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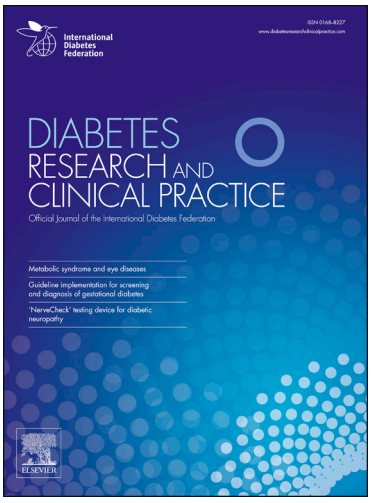

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Impact of maternal height and gestational diabetes mellitus on offspring birthweight

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Abstract

Aims To evaluate the impact of gestational diabetes mellitus (GDM) and maternal height on offspring birthweight.

Methods This is an observational cohort study, encompassing 4 111 Finnish primiparous women from Vantaa city, Finland, with singleton deliveries between 2009-2015. Data were obtained from the Finnish Medical Birth Register. The study population was divided into five groups according to maternal height. Cut-offs for height levels were I ≤ 158 cm, II 159-163 cm, III 164-167 cm, IV 168-172 cm, V ≥ 173 cm. The main outcome measure was offspring birthweight, expressed as Z-scores according to sex and gestational age.

Results Independently, both maternal height and GDM increased offspring birthweight ($p<0.001$ for height and GDM). When studying the interaction, a significant increase in offspring birthweight was noted only in extreme height categories; group I ≤ 158 cm ($p = 0.011$), group IV 168-172 cm ($p = 0.010$) and group V ≥ 173 cm ($p < 0.001$) and the impact was similar in both sexes. Maternal height had no impact on offspring ponderal index ($p=0.20$ for trend).

Conclusions In extreme height categories, short and tall primiparous women with GDM are at risk for delivering larger offspring compared to women without GDM of similar height.

Keywords birthweight, gestational diabetes mellitus, maternal height, offspring, primiparous, stature

1. Introduction

Fetal growth is a complex and multifactorial process influenced by several factors including genetic factors, in utero environment, maternal metabolism, duration of pregnancy and neonatal sex [1,2]. Of pregnancy complications, hypertensive disorders and gestational diabetes mellitus (GDM) are the best known underlying factors affecting fetal growth [3-5]. Offspring birth size, especially when considered macrosomic, increases the risk for delivery complications such as prolonged labor, operative vaginal delivery, cesarean section and admission of the newborn to neonatal centers [6]. Furthermore, a non-optimal fetal growth environment has been shown to have long-term effects on cardiovascular and metabolic disturbances, partly through its impact on birth size [7]. Due to short- and long-term health consequences associated with body size at birth, it is of interest to study factors potentially influencing fetal growth.

GDM is a common pregnancy complication and has long been defined as any kind of abnormal glucose metabolism with onset or first detection during pregnancy [8]. Recent definitions are more precise in differentiating between pre-existing diabetes mellitus and GDM, depending on either different diagnostic criteria using 2-h 75-g oral glucose tolerance test (OGTT) or timing of diagnosis during pregnancy [9-11]. The prevalence of GDM varies between 2% to 32% with a 9% median estimate for North America and 6% for Europe [12]. GDM is known to increase the risk of macrosomia and metabolic disturbances for both mother and child later in life [13-16].

Maternal anthropometry and its effects on fetal growth have been widely studied. Pre-pregnancy body mass index (BMI) has a direct effect on offspring birthweight and obesity increases the risk of macrosomia [17]. It has also been shown that GDM augments the effects of maternal BMI on

offspring birthweight when combined [5,18,19]. Maternal stature has been shown to be positively associated with newborn size at birth [20-22].

Glucose metabolism itself is also affected by anthropometry. In non-pregnant, non-diabetic individuals it has been shown that taller people with a BMI below 35 kg/m^2 tend to have lower postprandial glucose levels compared to shorter people with the same BMI, using standard 2-h 75-g OGTT, with no difference in fasting glucose levels [23]. It has also been shown that short stature in pregnant women is associated with elevated postprandial glucose levels with no difference in fasting glucose levels [24,25].

In 2016, we initiated a long-term follow-up cohort study in the city of Vantaa, Finland, to assess both short- and long-term consequences of disturbances in glucose regulation on women's and their offspring's health. Since it has been shown that stature in pregnant women affects offspring size at birth and alters glucose metabolism, the aim of this study is to simultaneously study the impact of maternal height and GDM on offspring birthweight.

2. Materials and Methods

2.1. Subjects

This study is an observational cohort study in the city of Vantaa, the fourth biggest city in Finland. Between January 1st 2009 and December 31st 2015, 7 750 primiparous women without a history of previously diagnosed diabetes mellitus gave birth. Of those, 4 111 women with Finnish background (born in Finland with Finnish or Swedish as mother tongue) and aged ≥ 18 years gave birth to a singleton offspring between gestational weeks 37 and 42 and had complete height and weight data together with complete data from a standard 2-h 75-g OGTT. The Finnish Current Care Guidelines for GDM recommends screening of all pregnant women during their first pregnancy for GDM using

2-h 75-g OGTT, except in low-risk patients, i.e. women aged under 25 years, with a BMI between 18.5- 25 kg/m^2 and with no family history of diabetes [26].

Data on maternal-fetal characteristics and pregnancy outcomes were obtained from the Medical Birth Register, which is administrated by the National Institute for Health and Welfare in Finland and receives the information from all Finnish maternity hospitals. The following information on the primiparous women was obtained from this source: pre-gestational weight, height, previous pregnancies (miscarriages, induced abortions or ectopic pregnancies) and deliveries, infertility treatment, smoking during pregnancy, and hospitalization due to hypertension during pregnancy [27]. The following information on the offspring was collected: sex, birth length, birthweight, and head circumference.

GDM was defined according to the Finnish Current Care Guidelines for GDM as one or more pathological glucose values in a standard 2-h 75-g OGTT [26]. The diagnostic thresholds were: fasting plasma glucose ≥ 5.3 mmol/L, 1-h glucose ≥ 10.0 mmol/L, and 2-h glucose ≥ 8.6 mmol/L [26].

