparity, smoking during pregnancy, alcohol use during pregnancy, pregnancy complication (defined as the presence of gestational diabetes or preeclampsia), and male infant. Omega study additionally adjusts for marital status (binary) and HAPO study additionally adjusts for study site (grouped categorical variable for six study sites).

[c] Fully adjusted models adjust for all the variables in partially adjusted model but additionally adjusts for pregnancy complication (binary)
[d] ß for linear height represents the change in infant birth weight in gram per 5 cm greater height of the mother.
P-value for the linear height represents Wald p-value for the continuous term ß1 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1 *X_{height} + ß *$ Covariates, where Y = birth weight in grams.
[e] Definitions of short and tall height were cohort specific. p-value for categorical height represents Wald p-value for terms ß1 and ß2 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*X_{height\text{-}short} + ß2*X_{height\text{-}tall} + ß *$ Covariates, where Y = birth weight in grams. ß1 =0 tests whether the mean birth weight among short women is significantly different from the mean birth weight of babies among women of average height. ß2 =0 tests whether the mean birth weight among tall women is significantly different from the mean birth weight of babies among women of average height.
[f] Nodes for restricted cubic spline model were placed at 5th, 25th, 50th, 75th, and 95th percentiles of height for each cohort. Overall p-value for cubic spline models represent the p-value from likelihood ratio test comparing fully adjusted regression models with linear height to fully adjusted regression models with height modelled using cubic splines.

Table 1.6 Associations of maternal height with **infant birth length** among Omega, HAPO and GUSTO study participants

	Unadjusted model [a]			Partially adjusted model [b]			Fully adjusted model [c]		
	ß	95% CI	p-value	ß	95% CI	p-value	ß	95% CI	p-value
Omega study									
Linear height (5 cm increase) [d]	0.34	(0.27, 0.41)	**0.00**	0.23	(0.16, 0.29)	**0.00**	0.23	(0.16, 0.30)	**0.00**
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.71	(-0.98, -0.43)	**0.00**	-0.43	(-0.69, -0.18)	**0.00**	-0.44	(-0.69, -0.19)	**0.00**
Tall height	0.65	(0.37, 0.92)	**0.00**	0.39	(0.15, 0.63)	**0.00**	0.40	(0.16, 0.64)	**0.00**
Cubic spline [f]									0.78
Spline 1	0.23	(0, 0.46)	0.05	0.12	(-0.1, 0.33)	0.29	0.12	(-0.1, 0.33)	0.29
Spline 2	-0.88	(-2.31, 0.55)	0.23	-0.24	(-1.55, 1.07)	0.72	-0.23	(-1.55, 1.08)	0.73
Spline 3	3.19	(-4.09, 10.46)	0.39	-0.21	(-6.77, 6.35)	0.95	-0.25	(-6.81, 6.31)	0.94
Spline 4	-2.62	(-17.78, 12.55)	0.74	4.11	(-9.23, 17.45)	0.55	4.16	(-9.18, 17.51)	0.54
Spline 5	-0.78	(-19.02, 17.47)	0.93	-7.6	(-23.34, 8.14)	0.34	-7.64	(-23.39, 8.1)	0.34
Spline 6	1.53	(-11.27, 14.32)	0.82	5.46	(-5.45, 16.37)	0.33	5.48	(-5.43, 16.39)	0.33
HAPO study									
Linear height (5 cm increase) [d]	0.29	(0.25, 0.33)	**0.00**	0.25	(0.2, 0.3)	**0.00**	0.26	(0.20, 0.31)	**0.00**
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.66	(-0.81, -0.5)	**0.00**	-0.66	(-0.81, -0.5)	**0.00**	-0.44	(-0.63, -0.24)	**0.00**
Tall height	0.56	(0.41, 0.71)	**0.00**	0.56	(0.41, 0.71)	**0.00**	0.53	(0.36, 0.69)	**0.00**
Cubic spline [f]									0.39
Spline 1	0.06	(-0.09, 0.21)	0.43	0.03	(-0.15, 0.2)	0.74	0.03	(-0.15, 0.2)	0.74

Spline 2	0.31	(-1.7, 2.32)	0.76	0.47	(-1.86, 2.79)	0.69	0.51	(-1.82, 2.83)	0.67
Spline 3	-1.27	(-8.24, 5.71)	0.72	-1.94	(-9.84, 5.96)	0.63	-2.09	(-9.99, 5.8)	0.6
Spline 4	0.74	(-10.03, 11.51)	0.89	2.43	(-9.33, 14.19)	0.69	2.66	(-9.09, 14.41)	0.66
Spline 5	2.42	(-7.66, 12.49)	0.64	0.51	(-10.11, 11.14)	0.92	0.31	(-10.3, 10.93)	0.95
Spline 6	-4.15	(-10.74, 2.44)	0.22	-3.47	(-10.26, 3.31)	0.32	-3.34	(-10.12, 3.44)	0.33
GUSTO study									
Linear height (5 cm increase) [d]	0.29	(0.17, 0.41)	**0.00**	0.16	(0.05, 0.28)	**0.00**	0.17	(0.06, 0.29)	**0.00**
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.45	(-0.80, -0.10)	**0.01**	-0.20	(-0.50, 0.10)	0.19	-0.22	(-0.53, 0.08)	0.15
Tall height	0.62	(0.27, 0.96)	**0.00**	0.43	(0.12, 0.74)	**0.01**	0.43	(0.12, 0.74)	**0.01**
Cubic spline [f]									0.25
Spline 1	0.20	(-0.22, 0.62)	0.35	0.06	(-0.29, 0.41)	0.74	0.05	(-0.3, 0.4)	0.76
Spline 2	-1.74	(-5.58, 2.1)	0.38	-0.88	(-4.10, 2.34)	0.59	-0.80	(-4.02, 2.42)	0.63
Spline 3	7.35	(-6.21, 20.9)	0.29	4.78	(-6.63, 16.20)	0.41	4.51	(-6.91, 15.93)	0.44
Spline 4	-18.46	(-44.49, 7.56)	0.16	-14.59	(-36.71, 7.53)	0.20	-14.14	(-36.27, 7.98)	0.21
Spline 5	24.76	(-3.91, 53.43)	0.09	20.84	(-3.71, 45.4)	0.10	20.37	(-4.19, 44.94)	0.10
Spline 6	-18.38	(-35.97, -0.78)	0.04	-16.20	(-31.38, -1.02)	0.04	-15.84	(-31.03, -0.66)	0.04

[a] Unadjusted model included term (s) for height, measured in cm and birth length, measured in cm.

[b] Partially adjusted models adjust for continuous variables -maternal age (years), pre-pregnancy weight (kg), gestational age (weeks) and binary variables- post-high school education married marital status, nulliparity, smoking during pregnancy, alcohol use during pregnancy, pregnancy complication (defined as the presence of gestational diabetes or preeclampsia), and male infant. Omega study additionally adjusts for marital status (binary) and HAPO study additionally adjusts for study site (grouped categorical variable for six study sites).

[c] Fully adjusted models adjust for all the variables in partially adjusted model but additionally adjusts for pregnancy complication (binary)

[d] **ß** for linear height represents the change in infant birth length in cm per 5 cm greater height of the mother

P-value for the linear height represents Wald p-value for the continuous term ß1 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*X_{height} + ß *$ Covariates, where Y = birth length in cm.

[e] Definitions of short and tall height were cohort specific. p-value for categorical height represents Wald p-value for terms ß1 and ß2 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*X_{height\text{-}short} + ß2*X_{height\text{-}tall} + ß *$ Covariates, where Y = birth length in cm. ß1 =0 tests whether the mean birth length among short women is significantly different from the mean birth length of babies among women of average height. ß2 =0 tests whether the mean birth length among tall women is significantly different from the mean birth length of babies among women of average height.

[f] Nodes for restricted cubic spline model were placed at 5th, 25th, 50th, 75th, and 95th percentiles of height for each cohort. Overall p-value for cubic spline models represent the p-value from likelihood ratio test comparing fully adjusted regression models with linear height to fully adjusted regression models with height modelled using cubic splines.

Table 1.7 Associations of maternal height with **infant head circumference** among Omega, HAPO and GUSTO study participants

	Unadjusted model [a]			Partially adjusted model [b]			Fully adjusted model [c]		
	ß	95% CI	p-value	ß	95% CI	p-value	ß	95% CI	p-value
Omega study									
Linear height (5 cm increase) [d]	0.14	(0.1, 0.19)	**0.00**	0.05	(0.01, 0.1)	**0.02**	0.05	(0.01, 0.1)	**0.03**
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.34	(-0.52, -0.16)	**0.00**	-0.15	(-0.33, 0.02)	0.09	-0.15	(-0.32, 0.03)	0.11
Tall height	0.19	(0.01, 0.37)	**0.04**	-0.01	(-0.18, 0.16)	0.87	-0.02	(-0.19, 0.15)	0.84
Cubic spline [f]									0.24
Spline 1	0.2	(0.05, 0.35)	0.01	0.15	(0, 0.3)	0.05	0.15	(0, 0.3)	0.05
Spline 2	-0.9	(-1.84, 0.03)	0.06	-0.68	(-1.6, 0.25)	0.15	-0.68	(-1.61, 0.24)	0.15
Spline 3	3.91	(-0.83, 8.66)	0.11	2.62	(-2, 7.23)	0.27	2.65	(-1.97, 7.27)	0.26
Spline 4	-6.43	(-16.32, 3.46)	0.20	-4.07	(-13.46, 5.31)	0.40	-4.13	(-13.51, 5.26)	0.39
Spline 5	5.68	(-6.21, 17.58)	0.35	4.09	(-6.99, 15.17)	0.47	4.13	(-6.95, 15.21)	0.47
Spline 6	-2.52	(-10.86, 5.83)	0.55	-2.32	(-10, 5.36)	0.55	-2.34	(-10.02, 5.34)	0.55
HAPO study									
Linear height (5 cm increase) [d]	0.15	(0.12, 0.18)	**0.00**	0.05	(0.02, 0.09)	**<0.01**	0.06	(0.02, 0.09)	**<0.01**
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.3	(-0.4, -0.19)	**0.00**	-0.3	(-0.4, -0.19)	**0.00**	0	(-0.13, 0.13)	0.96
Tall height	0.29	(0.19, 0.39)	**0.00**	0.29	(0.19, 0.39)	**0.00**	0.15	(0.04, 0.27)	**0.01**
Cubic spline [f]									0.28
Spline 1	0.07	(-0.03, 0.17)	0.15	0.09	(-0.03, 0.21)	0.13	0.09	(-0.03, 0.21)	0.13

Spline 2	-0.68	(-2.04, 0.68)	0.33	-1.17	(-2.74, 0.41)	0.15	-1.15	(-2.72, 0.43)	0.15
Spline 3	2.35	(-2.37, 7.06)	0.33	3.46	(-1.88, 8.81)	0.2	3.39	(-1.95, 8.73)	0.21
Spline 4	-2.74	(-10.03, 4.54)	0.46	-2.82	(-10.78, 5.13)	0.49	-2.71	(-10.66, 5.24)	0.5
Spline 5	0.72	(-6.09, 7.53)	0.84	-0.06	(-7.24, 7.13)	0.99	-0.15	(-7.34, 7.03)	0.97
Spline 6	0.87	(-3.59, 5.33)	0.7	0.83	(-3.76, 5.42)	0.72	0.9	(-3.69, 5.49)	0.7
GUSTO study									
Linear height (5 cm increase) [d]	0.10	(0.02, 0.17)	**<0.01**	0.02	(-0.05, 0.10)	0.55	0.03	(-0.05, 0.10)	0.49
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.21	(-0.43, 0.01)	0.06	-0.05	(-0.25, 0.15)	0.65	-0.06	(-0.26, 0.15)	0.59
Tall height	0.15	(-0.07, 0.37)	0.18	0.05	(-0.16, 0.25)	0.64	0.05	(-0.16, 0.26)	0.63
Cubic spline [f]									0.17
Spline 1	0.20	(-0.22, 0.62)	0.35	0.06	(-0.29, 0.41)	0.74	0.05	(-0.30, 0.40)	0.76
Spline 2	-1.74	(-5.58, 2.10)	0.38	-0.88	(-4.10, 2.34)	0.59	-0.80	(-4.02, 2.42)	0.63
Spline 3	7.35	(-6.21, 20.9)	0.29	4.78	(-6.63, 16.20)	0.41	4.51	(-6.91, 15.93)	0.44
Spline 4	-18.46	(-44.49, 7.56)	0.16	-14.59	(-36.71, 7.53)	0.20	-14.14	(-36.27, 7.98)	0.21
Spline 5	24.76	(-3.91, 53.43)	0.09	20.84	(-3.71, 45.4)	0.10	20.37	(-4.19, 44.94)	0.10
Spline 6	-18.38	(-35.97, -0.78)	0.04	-16.20	(-31.38, -1.02)	0.04	-15.84	(-31.03, -0.66)	0.04

[a] Unadjusted model included term (s) for height, measured in cm and head circumference, measured in cm.

[b] Partially adjusted models adjust for continuous variables -maternal age (years), pre-pregnancy weight (kg), gestational age (weeks) and binary variables- post-high school education married marital status, nulliparity, smoking during pregnancy, alcohol use during pregnancy, pregnancy complication (defined as the presence of gestational diabetes or preeclampsia), and male infant. Omega study additionally adjusts for marital status (binary) and HAPO study additionally adjusts for study site (grouped categorical variable for six study sites).

[c] Fully adjusted models adjust for all the variables in partially adjusted model but additionally adjusts for pregnancy complication (binary)

[d] **ß** for linear height represents the change in infant head circumference in cm per 5 cm greater height of the mother

P-value for the linear height represents Wald p-value for the continuous term ß1 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*X_{height} + ß *$ Covariates, where Y = head circumference in cm.

[e] Definitions of short and tall height were cohort specific. p-value for categorical height represents Wald p-value for terms ß1 and ß2 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*X_{height\text{-}short} + ß2*X_{height\text{-}tall} + ß *$ Covariates, where Y = head circumference in cm. ß1 =0 tests whether the mean head circumference among short women is significantly different from the mean head circumference of babies among women of average height. ß2 =0 tests whether the mean birth weight among tall women is significantly different from the mean birth weight of babies among women of average height.

[f] Nodes for restricted cubic spline model were placed at 5th, 25th, 50th, 75th, and 95th percentiles of height for each cohort. Overall p-value for cubic spline models represent the p-value from likelihood ratio test comparing fully adjusted regression models with linear height to fully adjusted regression models with height modelled using cubic splines.

Table 1.8 Associations of maternal height with **sex-specific birth weight Z-score** among Omega, HAPO and GUSTO study participants

	Unadjusted model [a]			Partially adjusted model [b]			Fully adjusted model [c]		
	ß	95% CI	p-value	ß	95% CI	p-value	ß	95% CI	p-value
Omega study									
Linear height (5 cm increase) [d]	0.12	(0.1, 0.14)	**0.00**	0.06	(0.05, 0.08)	**0.00**	0.06	(0.05, 0.08)	**0.00**
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.28	(-0.36, -0.2)	0	-0.18	(-0.24, -0.11)	0	-0.18	(-0.24, -0.11)	0
Tall height	0.22	(0.14, 0.3)	0	0.1	(0.04, 0.16)	0	0.1	(0.04, 0.16)	0
Cubic spline [f]									
Spline 1	0.03	(-0.03, 0.1)	0.32	-0.03	(-0.08, 0.03)	0.37	-0.03	(-0.08, 0.03)	0.36
Spline 2	-0.13	(-0.54, 0.29)	0.54	0.21	(-0.13, 0.56)	0.23	0.21	(-0.13, 0.56)	0.23
Spline 3	1.01	(-1.1, 3.12)	0.35	-0.75	(-2.47, 0.97)	0.39	-0.76	(-2.48, 0.96)	0.39
Spline 4	-2.83	(-7.23, 1.56)	0.21	0.55	(-2.95, 4.04)	0.76	0.55	(-2.94, 4.05)	0.76
Spline 5	3.63	(-1.66, 8.92)	0.18	0.35	(-3.78, 4.48)	0.87	0.34	(-3.78, 4.47)	0.87
Spline 6	-2.27	(-5.98, 1.44)	0.23	-0.57	(-3.43, 2.29)	0.7	-0.56	(-3.42, 2.3)	0.7
HAPO study									
Linear height (5 cm increase) [d]	0.17	(0.16, 0.19)	0	0.09	(0.07, 0.12)	0	0.1	(0.07, 0.12)	0
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.38	(-0.45, -0.3)	0	-0.38	(-0.45, -0.3)	0	-0.15	(-0.24, -0.06)	0
Tall height	0.34	(0.27, 0.4)	0	0.34	(0.27, 0.4)	0	0.21	(0.14, 0.29)	0
Cubic spline [f]									
Spline 1	0.02	(-0.05, 0.09)	0.55	0	(-0.08, 0.08)	0.91	-0.01	(-0.08, 0.07)	0.9
Spline 2	0.24	(-0.68, 1.15)	0.61	0.37	(-0.69, 1.44)	0.49	0.41	(-0.65, 1.47)	0.45
Spline 3	-0.81	(-3.98, 2.36)	0.62	-1.64	(-5.25, 1.97)	0.37	-1.76	(-5.36, 1.84)	0.34
Spline 4	1.19	(-3.71, 6.08)	0.63	3.42	(-1.95, 8.8)	0.21	3.61	(-1.75, 8.97)	0.19

Spline 5	-1.24	(-5.82, 3.34)	0.6	-3.57	(-8.43, 1.29)	0.15	-3.73	(-8.57, 1.11)	0.13
Spline 6	0.95	(-2.05, 3.95)	0.53	1.76	(-1.34, 4.86)	0.27	1.86	(-1.23, 4.96)	0.24
GUSTO study									
Linear height (5 cm increase) [d]	0.11	(0.06, 0.16)	**0.00**	0.05	(0, 0.10)	**0.04**	0.05	(0.01, 0.10)	**0.03**
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.24	(-0.39, -0.09)	0.00	-0.12	(-0.24, 0.01)	0.07	-0.12	(-0.25, 0.00)	0.06
Tall height	0.15	(0.00, 0.3)	0.05	0.07	(-0.06, 0.20)	0.29	0.07	(-0.06, 0.20)	0.28
Cubic spline [f]									
Spline 1	-0.03	(-0.21, 0.15)	0.75	-0.05	(-0.20, 0.10)	0.52	-0.05	(-0.20, 0.10)	0.50
Spline 2	0.18	(-1.48, 1.83)	0.83	0.24	(-1.12, 1.60)	0.73	0.27	(-1.09, 1.63)	0.70
Spline 3	0.66	(-5.18, 6.50)	0.82	0.32	(-4.49, 5.14)	0.89	0.23	(-4.59, 5.04)	0.93
Spline 4	-6.21	(-17.42, 5.00)	0.28	-4.87	(-14.2, 4.46)	0.31	-4.71	(-14.04, 4.63)	0.32
Spline 5	10.61	(-1.74, 22.96)	0.09	8.62	(-1.74, 18.97)	0.10	8.45	(-1.91, 18.81)	0.11
Spline 6	-7.30	(-14.88, 0.29)	0.06	-6.45	(-12.86, -0.05)	0.05	-6.33	(-12.73, 0.08)	0.05

[a] Unadjusted model included term (s) for height, measured in cm and birth weight Z-score.

[b] Partially adjusted models adjust for continuous variables -maternal age (years), pre-pregnancy weight (kg), gestational age (weeks) and binary variables- post-high school education married marital status, nulliparity, smoking during pregnancy, alcohol use during pregnancy, pregnancy complication (defined as the presence of gestational diabetes or preeclampsia), and male infant. Omega study additionally adjusts for marital status (binary) and HAPO study additionally adjusts for study site (grouped categorical variable for six study sites).

[c] Fully adjusted models adjust for all the variables in partially adjusted model but additionally adjusts for pregnancy complication (binary)

[d] **ß** for linear height represents the change in infant birth weight in grams per 1 standard deviation greater height of the mother
P-value for the linear height represents Wald p-value for the continuous term ß1 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*X_{height} + ß *$ Covariates, where Y = sex-specific Z score for birth weight for each cohort.

[e] Definitions of short and tall height were cohort specific. p-value for categorical height represents Wald p-value for terms ß1 and ß2 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*X_{height\text{-}short} + ß2*X_{height\text{-}tall} + ß *$ Covariates, where Y = sex-specific Z score for birth weight for each cohort. ß1 =0 tests whether the change in birth weight Z score when comparing short women to average height women is 0. ß2 =0 tests whether the change in birth weight Z score when comparing tall women to average height women is 0.

[f] Nodes for restricted cubic spline model were placed at 5th, 25th, 50th, 75th, and 95th percentiles of height for each cohort.

Table 1.9 Associations of maternal height with **sex-specific birth length Z-score** among Omega, HAPO and GUSTO study participants

	Unadjusted model [a]			Partially adjusted model [b]			Fully adjusted model [c]		
	ß	95% CI	p-value	ß	95% CI	p-value	ß	95% CI	p-value
Omega study									
Linear height (5 cm increase) [d]	0.1	(0.08, 0.12)	**0.00**	0.07	(0.05, 0.09)	**0.00**	0.07	(0.05, 0.09)	**0.00**
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.21	(-0.29, -0.13)	0	-0.13	(-0.2, -0.05)	0	-0.13	(-0.2, -0.05)	0
Tall height	0.19	(0.11, 0.27)	0	0.12	(0.05, 0.19)	0	0.12	(0.05, 0.19)	0
Cubic spline [f]									
Spline 1	0.07	(0.01, 0.14)	0.03	0.04	(-0.03, 0.1)	0.25	0.04	(-0.03, 0.1)	0.26
Spline 2	-0.29	(-0.71, 0.12)	0.17	-0.08	(-0.47, 0.3)	0.67	-0.08	(-0.47, 0.3)	0.68
Spline 3	1.13	(-0.99, 3.25)	0.29	-0.01	(-1.93, 1.92)	0.99	-0.02	(-1.95, 1.91)	0.98
Spline 4	-1.24	(-5.66, 3.17)	0.58	1.14	(-2.78, 5.05)	0.57	1.16	(-2.76, 5.07)	0.56
Spline 5	0.4	(-4.91, 5.71)	0.88	-2.19	(-6.81, 2.43)	0.35	-2.2	(-6.83, 2.42)	0.35
Spline 6	0.04	(-3.69, 3.76)	0.98	1.58	(-1.62, 4.79)	0.33	1.59	(-1.61, 4.79)	0.33
HAPO study									
Linear height (5 cm increase) [d]	0.13	(0.12, 0.15)	0	0.12	(0.09, 0.14)	0	0.12	(0.09, 0.15)	0
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.3	(-0.38, -0.23)	0	-0.3	(-0.38, -0.23)	0	-0.2	(-0.29, -0.11)	0
Tall height	0.26	(0.19, 0.33)	0	0.26	(0.19, 0.33)	0	0.25	(0.17, 0.32)	0
Cubic spline [f]									
Spline 1	0.02	(-0.05, 0.09)	0.52	0.01	(-0.07, 0.09)	0.75	0.01	(-0.07, 0.09)	0.75
Spline 2	0.19	(-0.73, 1.12)	0.68	0.23	(-0.85, 1.31)	0.68	0.25	(-0.84, 1.33)	0.65
Spline 3	-0.71	(-3.93, 2.5)	0.66	-0.96	(-4.65, 2.72)	0.61	-1.03	(-4.71, 2.65)	0.58
Spline 4	0.41	(-4.55, 5.38)	0.87	1.26	(-4.22, 6.75)	0.65	1.37	(-4.1, 6.85)	0.62
Spline 5	1.12	(-3.53, 5.76)	0.64	0.09	(-4.86, 5.05)	0.97	0	(-4.95, 4.95)	1
Spline 6	-1.89	(-4.93, 1.15)	0.22	-1.54	(-4.7, 1.63)	0.34	-1.47	(-4.63, 1.69)	0.36

GUSTO study									
Linear height (5 cm increase) [d]	0.13	(0.08, 0.18)	**0.00**	0.07	(0.02, 0.12)	**0.01**	0.07	(0.02, 0.12)	**0.00**
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.19	(-0.34, -0.04)	0.01	-0.09	(-0.22, 0.05)	0.20	-0.09	(-0.22, 0.04)	0.16
Tall height	0.27	(0.12, 0.42)	0.00	0.18	(0.05, 0.32)	0.01	0.19	(0.05, 0.32)	0.01
Cubic spline [f]									
Spline 1	0.05	(-0.13, 0.24)	0.55	0.02	(-0.13, 0.17)	0.77	0.02	(-0.13, 0.17)	0.80
Spline 2	-0.52	(-2.18, 1.13)	0.53	-0.35	(-1.75, 1.05)	0.62	-0.32	(-1.71, 1.08)	0.66
Spline 3	2.60	(-3.22, 8.43)	0.38	1.97	(-2.99, 6.93)	0.44	1.86	(-3.1, 6.81)	0.46
Spline 4	-7.63	(-18.81, 3.55)	0.18	-6.14	(-15.74, 3.47)	0.21	-5.95	(-15.56, 3.66)	0.23
Spline 5	10.78	(-1.54, 23.10)	0.09	8.86	(-1.81, 19.52)	0.10	8.66	(-2.01, 19.32)	0.11
Spline 6	-8.02	(-15.58, -0.46)	0.04	-6.93	(-13.52, -0.34)	0.04	-6.78	(-13.37, -0.18)	0.04

[a] Unadjusted model included term (s) for height, measured in cm and birth length Z-score.