Macrosomia was defined as offspring birthweight ≥ 4 500g. Large for gestational age (LGA) and small for gestational age (SGA) were defined as a birthweight > 90th percentile and <10th percentile, respectively, according to gestational age and sex. Ponderal index (PI), was calculated for estimating body proportionality at birth and was defined as birth weight (kg) divided by birth length (m) in third power: PI = kg/m^3 [28].

Educational attainment was defined according to years of schooling, as obtained from Statistics Finland [29].

2.2. Statistical analysis

Data are presented as means with range or standard deviations (SD) or as counts with percentages. Standardized values were divided into five height level categories using z-scores: 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) corresponding to grades containing 12.5, 25, 25, 25, and 12.5% of the total distribution. Cut-offs for maternal height levels were I ≤ 158 cm, II 159-163 cm, III 164-167 cm, IV 168-172 cm, V ≥ 173 cm. Offspring birthweight and PI were calculated as Z-scores (according to sex and gestational age). Statistical significances for the unadjusted hypothesis of linearity across categories of height levels were evaluated by using the Cochran-Armitage test for trend and analysis of variance with an appropriate contrast. Adjusted hypothesis of linearity (orthogonal polynomial) was evaluated using generalized linear models (e.g. analysis of covariance and logistic models) with appropriate distribution and link function. Models included age, education years and pre-pregnancy body mass as covariates. A possible nonlinear relationship between prevalence of GDM or offspring birthweight and the maternal standardized height was assessed by using 5-knot-restricted cubic spline regression. The length of the distribution of knots was located at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles corresponding to standardized height values of -1.66, -0.66, 0.01, 0.67 and 1.67. For restricted cubic splines, also known as natural splines, knot locations are based on Harrell's recommended percentiles or user-specified points [30]. The normality of the variables was tested by using the Shapiro–Wilk W test. Statistical significance was set at $p < 0.05$. Stata 15.0 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analysis.

2.3. Ethical approval

This study has been approved by the ethics committee of the Hospital District of Helsinki and Uusimaa (356/13/03/03/2015, November 2nd 2015), and by the health authority of Vantaa city, Finland. Permission to use register data for this study were given by the National Institute for Health and Welfare, and Statistics Finland. According to the ethics committee of Hospital District of Helsinki and Uusimaa, and the health authority of Vantaa city, the study participants do not need

to provide the Statement of Informed Consent, since this is an observational register-based study and the registered people were not contacted.

3. Results

3.1. Characteristics of the study participants

Baseline characteristics of the 4 111 study participants divided into five height levels are shown in Table 1. The cut-offs were: I ≤ 158 cm, II 159-163 cm, III 164-167 cm, IV 168-172 cm, and V ≥ 173 cm. Mean height of the study participants was 166.0 (SD 6.0) cm. Height was positively associated with age and educational attainment (both $p < 0.001$).

Baseline characteristics of the offspring according to maternal height levels are shown in Table 2. Boys had a mean birthweight of 3 564 (SD 466) g, birth length 50.7 (SD 2.0) cm, and head circumference 35.3 (SD 1.4) cm, while the corresponding values for girls were 3 458 (SD 446) g, 49.9 (SD 2.0) cm, and 34.8 (SD 1.4) cm, respectively. Maternal height was positively associated with offspring birthweight, birth length, and head circumference in both sexes, as well as with a higher prevalence of macrosomia and large for gestational age (LGA) newborns (all $p < 0.001$). In contrast, maternal height was inversely associated with small for gestational age (SGA) newborns ($p < 0.001$). Ponderal index of newborns did not differ across different maternal height levels.

3.2. Maternal height and prevalence of gestational diabetes

Figure 1 shows the prevalence of GDM at five different height levels and on a continuous scale with standardized height, adjusted for age and educational attainment. The prevalence of GDM was highest among the shortest women (≤ 158 cm) with a prevalence of 23.9% (95% CI 19.9- 27.9) and lowest in the group of average height women (164-167 cm) with a prevalence of 18.7% (95% CI

15.5- 21.9) (Figure 1B). There was an inverse relationship across maternal height levels and prevalence of GDM ($p = 0.018$ for linearity).

3.3. Effect of maternal height and gestational diabetes on offspring birthweight and ponderal index

Figure 2 shows the impact of maternal height and GDM and their interaction on offspring birthweight, adjusted for maternal age, pre-pregnancy BMI and educational attainment. In primiparous women without GDM, offspring birthweight increased with maternal height ($p < 0.001$ for trend). Similarly, in primiparous women with GDM offspring birthweight increased with maternal height ($p < 0.001$ for trend), except in women of average height (159-167cm) which included about half of the study participants, in whom GDM had no significant influence on offspring birthweight. Maternal height had no impact on offspring PI ($p=0.20$ for trend, adjusted for maternal age, pre-pregnancy BMI and educational attainment) (Figure 3). The impact of maternal height and GDM on offspring birthweight was similar for both sexes, as shown in Figure 4.

4. Discussion

According to the study findings in our cohort including Finnish women and their offspring, in primiparous women without GDM, offspring birthweight increased with maternal height. Interestingly, in primiparous women with GDM such an association with offspring birthweight was observed only in the extreme height categories of short and tall women, but not in women of average height. There was a significant interaction between maternal height and GDM on offspring birthweight, and the same trend was observed in both sexes. Tall primiparous women had an increased risk of newborn macrosomia and LGA newborns. Similarly, short stature was associated with SGA newborns. PI, in contrast, did not differ across different maternal height levels. Moreover, maternal height and GDM had no impact on PI.

The nationwide prevalence of GDM in Finland increased during our study period from 11.2% to 15.9% in 2015 [27]. The high prevalence of GDM in our cohort is in line with nationwide findings. Overall, GDM prevalence can be considered high in Finland, when compared to a median estimate of 6% in Europe, even though GDM prevalence have been shown to vary between 2-32% globally [12]. The comprehensive screening for GDM since 2008 in Finland might possibly explain this rather high prevalence in our country and particularly in this study, in which only women with high-risk for GDM with complete OGTT data were included.

Our findings regarding maternal height and offspring birthweight in pregnancies without GDM were expected. Many other studies have shown a positive association between maternal height and offspring birth size [20-22,31]. Moreover, the positive association between maternal height and LGA babies, as well as the negative association between maternal height and SGA babies have been recognized previously. In fact, a recent German study reported similar relationships [32]. Interestingly, neither maternal height nor GDM had any impact on PI. This might indicate that body proportionalities did not differ across different maternal height levels at term.

The association between maternal height and offspring birth size has been thought to reflect mainly genetic factors [21], although the height of the mother and offspring body size, especially in developing countries, are also consequences of the nutritional status early in life [33]. Further, some physical aspects are thought to explain the correlation, including maternal constraint. In shorter mothers, there can be physical limitations for the growth of the uterus that can restrict fetal growth [34].

In most previous studies, a positive correlation between GDM and offspring birth size has been reported, but the effect of GDM on offspring birth size has been studied with no distinction of maternal stature [4,13,35]. In 1952, Jørgen Pedersen theorized that hyperglycemia of the mother led to hyperglycemia of the fetus and that this, in turn, amplified the fetal response to insulin [36].

Pedersen´s hypothesis has formed the basic understanding of the pathophysiological consequences of diabetes during pregnancy. Modifying Pedersen´s hypothesis has led to the idea, that the impact of GDM on birth size is thought to be due to insulin resistance in diabetic mothers and an elevated glucose level that passes through the placenta. This, in turn, increases the insulin levels of the fetus and leads to an excessive uptake of glucose, storage of glycogen and the formation of adipose tissue, resulting in macrosomia [13]. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study showed no threshold for glucose in relation to adverse pregnancy outcomes [4]. The results indicated a strong, positive and continuous association between increasing maternal glucose concentrations, already below those that are diagnostic for diabetes mellitus, and an increased birthweight [4].

GDM is a heterogenic metabolic disorder and is thought to be caused by increasing insulin resistance due to placental hormonal influence and maternal adiposity in late pregnancy, impaired beta-cell function, genetic predisposition and in some cases autoimmunity [37]. Glucose metabolism has been shown to be affected by stature both in non-pregnant and pregnant individuals. In non-pregnant individuals, studies have shown that taller individuals tend to have lower postprandial glucose levels compared to shorter individuals using standard OGTT, with no difference in fasting glucose levels [23-25,38-40]. In line with our findings, previous studies have also proven GDM to be more common in shorter women [24-25,41], although some findings show no differences in stature between GDM and non-GDM women [42].

It is not fully understood how stature influences glucose metabolism, but there are several hypotheses trying to explain the association. Taller people have more muscle mass, although not necessarily a higher percentage of muscle tissue in relation to total body mass. It is generally accepted that muscle tissue is the major tissue involved in glucose metabolism [39]. It has been theorized that the inverse association between height and postprandial glucose levels after a standard 2-h OGTT reflects the larger amount of metabolically active muscle tissue that taller

individuals, compared to shorter individuals, have to metabolize the same fixed load of glucose [39]. Height has also been positively associated with both pancreatic beta cell function and insulin sensitivity [38], possibly indicating a more favorable glucose regulation in tall, compared to short individuals.

According to our findings, the simultaneous effect of maternal height and GDM affects offspring birthweight only in the extreme height categories of short and tall women. In Finland, GDM is diagnosed using a fixed load of 75-g glucose in association with a 2-h OGTT, regardless of maternal height, weight or body composition. The varying effect of GDM on offspring birthweight observed in different maternal height levels can probably partly be explained by differences in maternal anthropometrics including body composition. Perhaps, taller women with GDM might have a more severe degree of impairment in their glucose regulation compared to shorter women, consequently more often leading to macrosomia among the offspring. Among short women, it is possible that the muscle mass is limited – both quantitatively and qualitatively - and thus already a mild elevation in glucose concentration is more likely to affect the fetus.

One can also speculate about possible effects of assortative mating on stature and paternal genetic imprinting on traits and disease burden in the fetus. According to a meta-analysis about assortative mating for human heights there is a moderate positive trend for assortative mating for height despite ethnicities, although, height cannot be considered as a major factor when choosing a partner [43]. Similarly, it is important to knowledge the possible impact of a short mothers' own early growth and nutritional status. Birth size is known to be positively associated with adult height [44], in other words might short individuals have had a low birthweight and a non-optimal prenatal growth. There are several studies indicating that intrauterine growth restriction and malnutrition in infancy can lead to impaired glucose regulation and impaired endogenous pancreatic function in adulthood, predisposing to type 2 diabetes [45,46].

The question remains why offspring birthweight is not affected by GDM in women of average height? Interestingly, a recent Australian study shows no elevation at macrosomia rates in diet-treated GDM women compared to non-diabetic controls, suggesting that a milder and diet-treated GDM could have a lower impact on risk of macrosomia [47]. Possibly, GDM is milder in women of average height where the influence of stature on glucose metabolism would be less.

To the best of our knowledge, this is the first study to investigate the simultaneous effect of maternal height and GDM on offspring birthweight. According to our study findings, GDM increased offspring birthweight only in women with short or tall stature, while among the majority of women of average height no impact of GDM on birth size was observed. In clinical practice, this might indicate that both short and tall primiparous women with GDM should have a more intense follow up during pregnancy, and if needed, a customized plan for delivery. This area needs to be further explored, also taking into account the mother´s own birthweight and potential transgenerational aspects.

The strength of this study is that the study cohort encompasses all adult Finnish primiparous women from the city of Vantaa, the fourth largest city in Finland, who gave birth to a singleton infant at term during a seven-year follow-up. The diagnosis of GDM is based on a 2-h 75-g oral glucose tolerance test and is considered reliable while it is standardized nationwide, and the diagnostic criteria have been the same during the follow-up period.

The study has some limitations. We had no information on measures of insulin resistance, gestational weight gain, family history of diabetes, physical activity nor dietary habits. We also missed data on paternal anthropometry. Body composition and birthweight of the mothers´ were unknown. In this cohort all study participants were Finnish, therefore the generalization of our results globally can be limited. Noteworthy is that even if all women included in the study had a reliable GDM diagnosis based upon OGTT results, we have no other information on metabolic parameters and associations between these and offspring birthweight were unknown.

In conclusion, short and tall Finnish primiparous women with GDM are at risk of delivering larger infants compared to women without GDM with the same height. GDM does not affect offspring birthweight in Finnish primiparous women of average height. Among tall Finnish women with GDM, the prevalence of macrosomia is increased. Maternal height had no impact on offspring PI. To minimize the adverse effects of an increased birthweight and/or macrosomia, special attention should be paid to women with GDM, especially in the subgroups of short and tall women.