[b] Partially adjusted models adjust for continuous variables -maternal age (years), pre-pregnancy weight (kg), gestational age (weeks) and binary variables- post-high school education married marital status, nulliparity, smoking during pregnancy, alcohol use during pregnancy, pregnancy complication (defined as the presence of gestational diabetes or preeclampsia), and male infant. Omega study additionally adjusts for marital status (binary) and HAPO study additionally adjusts for study site (grouped categorical variable for six study sites).

[c] Fully adjusted models adjust for all the variables in partially adjusted model but additionally adjusts for pregnancy complication (binary)

[d] **ß** for linear height represents the change in infant birth length in cm per 1 standard deviation greater height of the mother

P-value for the linear height represents Wald p-value for the continuous term ß1 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*X_{height} + ß *$ Covariates, where Y = sex-specific Z score for birth length for each cohort.

[e] Definitions of short and tall height were cohort specific. p-value for categorical height represents Wald p-value for terms ß1 and ß2 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*X_{height\text{-}short} + ß2*X_{height\text{-}tall} + ß *$ Covariates, where Y = sex-specific Z score for birth length for each cohort. ß1 =0 tests whether the change in birth length Z score when comparing short women to average height women is 0. ß2 =0 tests whether the change in birth length Z score when comparing tall women to average height women is 0.

[f] Nodes for restricted cubic spline model were placed at 5th, 25th, 50th, 75th, and 95th percentiles of height for each cohort.

Table 1.10 Associations of maternal height with **sex-specific head circumference Z-score** among Omega, HAPO and GUSTO study participants

	Unadjusted model [a]			Partially adjusted model [b]			Fully adjusted model [c]		
	ß	95% CI	p-value	ß	95% CI	p-value	ß	95% CI	p-value
Omega study									
Linear height (5 cm increase) [d]	0.07	(0.05, 0.09)	0	0.03	(0, 0.05)	0.0171	0.02	(0, 0.05)	0.02226
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.16	(-0.24, -0.08)	0	-0.07	(-0.15, 0.01)	0.09	-0.07	(-0.15, 0.01)	0.11
Tall height	0.08	(0, 0.16)	0.04	0	(-0.08, 0.07)	0.92	-0.01	(-0.08, 0.07)	0.88
Cubic spline [f]									
Spline 1	0.1	(0.03, 0.16)	0.01	0.07	(0, 0.14)	0.04	0.07	(0, 0.14)	0.04
Spline 2	-0.45	(-0.87, -0.03)	0.04	-0.32	(-0.74, 0.1)	0.14	-0.32	(-0.74, 0.1)	0.13
Spline 3	2.01	(-0.12, 4.14)	0.06	1.25	(-0.84, 3.35)	0.24	1.27	(-0.82, 3.37)	0.23
Spline 4	-3.54	(-7.98, 0.9)	0.12	-2	(-6.26, 2.26)	0.36	-2.03	(-6.29, 2.23)	0.35
Spline 5	3.47	(-1.87, 8.81)	0.2	2.06	(-2.97, 7.09)	0.42	2.08	(-2.95, 7.11)	0.42
Spline 6	-1.73	(-5.48, 2.01)	0.36	-1.18	(-4.67, 2.3)	0.51	-1.19	(-4.68, 2.29)	0.5
HAPO study									
Linear height (5 cm increase) [d]	0.1	(0.09, 0.12)	0	0.04	(0.01, 0.06)	0.00357	0.04	(0.01, 0.07)	0.00196
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.2	(-0.28, -0.13)	0	-0.2	(-0.28, -0.13)	0	0	(-0.09, 0.09)	0.96
Tall height	0.2	(0.13, 0.27)	0	0.2	(0.13, 0.27)	0	0.11	(0.03, 0.19)	0.01
Cubic spline [f]									

Spline 1	0.04	(-0.02, 0.11)	0.2	0.06	(-0.02, 0.14)	0.14	0.06	(-0.02, 0.14)	0.14
Spline 2	-0.4	(-1.34, 0.53)	0.4	-0.78	(-1.88, 0.31)	0.16	-0.77	(-1.87, 0.32)	0.17
Spline 3	1.46	(-1.79, 4.71)	0.38	2.31	(-1.42, 6.03)	0.22	2.25	(-1.47, 5.97)	0.24
Spline 4	-1.8	(-6.81, 3.22)	0.48	-1.78	(-7.32, 3.76)	0.53	-1.7	(-7.24, 3.84)	0.55
Spline 5	0.48	(-4.21, 5.16)	0.84	-0.23	(-5.23, 4.78)	0.93	-0.3	(-5.3, 4.71)	0.91
Spline 6	0.67	(-2.4, 3.73)	0.67	0.69	(-2.5, 3.89)	0.67	0.74	(-2.45, 3.93)	0.65
GUSTO study									
Linear height (5 cm increase) [d]	0.07	(0.02, 0.12)	**0.01**	0.02	(-0.04, 0.07)	**0.56**	0.02	(-0.03, 0.07)	**0.51**
Categorical height [e]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	-0.14	(-0.29, 0.01)	0.07	-0.03	(-0.17, 0.11)	0.67	-0.04	(-0.18, 0.10)	0.61
Tall height	0.11	(-0.04, 0.26)	0.15	0.03	(-0.11, 0.18)	0.66	0.03	(-0.11, 0.18)	0.65
Cubic spline [f]									
Spline 1	0.02	(-0.16, 0.20)	0.82	0.00	(-0.16, 0.17)	0.96	0	(-0.16, 0.16)	0.98
Spline 2	-0.44	(-2.1, 1.22)	0.60	-0.37	(-1.87, 1.12)	0.62	-0.35	(-1.85, 1.14)	0.65
Spline 3	2.78	(-3.07, 8.64)	0.35	2.42	(-2.87, 7.72)	0.37	2.35	(-2.95, 7.65)	0.39
Spline 4	-9.81	(-21.06, 1.44)	0.09	-8.51	(-18.77, 1.75)	0.10	-8.39	(-18.65, 1.88)	0.11
Spline 5	14.3	(1.91, 26.69)	0.02	12.48	(1.09, 23.87)	0.03	12.35	(0.95, 23.74)	0.03
Spline 6	-9.46	(-17.07, -1.85)	0.01	-8.62	(-15.66, -1.57)	0.02	-8.52	(-15.56, -1.47)	0.02

[a] Unadjusted model included term (s) for height, measured in cm and head circumference Z-score.

[b] Partially adjusted models adjust for continuous variables -maternal age (years), pre-pregnancy weight (kg), gestational age (weeks) and binary variables- post-high school education married marital status, nulliparity, smoking during pregnancy, alcohol use during pregnancy, pregnancy complication (defined as the presence of gestational diabetes or preeclampsia), and male infant. Omega study additionally adjusts for marital status (binary) and HAPO study additionally adjusts for study site (grouped categorical variable for six study sites).

[c] Fully adjusted models adjust for all the variables in partially adjusted model but additionally adjusts for pregnancy complication (binary)
[d] **ß** for linear height represents the change in infant head circumference in cm per 1 standard deviation greater height of the mother
P-value for the linear height represents Wald p-value for the continuous term ß1 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*X_{height} + ß *$ Covariates, where Y = sex-specific Z score for head circumference for each cohort.
[e] Definitions of short and tall height were cohort specific. p-value for categorical height represents Wald p-value for terms ß1 and ß2 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*X_{height\text{-}short} + ß2*X_{height\text{-}tall} + ß *$ Covariates, where Y = sex-specific Z score for head circumference for each cohort. ß1 =0 tests whether the change in head circumference Z score when comparing short women to average height women is 0. ß2 =0 tests whether the change in head circumference Z score when comparing tall women to average height women is 0.
[f] Nodes for restricted cubic spline model were placed at 5th, 25th, 50th, 75th, and 95th percentiles of height for each cohort.

Table 1.11 Associations of maternal height with **low birth weight** among Omega, HAPO and GUSTO study participants

	Unadjusted model [a]			Partially adjusted model [b]			Fully adjusted model [c]		
	RR	95% CI	p-value	aRR	95% CI	p-value	aRR	95% CI	p-value
Omega study									
Linear height (5 cm increase) [d]	0.85	(0.78, 0.92)	**0.00**	0.83	(0.63, 1.09)	0.18	0.86	(0.67, 1.09)	0.21
Categorical height [e]									
Average height	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)
Short height	1.38	(1.01, 1.87)	**0.04**	1.48	(0.58, 3.79)	0.42	1.34	(0.58, 3.1)	0.50
Tall height	0.79	(0.54, 1.15)	0.22	0.96	(0.44, 2.1)	0.91	1.01	(0.46, 2.2)	0.98
HAPO study									
Linear height (5 cm increase) [d]	0.88	(0.80, 0.98)	0.02	0.96	(0.81, 1.14)	0.64	0.96	(0.81, 1.14)	0.65
Categorical height [e]									
Average height	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)
Short height	1.32	(0.91, 1.91)	0.14	1.05	(0.59, 1.9)	0.86	1.05	(0.59, 1.9)	0.86
Tall height	0.86	(0.57, 1.3)	0.48	1	(0.6, 1.67)	0.98	1	(0.6, 1.67)	0.98
GUSTO study									
Linear height (5 cm increase) [d]	0.81	(0.69, 0.96)	**0.01**	0.84	(0.68, 1.03)	0.09	0.84	(0.68, 1.03)	0.09
Categorical height [e]									
Average height	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)
Short height	1.62	(1.06, 2.48)	**0.03**	1.29	(0.79, 2.12)	0.31	1.29	(0.79, 2.12)	0.31
Tall height	0.65	(0.35, 1.19)	0.16	0.54	(0.22, 1.34)	0.19	0.54	(0.22, 1.34)	0.19

[a] Unadjusted model included terms for short height and tall height and low birth weight (binary).

[b] Partially adjusted models adjust for continuous variables -maternal age (years), pre-pregnancy weight (kg), gestational age (weeks) and binary variables- post-high school education married marital status, nulliparity, smoking during pregnancy, alcohol use during pregnancy, pregnancy complication (defined as the presence of gestational diabetes or preeclampsia), and male infant. Omega study additionally adjusts for marital status (binary) and HAPO study additionally adjusts for study site (grouped categorical variable for six study sites).

[c] Fully adjusted models adjust for all the variables in partially adjusted model but additionally adjusts for pregnancy complication (binary)

[d] **ß** for linear height represents the relative risk of low birth weight associated with 5 cm greater height of the mother.

P-value for the linear height represents Wald p-value for the term ß1 (associated with log transformed continuous height) from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*\ln(X_{height}) + ß * \text{Covariates}$, where Y = low birth weight

[e] Definitions of short and tall height were cohort specific. p-values for categorical height represents Wald p-value for terms ß1 and ß2 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*\ln(X_{height\text{-}short}) + ß2*\ln(X_{height\text{-}tall}) + ß * \text{Covariates}$, where Y = low birth weight. ß1 =0 tests whether the risk of low birth weight when comparing short women to average height women is different from 1. ß2 =0 tests whether the risk of low birth weight when comparing tall women to average height women is different from 1.
RR: Relative Risk
aRR: adjusted RR

Table 1.12 The associations of short and tall maternal height with infant birth measures by **maternal age, race/ethnicity, and infant sex** among Omega, HAPO, and GUSTO study participants.

	Birth weight [a,b]						Birth length [a,b]						Head circumference [a,b]					
		Short height		Tall height				Short height		Tall height				Short height		Tall height		
	Mean (SD)	ß	95% CI	ß	95% CI	p-value	Mean (SD	ß	95% CI	ß	95% CI	p-value	Mean (SD	ß	95% CI	ß	95% CI	p-value
Omega study																		
Infant sex						0.67						0.43						0.97
Male infant	3490 (570)	-86.48	(-138.66, -34.29)	66.58	(15.89, 117.27)		51.0(3.51)	-0.52	(-0.87, -0.17)	0.3	(-0.04, 0.64)		35.0(2.34)	-0.15	(-0.41, 0.1)	-0.02	(-0.27, 0.23)	
Female infant	3360 (544)	-107.33	(-159.32, -55.33)	42.77	(-5.87, 91.4)		50.2(3.31)	-0.34	(-0.7, 0.03)	0.5	(0.16, 0.84)		34.4 (2.05)	-0.15	(-0.4, 0.09)	-0.02	(-0.25, 0.21)	
Age group						0.28						**0.04**						0.38
Age ≥ 35 years	3410 (582)	-108.59	(-176.33, -40.85)	28.66	(-31.81, 89.12)		50.6 (3.31)	-0.62	(-1.03, -0.2)	0.04	(-0.33, 0.41)		34.6 (2.16)	-0.03	(-0.33, 0.27)	0.11	(-0.15, 0.38)	
Age <35 years	3440 (550)	-91.83	(-135.29, -48.37)	71.83	(28.72, 114.95)		50.6 (3.50)	-0.36	(-0.68, -0.05)	0.6	(0.29, 0.92)		34.7 (2.26)	-0.19	(-0.41, 0.03)	-0.09	(-0.31, 0.13)	
Parity						0.50						**0.03**						0.16
Nulliparous	3390 (560)	-85.76	(-133.2, -38.31)	75.28	(29.97, 120.58)		50.4 (2.28)	-0.52	(-0.85, -0.19)	0.58	(0.26, 0.89)			(-0.33, 0.14)	0.08	(-0.15, 0.31)		
Multiparous	3480 (559)	-110.76	(-168.75, -52.77)	13.14	(-42.45, 68.73)		50.1 (2.33)	-0.3	(-0.69, 0.09)	0.06	(-0.32, 0.43)			(-0.46, 0.06)	-0.23	(-0.48, 0.03)		
Race/ethnicity						0.68						0.99						0.87
White	3440 (553)	-107.33	(-148.71, -65.95)	59.01	(22.6, 95.43)		50.6 (3.43)	-0.4	(-0.69, -0.11)	0.41	(0.16, 0.66)		34.6 (2.27)	-0.2	(-0.4, 0)	-0.03	(-0.21, 0.14)	
African-American	3230 (778)	9.26	(-267.25, 285.77)	194.54	(-98.4, 487.48)		50.6 (3.49)	-0.62	(-2.59, 1.35)	0.76	(-1.32, 2.85)		34.8 (2.16)	0.21	(-0.9, 1.31)	0.46	(-0.72, 1.63)	
Asian	3320 (578)	-70.51	(-176.19, 35.16)	-23.69	(-260.2, 212.81)		50.6 (3.34)	-0.34	(-1.07, 0.38)	0.04	(-1.58, 1.67)		34.8 (2.20)	0.01	(-0.55, 0.56)	0.26	(-0.98, 1.49)	
Hispanic	3420 (561)	-95.68	(-249.5, 58.13)	-62.14	(-278.56, 154.27)		49.8 (4.58)	-0.88	(-1.85, 0.08)	0.53	(-0.83, 1.88)		33.7 (2.71)	0.02	(-0.67, 0.72)	-0.2	(-1.18, 0.79)	
HAPO study																		
Infant sex						0.48						0.68						0.97
Male infant	3350 (478)	-70.43	(-129.65, -11.22)	106.91	(56.99, 156.83)		50.3 (2.19)	-0.5	(-0.78, -0.21)	0.49	(0.25, 0.73)		34.5 (1.51)	0	(-0.19, 0.2)	0.13	(-0.04, 0.29)	
Female infant	3230 (453)	-76.92	(-133.91, -19.92)	89.92	(41.92, 137.91)		49.6 (2.09)	-0.38	(-0.65, -0.12)	0.56	(0.33, 0.78)		34.0 (1.36)	-0.02	(-0.2, 0.15)	0.18	(0.03, 0.32)	
Age group						0.68						0.54						0.64
Age ≥ 35 years	3370 (476)	-84.47	(-190.54, 21.59)	122.17	(39.25, 205.09)		50.3 (2.13)	-0.57	(-1.05, -0.08)	0.55	(0.17, 0.93)		34.5 (1.39)	-0.25	(-0.57, 0.07)	0.09	(-0.16, 0.34)	
Age <35 years	3280 (468)	-67.82	(-112.46, -23.18)	93.5	(55.2, 131.79)		49.9 (2.17)	-0.4	(-0.61, -0.19)	0.53	(0.35, 0.71)		34.2 (1.46)	0.04	(-0.1, 0.19)	0.17	(0.05, 0.3)	
Parity						0.76						0.18						0.47
Nulliparous	3290 (468)	-76.65	(-122.39, -30.91)	99.26	(61.98, 136.54)		50.0 (2.22)	-0.3	(-0.52, -0.09)	0.47	(0.29, 0.65)		34.2 (1.49)	-0.01	(-0.16, 0.14)	0.19	(0.07, 0.31)	
Multiparous	3410 (468)	-52.99	(-135.57, 29.59)	88.73	(7.73, 169.74)		50.3 (2.20)	-0.24	(-0.63, 0.14)	0.07	(-0.31, 0.45)		34.4 (1.39)	-0.13	(-0.38, 0.13)	0.2	(-0.05, 0.45)	
Race/ethnicity						0.11						0.09						0.89
White	3420 (505)	-113.05	(-219.86, -6.25)	120.02	(68.39, 171.66)		50.6 (2.26)	-0.77	(-1.26, -0.28)	0.6	(0.37, 0.84)		34.9 (1.53)	-0.07	(-0.42, 0.28)	0.16	(0, 0.33)	
Black	3220 (453)	-32.36	(-153.72, 89.01)	68.28	(3.38, 133.17)		49.3 (2.51)	-0.24	(-0.93, 0.45)	0.54	(0.17, 0.91)		33.7 (1.48)	0.13	(-0.28, 0.53)	0.12	(-0.09, 0.34)	
Hispanic	3430 (425)	-86.45	(-154.88, -18.01)	86.57	(2.27, 170.88)		50.6 (1.71)	-0.35	(-0.64, -0.06)	0.24	(-0.11, 0.59)		34.4 (1.14)	0	(-0.2, 0.19)	0.24	(0.01, 0.48)	
Asian	3100 (389)	0.87	(-56.57, 58.32)	-247.89	(-526.07, 30.3)		49.5 (1.53)	-0.27	(-0.49, -0.04)	-0.65	(-1.74, 0.44)		33.9 (1.21)	0.12	(-0.06, 0.31)	-0.32	(-1.23, 0.59)	

GUSTO study																	
Infant sex					**<0.001**						0.17						0.29
Male infant	3140 (442)	-23.80	(-106.3, 58.7)	-4.70	(-87.60, 78.20)	48.9 (2.26)	0.07	(-0.37, 0.5)	0.28	(-0.16, 0.72)	33.6 (1.41)	0.11	(-0.17, 0.4)	-0.09	(-0.37, 0.2)		
Female infant	3020 (445)	-77.4	(-154.20, -0.57)	61.50	(-18.70, 141.76)	48.2 (2.36)	-0.5	(-0.92, -0.07)	0.58	(0.14, 1.02)	33.1 (1.46)	-0.21	(-0.49, 0.08)	0.16	(-0.14, 0.46)		
Age group					0.17						0.69						0.54
Age ≥ 35 years	3120 (481)	-76.45	(-205.66, 52.76)	126.56	(-9.82, 262.94)	48.6 (2.49)	-0.19	(-0.85, 0.47)	0.78	(0.09, 1.48)	33.5 (1.51)	-0.07	(-0.51, 0.36)	0.36	(-0.1, 0.82)		
Age <35 years	3070 (439)	-42.9	(-105.22, 19.42)	15.92	(-47.16, 79)	48.5 (2.28)	-0.22	(-0.56, 0.12)	0.38	(0.03, 0.72)	33.3 (1.44)	-0.04	(-0.27, 0.19)	0	(-0.23, 0.23)		
Parity					0.09						**0.03**						0.46
Nulliparous	3060 (443)	-101.62	(-182.88, -20.36)	-21.35	(-97.26, 54.55)	48.5 (2.43)	-0.58	(-1.03, -0.12)	0.15	(-0.27, 0.58)	33.2 (1.52)	-0.12	(-0.44, 0.19)	-0.07	(-0.36, 0.22)		
Multiparous	3100 (451)	-14.42	(-93.51, 64.67)	93.6	(5.82, 181.39)	48.6 (2.23)	0.09	(-0.31, 0.5)	0.75	(0.3, 1.2)	33.4 (1.39)	0.02	(-0.25, 0.28)	0.2	(-0.1, 0.49)		
Race/ethnicity					**<0.001**						**<0.001**						**<0.001**
Chinese	3090 (449)	-49.08	(-124.9, 26.74)	7.98	(-60.82, 76.78)	48.7 (2.38)	-0.09	(-0.48, 0.30)	0.02	(-0.23, 0.27)	33.4 (1.46)	-0.04	(-0.31, 0.23)	0.02	(-0.23, 0.27)		
Indian	3030 (476)	-11.6	(-157.55, 134.34)	131.28	(-28.08, 290.65)	48.6 (2.48)	0.26	(-0.48, 1)	0.51	(-0.3, 1.32)	33.2 (1.53)	-0.16	(-0.66, 0.35)	-0.13	(-0.68, 0.42)		
Malay	3100 (422)	-89.21	(-199.43, 21.01)	14.39	(-136.34, 165.12)	48.3 (2.05)	-0.31	(-0.85, 0.23)	0.43	(-0.31, 1.16)	33.4 (1.38)	-0.09	(-0.48, 0.3)	0.1	(-0.44, 0.63)		

[a] The estimates are in comparison to average height women. P-value is from likelihood ratio test comparing the fully adjusted model with model with an interaction term between short height and effect modifier and tall height and effect modifier.

[b] Measurements of birth weight was in g, birth length in cm and head circumference in cm.

Chapter 2. ASSOCIATION OF MATERNAL HEIGHT WITH PREGNANCY COMPLICATIONS

2.1 ABSTRACT

Background: Increasing evidence suggests an inverse association of height with the risk of cardiovascular and metabolic conditions among men and non-pregnant women. Studies of maternal height and pregnancy complications, however, are limited. The objective of the current study was to examine associations of maternal height with pregnancy complications, independent of maternal pre-pregnancy weight.

Methods: We used data from two prospective cohort studies of pregnant women: Omega and Hyperglycemia, and Adverse Pregnancy Outcome (HAPO) studies. We categorized the height of participants as short (< 20^{th}), average (20^{th}–80^{th}), or tall (≥ 80^{th}) based on the percentile values of height for each population. We considered gestational diabetes, preterm birth, and preeclampsia as outcomes. To estimate associations between height and outcomes, we fit cohort-specific unadjusted and adjusted modified Poisson regression models with robust standard errors. We estimated relative risks (RR) and 95% confidence intervals (95% CI) associated with 1) a 5 cm change in maternal height (linear), and 2) tall height and short height, compared to cohort-specific average height (categorical). We used the p-value of the interaction term to determine if the interaction between height and potential effect modifiers (race/ethnicity, infant sex) were significant in the multiplicative scale and fit stratified regression models based on significant effect modifiers.