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Conflict of interest

Declarations of interest: None.

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References

[1] Catalano PM, Kirwan JP. Maternal factors that determine neonatal size and body fat. *Current diabetes reports.* 2001;1(1):71-77.

[2] Love EJ, Kinch RA. Factors influencing the birth weight in normal pregnancy. *American journal of obstetrics and gynecology.* 1965;91:342-349.

[3] Shen M, Smith GN, Rodger M, White RR, Walker MC, Wen SW. Comparison of risk factors and outcomes of gestational hypertension and pre-eclampsia. *PloS one.* 2017;12(4):e0175914. https://doi.org/10.1371/journal.pone.0175914

[4] Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. *The New England journal of medicine.* 2008;358(19):1991-2002. https://doi.org/10.1056/NEJMoa0707943

[5] Catalano PM, McIntyre HD, Cruickshank JK, McCance DR, Dyer AR, Metzger BE, et al. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes care.* 2012;35(4):780-786. https://doi.org/10.2337/dc11-1790

[6] Mocanu EV, Greene RA, Byrne BM, Turner MJ. Obstetric and neonatal outcome of babies weighing more than 4.5 kg: an analysis by parity. *European journal of obstetrics, gynecology, and reproductive biology.* 2000;92(2):229-233. https://doi.org/10.1016/S0301-2116(99)00280-8

[7] Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *The New England journal of medicine.* 2008;359(1):61-73. https://doi.org/10.1056/NEJMra0708473

[8] Gestational diabetes mellitus. *Diabetes care.* 2004;27 Suppl 1:S88-90. https://doi.org/10.2337/diacare.27.2007

[9] WHO Guidelines Approved by the Guidelines Review Committee. In: *Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy.* Geneva: World Health Organization Copyright (c) World Health Organization 2013.; 2013.

[10] 2. Classification and Diagnosis of Diabetes. *Diabetes care.* 2017;40(Suppl 1):S11-s24. https://doi.org/10.2337/dc17-S005

[11] Agarwal MM. Gestational diabetes mellitus: An update on the current international diagnostic criteria. *World journal of diabetes.* 2015;6(6):782-791. https://doi.org/10.4239/wjd.v6.i6.782

[12] Zhu Y, Zhang C. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. *Current diabetes reports.* 2016;16(1):7. https://doi.org/10.1007/s11892-015-0699-x

[13] Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. *Annals of nutrition & metabolism.* 2015;66 Suppl 2:14-20. https://doi.org/10.1159/000371628

[14] Mitanchez D, Yzydorczyk C, Siddeek B, Boubred F, Benahmed M, Simeoni U. The offspring of the diabetic mother--short- and long-term implications. *Best practice & research Clinical obstetrics & gynaecology.* 2015;29(2):256-269. https://doi.org/10.1016/j.bpobgyn.2014.08.004

[15] Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet (London, England).* 2009;373(9677):1773-1779. https://doi.org/10.1016/S0140-6736(09)60731-5

[16] Tobias DK, Stuart JJ, Li S, Chavarro J, Rimm EB, Rich-Edwards J, et al. Association of History of Gestational Diabetes With Long-term Cardiovascular Disease Risk in a Large Prospective Cohort of US Women. *JAMA internal medicine.* 2017. https://doi.org/10.1001/jamainternmed.2017.2790

[17] Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. *PloS one.* 2013;8(4):e61627. https://doi.org/10.1371/journal.pone.0061627

[18] Bystrom M, Liu A, Quinton AE, Champion BL, Mann K, Peek M, Nanan RK, et al. Gestational Diabetes Independently Increases Birth Length and Augments the Effects of Maternal BMI on Birth Weight: A Retrospective Cohort Study. *Frontiers in pediatrics.* 2014;2:112. https://doi.org/10.3389/fped.2014.00112

[19] Miao M, Dai M, Zhang Y, Sun F, Guo X, Sun G. Influence of maternal overweight, obesity and gestational weight gain on the perinatal outcomes in women with gestational diabetes mellitus. *Scientific reports.* 2017;7(1):305. https://doi.org/10.1038/s41598-017-00441-z

[20] Polzlberger E, Hartmann B, Hafner E, Stumpflein I, Kirchengast S. Maternal height and pre-pregnancy weight status are associated with fetal growth patterns and newborn size. *Journal of biosocial science.* 2017;49(3):392-407. https://doi.org/10.1017/S0021932016000493

[21] Kirchengast S, Hartmann B, Schweppe KW, Husslein P. Impact of maternal body build characteristics on newborn size in two different European populations. *Human biology.* 1998;70(4):761-774.

[22] Han Z, Lutsiv O, Mulla S, McDonald SD. Maternal height and the risk of preterm birth and low birth weight: a systematic review and meta-analyses. *Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC.* 2012;34(8):721-746. https://doi.org/10.1016/S1701-2163(16)35337-3

[23] Rehunen SKJ, Kautiainen H, Eriksson JG, Korhonen PE. Adult height and glucose tolerance: a re-appraisal of the importance of body mass index. *Diabetic medicine : a journal of the British Diabetic Association.* 2017;34(8):1129-1135. https://doi.org/10.1111/dme.13382

[24] Jang HC, Min HK, Lee HK, Cho NH, Metzger BE. Short stature in Korean women: a contribution to the multifactorial predisposition to gestational diabetes mellitus. *Diabetologia.* 1998;41(7):778-783. https://doi.org/10.1007/s001250050987

[25] Branchtein L, Schmidt MI, Matos MC, Yamashita T, Pousada JM, Duncan BB. Short stature and gestational diabetes in Brazil. Brazilian Gestational Diabetes Study Group. *Diabetologia.* 2000;43(7):848-851.

[26] [Update on current care guideline: gestational diabetes]. *Duodecim; laaketieteellinen aikakauskirja.* 2013;129(17):1798-1799.

[27] THL. Medical Birth Register 2015. Available at: *http://www.thl.fi/en/statistics/parturients.* (Accessed 12/17, 2017).