Results: Mean height and mean pre-pregnancy weight of the participants were 168 (standard deviation [SD]: 7.68) cm and 65.8 (SD: 13.5) kg in the Omega cohort and 161 (SD: 7.51) cm and

64.8 (13.5) kg in the HAPO cohort, respectively. A 5 cm greater maternal height was associated with 1% and 16% lower risk of gestational diabetes in Omega and HAPO cohorts, respectively (adjusted RR, aRR = 0.99, 95% CI: 0.98, 0.99; $p < 0.01$ in Omega and aRR = 0.84, 95% CI: 0.78, 0.90; $p < 0.001$ in HAPO). Women with short height (compared to women with average height) had a 1.05-fold (aRR = 1.05, 95% CI: 1.03, 1.07; $p < 0.01$ in Omega) to 1.44-fold (aRR = 1.44, 95% CI: 1.18, 1.75; $p < 0.001$ in HAPO) higher risk of gestational diabetes, while tall women were at a lower risk (aRR = 0.98, 95% CI: 0.96, 0.99; $p < 0.01$ in Omega and aRR = 0.71, 95% CI: 0.56, 0.89; $p < 0.001$ in HAPO). Results for the association of linear height with outcomes in Omega showed significant association for both preeclampsia (aRR = 0.99, 95% CI: 0.99, 0.99; $p < 0.01$) and preterm birth (aRR = 1.006, 95% CI: 1.001, 1.012; $p = 0.03$), though the association with preterm birth was only marginally positive. We did not find association of maternal height with preeclampsia in the HAPO study (aRR = 0.89, 95% CI: 0.75, 1.08; $p = 0.24$). Test of effect modification by infant sex or race/ethnicity was not statistically significant (all interaction $p > 0.05$, both cohorts).

Conclusion: Maternal height had a strong inverse association with the risk of gestation diabetes. There was a significant but marginally positive association of maternal height with preterm birth and a significant inverse association with preeclampsia in the Omega study. Future studies that replicate the findings in other large sample size cohorts and/or apply a causal framework to examine the relationship of maternal height with pregnancy complications and outcomes may be needed.

2.2 BACKGROUND

About 19%–44% of the pregnancies are complicated by gestational diabetes (8%–24%) (68), preeclampsia (2.7%–8.2%) (69), or preterm birth (9%–12%) (70). These pregnancy complications have been consistently shown to be associated with cardiometabolic risk factors such as hypertension and later-life morbidity and mortality from cardiovascular and metabolic diseases (13). Older age, family history, physical activity, and obesity, measured by body mass index (BMI) are well established risk factors for these complications, while less strong evidence exists for other factors, such as height (71–73).

Increasing evidence suggests an inverse association of height with the risk of cardiovascular and metabolic conditions among men and non-pregnant women (2–7). Studies of maternal height and pregnancy complications, however, are limited with inconsistent results (14–20). Further, the independent association of maternal height, independent of other body measures, particularly maternal pre-pregnancy weight, has not been examined (18,19,22,74). To add, reports of potential difference in the association of maternal height with gestational diabetes by infant sex or maternal race/ethnicity is sparse despite recent evidence of sex-specific associations of various maternal exposures on pregnancy outcomes (53,54) and race/ethnicity-specific association of maternal height on gestational diabetes (34).

Although the exact mechanism of the association between maternal height and pregnancy complications is not been fully understood, several authors have reported associations of short maternal height with a greater risk of gestational diabetes (15,16,20,21), preeclampsia (17–19,22), and preterm birth (20,23). Findings from other observational studies did not support this association (17,75). Inconsistencies in findings may be related to inadequate adjustment for important confounders, particularly body weight, weaker study designs (many were cross-

sectional studies), limited generalizability (racially/ethnically homogeneous populations), lack of consideration of potential effect modifiers (infant sex, race/ethnicity) and potential misclassification of exposure due to self-reported height.

The objective of the current study was to examine the associations of maternal height, independent of maternal pre-pregnancy weight, with pregnancy complications (gestational diabetes, preeclampsia, and preterm birth). Extensive data from two geographically and racially/ethnically diverse prospective cohorts of pregnant women enabled us to comprehensively adjust for confounders in our study and obtain a robust estimate of associations of interest. In this study, we also explored if infant sex or maternal race/ethnicity modified the associations between maternal height and gestational diabetes.

2.3 METHODS

2.3.1 *Study Settings and Study Populations*

Data from two prospective cohort studies of pregnant women, Omega, and Hyperglycemia, and Adverse Pregnancy Outcome (HAPO) cohorts, were used for the analysis in this study. Details on the study objectives, study designs, inclusion and exclusion criteria, and data collection have been reported in prior publications (55–59). Briefly, study participants in the Omega study were recruited from among pregnant women attending prenatal care clinics affiliated with Swedish Medical Center and Tacoma General Hospital in Seattle and Tacoma, Washington State, respectively, between 1996 and 2008. Women were eligible if they were 18 years of age or older, able to speak and read English, initiated prenatal care before 16 weeks of gestation, and planned to carry the pregnancy to term and deliver at one of the two study hospitals. The primary goal of the Omega study was to examine dietary and metabolic risk factors of pregnancy complications (15). Out of 5,063 eligible women, 4,602 (91%) provided informed consent and were enrolled in

the cohort. The study was approved by the institutional review boards of Swedish Medical Center and Tacoma General Hospital.

Study participants in the HAPO study were recruited among pregnant women less than 31 weeks of gestation from 15 field centers located in Asia, Australia, Europe, North America, and the Middle East, between July 2000 and April 2006. Women were eligible if they were 18 years of age or older, planned delivery at participating health centers, were able to complete the oral glucose tolerance test (OGTT) by 32 weeks gestation, and were either certain of the date of last menstrual period or had ultrasound estimation between 6–24 weeks of gestation. Women with multiple pregnancy, conception using gonadotropin ovulation induction or by in vitro fertilization, diabetes antedating pregnancy requiring treatment with medication, known to be HIV positive or to have hepatitis B or C, or inability to converse in the languages used in field center forms without the aid of an interpreter were excluded. If glucose measurements were made outside of the HAPO study after initial enrollment, or if the fasting blood glucose level exceeded 105 mg/dl, or two-hour glucose exceeded 200 mg/dl, or random glucose exceeded 160 mg/dl, or any glucose level was below 45 mg/dl the participant was excluded from further participation in the HAPO study. All participants provided written informed consent. The objective of the HAPO study was to clarify unanswered questions on associations of maternal glycemia that was below the threshold for diagnosis of overt diabetes mellitus with risks of adverse pregnancy outcome particularly increased birth weight, increased cord-blood serum C-peptide, and primary cesarean delivery (76,77). Of 53,295 eligible women (all centers), 28,562 (53.59%) agreed to participate and among those, 25,505 (89.29%) completed an OGTT. The study was approved by the institutional review boards at all 15 field centers. For the HAPO study, we had access to publicly available data on

only 4,994 genotyped mother/infant pairs which we downloaded from the Database of Genotypes and Phenotypes (dbGaP) website, under phs000096.v4.p1.

For the current study, we excluded participants with pre-existing diabetes (N = 61 Omega, N = 0 HAPO), pre-existing hypertension (N = 201 Omega, N = 142 HAPO), or multiple pregnancy (N = 146 Omega, N = 0 HAPO). Participants with missing information on height (N = 208 Omega, N = 0 HAPO) or height less than 140 cm or greater than 200 cm (N = 5 Omega, N = 6 HAPO) were also excluded. Participants with missing data on gestational diabetes (N = 2 Omega, N = 0 HAPO), preeclampsia (N = 1 Omega, N = 0 HAPO), or preterm birth (N = 0 Omega, N = 3 HAPO) were excluded from all analysis. Our final analytic data set for the current study included 3,880 women from the Omega study and 4,843 from the HAPO study.

2.3.2 *Data Collection*

In the Omega study, information on maternal socio-demographic and medical characteristics, family and medical history, height, and pre-pregnancy weight, smoking and alcohol drinking habits was collected through interviewer-administered questionnaire at an average of 15 weeks of gestation. Information on gestational age at delivery, maternal health during the pregnancy and at the time of delivery, and pregnancy outcomes were abstracted from hospital labor and delivery medical records and clinic records by trained study personnel after delivery (15).

The participants in the HAPO study underwent 75 g OGTT as close to 28 weeks gestation as possible (range 24–32 weeks' gestation). At the OGTT visit, height, weight, and blood pressure were measured while other prenatal information, including sociodemographic characteristics and participant's report of pre-pregnancy weight, was collected using questionnaires. Following OGTT, routine pregnancy care was continued at the field centers. Neonatal anthropometric

measures were taken after delivery, and follow-up data were collected 4-6 weeks after delivery. In both the study cohorts, we used self-reported pre-pregnancy weight for our analyses.

For each study population, we defined quintiles of height (centimeter) using the self-reported (Omega) or measured height (HAPO). There are limited studies regarding the best way to classify maternal height. Similar to a previous study (20), based on the quintiles, we further categorized height as short height if the maternal height was less than 20^{th} percentile in that cohort, average height if the height was in between 20^{th} and 80^{th} percentiles and tall if the height was greater than or equal to the 80^{th} percentile value.

Diagnosis of gestational diabetes was made post hoc in HAPO data based on current International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (62). Using blood glucose values from 75 g OGTT done in the fasting state at 24–28 weeks of gestation, gestational diabetes mellitus was diagnosed if any of the following cut-off was met 1) fasting ≥ 92 mg/dl (≥ 5.2 mmol/l) or 2) one-hour ≥ 180 mg/dl (≥ 10 mmol/l) or 3) two-hour ≥ 153 mg/dl (≥ 8.5 mmol/l). In the Omega study, diagnosis of gestational diabetes was based on American Diabetes Association guidelines in use at the time (62,78). All women were screened for gestational diabetes between 24 and 28 weeks' gestation using a 50 g glucose challenge test. A 3-hour OGTT with a 100 g glucose was conducted among women who failed the screening test (post-load glucose ≥ 140 mg/dl). Women were diagnosed with gestational diabetes if ≥ 2 of the following cut-offs were met 1) fasting ≥ 105 mg/dl (≥ 5.8 mmol/l) or 2) one-hour ≥ 190 mg/dl (≥ 10.6 mmol/l) or 3) two-hour ≥ 165 mg/dl (≥ 9.2 mmol/l 4) 3-hour ≥ 145 mg/dl (≥ 8.1 mmol/dl) and no indication of prior chronic diabetes was noted.

Preeclampsia diagnosis was based on clinical records. In both HAPO and Omega cohorts, preeclampsia was diagnosed after 20 weeks of gestation and in absence of chronic hypertension if

1) systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg on ≥ 2 occasions at least 6 hours apart, and 2) proteinuria of ≥ 1+ dipstick or ≥ 300 mg per 24 hours, (or elevated protein/creatinine ratio where 24 hour urine protein was not available) (76).

Preterm birth was defined as birth that occurred before 37 completed weeks of gestation. In Omega, the date of the last menstrual period (LMP) or early pregnancy ultrasound (if available) was used to estimate the gestational age. In the HAPO study, if the participant was certain of her dates, LMP was used to determine the gestational age. If uncertain, ultrasound was performed between 6 and 24 weeks gestation to estimate the gestational age (77).

Self-reports of maternal age, race/ethnicity, pre-pregnancy weight, parity, and other important characteristics were collected in both studies during enrollment.

2.3.3 *Statistical Analysis*

We summarized selected characteristics of the participants overall and by the quintiles of height using mean and standard deviation (SD) for continuous variables and number (count) and percent of total for categorical variables.

To estimate the associations between height and outcomes, we fit cohort-specific (Omega or HAPO) unadjusted and adjusted modified Poisson regression models with robust standard errors (61) for each of the outcomes (gestational diabetes, preterm birth, and preeclampsia). We estimated the relative risks (RR) and 95% confidence intervals (95% CI) associated with 1) a 5 cm change in maternal height (linear), and 2) tall height and short height, compared to cohort-specific average height (categorical).

To estimate the adjusted associations between maternal height and the outcomes, the following covariates were identified a *priori* and added to the unadjusted regression models, either

as confounder or precision variables: Maternal age (years), pre-pregnancy weight (kg), and gestational age at delivery (week) were included as continuous variables. Post-high school education, married marital status, nulliparity, smoking during pregnancy, alcohol use during pregnancy and infant sex were included as binary variables. Of note, information on marital status was available only in the Omega study. We modeled maternal race/ethnicity as an indicator variable in the adjusted models and was categorized as White/African-American/Asian/Hispanic in Omega and HAPO studies. We additionally included study sites as a grouped categorical variable in adjusted models for the HAPO analysis.

To examine potential effect modification of the height-gestational diabetes association, we re-ran the fully adjusted regression models for categorical height stratified by the potential effect modifiers: infant sex (male/female) and race/ethnicity (categorized as above). Next, we included interaction terms between maternal height and each effect modifier in the fully adjusted regression models for gestational diabetes. We used the p-value of the interaction term to determine the significance of multiplicative interaction between height and potential effect modifiers.

We conducted sensitivity analyses using the values from the fasting, one-hour, and two-hour OGTT in the HAPO study to explore the association between height and maternal blood glucose levels (instead of gestational diabetes). The rationale for this analysis is that classifying gestational diabetes into yes or no based on a cut-off value may fail to identify linear relationships between maternal height and maternal glycemia.

In all analyses, a p-value of less than 0.05 in a two-sided test was considered statistically significant. All calculations and analyses were done separately for each of the two cohorts as well as outcomes. Analyses were conducted using R studio software (R Version 4.1.1 [2021-08-10]).

2.4 RESULTS

Mean height for women in the analytic population was 168 (SD: 7.68) cm in the Omega study and 161 (SD: 7.51) cm in HAPO. Based on the quintile values of height, women were considered short if their height was less than 161.35 cm or 154.05 cm (corresponding to the first quintile value) in the Omega and HAPO studies, respectively (Tables 2.1 and 2.2). Similarly, women were considered tall if their height was greater than or equal to 173.99 cm or 167.0 cm (corresponding to last quintile value), in Omega and HAPO, respectively. Mean pre-pregnancy weight was 65.8 (SD: 13.5) kg and 64.8 (SD: 13.5) kg for participants in Omega and HAPO cohorts, respectively. Overall, 85.3% and 61.7% of the participants were White and nulliparous, respectively in the Omega study and 30.0% and 67.9%, respectively in the HAPO study. The prevalence of gestational diabetes, preeclampsia, and preterm birth in the Omega cohort was 4.9%, 1.8%, and 7.8%, respectively, while the corresponding values in the HAPO cohort were 15%, 2.1%, and 0.1%, respectively.

Table 2.3 shows the unadjusted and adjusted RR (aRR) obtained from modified Poisson regression models for the outcomes considered (gestational diabetes, preeclampsia, and preterm birth) in relation to maternal height in the two study populations. Due to the limited number of preterm delivery cases (N = 6), we did not conduct any analysis for this outcome in HAPO.

After covariate adjustment, a 5 cm greater maternal height was associated with 1% and 16% lower risk of gestational diabetes in Omega and HAPO cohorts, respectively (adjusted RR [aRR] = 0.99, 95% CI: 0.98, 0.99; $p < 0.01$ in Omega and aRR = 0.84, 95% CI: 0.78, 0.90; $p < 0.001$ in HAPO) (Table 2.3). Women with short height, compared to women with average height, had significantly greater risk of gestational diabetes in both studies (aRR = 1.05, 95% CI: 1.03, 1.07; $p < 0.01$ in Omega and aRR = 1.44, 95% CI: 1.18, 1.75; $p < 0.001$ in HAPO). Further, tall women

had significantly lower risk of gestational diabetes compared to women with average height (aRR = 0.98, 95% CI: 0.96, 0.99; $p < 0.01$ in Omega and aRR = 0.71, 95% CI: 0.56, 0.89; $p < 0.001$ in HAPO).

Results for the association of linear height with outcomes in Omega showed significant association for both preeclampsia (aRR = 0.99, 95% CI: 0.99, 0.99; $p < 0.01$) and preterm birth (aRR = 1.006, 95% CI: 1.001, 1.012; $p = 0.03$), though there was a positive and marginal association with preterm birth. We did not find association of maternal height with preeclampsia in the HAPO study (aRR = 0.89, 95% CI: 0.75, 1.08; $p = 0.24$) (Table 2.4).

Test of interaction showed that the multiplicative interaction terms between overall height (in the model that includes indicator variables for short, tall and average height) and infant sex, or race/ethnicity were not significant in either cohort (all $p>0.05$).

Findings from sensitivity analyses using continuous values for fasting, one-hour, and two-hour blood glucose levels from the HAPO study showed significant inverse associations of maternal height with blood glucose levels, similar to our main findings reported above (Table 2.5).

2.5 DISCUSSION

In the current study, we found associations of shorter maternal height with a higher risk of gestational diabetes after adjusting for pre-pregnancy weight, among other variables. While maternal height, both as a continuous variable as well as a categorical variable, was significantly inversely associated with the risk of gestational diabetes, the estimates varied across the cohorts. A 5-cm greater maternal height was associated with a 1% and 16% lower risk of gestational diabetes in Omega and HAPO, respectively. Similarly, women with short height (compared to women with average height) had a 1.05- and 1.44-fold higher risk of gestational diabetes in Omega and HAPO, respectively. The corresponding lower risk among tall women were 98% and 71% in

Omega and HAPO. These associations did not vary by infant sex or maternal race/ethnicity. There was a significant positive association of maternal height with preterm birth and a significant inverse association with preeclampsia in the Omega study, although the association with preterm birth was marginal and the association with preeclampsia was not consistent with HAPO.

Our findings of height-gestational diabetes association are generally consistent with previous reports available in the literature (15,16,20,21). In a USA based study that included 135,861 pregnancies included in the Consortium on Safe Labor Study, Brite et al. found that with every 5 cm greater self-reported or measured maternal height, the risk of gestational diabetes was reduced by 20%, after adjusting for age, pre-pregnancy weight, race/ethnicity, insurance, and education (adjusted odds ratio [OR]: 0.80, 95% CI: 0.78, 0.82) (16). In another study using data from 1,644 pregnant women, Rudra et al. found that the risk of gestational diabetes was 60% lower in mothers taller than 170 cm (fourth quartile) compared to the mothers who were 160 cm or shorter (first quartile) after adjusting for race/ethnicity and years of education (aOR: 0.40, 95% CI: 0.17, 0.95) (15). While Rudra et al. used the same data source as ours (Omega), they did not adjust for pre-pregnancy weight, a potential confounder that is associated with both height and gestational diabetes risk and used different cut-offs (<160, 161-165, 166-170, and >170 cm) and comparison group (comparing tall vs short) than our study.

Among all California births that occurred between 2007 and 2010 (N = 2,094,220), Marshall et al. examined the associations of maternal height with gestational diabetes, preeclampsia, and preterm birth (20). They reported statistically significantly greater odds of gestational diabetes (aOR: 1.20, 95% CI: 1.19, 1.22), preeclampsia (aOR: 1.04, 95% CI: 1.02, 1.06), and preterm birth (aOR: 1.11, 95% CI: 1.10, 1.13), comparing short height women to average height women after adjusting for advanced maternal age, maternal education, parity, public insurance status, prenatal

care initiation in first trimester, chronic hypertension, and chronic diabetes. Similarly, tall maternal height, compared to average height, was also associated with a reduced risk gestational diabetes (aOR: 0.81, 95% CI: 0.80, 0.82) and preterm birth: aOR: 0.91, 95% CI: 0.90, 0.92) and an increased risk of preeclampsia (aOR: 1.03, 95% CI: 1.01, 1.05). Our results demonstrate a similar association in terms of direction and magnitude of association of short height or tall height with gestational diabetes in Omega (aRR = 1.05, 95% CI: 1.03, 1.07; $p < 0.01$ for short height and aRR = 0.98, 95% CI: 0.96, 0.99; $p < 0.01$ for tall height) and HAPO (aRR = 1.44, 95% CI: 1.18, 1.75; $p < 0.001$ for short height and aRR = 0.71, 95% CI: 0.56, 0.89; $p < 0.01$ for tall height) studies.

Unlike Marshall et al. and other studies (18,19,22,74), we did not observe associations of maternal height with preeclampsia in the HAPO cohort, but there was significant association of height with preeclampsia and preterm birth in the Omega study. Marshall et al reported a positive direction of association of height and preeclampsia in the Californian pregnancies in contrast to what we found in the Omega study. However, for a subset of normal weight women, the magnitude, direction, and significance of association were similar to our findings from the Omega study (aOR: 0.95, 95% CI: 0.92, 0.98). A study conducted in Uruguay (75) did not observe an association between maternal height and the risk of preeclampsia. The quintile-based definitions of short ($< 20^{th}$ percentile), average (20^{th}–80^{th} percentile), and tall ($\geq 80^{th}$ percentile) maternal height were similar in the California cohort study and HAPO and Omega studies. Despite the similarities, certain factors may account for the different findings in Omega, HAPO, and other previous studies. In contrast to our study in which we adjusted for pre-pregnancy weight, the effect of height was not independent of pre-pregnancy weight in previous studies (18,19,22,74). The characteristics of the study population varied substantially between these studies. Omega included predominantly White women (85.3%) whereas HAPO included racially/ethnically heterogeneous

group of women (30% White, 26.7% African-American, 18% Hispanic, and 25.4% Asian) from different geographic locations with greater variation in characteristic of the study participants. The mean height ranged from 162 cm (Asian) to 168 cm (Whites) in Omega whereas in HAPO the range was 154 (Asian)-164 (White and African-American). The majority of women in the Omega study were normal weight (71.5%) while 16.5% were overweight (as determined by BMI). In comparison, less than half of women in the HAPO study fell in the normal weight BMI category (45%), and 27.4% fell into the overweight (27.4%) BMI category. The diagnostic thresholds for glucose values used in the definition of gestational diabetes in HAPO were different from the Omega cohort. It should also be noted that given the small number of preeclampsia and preterm birth cases in each height category, our study may be underpowered to detect the association of maternal height with these outcomes. The prevalence of preterm birth in our study was lower compared to the prevalence in the larger HAPO cohort (N = 25,505) (0.1% vs. 6.9%), but we were unable to determine if this was due to any additional inclusion criteria for genotyping the study participants. To sum up, results from our study indicate that the risk of pregnancy complications associated with maternal height may vary depending upon the study population, analytic methods, and the outcome.

Our results provided suggestive evidence of associations of short or tall maternal height with gestational diabetes and possibly preeclampsia. To our knowledge, only a few studies have examined if the association between height and gestational diabetes varies by maternal race/ethnicity or infant sex. In the current study, we did not find evidence supporting potential effect modification by these factors.

Strengths of this study include the use of large racially/ethnically diverse well-characterized databases enabling us to compare the findings across the studies and provide evidence for

generalizability of the findings to a similar population. Results from Omega and HAPO study provide evidence to support that the association of height with gestational diabetes can be generalized to other populations, although the estimates may vary. In HAPO, we had access to detailed information on covariates (e.g., pre-pregnancy weight), which permitted us to adjust for various previously reported confounding variables as well as glucose values from the OGTT, which permitted us to perform sensitivity analyses and obtain robust estimates of the associations.

There are several limitations of our study that need to be acknowledged. There was high missingness for the pre-pregnancy weight variable in HAPO. However, excluding this covariate from the regression models did not change the statistical significance of our findings. Height was self-reported in the Omega cohort and self-reported height tends to be overestimated (36). For all analyses, some misclassification due to overreporting or underreporting of reported measures (such as pre-pregnancy weight in Omega) is a possibility. This may have resulted in non-differential misclassification of the height-birth size associations and hence underestimation of the effect size. As in all observational studies, we could not rule out bias due to residual or unmeasured confounding in this study, hence a causal relationship between material height and the outcomes cannot be concluded. There could be difference between participants who agreed to participate in the HAPO study (53.59%) and those who didn't (46.10%) affecting the risk estimates, but we were unable to determine this based on our data. Type I error due to multiple tests might be an issue because of the many statistical tests we have conducted. Data on only a subset of enrolled participants in HAPO was publicly available for download from dbGAP. The prevalence of preterm birth was substantially low in our analytic cohort. There is a possibility of selection bias because of inclusion of only term births in the publicly available HAPO data used in our analysis. Similar characteristics of the pregnant women in our analytic cohort and the full HAPO cohort

provided reassurance that restricting our analysis to term births is unlikely to bias our estimates of the association of maternal height with pregnancy complications (79) (Table 2.6).