[28] Landmann E, Irwin R, Misselwitz B, Gortner L. Ponderal index for discrimination between symmetric and asymmetric growth restriction: Percentiles for neonates from 30 weeks to 43

weeks of gestation. *The journal of Maternal-Fetal and Neonatal Medicine.* 2006;19(3):157-160. https://doi.org/10.1080/14767050600624786

[29] STAT. Koulutusaste 2016. Available at: *http://www.stat.fi/meta/luokitukset/koulutus/001-2016/kuvaus.* (Accessed 12/17, 2017).

[30] Harrell FE Jr. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. New York: Springer; 2001.

[31] Pickett KE, Abrams B, Selvin S. Maternal height, pregnancy weight gain, and birthweight. *American journal of human biology : the official journal of the Human Biology Council.* 2000;12(5):682-687. https://doi.org/10.1002/1520-6300(200009/10)12:5<682::AID-AJHB13>3.0.CO;2-X

[32] Olbertz BM, Knie A, Straube S, Hentschel R, Schleußner E, Hagenah HP, et al. Somatic development at birth as influenced by maternal characteristics- an analysis of the German Perinatal Survey. *J Perinat Med.* 2018;46(8):889-892. https://doi.org/10.1515/jpm-2017-0039

[33] Camilleri AP. The obstetric significance of short stature. *European Journal of Obstetrics and Gynecology and reproductive Biology.* 1981;12(6):347-356.

[34] Hisham TJ, Moawed SA. The relation of low birth weight to psychosocial stress and maternal anthropometric measurements. *Saudi Medical Journal.* 2000;21(7):649-54.

[35] Yang J, Cummings EA, O'Connell C, Jangard K. Fetal and neonatal outcomes of diabetic pregnancies. *Obstetrics and gynecology.* 2006;108(3 Pt 1):644-650. https://doi.org/10.1097/01.AOG.0000231688.08263.47

[36] Pedersen J. Diabetes and pregnancy; blood sugar of newborn infants during fasting and glucose administration. *Nordisk medicin.* 1952;47(30):1049.

[37] Buchanan TA, Xiang AH. Gestational diabetes mellitus. *The Journal of clinical investigation.* 2005;115(3):485-491. https://doi.org/10.1172/JCI24531

[38] Vangipurapu J, Stancakova A, Jauhiainen R, Kuusisto J, Laakso M. Short Adult Stature Predicts Impaired beta-Cell Function, Insulin Resistance, Glycemia, and Type 2 Diabetes in Finnish Men. *The Journal of clinical endocrinology and metabolism.* 2017;102(2):443-450. https://doi.org/10.1210/jc.2016-2933

[39] Sicree RA, Zimmet PZ, Dunstan DW, Cameron AJ, Welborn TA, Shaw JE. Differences in height explain gender differences in the response to the oral glucose tolerance test- the AusDiab study. *Diabetic medicine : a journal of the British Diabetic Association.* 2008;25(3):296-302. https://doi.org/10.1111/j.1464-5491.2007.02362.x

[40] Faerch K, Borch-Johnsen K, Vaag A, Jorgensen T, Witte DR. Sex differences in glucose levels: a consequence of physiology or methodological convenience? The Inter99 study. *Diabetologia.* 2010;53(5):858-865. https://doi.org/10.1007/s00125-010-1673-4

[41] Anastasiou E, Alevizaki M, Grigorakis SJ, Philippou G, Kyprianou M, Souvatzoglou A. Decreased stature in gestational diabetes mellitus. *Diabetologia.* 1998;41(9):997-1001. https://doi.org/10.1007/s001250051022

[42] Tabak AG, Kerenyi Z, Nagy E, Bosnyak Z, Madarasz E, Tamas G. Height and gestational diabetes mellitus. *Diabetic medicine : a journal of the British Diabetic Association.* 2002;19(4):344-345.

[43] Stulp G, Simons MJ, Grasman S, Pollet TV. Assortative mating for human height: A meta-analysis. *American Journal of Human Biology.* 2017;29(01):e22917. https://doi.org/10.1002/ajhb.22917

[44] Pietilainen KH, Kaprio J, Rasanen M, Winter T, Rissanen A, Rose RJ. Tracking of body size from birth to late adolescence: contributions of birth length, birth weight, duration of gestation, parents' body size, and twinship. *American journal of epidemiology.* 2001;154(1):21-29.

[45] Phipps K, Barker DJ, Hales CN, Fall CH, Osmond C, Clark PM. Fetal growth and impaired glucose tolerance in men and women. *Diabetologia.* 1993;36(3):225-228.

[46] Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, et al. Birth weight and risk of type 2 diabetes: a systematic review. *JAMA.* 2008 Dec 24;300(24):2886-97. https://doi.org/10.1001/jama.2008.886

[47] Vally F, Presneill J, Cade T. Macrosomia Rates in Women with Diet-Controlled Gestational Diabetes: A Retrospective Study. *Journal of pregnancy.* 2017;2017:4935397. https://doi.org/10.1155/2017/4935397

Table 1

Baseline characteristics of the 4 111 primiparous women according to height levels

Characteristics of the women	Height levels I N=442	II N=990	III N=974	IV N=1132	V N=573	p-value for linearity
Height (cm), mean (range)	156 (137- 158)	161 (159-163)	165 (164- 167)	170 (168- 172)	176 (173- 190)	
Age (years), mean (SD)	28.7 (4.7)	29.3 (4.8)	29.6 (4.8)	29.6 (4.8)	30.1 (4.6)	< 0.001
Cohabiting, n (%)	352 (80)	802 (81)	803 (82)	936 (83)	489 (85)	0.012
Smokers [a], n (%)	79 (18)	158 (16)	141 (14)	174 (15)	79 (14)	0.10
Years of education, mean (SD)	13.5 (2.5)	13.8 (2.5)	13.8 (2.4)	13.9 (2.5)	14.2 (2.5)	< 0.001
Prepregnancy BMI (kg/m^2), mean (SD)	24.9 (4.7)	24.6 (4.3)	24.8 (4.6)	24.9 (5.0)	24.7 (5.0)	0.93
Previous pregnancies, n (%)	93 (21)	202 (20)	189 (19)	245 (22)	89 (16)	0.15
Fertility treatment, n (%)	34 (8)	92 (9)	94 (10)	122 (11)	60 (10)	0.068
Hypertensive disorders [b], n (%)	31 (7)	54 (5)	73 (7)	79 (7)	31 (5)	0.94

BMI, body mass index; *SD*, standard deviation

[a] Included those who quitted smoking during pregnancy; [b] Hospitalization due to hypertension during pregnancy

Statistical significances for the unadjusted hypothesis of linearity across categories of height levels were evaluated by using the Cochran-Armitage test for trend and analysis of variance.