In conclusion, we found that maternal height had a strong inverse association with gestational diabetes in Omega and HAPO. Short women were at a higher risk of gestational diabetes compared to average height women, while the risk was lower for tall women. We observed an inverse association between maternal height and preeclampsia risk in the Omega study and found suggestive evidence of possible associations of short or tall maternal height with preeclampsia. Our results highlight that risk stratification of short women early in pregnancy or even as early as the pre-conception period may help to initiate monitoring approaches and prevention strategies. Examples of such strategies and approaches include starting early fetal assessment and monitoring and early and frequent screening of short women through OGTT to provide better opportunities to ensure pregnancy glucose control. Future studies to replicate the findings in other large sample size cohorts and/or to apply causal frameworks to examine the relationship of maternal height with pregnancy complications and outcomes may be needed.

Table 2.1 Selected characteristics of **Omega** study participants enrolled at Swedish Medical Center and Tacoma General Hospital in Washington State between1996 and 2008 by height quintiles

Characteristics [a]	First quintile[b] (N = 776)	Second quintile[c] (N=775)	Third quintile[d] (N=777)	Fourth quintile[e] (N=776)	Last quintile[f] (N=776)	Overall (N=3880)
Mother						
Race/ethnicity						
White	536 (69.1%)	659 (845.0%)	685 (88.2%)	699 (90.1%)	730 (94.1%)	3309 (85.3%)
African-American	20 (2.6%)	14 (1.8%)	9 (1.2%)	14 (1.8%)	9 (1.2%)	66 (1.7%)
Asian	156 (20.1%)	64 (8.3%)	44 (5.7%)	24 (3.1%)	14 (1.8%)	302 (7.8%)
Hispanic	64 (8.2%)	38 (4.9%)	39 (5.0%)	39 (5.0%)	23 (3.0%)	203 (5.2%)
Age (years)	32.0 (4.82)	32.6 (4.53)	33.0 (4.31)	33.0 (4.33)	32.9 (4.32)	32.7 (4.48)
Age ≥ 35 years	240 (30.9%)	261 (33.7%)	284 (36.6%)	279 (36.0%)	279 (36.0%)	1343 (34.6%)
Married	89 (11.5%)	65 (8.4%)	64 (8.2%)	63 (8.1%)	70 (9.0%)	351 (9.0%)
Nulliparous [g]	464 (59.8%)	470 (60.6%)	497 (64.0%)	481 (62.0%)	482 (62.1%)	2394 (61.7%)
Post high school education [h]	662 (85.3%)	690 (89.0%)	720 (92.7%)	722 (93.0%)	731 (94.2%)	3525 (90.9%)
Smoked during pregnancy [i]	117 (15.1%)	166 (21.4%)	155 (19.9%)	145 (18.7%)	187 (24.1%)	770 (19.8%)
Intake of any alcohol during pregnancy [j]	69 (8.9%)	67 (8.6%)	82 (10.6%)	78 (10.1%)	66 (8.5%)	362 (9.3%)
Pre-pregnancy weight (kg)	59.4 (11.9)	63.5 (12.5)	65.1 (11.9)	68.0 (13.1)	73.1 (14.2)	65.8 (13.5)
Pre-pregnancy body mass index (kg/m^2)	24.0 (4.81)	23.7 (4.70)	23.2 (4.24)	23.1 (4.45)	22.9 (4.22)	23.4 (4.51)
Pre-pregnancy body mass index category (kg/m^2)						
Underweight (<18.5)	27 (3.5%)	30 (3.9%)	31 (4.0%)	39 (5.0%)	43 (5.5%)	170 (4.4%)
Normal (18.5–24.9)	542 (69.8%)	553 (71.4%)	560 (72.1%)	560 (72.2%)	560 (72.2%)	2775 (71.5%)
Overweight (25–29.9)	122 (15.7%)	126 (16.3%)	131 (16.9%)	125 (16.1%)	137 (17.7%)	641 (16.5%)
Obesity (≥ 30)	85 (11.0%)	66 (8.5%)	55 (7.1%)	52 (6.7%)	36 (4.6%)	294 (7.6%)
Gestational age at delivery (weeks) [k]	38.8 (2.71)	38.8 (2.00)	39.0 (1.55)	39.0 (1.93)	39.0 (1.97)	38.9 (2.07)
Gestational diabetes	67 (8.6%)	36 (4.6%)	30 (3.9%)	33 (4.3%)	26 (3.4%)	192 (4.9%)
Pre-eclampsia	13 (1.7%)	22 (2.8%)	10 (1.3%)	15 (1.9%)	10 (1.3%)	70 (1.8%)
Newborn						
Male infant [l]	414 (53.4%)	390 (50.3%)	378 (48.6%)	406 (52.3%)	400 (51.5%)	1988 (51.2%)
Preterm (<37 weeks)	79 (10.2%)	77 (9.9%)	50 (6.4%)	52 (6.7%)	43 (5.5%)	301 (7.8%)

Birth weight	3300 (546)	3390 (567)	3480 (613)	3520 (491)	3620 (708)	3460 (599)

[a] Values are N (%) or mean (Standard Deviation)
[b] First quintile, height <161.35 cm.
[c] Second quintile, height ≥ 161.35 cm to <165.44 cm.
[d] Third quintile, height ≥ 165.44 cm to <169.53 cm.
[e] Fourth quintile, height ≥ 169.53 cm to >173.99 cm.
[f] Fifth quintile, height ≥ 173.99 cm
[g] Information on parity missing for 1 subject. For each quintile: 1 (quintile 1) was missing.
[h] Educational status missing for 231 subjects. For each quintile: 82 (quintile 1), 58 (quintile 2), 33 (quintile 3), 38 (quintile 4), 20 (quintile 5)
[i] Smoking status missing for 247 subjects. For each quintile: 85 (quintile 1), 62 (quintile 2), 37 (quintile 3), 41 (quintile 4), 22 (quintile 5)
[j] Alcohol intake missing for 54 subjects. For each quintile: 13 (quintile 1), 14 (quintile 2), 11 (quintile 3), 3 (quintile 4), 13 (quintile 5)
[k] Gestational age at delivery missing for 4 subjects. For each quintile: 2 (quintile 3), 2 (quintile 4)
[l] Infant sex missing for 11 subjects. For each quintile: 1 (quintile 1), 2 (quintile 3), 1 (quintile 4), 7 (quintile 5)

Table 2.2 Selected characteristics of **HAPO** study participants enrolled at field centers between July 2000 and April 2006 by height quintiles

Characteristics [a]	First quintile[b] (N=936)	Second quintile[c] (N=996)	Third quintile[d] (N=913)	Fourth quintile[e] (N=940)	Last quintile[f] (N=1058)	Overall (N=4843)
Mother						
Race/ethnicity						
White	74 (7.9%)	217 (21.8%)	285 (31.2%)	376 (40.0%)	499 (47.2%)	1451 (30.0%)
African-American	91 (9.7%)	188 (18.9%)	261 (28.6%)	301 (32.0%)	450 (42.5%)	1291 (26.7%)
Hispanic	152 (16.2%)	188 (18.9%)	229 (25.1%)	206 (21.9%)	96 (9.1%)	871 (18.0%)
Asian	619 (66.1%)	403 (40.5%)	138 (15.1%)	57 (6.1%)	13 (1.2%)	1230 (25.4%)
Age (years)	28.3 (5.64)	28.1 (5.68)	28.4 (5.91)	28.5 (5.90)	28.7 (6.19)	28.4 (5.87)
Age ≥ 35 years	122 (13.0%)	126 (12.7%)	129 (14.1%)	139 (14.8%)	188 (17.8%)	704 (14.5%)
Nulliparous [g]	502 (53.6%)	617 (61.9%)	625 (68.5%)	703 (74.8%)	841 (79.5%)	3288 (67.9%)
Post high school education [h]	257 (27.5%)	438 (44.0%)	482 (52.8%)	535 (56.9%)	655 (61.9%)	2367 (48.9%)
Smoking habits						
Smoking during pregnancy	13 (1.4%)	39 (3.9%)	47 (5.1%)	59 (6.3%)	61 (5.8%)	219 (4.5%)
Number of cigarettes/days during pregnancy	1.02 (0.163)	1.05 (0.253)	1.07 (0.305)	1.08 (0.319)	1.07 (0.304)	1.06 (0.276)
Alcohol drinking habits						
Alcohol during pregnancy	22 (2.4%)	55 (5.5%)	69 (7.6%)	84 (8.9%)	119 (11.2%)	349 (7.2%)
Number of alcoholic drinks/days during pregnancy						
<1 per day	19 (2.0%)	55 (5.5%)	68 (7.4%)	84 (8.9%)	116 (11.0%)	342 (7.1%)
1–2 per day	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	3 (0.3%)	4 (0.1%)
Illicit drug use in pregnancy	0 (0%)	3 (0.3%)	5 (0.5%)	7 (0.7%)	8 (0.8%)	23 (0.5%)
Pre-pregnancy weight (kg) [i]	58.7 (9.65)	62.5 (11.4)	64.6 (12.7)	67.4 (14.0)	70.9 (15.9)	64.8 (13.5)
Pre-pregnancy body mass index (kg/m^2) [i]	26.1 (4.18)	25.6 (4.67)	25.1 (4.96)	24.9 (5.17)	24.3 (5.32)	25.2 (4.91)
Pre-pregnancy body mass index category (kg/m^2)						

Underweight (<18.5)	10 (1.1%)	17 (1.7%)	35 (3.8%)	37 (3.9%)	82 (7.8%)	181 (3.7%)
Normal (18.5–24.9)	394 (42.1%)	445 (44.7%)	415 (45.5%)	444 (47.2%)	479 (45.3%)	2177 (45.0%)
Overweight (25–29.9)	356 (38.0%)	301 (30.2%)	250 (27.4%)	215 (22.9%)	204 (19.3%)	1326 (27.4%)
Obesity (≥ 30)	131 (14.0%)	128 (12.9%)	107 (11.7%)	120 (12.8%)	102 (9.6%)	588 (12.1%)
Gestational age at delivery (weeks)	39.5 (1.24)	39.6 (1.23)	39.7 (1.18)	39.8 (1.24)	39.8 (1.22)	39.7 (1.23)
Blood glucose level at OGTT (mg/dl)						
Fasting	81.0 (7.38)	81.1 (6.87)	81.9 (7.49)	81.9 (7.41)	81.4 (7.14)	81.4 (7.26)
One hour	145 (33.0)	137 (31.8)	133 (31.1)	131 (30.7)	127 (28.8)	134 (31.7)
Two hour	119 (25.7)	115 (23.7)	110 (22.5)	110 (22.3)	106 (21.3)	112 (23.5)
Gestational diabetes[j]	209 (22.3%)	164 (16.5%)	129 (14.1%)	122 (13.0%)	101 (9.5%)	725 (15.0%)
Pre-eclampsia	12 (1.3%)	15 (1.5%)	27 (3.0%)	24 (2.6%)	23 (2.2%)	101 (2.1%)
Newborn						
Male infant	463 (49.5%)	500 (50.2%)	455 (49.8%)	477 (50.7%)	550 (52.0%)	2445 (50.5%)
Preterm (<37 weeks)	0 (0%)	0 (0%)	1 (0.1%)	2 (0.2%)	3 (0.3%)	6 (0.1%)
Birth weight (g)	3110 (408)	3210 (428)	3290 (458)	3370 (465)	3450 (505)	3290 (470)

[a] Values are N (%) or mean (Standard Deviation)

[b] First quintile, height <154.05 cm.

[c] Second quintile, height ≥ 154.05 cm to <158.75 cm.

[d] Third quintile, height ≥ 158.75 cm to <162.56 cm.

[e] Fourth quintile, height ≥ 162.56 cm to <167.00 cm.

[f] Fifth quintile, height ≥ 167.00 cm

[g] Information on parity missing for 588 subjects. For each quintile: 261 (quintile 1), 173 (quintile 2), 81 (quintile 3), 47 (quintile 4), 26 (quintile 5)

[h] Educational status missing for 239 subjects. For each quintile: 90 (quintile 1), 44 (quintile 2), 38 (quintile 3), 36 (quintile 4), 31 (quintile 5)

[i] Pre-pregnancy weight and BMI missing for 571 subjects. For each quintile: 45 (quintile 1), 105 (quintile 2), 106 (quintile 3), 124 (quintile 4), 191 (quintile 5)

[j] Diagnosis of gestational diabetes was made post hoc based on IADPSG criteria (1 or more values exceeding the thresholds: fasting ≥92 mg/dl, one-hour ≥180 mg/dl, and two-hour ≥153 mg/dl)

Table 2.3 Associations of maternal height with **gestational diabetes, preeclampsia, and preterm birth** among Omega and HAPO study participants

	Gestational Diabetes						Preeclampsia						Preterm birth					
	Unadjusted model [a]			Adjusted model [b]			Unadjusted model [a]			Adjusted model [b]			Unadjusted model [a]			Adjusted model [b]		
	RR	95% CI	p-value	RR	95% CI	p-value	RR	95% CI	p-value	RR	95% CI	p-value	RR	95% CI	p-value	RR	95% CI	p-value
Omega study																		
Linear height (5 cm increase) (cm) [c]	0.99	(0.98, 0.99)	**0.00**	0.986	(0.981, 0.991)	**0.000**	0.99	(0.99, 1.00)	0.26	0.995	(0.992, 0.999)	**0.011**	1.01	(1.00, 1.02)	**0.00**	1.00	(1.001, 1.012)	**0.03**
Categorical height [d]																		
Average height	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)
Short height	1.04	(1.02, 1.06)	**0.00**	1.052	(1.030, 1.075)	**0.040**	1.00	(0.99, 1.01)	0.53	1.000	(0.989, 1.011)	0.970	0.97	(0.95, 1.00)	0.04	0.980	(0.959, 1.002)	0.07
Tall height	0.99	(0.98, 1.01)	0.24	0.978	(0.963, 0.993)	**0.004**	0.99	(0.98, 1.00)	0.14	0.986	(0.975, 0.997)	**0.013**	1.02	(1.00, 1.04)	0.03	1.006	(0.988, 1.024)	0.54
HAPO study																		
Linear height (5 cm increase) (cm) [c]	0.82	(0.79, 0.86)	**0.00**	0.84	(0.78, 0.90)	**0.000**	1.10	(0.98, 1.24)	0.08	0.89	(0.75, 1.08)	0.238						
Categorical height [d]																		
Average height	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)	(referent)						
Short height	1.53	(1.32, 1.78)	**0.00**	1.44	(1.18, 1.75)	**0.00**	0.55	(0.30, 1.02)	0.06	0.89	(0.41, 1.95)	0.77						
Tall height	0.66	(0.53, 0.80)	**0.00**	0.71	(0.56, 0.89)	**0.00**	0.94	(0.59, 1.50)	0.79	0.83	(0.48, 1.44)	0.51						

[a] Unadjusted model included terms for linear height or categorical height (indicator variable; short height, tall height, average height) and each outcome (binary).

[b] Adjusted models adjust for continuous variables -maternal age (years), pre-pregnancy weight (kg), gestational age (weeks) and binary variables- post-high school education married marital status, nulliparity, smoking during pregnancy, alcohol use during pregnancy, and male infant. Omega study additionally adjusts for marital status (binary) and HAPO study additionally adjusts for study site (grouped categorical variable for six study sites).

[c] **ß** for linear height represents the relative risk of outcome associated with 5 cm greater height of the mother.

P-value for the linear height represents Wald p-value for the term ß1 (associated with log transformed continuous height) from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*ln(X_{height}) + ß * Covariates$, where Y = outcome

[d] Definitions of short and tall height were cohort specific. p-values for categorical height represents Wald p-value for terms ß1 and ß2 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1*ln(X_{height\text{-}short}) + ß2*ln(X_{height\text{-}tall}) + ß * Covariates$, where Y = outcome. ß1 =0 tests whether the risk of outcome when comparing short women to average height women is different from 1. ß2 =0 tests whether the risk of outcome when comparing tall women to average height women is different from 1.

P-values < 0.05 are bold

Table 2.4 The associations of short and tall maternal height with gestational diabetes by **maternal race/ethnicity and infant sex** among Omega and HAPO study participants.

	Omega study[a]					HAPO study[a]				
	Short height		Tall height			Short height		Tall height		
	RR	95% CI	RR	95% CI	p-value	RR	95% CI	RR	95% CI	p-value
Infant sex					0.90					0.30
Male infant	**1.07**	**(1.04, 1.10)**	0.99	(0.97, 1.01)		1.04	(0.98, 1.12)	**0.95**	**(0.91, 0.98)**	
Female infant	1.03	(1.00, 1.06)	**0.97**	**(0.95, 0.99)**		**1.10**	**(1.04, 1.16)**	0.97	(0.94, 1.01)	
Race/ethnicity					>0.90					0.50
White	**1.05**	**(1.03, 1.07)**	**0.98**	**(0.96, 0.99)**		1.10	(1.00, 1.22)	**0.96**	**(0.92, 0.99)**	
African-American	1.02	(0.87, 1.19)	0.94	(0.78, 1.14)		0.99	(0.94, 1.05)	0.99	(0.95, 1.02)	
Asian	1.05	(0.97, 1.14)	0.97	(0.82, 1.15)		**1.09**	**(1.02, 1.16)**	1.19	(0.80, 1.76)	
Hispanic	1.07	(0.98, 1.18)	1.02	(0.93, 1.12)		1.08	(1.00, 1.17)	**0.90**	**(0.84, 0.98)**	

[a] The estimates are in comparison to average height women. P-value denotes the p-value of the interaction term between height and effect modifier in the adjusted model.

Table 2.5 Associations of maternal height with **fasting, one-hour and two-hour blood glucose levels** among HAPO study participants

	Fasting blood glucose [a,b]			One-hour blood glucose [a,b]			Two-hour blood glucose [a,b]		
	aß	95% CI	p-value	aß	95% CI	p-value	aß	95% CI	p-value
Linear height (5 cm increase) [c]	-0.54	(-0.73, -0.35)	**<0.001**	-3.08	(-3.91, -2.26)	**<0.001**	-2.96	(-3.58, -2.33)	**<0.001**
Categorical height [d]									
Average height	(referent)	(referent)	-	(referent)	(referent)	-	(referent)	(referent)	-
Short height	0.97	(0.29, 1.65)	**0.01**	5.83	(2.89, 8.76)	**<0.001**	4.73	(2.51, 6.94)	**<0.001**
Tall height	-1.25	(-1.82, -0.67)	**0.00**	-5.25	(-7.73, -2.77)	**<0.001**	-6.14	(-8.01, -4.27)	**<0.001**

[a] Model included term (s) for height, measured in cm and blood glucose level, measured in mg/dl.

[b] Models adjust for continuous variables -maternal age (years), pre-pregnancy weight (kg), gestational age (weeks) and binary variables- post-high school education married marital status, nulliparity, smoking during pregnancy, alcohol use during pregnancy, male infant, and study site (grouped categorical variable for six study sites).

[c] ß for linear height represents the change in blood glucose level in mg/dl per 5 cm greater height of the mother.

P-value for the linear height represents Wald p-value for the continuous term ß1 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1 * X_{height} + ß * Covariates$, where Y = birth weight in grams.

[d] Definitions of short and tall height were cohort specific. p-value for categorical height represents Wald p-value for terms ß1 and ß2 from the model, $E(Y| X_{height}, X_{covariates}) = ß0 + ß1 * X_{height\text{-}short} + ß2 * X_{height\text{-}tall} + ß * Covariates$, where Y = blood glucose level in mg/dl. ß1 =0 tests whether the mean glucose level among short women is significantly different from the mean glucose level among women of average height. ß2 =0 tests whether the mean glucose level among tall women is significantly different from the mean glucose level among women of average height.

Table 2.6 Maternal and infant characteristics of analytic cohort and full cohort in HAPO study

Characteristics [ab]	Analytic Cohort (N=4843)	Full Cohort (N=23316)	Range of Means among study centers in Full Cohort
Mother			
Age (years)	28.4 (5.87)	29.2 (5.80)	25.4-33.6
Any smoking during pregnancy	219 (4.5%)	1581 (6.8%)	0.2-23.6%
Any alcohol during pregnancy	349 (7.2%)	1612 (6.9%)	0.1-26.5%
Pre-pregnancy body mass index (kg/m^2)	25.2 (4.91)	27.7 (5.10)	24.4-29.9
Gestational age at delivery (weeks)	39.7 (1.23)	39.4 (1.7)	38.7-39.9
Blood glucose level at OGTT (mg/dl)			
Fasting	81.4 (7.26)	80.9 (6.90)	78.2-83.7
One hour	134 (31.7)	134.1 (30.9)	119.5-148.2
Two hour	112 (23.5)	111 (23.5)	99.6-120.9
Pre-eclampsia	101 (2.1%)	1116 (4.8)	1.4-11.4%
Newborn			
Male infant	2445 (50.5%)	12003 (51.5%)	49.3-54.0%
Preterm (<37 weeks)	6 (0.1%)	1608 (6.9%)	3.9-9.1%
Birth weight (g)	3290 (470)	3292 (529)	3109-3526

[a] Values are N (%) or mean (Standard Deviation)

[b] Information on data for full cohort was obtained from Reference (79)

Chapter 3. JOINT ASSOCIATION OF MATERNAL HEIGHT AND GESTATIONAL DIABETES ON INFANT OUTCOMES

3.1 ABSTRACT

Background: Despite the associations of maternal height with gestational diabetes and neonatal birth measures, the joint association of gestational diabetes and maternal height on infant birth outcomes has not been widely studied. Hence, our primary aim was to examine the joint association of maternal height and gestational diabetes with infant outcomes.

Methods: Based on the percentile values of height for each study populations (N = 3,763 in the Omega and N = 4,813 in the Hyperglycemia, and Adverse Pregnancy Outcome [HAPO] study), we categorized height of participants as short (< 20^{th}), average (20^{th}–80^{th}), or tall (≥ 80^{th}). We considered birth weight, birth length, and head circumference as continuous outcomes of interest, and infant macrosomia as a binary outcome. We estimated the average difference in mean of the continuous outcomes or relative risk (RR) of binary outcomes and their corresponding 95% confidence interval (CI) using unadjusted and adjusted linear regression models (for continuous outcome) or Poisson regression models with robust standard errors (for binary outcomes) for each height category. We estimated the p-value of the cross-product term between overall height (short, average, or tall) and gestational diabetes to determine if the associations between gestational diabetes and outcomes were statistically significantly modified by maternal height.

Results: Gestational diabetes was associated with significantly increased risk of macrosomia in infants among short height mothers (adjusted RR, aRR = 2.77, 95% CI: 1.06, 7.19; p = 0.03) and tall height mothers (aRR = 1.58, 95% CI: 1.02, 2.43; p = 0.03) but not among mothers with average

height (aRR = 1.34, 95% CI: 0.91, 1.98; p = 0.13) in the HAPO cohort. Gestational diabetes was associated with a higher infant birth length among short height mothers (0.44 cm, 95% CI: 0.09, 0.79; p = 0.01) or tall height mothers (0.57 cm, 95% CI: 0.06, 1.08; p = 0.02), but not among mothers who fell in average height category (0.12 cm, 95% CI: -0.13, 0.37; p = 0.36). Results from Omega showed no significant association of gestational diabetes with outcomes within categories of short, average, or tall height women. There was no significant interaction between gestational diabetes and maternal height on macrosomia, birth weight, birth length, or head circumference in either cohort (interaction p > 0.05).

Conclusions: Our study extends the literature on the role of maternal height and gestational diabetes in infant birth size. The findings suggest that both short women and tall women with gestational diabetes may be at higher risk for gestational diabetes-related complications and need to be monitored more closely than average height women. Further research in similar large studies may be needed to establish if gestational diabetes is associated differently with infant birth size depending on maternal height.

3.2 BACKGROUND

Gestational diabetes is a major pregnancy complication that occurs in 1%–14% of pregnancies in the US (80–82). It is defined as glucose intolerance of varying severity resulting in hyperglycemia that is first diagnosed in pregnancy among women without overt diabetes (83). Gestational diabetes is associated with a wide range of perinatal complications including fetal hypoxia and fetal macrosomia (84). Infant birth size reflected by birth weight, birth length, and head circumference has been associated with perinatal morbidity and mortality and with adverse health outcomes in adulthood (29,39–43,45–49,85,86).

Adult height reflects not only an individual's genetic make-up but also their early life environmental exposures, socioeconomic status, infection, nutrition, and growth and development (36,37). Among pregnant women, studies suggest inverse associations of short maternal height with a greater risk of gestational diabetes (15,16,20,21). Further, maternal hyperglycemia in gestational diabetes is an important risk factor for increased fetal growth and macrosomia (87).

Although associations of maternal height with gestational diabetes (15,16,20,21) and infant birth size (20,24–27) have been reported many times, the joint association of gestational diabetes and maternal height on neonatal birth outcomes has not been widely studied and has been examined in only two previous studies (34,35). The findings suggest a significant interaction between maternal height and gestational diabetes on infant birth weight where, unlike other height groups, average height women with gestational diabetes did not have a significantly greater infant birth weight, compared to average height women without gestational diabetes (35). Tall women with gestational diabetes, compared to tall women without, were reported to be more likely to deliver larger babies than short women with gestational diabetes (34). Similar associations have not been examined in a racially/ethnically diverse population. Hence, in this multi-cohort study,

our primary aim was to examine the joint association of maternal height and gestational diabetes with neonatal outcomes: birth weight, birth length, head circumferences, and infant macrosomia. We hypothesized that the impact of gestational diabetes on infant outcomes would be modified by maternal height such that the effect of gestational diabetes on the outcomes is more evident in women with tall or short height due to their 'intense' hyperglycemia than in women with an average height who may have a 'milder' hyperglycemia.

3.3 METHODS

3.3.1 *Study Settings and Study Populations*

The current study was conducted in the setting of two studies 1) Hyperglycemia, and Adverse Pregnancy Outcome (HAPO) study, a prospective cohort study that recruited pregnant women less than 31 weeks of gestation from 15 field centers located in Asia, Australia, Europe, North America, and the Middle East, between July 2000 and April 2006, and 2) the Omega study that recruited participants from pregnant women less than 30 weeks attending prenatal care clinics affiliated with Swedish Medical Center and Tacoma General Hospital in Seattle and Tacoma, Washington State, respectively, between 1996 and 2008.

The HAPO study was designed to examine associations of maternal glycemia that was below the threshold for diagnosis of overt diabetes mellitus with risk of adverse pregnancy outcomes including increased birth weight, increased cord-blood serum C-peptide, and primary cesarean delivery (57,58). Exclusion criteria were age less than 18 years, planned delivery at another hospital, uncertain last menstrual period and ultrasound estimate from 6-24 weeks of gestation age unavailable, multiple pregnancy, conception using gonadotropin ovulation induction or by in vitro fertilization, any glucose testing in pregnancy before recruitment in HAPO or a diagnosis of diabetes during the current pregnancy, history of overt diabetes, current use of drugs affecting

glucose metabolism, known to be HIV positive or to have hepatitis B or C, or inability to converse in the languages used in field center forms without the aid of an interpreter. If glucose measurements were made outside of the HAPO study after initial enrollment, the participant was excluded from further participation. OGTT results remained blinded to HAPO participants. Participants whose fasting blood glucose level exceeded 105 mg/dl (5.8 mmol/l), two-hour glucose exceeded 200 mg/dl (11.1 mmol/l), random glucose exceeded 160 mg/dl (8.9 mmol/l) or greater, or any glucose level was below 45 mg/dl (2.5 mmol/l) were further excluded from HAPO after their test results were unblinded. Informed consent was obtained from all participants. Of 53,295 eligible women (all centers), 28,562 (53.59%) agreed to participate in the study. From among those, 25,505 (89.29%) completed an oral glucose tolerance test (OGTT). The study was approved by the institutional review boards at all 15 field centers. Additional information about the study procedures and data collection have been reported elsewhere (57,58). For HAPO analyses, we had access to publicly available phenotype data on only infants and their mothers who had consented to genetic studies. We downloaded data for 4,994 mother/infant pairs from the Database of Genotypes and Phenotypes (dbGaP) website, under phs000096.v4.p1.

The primary goal of the Omega study was to examine dietary and metabolic risk factors for pregnancy complications such as preeclampsia (15). Women were eligible if they were 18 years of age or older, were able to speak and read English, initiated prenatal care before 16 weeks of gestation, and planned to carry the pregnancy to term and deliver at one of the two study hospitals. Out of 5,063 eligible women, 4,602 (91%) provided informed consent and were enrolled in the cohort. The study was approved by the institutional review boards at Swedish Medical Center and Tacoma General Hospital. Details on the study objectives, study designs, inclusion and exclusion criteria, and data collection have been reported elsewhere (55,56).

Women with pre-existing diabetes or hypertension (N = 359 Omega, N = 142 HAPO), multiple pregnancy of any order (N = 148 Omega, N = 0 HAPO), missing data on maternal height (N = 208 Omega, N = 0 HAPO), gestational diabetes (N = 2 Omega, N = 0 HAPO), birth weight (N = 7 Omega, N = 26 HAPO), birth length (N = 57 Omega, N = 7 HAPO), or head circumference (N = 53 Omega, N = 0 HAPO), including those with implausible or extreme values of height (height < 140 cm or > 200 cm) (N = 5 Omega, N = 6 HAPO) were excluded. Our final analytic sample included 4,813 mother-newborn pairs from the HAPO study and 3,763 from Omega.

3.3.2 *Data Collection*

In the Omega study, information on maternal socio-demographic and medical characteristics, family and medical history, height, pre-pregnancy weight, smoking, and alcohol drinking habits were collected through an interviewer-administered questionnaire at an average of 15 weeks of gestation (range 4-23 weeks). Information on gestational age at delivery, maternal health during the pregnancy and at the time of delivery, and pregnancy outcomes (including newborn health) were abstracted from hospital labor and delivery medical records and clinic records by trained study personnel after the estimated delivery date (15).

HAPO participants underwent 75 g OGTT as close to 28 weeks gestation as possible (range 24–32 weeks' gestation). At the OGTT visit, height, weight, and blood pressure were measured while other prenatal information, including sociodemographic characteristics and self-reported pre-pregnancy weight and race/ethnicity, was collected using questionnaires. Following OGTT, routine pregnancy care was continued at the field centers. Neonatal anthropometric measures were taken after delivery, and follow-up data were collected 4-6 weeks after delivery.

3.3.3 *Exposures, Outcomes and Adjustment Variables*

One of the two primary exposures of interest was gestational diabetes. Diagnosis of gestational diabetes was made post hoc in HAPO data based on the current International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (62). Using blood glucose values from 75 g OGTT done in the fasting state at 24–28 weeks of gestation, gestational diabetes mellitus is diagnosed if any of the following cut-off is met 1) fasting ≥ 92 mg/dl (≥ 5.2 mmol/l) or 2) one-hour ≥ 180 mg/dl (≥ 10 mmol/l) or 3) two-hour ≥ 153mg/dl (≥ 8.5 mmol/l). In the Omega study, diagnosis of gestational diabetes was based on American Diabetes Association guidelines in use at the time (62,78). All women were screened for gestational diabetes between 24 and 28 weeks gestation using a 50 g glucose challenge test. A 3-hour OGTT with a 100 g glucose was done among women who failed the screening test (post-load glucose ≥ 140 mg/dl). Women were diagnosed with gestational diabetes if ≥ 2 of the following cut-offs were met 1) fasting ≥ 105 mg/dl (≥ 5.8 mmol/l) or 2) one-hour ≥ 190 mg/dl (≥ 10.6 mmol/l) or 3) two-hour ≥ 165mg/dl (≥ 9.2 mmol/l 4) 3-hour ≥ 145mg/dl (≥ 8.1 mmol/dl) and no indication of prior chronic diabetes was noted.

The primary exposure of interest, maternal height, was obtained through self-report in Omega study while in HAPO, it was measured during OGTT visit. We defined the categories of height based on the quintile values of height in centimeter separately for each study population: short height if the maternal height was less than 20^{th} percentile in that cohort, average height if the height was in between 20^{th} and 80^{th} percentile and tall if the height was greater than or equal to the 80^{th} percentile value.

Our primary outcomes of interest were birth weight (gram, g), birth length (cm), and head circumference (cm), information on which were abstracted from newborn medical records. We defined macrosomia as an infant's birth weight was ≥ 4000 g.

Based on our review of the literature, a *priori* confounding variables or precision variables were selected for inclusion in our study. Maternal age (years) and self-reported pre-pregnancy weight (kg) were included as continuous variables. Post-high school education, married marital status, nulliparity, smoking during pregnancy, alcohol use during pregnancy, and male infant were included as binary variables. Of note, information on marital status was available only in the Omega Study. We modeled maternal race/ethnicity as an indicator variable in the adjusted models. Maternal race/ethnicity was categorized as White/African-American/Asian/Hispanic in both cohorts. We additionally included study sites as a grouped categorical variable in all adjusted models for the HAPO study population.

3.3.4 *Statistical Analysis*

We first examined distributions of sociodemographic, pregnancy, and infant-related characteristics by gestational diabetes status and by quintiles of height using frequency distribution of categories or mean and standard deviation (SD) of continuous values.

Next, we examined the association of gestational diabetes with outcomes for each height category using regression models. We estimated the average difference in mean of the continuous outcomes or relative risk (RR) of binary outcomes and their corresponding 95% confidence interval (CI) using unadjusted and adjusted linear regression models (for continuous outcome) or Poisson regression models with robust standard errors (for binary outcomes) (61). Using unadjusted regression models, we estimated the crude association for each outcome by fitting a model with gestational diabetes as the primary exposure. We then added the covariates listed above

to each crude models to estimate the adjusted association of the gestational diabetes with each outcome.

The statistical significance effect of maternal height on gestational diabetes-outcome association was examined in additive scale for continuous outcomes and multiplicative scale for the binary outcome. Adjusted linear or modified Poisson regression models that included gestational diabetes, indicator variables for short, average, and tall maternal height, and their interactions, i.e., product of each indicator variable with gestational diabetes. We estimated the p-value of the interaction terms between overall height and gestational diabetes to determine if the association between gestational diabetes and outcomes was statistically significantly modified by maternal height.

Sensitivity analyses were conducted using the values from the fasting, one-hour, and two-hour OGTT instead of gestational diabetes to estimate the association of blood glucose levels with outcomes for each height category using adjusted regression models in the HAPO study.

In all analyses, a p-value of less than 0.05 in a two-sided test was considered statistically significant. All calculations and analyses were done in a cohort-specific manner. Analyses were conducted using R studio software (R Version 4.1.1 [2021-08-10]).

3.4 RESULTS

Pregnant women in the Omega study were on average 32.7 (SD: 4.45) years old with a mean body mass index (BMI) of 23.4 (SD: 4.52) kg/m^2, a mean pre-pregnancy body weight of 65.9 (SD: 13.6) kg and a mean height of 168 (SD: 7.67) cm (Tables 3.1). Overall, 85.3%, 8.8%, 91.0%, and 61.5% of the pregnant women were White, married, had completed post-high school education, or had no previous pregnancies at enrollment, respectively. Most of the participants in the HAPO study were White (30.0%), African-American (26.8%), or Asian (25.1%), nulliparous (68.0%), and younger,

with a mean age of 28.4 (SD: 5.88) years. The mean BMI, pre-pregnancy body weight and height of HAPO participants were 25.2 (SD: 4.91) kg/m^2, 64.8 (SD: 13.6) kg, and 161 (7.51) cm, respectively (Table 3.2). Based on the quintile values of height in the Omega and HAPO cohorts, women were considered short if their height was less than 161.37 cm or 154.05 cm (corresponding to the first quintile cutoff value) and tall if their height was greater than or equal to 173.99 cm or 167.00 cm (corresponding to the last quintile cutoff value), respectively.

Selected characteristics of pregnant women and their newborn in each study population are presented by height quintiles in Tables 3.1 to 3.2 and by gestational diabetes status in Tables 3.3 to 3.4. Compared to women in the higher quintiles of height, women in the lower quintiles were in general less educated and had lower pre-pregnancy body weight, higher pre-pregnancy BMI, and a greater likelihood of being diagnosed with gestational diabetes in both cohorts. Compared to women without gestational diabetes, women with gestational diabetes in each of the two cohorts were more likely to be Asian, be older, be heavier, have obesity and have a height in first quintile category (Omega and HAPO).

In the unadjusted regression models stratified by categories of maternal height in HAPO, gestational diabetes status was associated with an increased risk of all outcomes of interest among short, average height, or tall women except the risk estimate for head circumference among short and average women was not significant (Table 3.5). However, multivariable regression models indicated that the associations of gestational diabetes with mean head circumference and mean birth length of infants and the risk of macrosomia differed by categories of maternal height. Diagnosis of gestational diabetes was associated with significantly increased risk of macrosomia in infants among short height mothers (adjusted RR [aRR] = 2.77, 95% CI: 1.06, 7.19; p = 0.03) and tall height mothers (aRR = 1.58, 95% CI: 1.02, 2.43; p = 0.03) but not among mothers with

average height (aRR = 1.34, 95% CI: 0.891, 1.98; p = 0.13). Gestational diabetes was associated with a higher birth length of infants among tall height mothers (0.57 cm, 95% CI: 0.06, 1.08; p = 0.02) or short height mothers (0.44 cm, 95% CI: 0.09, 0.79; p = 0.01), but not among mothers who fell in average height category (0.12 cm, 95% CI: -0.13, 0.37; p = 0.36). Further, the average head circumference of infants born to tall mothers with gestational diabetes was greater than that of infants born to tall mothers without gestational diabetes (0.36 cm, 95% CI: 0.04, 0.68; p = 0.02). This association was not present among short height women (0.26 cm, 95% CI: -0.02, 0.55; p = 0.07) or average height women (0.07 cm, 95% CI: -0.09, 0.23; p = 0.37). However, associations of gestational diabetes and the outcomes (macrosomia, birth weight, birth length, and head circumference) did not show significant effect modification by maternal height (interaction p > 0.05 for each outcome).

Results from the Omega study showed no significant association of gestational diabetes with outcomes within categories of short, average, or tall height women (Table 3.5). The mean difference in the birth weight of infants associated with maternal gestational diabetes was 64.62 g (aß: 64.62, 95% CI: -74.21, 203.45; p = 0.36) among short mothers, 55.26 g (aß: -55.26, 95% CI: -170.01, 59.49; p = 0.34) among average height mothers, and 62.07 g (aß: 62.07, 95% CI: (-150.49, 274.64; p = 0.56) among tall mothers. In contrast to HAPO findings, results from Omega study did not provide any evidence to support the hypothesis that gestational diabetes-infant outcome associations varied by maternal height.

In sensitivity analyses conducted using the individual glucose measures from the OGTT, similar to our findings from the height-stratified analyses reported above, higher blood plasma glucose values were associated with a higher infant birth weight among women of all height categories (Table 3.6). A 10 mg/dl greater fasting, one-hour, or two-hour glucose levels was

associated with a significantly higher risk of macrosomia among tall women (fasting: aRR = 1.59, 95% CI: 1.29, 1.96; p < 0.001, one-hour: aRR = 1.09, 95% CI: 1.03, 1.15; p = 0.002, and two-hour: aRR = 1.11, 95% CI: 1.03, 1.20; p = 0.003) and average height women (fasting: aRR = 1.32, 95% CI: 1.09, 1.60; p = 0.003, one-hour: aRR = 1.06, 95% CI: 1.01, 1.12; p = 0.01, and two-hour: aRR = 1.10, 95% CI: 1.03, 1.17; p = 0.02), but not among short women (fasting: aRR = 1.38, 95% CI: 0.79, 2.41; p = 0.25, one-hour: aRR = 1.11, 95% CI: 0.94, 1.31; p = 0.19, and two-hour: aRR = 1.16, 95% CI: 0.97, 1.37; p = 0.09). The significance of the findings, in general, did not differ by fasting or post load status of the blood glucose and no single measure of blood glucose was superior in predicting the outcomes.

3.5 DISCUSSION

Gestational diabetes was associated with significantly greater risk of macrosomia and greater birth length among infants born to short height mothers and tall height mothers but not among mothers with average height in the HAPO study. Higher fasting, one-hour, or two-hour glucose levels in HAPO were associated with a significantly greater risk of macrosomia among tall women and average height women, but not among short women. Results from Omega showed no significant association of gestational diabetes with outcomes within categories of short, average, or tall height women. There was no significant interaction between gestational diabetes and maternal height on birth weight, birth length, head circumference, and macrosomia in either cohort (interaction p > 0.05).

To the best of our knowledge, only two studies have investigated whether the associations of gestational diabetes with pregnancy outcomes and complications varied by maternal height (34,35). In a study conducted among 4,111 primiparous women in Finland, Masalin et al. (35) found that after adjustment for age, pre-pregnancy BMI, and educational attainment, gestational

diabetes was associated with a significant increase in infant birth weight among women who fell in lowest and highest height categories defined by Z-score: I (< 1.5), II (1.5 to < 0.319), III (0.319 to < 0.319), IV (0.319 to < 1.15), and V (≥ 1.15). Among average height women in the second and third height levels (159 cm–167 cm), gestational diabetes had no impact on infant birth weight Z-score. This is in line with our findings of greater risk of macrosomia in infants included in the HAPO study among short height mothers (<154.05 cm) and tall height mothers (≥ 167.0 cm) but not among mothers with average height, although infant birth weight did not vary by maternal height levels in our study. Unlike our findings in the current study, the interaction between maternal height and gestational diabetes on infant birth weight was reported to be significant by Masalin et al. (interaction p = 0.016). There was a significant association of gestational diabetes with infant birth weight among short height and tall height mothers, but not among average height (35). Despite the similarity in analytic methods (e.g., categorizing height using percentiles), certain factors may account for a part of the difference in findings between HAPO, Omega, and the Finnish cohort. Since participants were not blinded to their OGTT results, the lack of association in the Omega cohort may be due to treatment effect or lifestyle interventions which may have reduced the risk of gestational diabetes related complications in all groups defined by height. In a different analysis (using data from Omega), we also found that gestational diabetes was not associated with birth outcomes evaluated in this study, contrary to several other previous reports. In addition, Omega women are generally tall with less variation in height. The mean height of women in the Omega study was 168 cm (SD: 7.67) while women in the other two studies were shorter (Finnish study: mean height: 166 cm; SD: 6.00 and HAPO study: mean height 161cm; SD: 7.51). The diagnostic thresholds for glucose values used in the definition of gestational diabetes were similar in HAPO and the Finnish study but different from the Omega cohort. To add, HAPO participants

who were applied the lower IADPSG diagnostic threshold for post hoc gestational diabetes in our study possibly had a "milder" gestational diabetes because of the exclusion of women with blood glucose levels above a threshold in HAPO. Masalin et al. defined macrosomia as birth weight ≥ 4500 g while in HAPO and Omega studies, we used 4000 g or greater as the cut-off definition of macrosomia. The prevalence of macrosomia varied greatly between the studies with Omega having the highest prevalence of 14.24% (HAPO: 7.1% and the Finnish study: 8.4%). However, we were unable to determine whether the lack of any significant associations in the Omega study, as opposed to the results from HAPO and the Finnish study, could be attributed to different diagnostic criteria for gestational diabetes, less variation in height of the women, differing prevalence of macrosomia, or unmeasured or residual confounding in the Omega study including any factors that may be different between predominantly White Omega cohort (vs. the predominantly European Finnish cohort or a more heterogenous HAPO cohort).

Using data from two Singaporean cohorts (the Growing Up in Singapore Towards healthy Outcomes (GUSTO) mother-infant cohort study and the National University Hospital (NUH) cohort, Chu et al. investigated the associations between gestational diabetes and pregnancy complications among mothers in short and tall height categories (N = 5,168) (34). Consistent with our findings from HAPO, they reported association of maternal height on macrosomia varied by height levels. Using WHO-1999 criteria for diagnosis of gestational diabetes (fasting ≥ 7.0 mmol/l and/or two-hour post 75 g OGTT ≥ 7.8 mmol/l), they found that among tall women, but not short women, gestational diabetes was associated with a greater odds of macrosomia among infants, after adjustment for age, ethnicity, BMI, parity, and gestational age (aOR: 1.85, 95% CI: 1.02, 3.36; p = 0.044 among tall women and aOR: 0.56, 95% CI: 0.19, 1.63; p = 0.286 among short women). However, when they used WHO-2013 criteria, which was same as the post hoc IADPSG

diagnostic criteria used in HAPO, the risk of macrosomia was not statistically significant among both short (aOR: 0.80, 95% CI: 0.26, 2.49; p = 0.702) and tall women (aOR: 1.97, 95% CI: 0.97, 3.98; p = 0.060), suggesting that the difference in gestational diabetes diagnostic criteria may account for at least some part of the difference in findings in between Omega and HAPO studies. They found that among tall women, but not short, gestational diabetes diagnosed using WHO-1999 criteria was associated with a greater birth weight of infants, after adjustment for age, ethnicity, BMI, parity, and gestational age (aß [adjusted difference in mean]: 31.72, 95% CI: 0.10, 63.33; p = 0.049 for short women and aß: 57.16, 95% CI: 20.95, 93.38; p = 0.002 for tall women). Using GDM-2013 criteria, the effect estimates were aß: 42.03, 95% CI: 1.65, 82.41; p = 0.041 for tall women and aß: 8.56, 95% CI: -27.53, 44.66; p = 0.642 for short women. They used the height of each ethnic group (Chinese, Malay, Indian, Caucasian, Eurasian, and Others) and categorized women into two categories of short height group and tall height group using the median value of height for that ethnic group: Chinese: 159 cm, Malay: 157 cm, Indian: 158 cm, Caucasian: 166 cm, Eurasian: 161.5 cm, Others: 157 cm. In our study, we did not adjust for gestational age as it may be in the causal pathway, linking gestational diabetes with the pregnancy outcomes, nor used ethnicity-specific height that could account for some difference in the observed association in Chu et al. and our study.

The association of gestational diabetes with macrosomia and birth length among short and tall women, but not among average height women indicates a potential role of body composition in these relationships. The association of height with gestational diabetes has partly been attributed to the diagnostic test, OGTT, where all women regardless of their height are given a fixed load of glucose (21). Shorter women have a smaller amount of metabolically active muscle tissue to metabolize the same fixed glucose load during OGTT, as compared to taller women. Therefore,

they have a higher post-load glucose level and may be more often diagnosed with gestational diabetes (39). However, we observed that the risk of complications of gestational diabetes increased for short height women (compared to average height) indicating a true pathophysiological relationship between height and gestational diabetes suggesting that the association between short height and gestational diabetes risk is not completely a result of this artifact. If this is the case, the lack of association of gestational diabetes with macrosomia among average height women may be attributed to a milder form of diabetes or to less hyperglycemia in this group of women. Consistent with this possibility, the mean one hour and two-hour OGTT glucose levels for average height women in our study were lower than that for short women (one-hour: 175 vs 185 mg/dl and two-hour 146 vs 139 mg/dl). On the other hand, despite an higher insulin sensitivity (88,89), tall women had an increased risk of gestational diabetes complications similar to short women in our study. This might indicate that hyperglycemia in tall women may be of severe form leading to complications despite the higher insulin sensitivity (35). Among women with gestational diabetes, the mean fasting glucose level was highest for tall women in our study (tall: 92.4 mg/dl, medium 90.8 mg/dl, and short 87.5 mg/dl). On the other hand, the muscle mass in short women is limited and even a small increase in maternal glucose level impacts the infant outcome negatively (35).

Strengths of this study include the use of data from two heterogeneous and ethnically diverse prospective cohorts with rich individual-level data, one of which was designed to investigate the associations of maternal hyperglycemia with adverse pregnancy outcomes. This enabled us to incorporate many confounders in our analysis to obtain non-biased estimates of the associations. To the best of our knowledge, this is the first study to examine the interaction of maternal height with gestational diabetes on pregnancy outcomes outside of Finland or Singapore. We used

continuous blood glucose values, in addition to the use of gestational diabetes status to ensure the robustness of our results.