Table 2

Baseline characteristics of the 4 111 offspring according to maternal height [a]

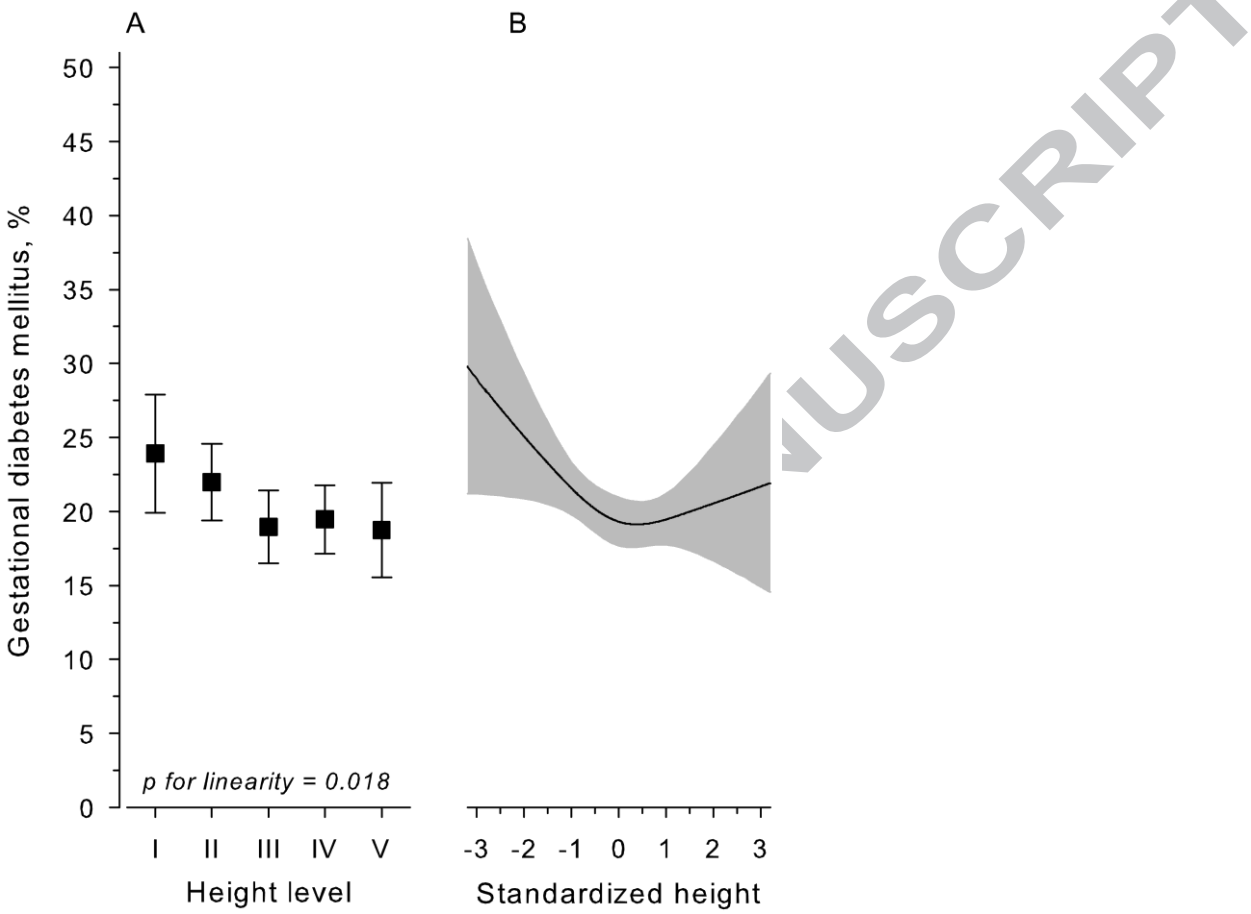
Characteristics of the offspring	Height levels I N=442	II N=990	III N=974	IV N=1132	V N=573	p-value for linearity
Boys, n (%)	238 (54)	516 (52)	527 (54)	572 (51)	298 (52)	0.37
Birthweight (g), mean (SD)						
Boys	3 435 (451)	3 483 (443)	3 529 (478)	3 653 (461)	3 700 (445)	< 0.001
Girls	3 304 (441)	3 406 (415)	3 466 (448)	3 511 (465)	3 539 (423)	< 0.001
Birth length (cm), mean (SD)						
Boys	50.0 (2.0)	50.3 (1.9)	50.5 (1.9)	51.0 (2.0)	51.3 (1.9)	< 0.001
Girls	49.1 (2.0)	49.7 (1.9)	49.8 (1.9)	50.1 (2.0)	50.4 (1.9)	< 0.001
Birth weight (Z-score), mean (SD)						
Boys	-0.31 (0.94)	-0.18 (0.95)	-0.07 (1.00)	0.19 (0.99)	0.33 (0.99)	< 0.001
Girls	-0.37 (0.94)	-0.17 (0.91)	0.04 (1.01)	0.15 (1.02)	0.19 (1.01)	< 0.001
Ponderal Index, (weight [kg]/ height $[m]^3$), mean (SD)						
Boys	27.4 (2.6)	27.2 (2.4)	27.3 (2.5)	27.5 (2.4)	27.4 (2.5)	0.42
Girls	27.4 (2.6)	27.8 (2.3)	27.9 (2.5)	27.9 (2.5)	27.7 (2.5)	0.76
Head circumference (cm), mean (SD)						

Boys	35.0 (1.5)	35.1 (1.4)	35.3 (1.5)	35.5 (1.4)	35.6 (1.4)	< 0.001
Girls	34.3 (1.5)	34.7 (1.3)	34.8 (1.4)	35.0 (1.4)	35.0 (1.3)	< 0.001
Macrosomia (birthweight ≥ 4500g), n (%)	2 (0.5)	12 (1.2)	23 (2.4)	37 (3.2)	20 (3.5)	< 0.001
LGA (>90h percentile), n (%)	22 (5.0)	66 (6.7)	100 (10.3)	148 (13.1)	75 (13.1)	< 0.001
SGA (<10h percentile), n (%)	69 (15.6)	122 (12.3)	107 (11.0)	78 (6.9)	34 (5.9)	< 0.001