Several limitations of our study are worth mentioning. Height was self-reported in the Omega study and self-reported height tends to be overestimated (36). Misclassification due to overreporting or underreporting of reported measures (such as pre-pregnancy weight in Omega) is a possibility. Residual confounding due to incomplete adjustment of confounders and unmeasured confounding in the findings of an observational study such as ours is another limitation. Type I error due to multiple tests might be an issue because of the many statistical tests we conducted. The findings from this study are not generalizable to the groups of women that were excluded from the analysis (e.g., women with pre-existing diabetes or hypertension). There could be a difference between participants who agreed to participate in the HAPO study (53.59%) and those who didn't (46.10%) affecting the risk estimates, but we were unable to determine this based on our data. Further, data on only a subset of enrolled participants in HAPO was publicly available for download from dbGAP. There is a possibility of selection bias because of substantially greater proportion of term births in the analytic cohort. However, other characteristics of the pregnant women in our analytic cohort were similar to those in the full cohort (79) (Table 3.8). Women who exceeded a certain threshold of blood glucose values were excluded in the HAPO study which may lead to an underestimation of the association of gestational diabetes with neonatal outcomes due to exclusion of more severe cases of hyperglycemia.

In summary, our results indicate heterogeneity in associations of gestational diabetes with infant birth size by maternal height as well as cohort. Gestational diabetes was associated with a significantly increased risk of macrosomia and birth length in infants among short and tall mothers but not among mothers with average height in HAPO cohort. Results from Omega showed no

significant association of gestational diabetes with outcomes within categories of short, average, or tall height women. Our study extends the literature on the role of maternal height and gestational diabetes in infant birth size. Through better risk categorization based on maternal height, women at a greater risk of gestational diabetes related macrosomia can be identified and monitoring approaches and prevention strategies can be implemented. Findings from these analyses highlight that though tall height may be protective against gestational diabetes, both short women with gestational diabetes and tall women with gestational diabetes may need to be monitored closely for gestational diabetes-related complications during pregnancy. Further research in similar large studies may be needed to establish if gestational diabetes is associated differently with infant birth size depending on maternal height.

Table 3.1 Selected characteristics of **Omega** study participants enrolled at Swedish Medical Center and Tacoma General Hospital in Washington State between1996 and 2008 by height quintiles

Characteristics [a]	First quintile[b] (N=753)	Second quintile[c] (N=752)	Third quintile[d] (N=753)	Fourth quintile[e] (N=751)	Last quintile[f] (N=754)	Overall (N=3763)
Mother						
Race/ethnicity						
White	526 (69.9%)	636 (84.6%)	666 (88.4%)	674 (89.7%)	709 (94.0%)	3211 (85.3%)
African-American	17 (2.3%)	14 (1.9%)	9 (1.2%)	14 (1.9%)	9 (1.2%)	63 (1.7%)
Asian	149 (19.8%)	64 (8.5%)	42 (5.6%)	24 (3.2%)	14 (1.9%)	293 (7.8%)
Hispanic	61 (8.1%)	38 (5.1%)	36 (4.8%)	39 (5.2%)	22 (2.9%)	196 (5.2%)
Age (years)	32.1 (4.73)	32.6 (4.51)	32.9 (4.34)	33.0 (4.33)	33.0 (4.29)	32.7 (4.45)
Age ≥ 35 years	237 (31.5%)	254 (33.8%)	272 (36.1%)	271 (36.1%)	274 (36.3%)	1308 (34.8%)
Married	79 (10.5%)	61 (8.1%)	63 (8.4%)	62 (8.3%)	66 (8.8%)	331 (8.8%)
Nulliparous [g]	448 (59.5%)	453 (60.2%)	482 (64.0%)	464 (61.8%)	466 (61.8%)	2313 (61.5%)
Post high school education [h]	644 (85.5%)	669 (89.0%)	699 (92.8%)	699 (93.1%)	712 (94.4%)	3423 (91.0%)
Smoked during pregnancy [i]	111 (14.7%)	163 (21.7%)	150 (19.9%)	143 (19.0%)	179 (23.7%)	746 (19.8%)
Intake of any alcohol during pregnancy [j]	67 (8.9%)	66 (8.8%)	79 (10.5%)	77 (10.3%)	65 (8.6%)	354 (9.4%)
Pre-pregnancy weight (kg)	59.4 (11.9)	63.6 (12.4)	65.2 (12.0)	68.1 (13.2)	73.2 (14.2)	65.9 (13.6)
Height (cm)	157 (3.43)	164 (1.21)	168 (1.07)	172 (1.29)	179 (4.07)	168 (7.67)
Pre-pregnancy body mass index (kg/m^2)	24.0 (4.83)	23.7 (4.65)	23.2 (4.28)	23.2 (4.50)	22.9 (4.23)	23.4 (4.52)
Pre-pregnancy body mass index category (kg/m^2)						
Underweight (<18.5)	26 (3.5%)	28 (3.7%)	30 (4.0%)	39 (5.2%)	42 (5.6%)	165 (4.4%)
Normal (18.5–24.9)	529 (70.3%)	537 (71.4%)	542 (72.0%)	538 (71.6%)	542 (71.9%)	2688 (71.4%)
Overweight (25–29.9)	115 (15.3%)	124 (16.5%)	126 (16.7%)	123 (16.4%)	135 (17.9%)	623 (16.6%)
Obesity (≥ 30)	83 (11.0%)	63 (8.4%)	55 (7.3%)	51 (6.8%)	35 (4.6%)	287 (7.6%)
Gestational age at delivery (weeks) [k]	38.8 (2.60)	38.8 (1.83)	39.0 (1.54)	39.0 (1.83)	39.1 (1.73)	38.9 (1.94)
Gestational diabetes	66 (8.8%)	33 (4.4%)	28 (3.7%)	30 (4.0%)	26 (3.4%)	183 (4.9%)
Pre-eclampsia	13 (1.7%)	22 (2.9%)	10 (1.3%)	15 (2.0%)	10 (1.3%)	70 (1.9%)
Newborn						
Male infant [l]	400 (53.1%)	383 (50.9%)	367 (48.7%)	395 (52.6%)	394 (52.3%)	1939 (51.5%)

Preterm (<37 weeks)	75 (10.0%)	72 (9.6%)	48 (6.4%)	50 (6.7%)	38 (5.0%)	283 (7.5%)
Birth weight (g)	3310 (524)	3400 (552)	3470 (517)	3520 (480)	3600 (519)	3460 (528)
Birth length (cm)	50.0 (3.46)	50.5 (3.34)	50.6 (3.38)	51.1 (2.96)	51.4 (3.26)	50.7 (3.32)
Head circumference (cm)	34.5 (2.25)	34.6 (2.13)	34.8 (2.20)	34.9 (2.13)	35.0 (2.16)	34.8 (2.18)

[a] Values are N (%) or mean (Standard Deviation)
[b] First quintile, height <161.37 cm.
[c] Second quintile, height ≥ 161.37 cm to < 165.44 cm.
[d] Third quintile, height ≥ 165.44 cm to < 169.54 cm.
[e] Fourth quintile, height ≥ 169.54 cm to > 173.99 cm.
[f] Fifth quintile, height ≥ 173.99 cm
[g] Information on parity missing for 1 subject. For each quintile: 1 (quintile 1) was missing.
[h] Educational status missing for 223 subjects. For each quintile: 82 (quintile 1), 57 (quintile 2), 31 (quintile 3), 36 (quintile 4), 17 (quintile 5)
[I] Smoking status missing for 238 subjects. For each quintile: 85 (quintile 1), 60 (quintile 2), 35 (quintile 3), 39 (quintile 4), 19 (quintile 5)
[j] Alcohol intake missing for 53 subjects. For each quintile: 13 (quintile 1), 14 (quintile 2), 10 (quintile 3), 3 (quintile 4), 13 (quintile 5)
[k] Gestational age at delivery missing for 1 subject. For each quintile: 1(quintile 3)
[l] Infant sex missing for 2 subjects. For each quintile: 1 (quintile 1), 1 (quintile 4)

Table 3.2 Selected characteristics of **HAPO** study participants enrolled at field centers between July 2000 and April 2006 by height quintiles

Characteristics [a]	First quintile[b] (N=928)	Second quintile[c] (N=984)	Third quintile[d] (N=909)	Fourth quintile[e] (N=936)	Last quintile[f] (N=1056)	Overall (N=4813)
Mother						
Race/ethnicity						
White	74 (8.0%)	215 (21.8%)	282 (31.0%)	374 (40.0%)	499 (47.3%)	1444 (30.0%)
African-American	91 (9.8%)	188 (19.1%)	261 (28.7%)	300 (32.1%)	448 (42.4%)	1288 (26.8%)
Hispanic	152 (16.4%)	188 (19.1%)	229 (25.2%)	206 (22.0%)	96 (9.1%)	871 (18.1%)
Asian	611 (65.8%)	393 (39.9%)	137 (15.1%)	56 (6.0%)	13 (1.2%)	1210 (25.1%)
Age (years)	28.3 (5.64)	28.1 (5.68)	28.4 (5.92)	28.5 (5.90)	28.7 (6.20)	28.4 (5.88)
Age ≥ 35 years	121 (13.0%)	124 (12.6%)	128 (14.1%)	139 (14.9%)	188 (17.8%)	700 (14.5%)
Nulliparous [g]	497 (53.6%)	610 (62.0%)	623 (68.5%)	702 (75.0%)	841 (79.6%)	3273 (68.0%)
Post high school education [h]	256 (27.6%)	435 (44.2%)	480 (52.8%)	533 (56.9%)	655 (62.0%)	2359 (49.0%)
Smoking habits						
Smoking during pregnancy	13 (1.4%)	39 (4.0%)	47 (5.2%)	59 (6.3%)	61 (5.8%)	219 (4.6%)
Number of cigarettes/days during pregnancy	1.02 (0.163)	1.05 (0.254)	1.07 (0.306)	1.08 (0.319)	1.07 (0.304)	1.06 (0.277)
Alcohol drinking habits						
Alcohol during pregnancy	22 (2.4%)	55 (5.6%)	68 (7.5%)	84 (9.0%)	119 (11.3%)	348 (7.2%)
Number of alcoholic drinks/days during pregnancy						
<1 per day	19 (2.0%)	55 (5.6%)	67 (7.4%)	84 (9.0%)	116 (11.0%)	341 (7.1%)
1–2 per day	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	3 (0.3%)	4 (0.1%)
Illicit drug use in pregnancy	0 (0%)	3 (0.3%)	5 (0.6%)	7 (0.7%)	8 (0.8%)	23 (0.5%)
Pre-pregnancy weight (kg) [i]	58.7 (9.64)	62.5 (11.4)	64.6 (12.7)	67.4 (14.0)	70.9 (15.9)	64.8 (13.6)
Height (cm)	150 (2.98)	156 (1.28)	160 (1.11)	164 (1.20)	171 (3.58)	161 (7.51)
Pre-pregnancy body mass index (kg/m^2) [i]	26.1 (4.18)	25.6 (4.66)	25.1 (4.97)	24.9 (5.17)	24.3 (5.32)	25.2 (4.91)

Pre-pregnancy body mass index category (kg/m^2)						
Underweight (<18.5)	10 (1.1%)	17 (1.7%)	35 (3.9%)	36 (3.8%)	82 (7.8%)	180 (3.7%)
Normal (18.5–24.9)	391 (42.1%)	437 (44.4%)	413 (45.4%)	442 (47.2%)	479 (45.4%)	2162 (44.9%)
Overweight (25–29.9)	354 (38.1%)	299 (30.4%)	249 (27.4%)	214 (22.9%)	202 (19.1%)	1318 (27.4%)
Obesity (≥ 30)	128 (13.8%)	126 (12.8%)	106 (11.7%)	120 (12.8%)	102 (9.7%)	582 (12.1%)
Gestational age at delivery (weeks)	39.5 (1.23)	39.6 (1.22)	39.7 (1.18)	39.8 (1.24)	39.9 (1.22)	39.7 (1.23)
Blood glucose level at OGTT (mg/dl)						
Fasting	81.0 (7.39)	81.1 (6.89)	81.9 (7.51)	81.9 (7.41)	81.4 (7.15)	81.5 (7.27)
One hour	145 (32.9)	137 (31.9)	133 (31.1)	131 (30.7)	127 (28.8)	134 (31.6)
Two hour	119 (25.7)	115 (23.8)	110 (22.5)	110 (22.3)	106 (21.3)	112 (23.5)
Gestational diabetes[j]	204 (22.0%)	163 (16.6%)	129 (14.2%)	122 (13.0%)	101 (9.6%)	719 (14.9%)
Pre-eclampsia	12 (1.3%)	15 (1.5%)	27 (3.0%)	24 (2.6%)	23 (2.2%)	101 (2.1%)
Newborn						
Male infant	457 (49.2%)	494 (50.2%)	453 (49.8%)	476 (50.9%)	548 (51.9%)	2428 (50.4%)
Preterm (<37 weeks)	0 (0%)	1 (0.1%)	1 (0.1%)	2 (0.3%)	2 (0.3%)	6 (0.2%)
Birth weight (g)	3110 (408)	3210 (428)	3290 (456)	3370 (465)	3450 (505)	3290 (470)
Birth length (cm)	49.3 (1.81)	49.7 (1.96)	50.0 (2.26)	50.2 (2.19)	50.5 (2.37)	50.0 (2.17)
Head circumference (cm)	33.9 (1.42)	34.1 (1.33)	34.2 (1.43)	34.4 (1.41)	34.5 (1.58)	34.2 (1.45)

[a] Values are N (%) or mean (Standard Deviation)

[b] First quintile, height <154.05 cm.

[c] Second quintile, height ≥ 154.05 cm to < 158.75 cm.

[d] Third quintile, height ≥ 158.75 cm to < 162.56 cm.

[e] Fourth quintile, height ≥ 162.56 cm to < 167.00 cm.

[f] Fifth quintile, height ≥ 167.00 cm

[g] Information on parity missing for 577 subjects. For each quintile: 258 (quintile 1), 169 (quintile 2), 80 (quintile 3), 45 (quintile 4), 25 (quintile 5)

[h] Educational status missing for 235 subjects. For each quintile: 89 (quintile 1), 42 (quintile 2), 37 (quintile 3), 36 (quintile 4), 31 (quintile 5)

[i] Pre-pregnancy weight and BMI missing for 571 subjects. For each quintile: 113 (quintile 1), 110 (quintile 2), 94 (quintile 3), 136 (quintile 4), 118 (quintile 5)

[j] Diagnosis of gestational diabetes was made post hoc based on IADPSG criteria (1 or more values exceeding the thresholds: fasting ≥92 mg/dl, one-hour ≥180 mg/dl, and two-hour ≥153 mg/dl)

Table 3.3 Selected characteristics of **Omega** study participants enrolled at Swedish Medical Center and Tacoma General Hospital in Washington State between1996 and 2008 by gestational diabetes status

Characteristics [a]	Gestational diabetes (N=183)	No gestational diabetes (N=3580)	Overall (N=3763)
Mother			
Race/ethnicity			
White	131 (71.6%)	3080 (86.0%)	3211 (85.3%)
African-American	5 (2.7%)	58 (1.6%)	63 (1.7%)
Asian	36 (19.7%)	257 (7.2%)	293 (7.8%)
Hispanic	11 (6.0%)	185 (5.2%)	196 (5.2%)
Age (years)	33.6 (4.69)	32.7 (4.44)	32.7 (4.45)
Age ≥ 35 years	79 (43.2%)	1229 (34.3%)	1308 (34.8%)
Married	21 (11.5%)	310 (8.7%)	331 (8.8%)
Nulliparous [b]	107 (58.5%)	2206 (61.6%)	2313 (61.5%)
Post high school education [c]	159 (86.9%)	3264 (91.2%)	3423 (91.0%)
Smoked during pregnancy [d]	33 (18.0%)	713 (19.9%)	746 (19.8%)
Intake of any alcohol during pregnancy [e]	20 (10.9%)	334 (9.3%)	354 (9.4%)
Pre-pregnancy weight (kg)	73.2 (21.7)	65.5 (12.9)	65.9 (13.6)
Maternal height (cm)	165 (8.75)	168 (7.60)	168 (7.67)
Maternal height quintiles			
First quintile (<161.37 cm)	66 (36.1%)	687 (19.2%)	753 (20.0%)
Second quintile (≥ 161.37 cm to <165.44 cm)	33 (18.0%)	719 (20.1%)	752 (20.0%)
Third quintile (≥ 165.44 cm to <169.54 cm)	28 (15.3%)	725 (20.3%)	753 (20.0%)
Fourth quintile (≥ 169.54 cm to >173.99 cm)	30 (16.4%)	721 (20.1%)	751 (20.0%)
Last quintile (≥ 173.99 cm)	26 (14.2%)	728 (20.3%)	754 (20.0%)
Pre-pregnancy body mass index (kg/m^2)	24.0 (4.81)	23.7 (4.70)	23.4 (4.51)
Pre-pregnancy body mass index category (kg/m^2)			
Underweight (<18.5)	4 (2.2%)	161 (4.5%)	165 (4.4%)
Normal (18.5–24.9)	92 (50.3%)	2596 (72.5%)	2688 (71.4%)
Overweight (25–29.9)	48 (26.2%)	575 (16.1%)	623 (16.6%)
Obesity (≥ 30)	39 (21.3%)	248 (6.9%)	287 (7.6%)
Gestational age at delivery (weeks) [f]	38.4 (1.71)	39.0 (1.95)	38.9 (1.94)
Pre-eclampsia	10 (5.5%)	60 (1.7%)	70 (1.9%)
Newborn			
Male infant [g]	88 (48.1%)	1851 (51.7%)	1939 (51.5%)
Preterm (<37 weeks)	22 (12.0%)	261 (7.3%)	283 (7.5%)

Birth weight (g)	3480 (557)	3460 (527)	3460 (528)
Birth length (cm)	50.7 (2.74)	50.7 (3.35)	50.7 (3.32)
Head circumference (cm)	34.7 (1.69)	34.8 (2.21)	34.8 (2.18)

[a] Values are N (%) or mean (Standard Deviation)
[b] Information on parity missing for 1 subject with gestational diabetes.
[c] Educational status missing for 15 subjects with gestational diabetes and 208 without gestational diabetes.
[d] Smoking status missing for 15 subjects with gestational diabetes and 223 without gestational diabetes.
[e] Alcohol intake missing for 2 subjects with gestational diabetes and 51 without gestational diabetes.
[f] Gestational age at delivery missing for 1 subject without gestational diabetes.
[g] Infant sex missing for 2 subjects without gestational diabetes.

Table 3.4 Selected characteristics of **HAPO** study participants enrolled at field centers between July 2000 and April 2006 by gestational diabetes status

Characteristics [a]	No gestational diabetes[b] (N=4094)	Gestational diabetes (N=719)	Overall (N=4813)
Mother			
Race/ethnicity			
White	1271 (31.0%)	173 (24.1%)	1444 (30.0%)
African-American	1182 (28.9%)	106 (14.7%)	1288 (26.8%)
Hispanic	685 (16.7%)	186 (25.9%)	871 (18.1%)
Asian	956 (23.4%)	254 (35.3%)	1210 (25.1%)
Age (years)	28.1 (5.85)	30.5 (5.62)	28.4 (5.88)
Age ≥ 35 years	542 (13.2%)	158 (22.0%)	700 (14.5%)
Nulliparous [c]	2849 (69.6%)	424 (59.0%)	3273 (68.0%)
Post high school education [d]	2042 (49.9%)	317 (44.1%)	2359 (49.0%)
Smoking habits			
Smoking during pregnancy	196 (4.8%)	23 (3.2%)	219 (4.6%)
Number of cigarettes/days during pregnancy	1.06 (0.284)	1.04 (0.227)	1.06 (0.277)
Alcohol drinking habits			
Alcohol during pregnancy	306 (7.5%)	42 (5.8%)	348 (7.2%)
Number of alcoholic drinks/days during pregnancy			
<1 per day	300 (7.3%)	41 (5.7%)	341 (7.1%)
1–2 per day	4 (0.1%)	0 (0%)	4 (0.1%)
Illicit drug use in pregnancy	20 (0.5%)	3 (0.4%)	23 (0.5%)
Pre-pregnancy weight (kg) [e]	64.0 (13.0)	69.0 (15.7)	64.8 (13.6)
Maternal height (cm)	161 (7.46)	159 (7.45)	161 (7.51)
Maternal height quintiles			
First quintile (<157.48 cm)	724 (17.7%)	204 (28.4%)	928 (19.3%)
Second quintile (≥ 157.48 cm to <161.20 cm)	821 (20.1%)	163 (22.7%)	984 (20.4%)
Third quintile (≥ 161.20 cm to <165.0 cm)	780 (19.1%)	129 (17.9%)	909 (18.9%)
Fourth quintile (≥ 165.0 cm to >168.50 cm)	814 (19.9%)	122 (17.0%)	936 (19.4%)
Last quintile (≥ 168.50 cm)	955 (23.3%)	101 (14.0%)	1056 (21.9%)
Pre-pregnancy body mass index (kg/m^2) [e]	24.8 (4.67)	27.5 (5.54)	25.2 (4.91)
Pre-pregnancy body mass index category (kg/m^2)			
Underweight (<18.5)	173 (4.2%)	7 (1.0%)	180 (3.7%)
Normal (18.5–24.9)	1922 (46.9%)	240 (33.4%)	2162 (44.9%)
Overweight (25–29.9)	1072 (26.2%)	246 (34.2%)	1318 (27.4%)
Obesity (≥ 30)	418 (10.2%)	164 (22.8%)	582 (12.1%)
Gestational age at delivery (weeks)	39.7 (1.23)	39.5 (1.21)	39.7 (1.23)

Blood glucose level at OGTT (mg/dl)			
Fasting	79.9 (5.67)	90.1 (9.16)	81.5 (7.27)
One hour	127 (25.1)	177 (31.0)	134 (31.6)
Two hour	107 (18.6)	140 (27.8)	112 (23.5)
Pre-eclampsia	83 (2.0%)	18 (2.5%)	101 (2.1%)
Newborn			
Male infant	2052 (50.1%)	376 (52.3%)	2428 (50.4%)
Preterm (<37 weeks)	5 (0.1%)	1 (0.1%)	6 (0.1%)
Birth weight (g)	3270 (464)	3390 (489)	3290 (470)
Birth length (cm)	49.9 (2.17)	50.3 (2.14)	50.0 (2.17)
Head circumference (cm)	34.2 (1.46)	34.4 (1.43)	34.2 (1.45)

[a] Values are N (%) or mean (Standard Deviation)

[b] Diagnosis of gestational diabetes was made post hoc based on IADPSG criteria (1 or more values exceeding the thresholds: fasting ≥92 mg/dl, one-hour ≥180 mg/dl, and two-hour ≥153 mg/dl)

[c] Information on parity missing for 106 subjects with gestational diabetes and 471 without gestational diabetes.

[d] Educational status missing for 40 subjects with gestational diabetes and 195 without gestational diabetes.

[e] Pre-pregnancy weight and BMI missing for 62 subjects with gestational diabetes and 509 without gestational diabetes.

Table 3.5 Associations of gestational diabetes with outcomes among Omega and HAPO study participants **stratified by height categories**

Outcome	Height category	Omega								HAPO							
		Mean (SD) GDM	Mean (SD) No GDM	Unadjusted model [abc]			Adjusted model [cde]			Mean (SD) GDM	Mean (SD) No GDM	Unadjusted model [abc]			Adjusted model [cde]		
				ß	95% CI	p-value	ß	95% CI	p-value			ß	95% CI	p-value	ß	95% CI	p-value
Birth weight (g)	Short	3380 (387)	3310 (530)	70.83	(-61.54, 203.19)	0.29	64.62	(-74.21, 203.45)	0.36	3220 (445)	3080 (392)	141.04	(78.2, 203.89)	**<0.001**	163.76	(87.82, 239.69)	**<0.01**
	Average	3490 (519)	3460 (519)	10.48	(-98.43, 119.4)	0.85	-55.26	(-170.01, 59.49)	0.34	3400 (473)	3270 (448)	126.69	(79.58, 173.79)	**<0.001**	86.39	(33.28, 139.5)	**<0.01**
	Tall	3510 (476)	3600 (521)	141.55	(-61.31, 344.42)	0.17	62.07	(-150.49, 274.64)	0.56	3710 (480)	3420 (500)	289.89	(187.7, 392.08)	**<0.001**	195.62	(85.07, 306.18)	**<0.01**
Birth length (cm)	Short	50.1 (2.74)	50.0 (3.49)	0.72	(-0.15, 1.59)	0.10	0.85	(-0.01, 1.71)	0.05	49.6 (1.72)	49.2 (1.82)	0.44	(0.16, 0.72)	**<0.01**	0.44	(0.09, 0.79)	**0.01**
	Average	51.1 (2.95)	50.7 (3.26)	-0.35	(-1.03, 0.33)	0.31	-0.57	(-1.29, 0.15)	0.12	50.3 (2.19)	49.90 (2.13)	0.37	(0.15, 0.59)	**<0.001**	0.12	(-0.13, 0.37)	0.36
	Tall	50.6 (2.84)	51.5 (3.28)	0.46	(-0.81, 1.74)	0.47	0.13	(-1.23, 1.49)	0.85	51.4 (2.21)	50.4 (2.36)	0.98	(0.50, 1.46)	**<0.01**	0.57	(0.06, 1.08)	**0.02**
Head circumference (cm)	Short	34.0 (2.24)	34.5 (2.25)	-0.01	(-0.58, 0.55)	0.96	-0.04	(-0.63, 0.55)	0.88	34.1 (1.33)	33.9 (1.44)	0.19	(-0.03, 0.41)	0.09	0.26	(-0.02, 0.55)	0.07
	Average	35.0 (2.20)	34.8 (2.16)	-0.25	(-0.7, 0.2)	0.28	-0.26	(-0.74, 0.22)	0.28	34.3 (1.38)	34.2 (1.40)	0.14	(0, 0.29)	0.05	0.07	(-0.09, 0.23)	0.37
	Tall	34.9 (2.59)	35.0 (2.14)	0.67	(-0.17, 1.52)	0.11	0.21	(-0.67, 1.1)	0.63	35.10 (1.57)	34.5 (1.57)	0.61	(0.29, 0.93)	**<0.01**	0.36	(0.04, 0.68)	**0.02**
Macrosomia [f]	Short	3 (8.1%)	65 (9.1%)	2.00	(1.10, 3.67)	**0.02**	1.58	(0.80, 3.14)	0.18	13 (1.8%)	10 (4.9%)	2.73	(1.21, 6.14)	**0.01**	2.77	(1.06, 7.19)	**0.03**

	Average	19 (18.4 %)	297 (13.8 %)	1.27	(0.8, 2.01)	0.31	0.92	(0.53, 1.61)	0.78	40 (9.7%)	140 (5.8%)	1.67	(1.19, 2.33)	**0.001**	1.34	(0.91, 1.98)	0.13
	Tall	4 (10.8 %)	148 (20.6 %)	1.15	(0.54, 2.42)	0.85	0.71	(0.40, 2.11)	0.85	27 (26.7 %)	113 (11.8 %)	2.25	(1.56, 3.26)	**<0.01**	1.58	(1.02, 2.43)	**0.03**

[a] Unadjusted model included terms for gestational diabetes (independent variable, binary) and the outcomes – birth weight (g, continuous), birth length (cm, continuous), or head circumference (cm, continuous).

[b] P-value for the gestational diabetes represents Wald p-value for the term ß1 (associated with log transformed gestational diabetes) from the model, $E(Y| X_{gdm}, X_{covariates}) = ß0 + ß1*\ln(X_{gdm})$, where Y = outcome. ß1 =0 tests whether the difference in mean of Y for continuous outcome or difference in mean of log(Y) for binary outcome when comparing women with gdm to women without is different from 0.

[c] P-values < 0.05 are bold

[d] Adjusted models adjust for continuous variables -maternal age (years), pre-pregnancy weight (kg), and binary variables- post-high school education, nulliparity, smoking during pregnancy, alcohol use during pregnancy, and male infant, including the indicator variable for race/ethnicity. Omega study additionally adjusts for marital status (binary) and HAPO study additionally adjusts for study site (grouped categorical variable for six study sites).

[e] P-value for the gestational diabetes represents Wald p-value for the term ß1 (associated with log transformed gestational diabetes) from the model, $E(Y| X_{gdm}, X_{covariates}) = ß0 + ß1*\ln(X_{gdm}) + ß * \text{Covariates}$, where Y = outcome. ß1 =0 tests whether the difference in mean of Y for continuous outcome or difference in mean of log(Y) for binary outcome when comparing women with gdm to women without is different from 0.

[f] Values are n (%) of all women in each height category, or relative risk (RR) and the corresponding 95% confidence interval

Among Omega participants, out of 753 short women, 37 had gestational diabetes; out of 2153 average height women, 103 had gestational diabetes; and out of 754 tall women, 37 had gestational diabetes.

Among HAPO participants, out of 928 short women, 204 had gestational diabetes; out of 2829 average height women, 414 had gestational diabetes; and out of 1056 tall women, 101 had gestational diabetes.

Table 3.6 Associations of **fasting, one-hour, and two-hour OGTT glucose values** with outcomes among HAPO study participants stratified by height categories (quintiles)

Outcome	Height category	HAPO[ab]								
		Fasting PG (10 mg/dl increase)			One-hour PG (10 mg/dl increase)			Two-hour PG (10 mg/dl increase)		
		ß	95% CI	p-value	ß	95% CI	p-value	ß	95% CI	p-value
Birth weight (g)	Short	57.36	(10.39, 104.33)	**0.001**	18.07	(7.54, 28.61)	**<0.01**	20.22	(7.22, 33.21)	**<0.01**
	Average	49.66	(23.1, 76.23)	**<0.001**	13.56	(7.42, 19.71)	**<0.001**	21.2	(12.92, 29.49)	**<0.001**
	Tall	152.87	(103.84, 201.9)	**<0.01**	24.19	(12.52, 35.86)	**<0.01**	32.57	(16.8, 48.33)	**<0.001**
Birth length (cm)	Short	0.17	(-0.05, 0.38)	0.18	0.07	(0.02, 0.12)	0.09	0.1	(0.04, 0.16)	**<0.01**
	Average	0.1	(-0.03, 0.22)	0.06	0.04	(0.01, 0.07)	**<0.01**	0.06	(0.02, 0.09)	**<0.01**
	Tall	0.47	(0.24, 0.69)	**<0.01**	0.06	(0.01, 0.12)	**<0.01**	0.12	(0.04, 0.19)	**<0.01**
Head circumference (cm)	Short	0.14	(-0.04, 0.31)	**0.02**	0.04	(0, 0.08)	**<0.01**	0.05	(0, 0.09)	0.07
	Average	0.04	(-0.04, 0.12)	**0.04**	0.03	(0.01, 0.04)	**0.01**	0.03	(0, 0.06)	**0.01**
	Tall	0.34	(0.2, 0.49)	**<0.01**	0.04	(0, 0.07)	0.09	0.07	(0.02, 0.12)	**0.01**
Macrosomia [c]	Short	1.38	(0.79, 2.41)	0.25	1.11	(0.94, 1.31)	0.19	1.16	(0.97, 1.37)	0.09
	Average	1.32	(1.09, 1.60)	**0.003**	1.06	(1.01, 1.12)	**0.01**	1.10	(1.03, 1.17)	**0.02**
	Tall	1.59	(1.29, 1.96)	**<0.001**	1.09	(1.03, 1.15)	**0.002**	1.11	(1.03, 1.20)	**0.003**

[a] P-values < 0.05 are bold

[b] All models adjust for continuous variables -maternal age (years), pre-pregnancy weight (kg), and binary variables- post-high school education, nulliparity, smoking during pregnancy, alcohol use during pregnancy, and male infant, including the indicator variable for race/ethnicity and grouped categorical variable for six study sites.
[c] Values are n (%) of all women in each height category, or relative risk (RR) and the corresponding 95% confidence interval

Table 3.7 Maternal and infant characteristics of **analytic cohort and full cohort** in HAPO study

Characteristics [ab]	Analytic Cohort (N=4813)	Full Cohort (N=23316)	Range of Means among study centers in Full Cohort
Mother			
Age (years)	28.4 (5.88)	29.2 (5.80)	25.4-33.6
Any smoking during pregnancy	219 (4.6%)	1581 (6.8%)	0.2-23.6%
Any alcohol during pregnancy	348 (7.2%)	1612 (6.9%)	0.1-26.5%
Pre-pregnancy body mass index (kg/m^2)	25.2 (4.91)	27.7 (5.10)	24.4-29.9
Gestational age at delivery (weeks)	39.7 (1.23)	39.4 (1.7)	38.7-39.9
Blood glucose level at OGTT (mg/dl)			
Fasting	81.5 (7.27)	80.9 (6.90)	78.2-83.7
One hour	134 (31.6)	134.1 (30.9)	119.5-148.2
Two hour	112 (23.5)	111 (23.5)	99.6-120.9
Pre-eclampsia	101 (2.1%)	1116 (4.8)	1.4-11.4%
Newborn			
Male infant	2428 (50.4%)	12003 (51.5%)	49.3-54.0%
Preterm (<37 weeks)	6 (0.2%)	1608 (6.9%)	3.9-9.1%
Birth weight (g)	3290 (470)	3292 (529)	3109-3526

[a] Values are N (%) or mean (Standard Deviation)

[b] Information on data for full cohort was obtained from Reference (79)

Chapter 4. CAUSAL EFFECT OF MATERNAL HEIGHT ON GLUCOSE INTOLERANCE DURING PREGNANCY USING A MENDELIAN RANDOMIZATION APPROACH

4.1 ABSTRACT

Background: Observational studies have reported that maternal height is inversely associated with glucose intolerance during pregnancy, including gestational diabetes, although reports were inconsistent. However, it is unclear whether the observed association of height with glucose intolerance reflects causal relationships. The purpose of this study was to examine the presence of a causal relationships between maternal height and glucose intolerance (including gestational diabetes risk) during pregnancy using a Mendelian randomization approach.

Methods: Using height-related single nucleotide polymorphisms (SNPs) (N = 36) and genotype data from 4,586 mothers in the Hyperglycemia, and Adverse Pregnancy Outcome (HAPO) study, we calculated two weighted genetic risk scores (GRS) for each individual—one using the effect size estimates (the increase in height Z-score per one additional risk allele) from a previous GWAS (external weight) and another from similar estimates derived from our analytical cohort (internal weight). A 75 g oral glucose tolerance test was done at 24–28 weeks of gestation for all participants in HAPO cohort and results for fasting, one-hour, and two-hour blood glucose levels were obtained. Diagnosis of gestational diabetes was made post hoc based on the current International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. We examined the association of the internally and externally weighted GRS with height using linear regression models. We used logistic regression adjusted for covariates to estimate the odds ratio (OR) and 95% confidence intervals (CI) for associations between height GRS (internally weighted GRS or

externally adjusted GRS) and gestational diabetes risk. Using linear regression models, we estimated mean glucose values and 95% confidence interval (CI) for the association of height GRS with fasting, one-hour, and two-hour glucose levels.

Results: The internally and externally weighted height GRS were strongly associated with maternal height. Each unit greater height GRS increased the maternal height by approximately 6.20 cm (95% CI: 4.57, 7.82) using internal weights and 1.95 cm (95% CI: 0.26, 3.65) using external weights. We did not find significant associations between the externally weighted (adjusted OR [aOR] 0.55, 95% CI: 0.23, 1.28, p = 0.160) or internally weighted height GRS (aOR 0.72, 95% CI: 0.32, 1.64, p = 0.449) and gestational diabetes. We found inverse associations between height GRS and blood glucose levels. One unit decrease in the internally weighted GRS was associated with a 1.99 mg/dl higher fasting (95% CI: -3.94, -0.03; p = 0.046) and 9.08 mg/dl higher two-hour glucose level (95% CI: -15.56, -2.59; p = 0.006), but not one-hour levels. One unit decrease in the externally weighted GRS was associated with a 2.37 mg/dl higher fasting (95% CI: -4.39, -0.34; p = 0.021) and 11.04 mg/dl higher one-hour glucose level (95% CI: -19.87, -2.21; p = 0.014), but not two-hour levels.

Conclusion: Genetic variants that predicted maternal height were significantly associated with maternal fasting, one-hour, and two-hour blood glucose levels during pregnancy. Associations with gestational diabetes risk were not statistically significant. Future studies to explore the effect of maternal height on other maternal health outcomes and long-term health in the post-natal period are needed.

4.2 BACKGROUND

Maternal height reflects an individual's genetics and past environmental influences, including nutrition and health, particularly those that occurred during prenatal and early postnatal life (36,37). Glucose intolerance during pregnancy, including gestational diabetes, is a major pregnancy complication associated with adverse perinatal and long-term outcomes for mothers and their infant (84). Observational studies have reported that maternal height is inversely associated with glucose intolerance, although the findings were inconsistent (15,16,20,21).

Observational studies may be biased and confounded by factors such as socioeconomic conditions, and reporting bias; therefore, the analyses of associations of height with glucose intolerance may have produced inconsistent results in different populations. Further, differences in analytical approaches, diagnostic criteria, study design, and other factors that varied across the studies may also contribute to the different findings. Despite the inconsistencies, evidence on potential biological (8,9), genetic (10) and epigenetic mechanisms (11,12) provide plausibility for the argument for the observed associations of height with glucose intolerance. These calls considerations of novel approaches such as Mendelian randomization design, which can provide stronger evidence for causal inference through control of measured and unmeasured confounding. Mendelian randomization, analogous to a randomized controlled trial where randomization to genotype takes place at conception (90), has been commonly used to detect unbiased causal estimates. While previous studies have demonstrated causal relationships of maternal height with offspring outcomes (preterm birth, birth weight, etc.), to our knowledge, no prior study investigated the causal effect of maternal height on glucose intolerance (28).

Recent advances in the field of genetics have led to the use of polygenic risk scores combining several genetic susceptibility or protective variants to predict an individual's risk of complex

phenotypes (e.g., height) or diseases (e.g., type 2 diabetes) with improved power and accuracy (91). The objective of the current study was to examine the presence of a causal association between maternal height and glucose intolerance (including gestational diabetes risk) during pregnancy using polygenic risk score and Mendelian randomization approaches.

4.3 METHODS

4.3.1 *Study Settings and Study Populations*

We conducted the study using individual-level data collected as a part of the Hyperglycemia, and Adverse Pregnancy Outcome (HAPO) study, an international, multi-center prospective cohort study of 25,505 pregnant women recruited between July 2000 and April 2006 in 15 field centers located in Asia, Australia, Europe, North America, and the Middle East. Participants 18 years or older were recruited unless they had one or more exclusion criteria, which included multiple pregnancies, gestational diabetes diagnosis prior to enrollment in the HAPO study, history of overt diabetes, and current use of drugs affecting glucose metabolism. Details on the study objectives, study designs, inclusion and exclusion criteria, and data collection have been reported elsewhere (55–59). For the current study, we additionally excluded mothers with missing information on height (N = 3), height less than 140 cm or greater than 200 cm (N = 6), or missing data on gestational diabetes (N = 0). The study was approved by the institutional review boards at all 15 field centers.

4.3.2 *Data Collection*

HAPO participants underwent a 75 g oral glucose tolerance test (OGTT) as close to 28 weeks' gestation as possible (range 24–32 weeks' gestation). At 34 to 37 weeks' gestation, random plasma glucose was collected. Participants whose fasting blood glucose level exceeded 105 mg/dl (5.8

mmol/h), two-hour glucose exceeded 200 mg/dl (11.1 mmol/l), random glucose exceeded 160 md/dl (8.9 mmol/l) or greater, or any glucose level was below 45 mg/dl (2.5 mmol/l) were further excluded from HAPO. Information on our phenotype of interest, maternal height, was obtained during the OGTT visit. Height, weight, and blood pressure were measured while other prenatal information, including socio-demographic characteristics and participant's report of pre-pregnancy weight, age, parity, and race/ethnicity, was collected using questionnaires at the OGTT visit. Following OGTT, routine pregnancy care was continued at the field centers. Maternal blood collected during the OGTT was used to isolate maternal DNA (92). Genotyping was conducted using the Illumina Human610 Quad (European ancestry participants), Human1M Duo (Afro-Caribbean and Hispanic participants), and Omni1-Quad_v1-0_B (Thai participants) platforms. Samples from 9,814 mothers and offspring, along with HapMap controls (N = 126) were submitted for genotyping in the HAPO study.

4.3.3 *Genotype QC Procedures and Estimation of Ancestry*

Complete reports of QC procedures at the genotyping centers are described in Laurie et al. (93) and are also available through http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000096.v4.p1. SNPs (single nucleotide polymorphisms) were excluded based on chromosomal abnormalities, gender discrepancies (annotated gender vs genetic), low call rate (<98%), <2% Minor Allele Frequency (MAF), deviation from Hardy-Weinberg equilibrium (HWE) ($p< 0.00004$), among others. We downloaded the genotype and phenotype data for our study from the Database of Genotypes and Phenotypes (dbGaP) under phs000096.v4.p1.

For the current analysis, we combined the genotype data of mothers and infants of Hispanic, Afro-Caribbean, European, and Thai ancestries and performed additional marker level

QC. We removed SNPs with high missingness (call rate < 90%), low MAF (< 10%), departure from HWE ($p < 0.00005$) and substantial linkage disequilibrium (LD) with other more significant SNPs ($r2 < 0.64$). We used GRAF-pop software to infer ancestry in the genotype data (94). GRAF-pop calculates the genetic distance of each subject to reference population of European, African, and Asian ancestry and has been used to accurately infer ancestry in data with even high non-random missingness of SNPs (94). We determined the proportion of European, African, and Asian ancestries for each participant in the dataset and included the estimates in the regression models.

4.3.4 *Phenotype*

Aliquots of all 75 g OGTT test specimens done in the fasting state at 24–28 weeks of gestation were analyzed at the central HAPO laboratory and results for fasting, one-hour, and two-hour blood glucose levels were obtained. Diagnosis of gestational diabetes was made post hoc in HAPO data based on the current International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (62). Using blood glucose values from OGTT, gestational diabetes mellitus was diagnosed if any of the following cut-offs was met 1) fasting ≥ 92 mg/dl (≥ 5.2 mmol/l) or 2) one-hour ≥ 180 mg/dl (≥ 10 mmol/l) or 3) two-hour ≥ 153mg/dl (≥ 8.5 mmol/l).

After all genomic and phenotypic quality control and exclusions, we studied 36 height SNPs identified from 4,586 mother-infant pairs in our analytic data set.

4.3.5 *Instrumental variable for Height for Mendelian Randomization*

We obtained information on 697 SNPs that were significantly associated with adult height in a recent genome-wide association study (GWAS) ($p < 5*10^{-8}$) (95). We removed SNPs with high missingness (call rate < 90%), low MAF (< 10%), departure from HWE ($p < 0.00005$) and substantial linkage disequilibrium (LD) with other SNPs ($r2 < 0.64$). After all genomic quality

control steps, we studied 36 height-related SNPs identified from 4,586 mother-infant pairs in our analytic data set. For each participant, we assigned a value of 0, 1, or 2 based on the number of alleles linked with increased height for each variant. Using 36 height SNPs, we calculated two weighted genetic (Polygenic) risk scores (GRS): 1) We used previously reported effect size estimates (the increase in height Z-score per one additional risk allele) from the GWAS analysis above (95) and weighted each variant (external weight). 2) Since the existing weights were derived mostly from individuals of European ancestry, we determined effect size estimates from our own study by regressing measured height (Z-score) by each genetic variant and used weights to calculate the GRS (internal weight) that will be most predictive within our population. The weighted variants were summed for everyone individually to create two height GRS for that individual based on the above weights.

4.3.6 *Statistical analysis*

We assessed distributions of sociodemographic, pregnancy, and infant-related characteristics using frequency distribution of categories or mean and standard deviation (SD) of continuous values. We examined the association of height GRS with height by fitting linear regression models adjusting for 1) only ancestry and 2) all covariates including ancestry. The F-statistics and estimates from the regression model was used to determine the validity of the instrumental variable for maternal height. An F-statistic greater than 10 was used to evaluate for the presence of weak instrument bias (96).

We determined whether genetically determined height was associated with the risk of gestational diabetes using logistic regression with ancestry-only and all-covariate adjustments. In these models, the exposure was height GRS, and the outcome was gestational diabetes. We estimated odds ratio (OR) and 95% confidence interval (CI) for the association. We determined

whether genetically determined height was associated with the fasting, one-hour, and two-hour glucose values using linear regression with ancestry-only and all-covariate adjustments. In these models, the exposure was height GRS, and the fasting, one-hour, and two-hour glucose values were the outcomes. We estimated the difference in mean glucose values and 95% confidence interval (CI) for the association. All analyses were conducted separately using internally weighted GRS and externally weighted GRS.

Since Mendelian randomization controls for most confounding factors with the exception of the influence of population level stratification, we included a minimal set of confounders and precision variables in all adjusted regression models: maternal age (years), pre-pregnancy weight (kg), European ancestry proportion, African ancestry proportion, and sex of the baby (male, female). We included the European and African proportions in all statistical models to prevent confounding by population ancestry (population stratification).

In all analyses, a p-value of less than 0.05 in a two-sided test was considered statistically significant. Analyses were conducted using R studio software (R Version 4.1.1 [2021-08-10]) or PLINK (www.cog-genomics.org/plink/1.9/) (97)

4.4 RESULTS

4.4.1 *Subject Characteristics*

Summary demographics of 4,586 pregnant women included in the analyses are presented in Table 4.1. The average age of participants was 28.5 (SD: 5.88) years and the average height of participants was 161 (7.52) cm. Most of the participants were normal weight (44.8%) based on their body mass index. Average fasting, one-hour, and two-hour blood glucose values were 81.5 (SD: 7.33) mg/dl, 135 (SD: 32) mg/dl, and 112 (SD: 23.8) mg/dl, respectively. The prevalence of

gestational diabetes in the analytic cohort was 15.5%. The 36 SNPs included in the genetic risk score are presented in Table 4.2.

4.4.2 *Association between weighted height GRS and height*

The weighted height GRS was strongly associated with maternal height when using internal weights and adjusting for ancestry ($p = 3.01 \times 10^{-16}$) (Table 4.3) such that each unit greater height GRS increased the maternal height by 6.82 cm (95% CI: 5.19, 8.46). The internally weighted height GRS explained 35.5% of the variation in height among all participants. This association persisted after all-covariate adjustment ($p = 9.67 \times 10^{-14}$). The externally weighted height GRS was associated with maternal height in the ancestry-adjusted model ($p = 0.0074$). After additional covariate adjustment, the association was still significant ($p = 0.023$), with each unit greater height GRS was associated with a 1.95 cm greater maternal height (95% CI: 0.26, 3.65). The externally weighted height GRS explained 34.5% of the variation in height among all participants. The weighted height GRS was a strong instrument for maternal height when using both internal and external weights (partial F statistics: 780 for internal weight and 749 for external weight).

4.4.3 *Association between weighted height GRS and glucose intolerance*

When an individual carried one additional height increasing risk allele, the GRS increases by one unit. After adjusting for age, pre-pregnancy weight, and infant sex (in addition to ancestry), a one-unit increase in the height GRS was associated with 28% lower odds of gestational diabetes (OR: 0.72; 95% CI: 0.32, 1.64; $p = 0.449$), although the finding was not statistically significant (Table 4.4). Further, we did not find significant associations between the externally weighted GRS for height and gestational diabetes (OR: 0.55; 95% CI: 0.23, 1.28; $p = 0.160$).

The associations between height GRS and blood glucose levels indicated that the blood glucose levels in general decreased with an increase in the GRS (Table 4.5). One unit decrease in the internally weighted GRS was associated with a 1.99 mg/dl higher fasting (95% CI: -3.94, -0.03; p = 0.046) and 9.08 mg/dl higher two-hour glucose level (95% CI: -15.56, -2.59; p = 0.006), but not one-hour levels (-5.93, 95% CI: -14.47, 2.60, p = 0.173). One unit decrease in the externally weighted GRS was associated with a 2.37 mg/dl higher fasting (95% CI: -4.39, -0.34; p = 0.021) and 11.04 mg/dl higher one-hour glucose level (95% CI: -19.87, -2.21; p = 0.014), but not two-hour levels (-3.26, 95% CI: -9.97, 3.44, p = 0.341).

4.5 DISCUSSION

Using individual-level genomic data from a large cohort of pregnant women, we applied the Mendelian randomization approach to examine causal association between maternal height and glucose intolerance (including risk of gestational diabetes). Our results demonstrate that variants that predicted adult height significantly influence the fasting, one-hour, and two-hour OGTT blood glucose levels during pregnancy. One unit decrease in the weighted GRS was associated with a 1.99 to 2.37 mg/dl higher fasting, 11.04 mg/dl higher one-hour and 9.08 mg/dl higher two-hour glucose levels. Associations with gestational diabetes were not statistically significant.