SD, standard deviation; [a]Cut-offs for the different height levels were I ≤ 158 cm, II 159 – 163 cm, III 164 – 167 cm, IV 168 – 172 cm, and V ≥ 173 cm. Statistical significances for the unadjusted hypothesis of linearity across categories of height levels were evaluated using Cochran-Armitage test for trend and analysis of variance

Figure 1

Prevalence of GDM according to height of the women

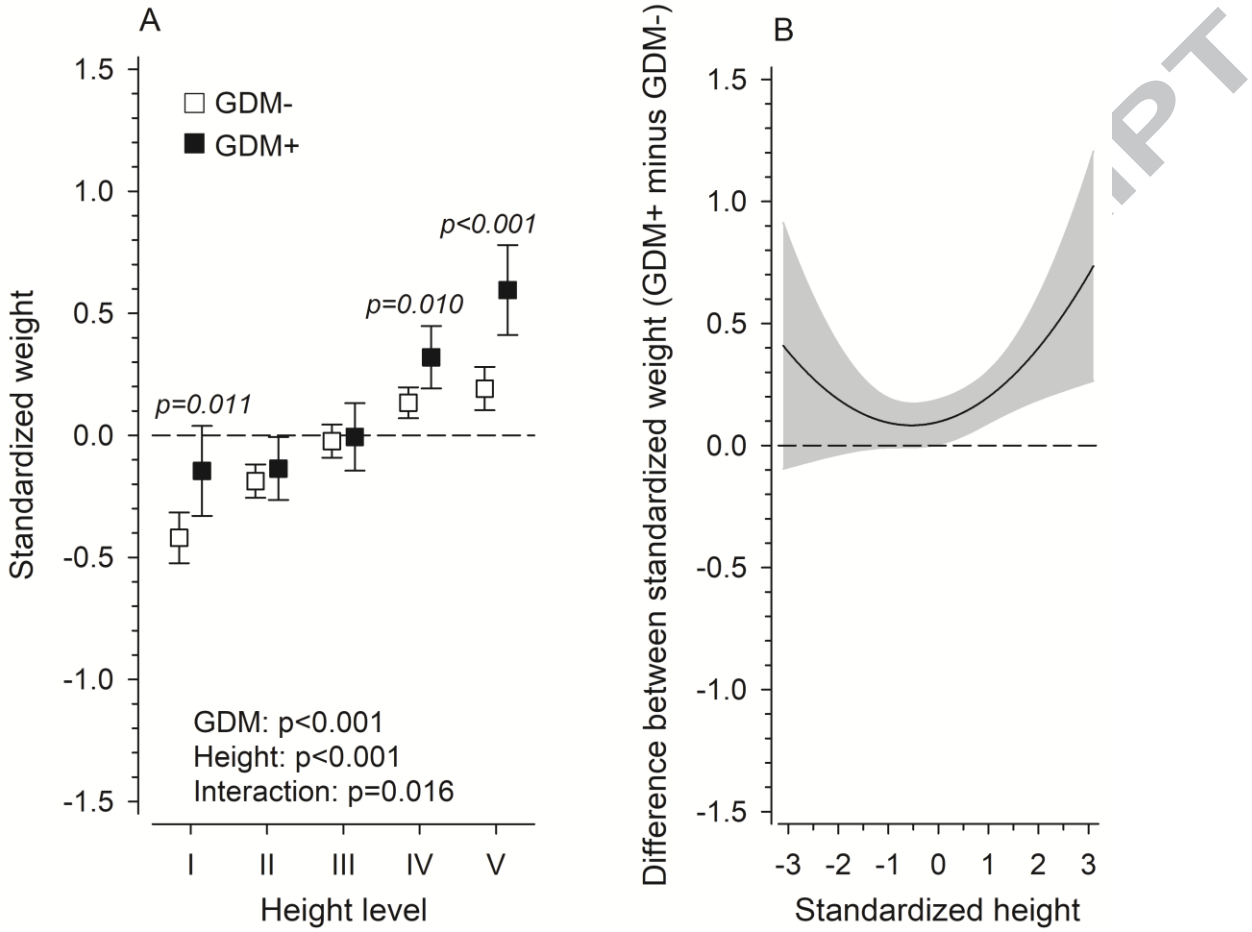


(A) Prevalence of GDM at five different height levels, with cut-offs for height levels at I ≤ 158 cm, II 159 – 163 cm, III 164 – 167 cm, IV 168 – 172 cm, and V ≥ 173 cm. Whiskers show 95% confidence intervals. (B) Prevalence of GDM on a continuous scale with standardized maternal height. The curve was derived from a 5-knot restricted cubic splines regression model and gray area represent 95% confidence interval. Both figures were adjusted for age and educational attainment.