In our current analysis, the weighted height GRS explained only 14.25% of the variation in maternal height in the unadjusted association and 35.5% in the ancestry-adjusted associations. The externally weighted height GRS based on 36 out of 697 SNPs associated with height (95) explained only 0.008% of the variation in maternal height in the unadjusted association and 34.5% in the ancestry-adjusted associations. The height GRS based on 697 SNPs explained approximately 16% of the variance in maternal height in a homogeneous sample of European population (95) and,

approximately 20% in a more homogeneous sample of north European pregnant women (28). These findings suggests that the height-related SNPs may be more predictive of height in more homogenous populations (e.g., European population) from whom the weights were derived. In a heterogeneous population like HAPO that includes European, African-American, Asian, and Hispanic population, there may be other determinants (genetic or non-genetic) of height that might be unique to each of these groups, reducing the level of predictions. Both the externally weighted and internally weighted height GRS were significantly predictive of maternal height in ancestry-adjusted and fully-adjusted models indicating that our instrument (height GRS) is valid.

While we did not find an association between height GRS and gestational diabetes according to IADPSG criteria in the current study, we found that lower maternal height (based on height GRS) was associated with higher blood glucose levels. There are several considerations to explain the potential null finding of associations of height GRS with gestational diabetes. Classifying women post hoc based on their blood glucose levels into categories of "gestational diabetes" and "no gestational diabetes" may have led to a loss of information and power, compared to using the continuous blood glucose values (98). We used the current IADPSG criteria to classify women with gestational diabetes. There are several diagnostic criteria for gestational diabetes with no consensus. The current IADPSG criteria include more women as having gestational diabetes than other diagnostic criteria, potentially resulting in misclassification of the participants based on gestational diabetes. This may have biased the effect estimates towards null. Additionally, women with blood glucose levels above a threshold were excluded from HAPO. Since more severe forms of gestational diabetes were excluded, we may not have detected a significant association between height GRS and gestational diabetes.

No previous analyses have used a Mendelian randomization framework to examine height as a causal risk factor for gestational diabetes. Observational studies of height and gestational diabetes have inconsistently reported short height as a risk factor for gestational diabetes (15,16,20,21). We have previously found that each 5 cm maternal height was associated with 16% lower the risk of gestational diabetes (aRR = 0.84, 95% CI: 0.78, 0.90; $p < 0.001$) (unpublished). Our finding of lower blood glucose levels in association with a one-unit increase in height GRS, however, was consistent with our observational analyses that found 0.54 to 3.08 mg/dl lower fasting, one-hour, and two-hour blood glucose levels with a 5cm greater height. Though observational studies are limited by the possibility of residual confounding, our finding is suggestive of a causal effect of maternal height on glucose intolerance (and possibly gestational diabetes risk). Future large, comprehensive studies conducted among diverse populations can expand on our understanding of height-gestational diabetes relationships.

Mechanisms by which height affects glucose tolerance are not clearly understood but recent evidence suggests several hypotheses. Height and glucose intolerance may have a shared risk factor. For example, a polymorphism in functional properties of genes that determine the height (for example, insulin-like growth factor [IGF]-1) was significantly related to both short adult height and an increased risk for type 2 diabetes in a study (39). According to a hypothesis of Developmental Origins of Health and Disease, epigenetic adaption takes place in fetal life to compensate for nutritional insufficiencies in response to maternal malnutrition and provides survival gains in utero and infancy (37). The adaptative alterations protecting women from undernourishment in utero could lead them to short height and subsequent glucose intolerance (20). Studies have also indicated that the association of height with glucose intolerance exists because of publication bias (height is generally available in all data sets and null results may not

have been published in the literature), as an artifact of the test (shorter women have a smaller amount of metabolically active muscle tissue to metabolize the same fixed glucose load during oral glucose tolerance test, as compared to taller women and therefore, they have a higher glucose level (39)), or as a residual and uncontrolled confounding factor (individuals who grew up in low socioeconomic status are likely to develop diabetes in later life (57,59) as well as have a shorter height (36)).

The strength of our study includes a large well-characterized sample that belonged to diverse ancestry groups with comparable representation from each ancestry in our sample. Availability of individual-level genetic data allowed us to use GRS to study the association between height and glucose intolerance. We used a novel GRS approach to examine the causal effect of maternal height on glucose tolerance.

Our study has several limitations. The validity of the Mendelian randomization approach to estimate the casual effect of maternal height with glucose intolerance is based on three assumptions. The first assumption is that maternal genetic instrumental variable is associated with maternal height. We demonstrated that in the current analyses. After adjustment, the height GRS was a strong instrument for height in our study (partial F statistics: 780 for internal weight and 749 for external weight). The second assumption is that the maternal genetic instrumental variable is not associated with potential confounders of the maternal height and gestational diabetes gestational diabetes association. Since the genetic variants are assigned at birth, they are less likely (than the maternal height itself) to be related to the socio-demographic and other characteristics (confounders). To validate the assumption, we explored the association of the maternal genetic variant for height with the observed confounders of the relationship between height and gestational diabetes (Table 4.6). The externally weighted GRS was not associated with the confounders,

though the internally weighted GRS showed significant association with the confounding variables. Nevertheless, we adjusted for important confounders and precision variables (age, pre-pregnancy weight, infant sex, and ancestry proportion) in our analyses. However, if the height-associated variants are associated with other traits (e.g., pre-pregnancy weight) that influence glucose tolerance, our estimates of causal association may be biased. The third assumption is that the maternal genetic variants for height are only related to glucose intolerance through their relationship with maternal height (biological pleiotropy), which is generally not possible to prove. Another limitation is that there is a possibility of selection bias because of inclusion of only term births in the publicly available HAPO data used in our analysis. Similar characteristics of the pregnant women in our analytic cohort and the full HAPO cohort provided reassurance that restricting our analysis to term births is unlikely to bias our estimates of height and glucose intolerance (79) (Table 4.7). Finally, genotyping bias due to use of slightly different BeadChips for different race/ethnicities is a possibility.

In conclusion, our results demonstrate that variants that predicted adult height are associated with the blood glucose levels during pregnancy. Together with the results of previous observational studies, our findings suggest that height has a role in glucose intolerance. Although adult height is not a modifiable risk factor, clinical implications of our findings may include the early start of dietary and lifestyle modifications for pregnant women to manage other modifiable risk factors of diabetes and the use of height in clinical models that predict maternal hyperglycemia. Future large studies are needed to replicate this association in other study populations along with the need to conduct GWAS studies of height in non-European populations, particularly women. The finding that shorter maternal height is associated with higher blood glucose levels provides opportunities for future studies to explore the effect of maternal height on

other maternal health outcomes and long-term health in the post-natal period, in addition to studies of gene-environment interaction for maternal height and these outcomes.

Table 4.1 Selected characteristics of **HAPO** study participants enrolled at field centers between July 2000 and April 2006

Characteristics	Overall (N=4,586)
Mother	
Race/ethnicity (self-reported)	
White	1396 (30.4%)
African-American	1151 (25.1%)
Hispanic	843 (18.4%)
Asian	1196 (26.1%)
Age (years)	28.5 (5.88)
Nulliparous	3097 (67.5%)
Pre-pregnancy weight (kg)	65.1 (13.8)
Height (cm)	161 (7.52)
Pre-pregnancy body mass index (kg/m^2) [i]	25.3 (4.99)
Pre-pregnancy body mass index category (kg/m^2)	
Underweight (<18.5)	166 (3.6%)
Normal (18.5–24.9)	2054 (44.8%)
Overweight (25–29.9)	1265 (27.6%)
Obesity (≥ 30)	591 (12.9%)
Gestational age at delivery (weeks)	39.7 (1.23)
Blood glucose level at OGTT (mg/dl)	
Fasting	81.5 (7.33)
One hour	135 (32.0)
Two hour	112 (23.8)
Gestational diabetes	710 (15.5%)
Newborn	
Male infant	2320 (50.6%)
Birth weight (g)	3290 (471)

Data are mean (SD) or n (%)

Table 4.2 Per-allele genetic associations for **36 genetic variants** in combined height genetic risk score

Chromosome	Variant	Effect allele	Other allele	Minor allele frequency	Estimate (HAPO)	SE (HAPO)	Estimate (GIANT)*	SE (GIANT)*	Nearest Gene
1	rs2298265	G	A	0.3498	0.0494	0.0329	0.3818	0.2484	*ZNF687*
1	rs10863936	A	G	0.1762	0.1211	0.0216	0.9031	0.1632	*DTL*
2	rs2278483	G	A	0.1437	0.2526	0.0271	1.8960	0.2048	*CENPO*
2	rs2166898	G	A	0.3387	0.0046	0.0298	0.0700	0.2255	*GLI2*
2	rs6733349	A	G	0.06051	0.1648	0.0217	1.2271	0.1642	*B3GNT7*
2	rs749052	A	G	0.258	0.3591	0.0425	2.6848	0.3211	*NPPC*
3	rs12330322	G	A	0.1877	-0.0418	0.0234	-0.3023	0.1769	*RYBP*
3	rs6439168	G	A	0.4593	0.0253	0.0265	0.1803	0.2005	*H1FX*
5	rs4624820	A	G	0.2522	-0.1552	0.0209	-1.1692	0.1579	*SPRY4*
5	rs4620037	A	C	0.4892	-0.0292	0.0239	-0.2200	0.1806	*FGF18*
6	rs9443804	A	G	0.4195	-0.1115	0.0208	-0.8484	0.1568	*BCKDHB*
6	rs6902771	G	A	0.2349	0.1243	0.0211	0.9523	0.1597	*ESR1*
7	rs12669267	G	A	0.2738	-0.1706	0.0242	-1.3336	0.1828	*WBSCR28*
9	rs10990303	G	A	0.2187	-0.1833	0.0230	-1.3597	0.1738	*PTCH1*
9	rs953199	C	A	0.4885	0.0376	0.0252	0.2798	0.1904	*XPA*
9	rs902143	A	G	0.1021	-0.0446	0.0207	-0.3325	0.1562	*ZNF462*
9	rs2451948	A	G	0.3265	0.1459	0.0339	1.1294	0.2565	*ZNF462*
9	rs999599	G	A	0.1118	-0.0576	0.0222	-0.4349	0.1677	*COL27A1*
11	rs2237886	G	A	0.3724	-0.1618	0.0331	-1.2519	0.2496	*KCNQ1*
11	rs7112925	G	A	0.2232	-0.0865	0.0215	-0.6249	0.1627	*RHOD*
12	rs3825199	A	G	0.4738	0.0856	0.0248	0.6682	0.1875	*SOCS2*
12	rs11835818	G	A	0.3529	-0.0309	0.0207	-0.2246	0.1560	*BCL7A*
13	rs6561319	A	C	0.34	0.1022	0.0216	0.7679	0.1635	*LRCH1*
14	rs1950500	G	A	0.2264	0.0486	0.0214	0.3650	0.1615	*NFATC4*
14	rs12435366	G	A	0.3685	-0.0189	0.0248	-0.1218	0.1871	*NFKBIA*
15	rs7181724	A	G	0.3601	-0.0224	0.0214	-0.1657	0.1617	*MCTP2*
16	rs2326458	A	C	0.3331	0.0243	0.0213	0.1740	0.1611	*ZDHHC7*
17	rs4640244	A	G	0.3539	-0.1323	0.0217	-0.9853	0.1644	*KCNJ12*
17	rs3760318	G	A	0.4012	0.1563	0.0214	1.1611	0.1618	*CENTA2*
17	rs2070776	G	A	0.3157	-0.2138	0.0209	-1.6285	0.1582	*CD79B*
19	rs891088	A	G	0.3143	0.0719	0.0222	0.5150	0.1674	*INSR*

19	rs6511689	A	G	0.2536	0.0293	0.0221	0.2046	0.1668	*S1PR2*
19	rs10401193	A	G	0.2548	-0.2941	0.0234	-2.2168	0.1766	*GATAD2A*
20	rs7273787	A	G	0.2486	0.1598	0.0238	1.2009	0.1796	*SMOX*
20	rs2057291	G	A	0.2646	0.1204	0.0239	0.9319	0.1807	*GNAS*
20	rs6061231	C	A	0.3498	0.0599	0.0238	0.4661	0.1799	*RPS21*

*Values are from (Reference (95))
beta-coefficients and standard errors [SE]) with maternal height from linear regression (1 Standard Deviation change)

Table 4.3 Associations of height genetic risk score with **maternal height** by weights used to determine the genetic risk score

Genetic Risk Score	SNPs (N)	Trait	Ancestry-adjusted			Fully adjusted	
			β (95% CI)	p-value	r2	β (95% CI)	p-value
Internal Weight	36	Height	6.82 (5.19, 8.46)	**$3.01*10^{-16}$**	35.5%	6.20 (4.57, 7.82)	**$9.67*10^{-14}$**
External Weight	36	Height	2.3 (0.62, 4.01)	**0.0074**	34.5%	1.957 (0.263, 3.651)	**0.023**

Multivariate models included age, pre-pregnancy weight, infant sex, European ancestry proportion, and African ancestry proportion as covariates.
Internal weights use effect estimates from our analytic cohort which was adjusted for ancestry proportions.
External weight use effect estimates from (Reference (95))

Table 4.4 Associations of height genetic risk score with **gestational diabetes**

Genetic Risk Score	Ancestry-adjusted		Fully Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Height (Internal Weight)	0.66 (0.31, 1.41)	0.29	0.72 (0.32, 1.64)	0.449
Height (External Weight)	0.52 (0.23, 1.14)	0.10	0.55 (0.23, 1.28)	0.160

Multivariate models included age, pre-pregnancy weight, infant sex, European ancestry proportion, and African ancestry proportion as covariates.
Internal weights use effect estimates from our analytic cohort which was adjusted for ancestry proportions.
External weight use effect estimates from (Reference (95))

Table 4.5 Associations of height genetic risk score with **blood glucose levels** from oral glucose tolerance test

Genetic Risk Score	Ancestry-adjusted		Fully Adjusted	
	β (95% CI)	p-value	β (95% CI)	p-value
Fasting				
Height (Internal Weight)	-1.68 (-3.64, 0.28)	0.093	-1.99 (-3.94, -0.03)	**0.046**
Height (External Weight)	-2.57 (-4.60, -0.54)	**0.013**	-2.37 (-4.39, -0.34)	**0.0216**
One-hour				
Height (Internal Weight)	-5.43 (-13.72, 2.85)	0.199	-5.93 (-14.47, 2.60)	0.173
Height (External Weight)	-12.05 (-20.60, -3.49)	**0.005**	-11.04 (-19.87, -2.21)	**0.0143**
Two-hour				
Height (Internal Weight)	-7.69 (-13.99, -1.40)	**0.0165**	-9.08 (-15.56, -2.59)	**0.0060**
Height (External Weight)	-3.75 (-10.25, 2.74)	0.258	-3.26 (-9.97, 3.44)	0.341

Multivariate models included age, pre-pregnancy weight, infant sex, European ancestry proportion, and African ancestry proportion as covariates.
Internal weights use effect estimates from our analytic cohort which was adjusted for ancestry proportions.
External weight use effect estimates from (Reference (95))

Table 4.6 Associations of height and the genetic risk score with **confounders of the observational association** between height and gestational diabetes

Characteristics	Height, cm Mean (SD)	p [a]	GRS (internal weight) Mean, (SD)	p [a]	GRS (external weight) Mean, (SD)	p [a]
Race/ethnicity (self-report)		<0.001		<0.001		<0.001
White	164 (6.36)		0.143 (0.448)		-0.070 (0.107)	
African-American	164 (6.69)		0.267 (0.485)		-0.070 (0.109)	
Hispanic	160 (5.76)		-0.233 (0.457)		-0.091 (0.013)	
Asian	154 (5.36)		-0.637 (0.467)		-0.058 (0.109)	
Age group		<0.001		0.21		0.93
Age< 35 years	160 (7.49)		-0.094 (0.592)		-0.071 (0.108)	
Age ≥ 35 years	162 (7.52)		-0.041 (0.536)		-0.071 (0.108)	
Parity at enrollment		<0.001		0.002		0.017
Nulliparous	160 (6.96)		-0.90 (0.559)		-0.081 (0.109)	
Primiparous/multiparous	162 (7.43)		-0.100 (0.568)		-0.071 (0.107)	
Post high school education		<0.001		<0.001		0.825
Yes	163 (6.99)		0.038 (0.530)		-0.072 (0.107)	
No	159 (7.46)		-0.204 (0.608)		-0.072 (0.109)	
Smoking during pregnancy		<0.001		<0.01		0.08
Yes	161 (7.53)		-0.096 (0.588)		-0.071 (0.108)	
No	163 (6.61)		0.117 (0.459)		-0.084 (0.103)	
Pre-pregnancy body mass index (kg/m^2)		<0.001		0.147		0.213
Underweight (<18.5)	166 (6.87)		0.130 (0.567)		-0.074 (0.106)	
Normal (18.5–24.9)	161 (7.32)		-0.093 (0.587)		-0.069 (0.108)	
Overweight (25–29.9)	159 (7.65)		-0.229 (0.574)		-0.069 (0.106)	
Obesity (≥ 30)	160 (7.38)		-0.099 (0.558)		-0.080 (0.110)	

[a]p-value from Student's t-test or ANOVA
GRS: genetic risk score

Table 4.7 Maternal and infant characteristics of **analytic cohort and full cohort** in HAPO study

Characteristics [ab]	Analytic Cohort (N=4,813)	Full Cohort (N=23,316)	Range of Means among study centers in Full Cohort
Mother			
Age (years)	28.4 (5.88)	29.2 (5.80)	25.4-33.6
Any smoking during pregnancy	219 (4.6%)	1581 (6.8%)	0.2-23.6%
Any alcohol during pregnancy	348 (7.2%)	1612 (6.9%)	0.1-26.5%
Pre-pregnancy body mass index (kg/m^2)	25.2 (4.91)	27.7 (5.10)	24.4-29.9
Gestational age at delivery (weeks)	39.7 (1.23)	39.4 (1.7)	38.7-39.9
Blood glucose level at OGTT (mg/dl)			
Fasting	81.5 (7.27)	80.9 (6.90)	78.2-83.7
One hour	134 (31.6)	134.1 (30.9)	119.5-148.2
Two hour	112 (23.5)	111 (23.5)	99.6-120.9
Pre-eclampsia	101 (2.1%)	1116 (4.8)	1.4-11.4%
Newborn			
Male infant	2428 (50.4%)	12003 (51.5%)	49.3-54.0%
Preterm (<37 weeks)	6 (0.2%)	1608 (6.9%)	3.9-9.1%
Birth weight (g)	3290 (470)	3292 (529)	3109-3526

[a] Values are N (%) or mean (Standard Deviation)

[b] Information on data for full cohort was obtained from Reference (79)

SUMMARY AND DISCUSSION

In this dissertation, we investigated the associations of maternal height with infant birth size and pregnancy complications. We investigated whether maternal height-infant birth size associations varied by infant sex and whether the gestational diabetes-infant birth size association varied by maternal height. We also examined the association between genetically determined height and glucose intolerance using the Mendelian randomization and novel polygenic risk score approaches. We used data from three prospective cohort studies of pregnant women (Omega, HAPO, and GUSTO) to address the specific aims.

A 5 cm greater height of the mother was associated with an average of 23.82 g to 46.26 g greater birth weight in the three cohorts, and 1% and 18% lower the risk of gestational diabetes in Omega and HAPO, respectively. We found associations of maternal height (continuous as well as short and tall categories) with birth weight, birth length, and gestational diabetes, but not head circumference. We did not find any evidence of a non-linear relationship between maternal height and infant birth size. We observed evidence of infant sex-specific association of maternal height with BW in one cohort (GUSTO) such that associations for short height were significant only among female infants. There was a significant positive association between maternal height and preterm birth and a significant inverse association with preeclampsia in the Omega study, although the association with preeclampsia was not seen in HAPO. Results from the Omega study showed no significant association of gestational diabetes with birth weight, birth length, head circumference, and macrosomia within categories of short, average, or tall height women. In HAPO, gestational diabetes was associated with a significantly increased risk of macrosomia as well as a greater birth length in infants among tall height mothers or short height mothers, but not

mothers of average height. There was no significant interaction between gestational diabetes and maternal height on birth weight, birth length, head circumference, or macrosomia in either cohort studied (interaction $p > 0.05$). The internal and external weighted height GRS were strongly associated with maternal height. Variants that predicted adult height were inversely associated with fasting, one-hour, and two-hour OGTT glucose levels. We did not find statistically significant associations between the externally weighted or internally weighted height GRS and gestational diabetes.

For this dissertation, we used data from three large prospective cohort studies of pregnant women to assess the role of maternal height on birth outcomes and pregnancy complications. The availability of extensive data in the three study cohorts, the racially/ethnically/geographically diverse and well-characterized population, standardized methods of data collection, and prospective designs are major strengths of this project. In HAPO, we had access to detailed information on glucose values from the OGTT that permitted us to perform assessment of glucose intolerance beyond gestational diabetes. We compared the findings across the studies and provided evidence for better generalizability of the findings to other study populations. We assessed the sex-specific association of maternal height on infant birth size, a relationship that hasn't been previously explored in the literature. Our analysis included in this dissertation project is the first to assess the interaction of maternal height and gestational diabetes on infant growth outcomes outside of Finland and Singapore (34,35). Further, our analyses to examine the causal association of height and glucose intolerance is the first study to use the Mendelian randomization approach for investigation of causal relationships between height and glucose intolerance including gestational diabetes. Considering inconsistent findings in the literature, we investigated the

association of maternal height with pregnancy outcomes within observational and non-observational study design frameworks.

The findings from this study, however, should be interpreted in light with the limitations. Type I error due to multiple tests might be an issue because of the many statistical tests we have conducted. Women with blood glucose levels above a threshold were excluded in HAPO. Since more severe forms of gestational diabetes were excluded, we may have underestimated significant associations. Application of different diagnostic criteria for gestational diabetes in the study population may make the comparison of findings across studies problematic.

The clinical and public health implications of our findings, including our recommendations for future studies are discussed below.

- The determinants of heights are linked across generations. Findings from these analyses have important public health implications as they highlight life-course risk development and the need for interventions aimed at determinants of women's height that are in play largely during early life. Maternal adult height cannot be modified and given the intergenerational linkage between height and various outcomes, the determinants of adult height functioning during early life (e.g., maternal education) can be focused to improve infant growth and pregnancy outcomes across generations.
- Our findings also highlight the importance for short women who are at risk of adverse pregnancy outcomes to focus on modifiable risk factors like smoking, gestational weight gain, prediabetes, hypertension, and alcohol/tobacco use.
- Our findings also support potential risk stratification of pregnant women based on height with the aim of applying monitoring approaches and prevention strategies in the prenatal care setting. Implementation of this approach will help to improve perinatal health

outcomes for the mother and their infant. Examples of such strategies and approaches include starting early fetal assessment and monitoring and early and frequent screening of short women through OGTT to provide better opportunities to ensure pregnancy glucose control.

- Our findings support consideration of maternal height in clinical models to predict the risk of pregnancy complications and adverse outcomes in clinical settings. Future study to investigate the improvement in pregnancy outcomes after the use of maternal height-incorporated prediction tools is needed.
- Our findings support consideration of maternal height in analyses that involve pregnancy complications and outcomes including the consideration of sex as an effect modifier for all infant health outcomes and examine its role in adult health outcomes.
- Further research to establish if maternal height is associated differently with infant birth size depending on age group, race/ethnicity or parity may be needed.
- Our findings highlight the need to investigate the causal association between maternal height and pregnancy complications and outcomes, including gestational diabetes, in future large studies. The finding that shorter maternal height is associated with higher blood glucose levels in late pregnancy provides opportunities for future studies to explore the effect of maternal height on other maternal health outcomes and long-term health in the post-natal period.
- Our study highlighted the need to conduct GWAS studies of height in non-European populations, particularly women, to improve the predictability of observed height based on genetic variants.

In sum, our findings support a critical role of maternal height on maternal and infant pregnancy outcomes and/or complications. Future studies in this area can help improve mechanistic understanding of the relationships and provide evidence to inform public health and clinical interventions aimed at improving maternal and child health outcomes.

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VITA

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