GDM, gestational diabetes

Figure 2

Impact of maternal height and GDM on offspring birthweight

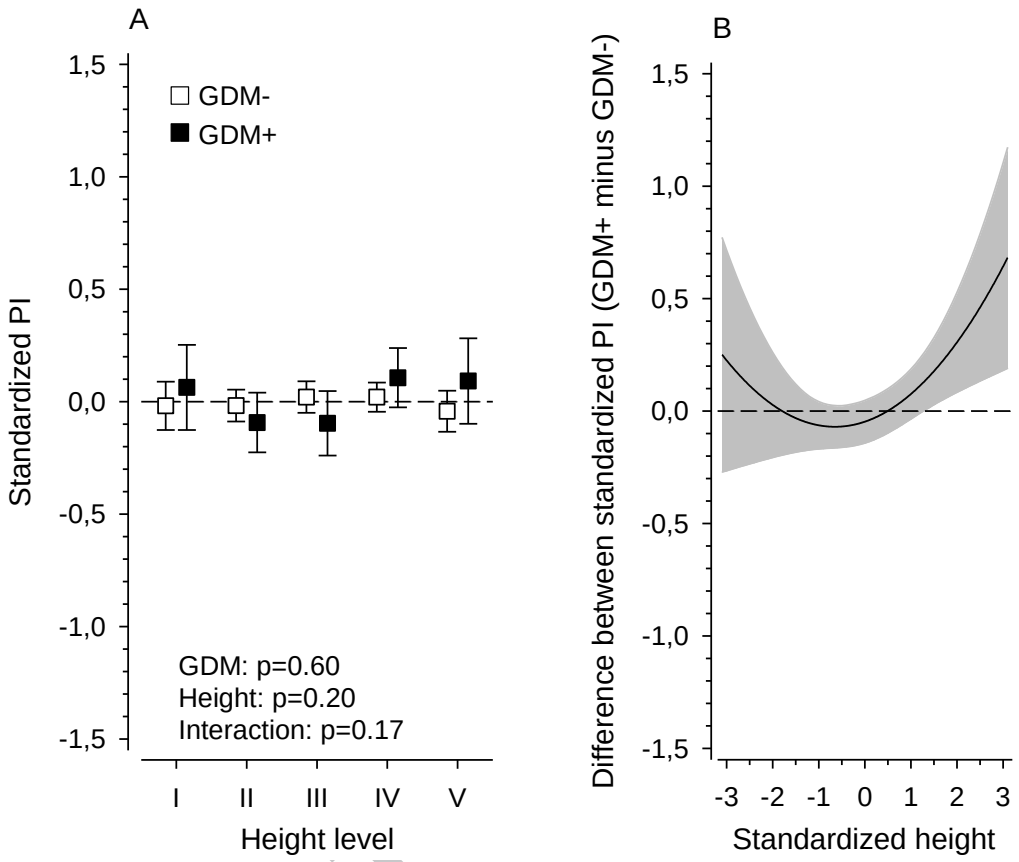


The impact of maternal height and GDM and their interaction on offspring birthweight in five different height levels (A) and as a continuum (B) with standardized maternal height adjusted for age, pre-pregnancy body mass index and educational attainment. Cut-offs for maternal height levels were I ≤ 158 cm, II 159-163 cm, III 164-167 cm, IV 168-172 cm, V ≥ 173 cm. Offspring birthweight was calculated as Z-scores (according to sex and gestational age).

GDM, Gestational diabetes mellitus

Figure 3

Impact of maternal height and GDM on offspring Ponderal Index



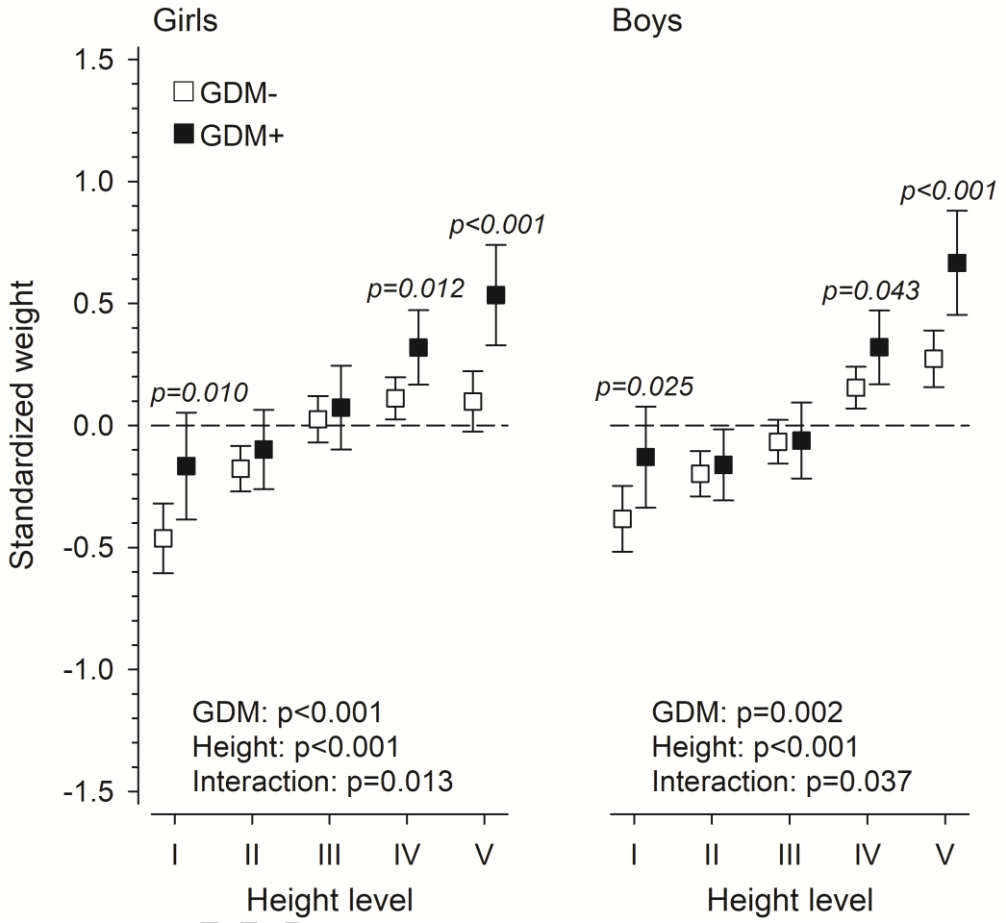
The impact of maternal height and GDM and their interaction on offspring Ponderal Index in five different height levels (A) and as a continuum (B) with standardized maternal height adjusted for age, pre-pregnancy body mass index and educational attainment. Cut-offs for maternal height levels were I ≤ 158 cm, II 159-163 cm, III 164-167 cm, IV 168-172 cm, V ≥ 173 cm. Offspring Ponderal Index was calculated as Z-scores (according to sex and gestational age).

GDM, Gestational diabetes mellitus

PI, Ponderal Index

Figure 4

Impact of maternal height and GDM on offspring birthweight in girls and boys



The impact of maternal height and GDM and their interaction on offspring birthweight in both girls (A) and boys (B) in five different height levels (age, pre-pregnancy body mass index and educational attainment adjusted). Cut-offs for height were I ≤ 158 cm, II 159-163 cm, III 164-167 cm, IV 168-172 cm, V ≥ 173 cm. Offspring birthweight was calculated as Z-scores (according to sex and gestational age).

GDM, Gestational diabetes mellitus