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ORIGINAL RESEARCH ARTICLE

Large maternal waist circumference in relation to height is associated with high glucose concentrations in an early-pregnancy oral glucose tolerance test: A population-based study

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Abstract

Introduction: To explore the role of maternal anthropometric characteristics in early-pregnancy glycemia, we analyzed the associations and interactions of maternal early-pregnancy waist circumference (WC), height and pre-pregnancy body mass index (BMI) with plasma glucose concentrations in an oral glucose tolerance test (OGTT) at 12–16 weeks' gestation.

Material and Methods: A population-based cohort of 1361 pregnant women was recruited in South Karelia, Finland, from March 2013 to December 2016. All participants had their WC, weight, height, HbA_{1c}, and blood pressure measured at 8–14 weeks' gestation and subsequently underwent a 2-h 75-g OGTT, including assessment of fasting insulin concentrations, at 12–16 weeks' gestation. BMI (kg/m^2) was calculated using self-reported pre-pregnancy weight. Maternal WC ≥80 cm was defined as large. Maternal height ≥166 cm was defined as tall. Data on gestational diabetes treatment was extracted from hospital records.

Results: In the total cohort, 901 (66%) of women had an early-pregnancy WC ≥80 cm, which was associated with higher early-pregnancy $HbA_{1c,}$ higher concentrations of fasting plasma glucose and serum insulin, higher post-load plasma glucose concentrations, higher HOMA-IR indices, higher blood pressure levels, and higher frequencies of pharmacologically treated gestational diabetes, than early-pregnancy WC <80 cm. Maternal height ≥166 cm was negatively associated with 1- and 2-h post-load plasma glucose concentrations. Waist-to-height ratio (WHtR) >0.5 was positively associated with both fasting and post-load plasma glucose concentrations at 12–16 weeks' gestation, even when adjusted for age, smoking, nulliparity, and family

Abbreviations: ANOVA, analysis of variance; AUC, areas under the curve; BMI, body mass index; CI, confidence interval; EDDIE, The Early Diagnosis of Diabetes in Pregnancy-study; GDM, gestational diabetes mellitus; HOMA-IR, insulin resistance index; LWS, large waist short; LWT, large waist tall; NWS, normal waist short; NWT, normal waist tall; OGTT, oral glucose tolerance test; SD, standard deviation; SKCH, South Karelia Central Hospital; WC, waist circumference; WHtR, waist-to-height ratio.

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history of type 2 diabetes. The best cut-offs for WHtR (0.58 for 1-h plasma glucose, and 0.54 for 2-h plasma glucose) were better predictors of post-load glucose concentrations >90th percentile than the best cut-offs for BMI (28.1 kg/m^2 for 1-h plasma glucose, and 26.6 kg/m^2 for 2-h plasma glucose), with areas-under-the-curve (95% confidence interval) 0.73 (0.68–0.79) and 0.73 (0.69–0.77), respectively, for WHtR, and 0.68 (0.63–0.74) and 0.69 (0.65–0.74), respectively, for BMI.

Conclusions: In our population-based cohort, early-pregnancy WHtR >0.5 was positively associated with both fasting and post-load glucose concentrations at 12–16 weeks' gestation and performed better than BMI in the prediction of post-load glucose concentrations >90th percentile. Overall, our results underline the importance of evaluating maternal abdominal adiposity in gestational diabetes risk assessment.

KEYWORDS

early pregnancy, gestational diabetes, height, oral glucose tolerance test, waist circumference, waist-to-height ratio

1 | INTRODUCTION

An increasing proportion of pregnancies are complicated by maternal hyperglycemia, most commonly gestational diabetes (gestational diabetes mellitus [GDM]).[1] Although less severe than overt diabetes, GDM predisposes to adverse perinatal outcomes, such as fetal macrosomia, and is associated with elevated risks of diabetes and cardiovascular diseases in both the mother and offspring.[1]

Currently, GDM screening is usually performed between 24 and 28 weeks' gestation utilizing an oral-glucose tolerance test (OGTT). Although the clinical benefits of diagnosing and treating late-pregnancy GDM have been well-documented, there is an urgent research gap around normal and abnormal glucose metabolism in early pregnancy.[2–5] Internationally accepted evidence-based guidelines are not available for standardized screening, diagnosis and treatment of "early-onset GDM" (ie mild hyperglycemia below the diagnostic thresholds of overt diabetes) before 20 weeks' gestation. Nevertheless, a growing number of studies from our group[6] and others[4,5] suggest that many women diagnosed with late-onset GDM display elevated glucose levels already earlier in gestation. Furthermore, there are indications that early GDM may be associated with poorer pregnancy outcomes than the late-onset form of the disease.[4,5] Pragmatic clinical tools are therefore needed for early-pregnancy identification of women with the highest metabolic risks.

Waist circumference (WC)—a simple anthropometric parameter that reflects central adiposity—has been established to predict metabolic disease in non-pregnant individuals.[7–9] In women, WC ≥80 cm is one of the diagnostic criteria of the metabolic syndrome.[7] Short stature is also associated with an increased risk of type 2 diabetes, especially in women.[9–11] In accordance with this, waist-to-height ratio (WHtR) has been shown to be a better predictor of cardiovascular risk in non-pregnant women than body mass index (BMI) or WC, with WHtR >0.5 suggested as a cut-off value.[12]

Key message

Maternal early-pregnancy waist-to-height ratio—an affordable but underutilized parameter that reflects abdominal adiposity—predicts plasma glucose concentrations >90th percentile in an oral glucose tolerance test at 12–16 weeks' gestation better than pre-pregnancy body mass index.

Despite strong evidence linking high WC and WHtR with poorer metabolic health, their measurement is rarely included in preconceptional care or maternal risk assessment at antenatal booking visits. WC changes minimally during pregnancy until the uterine fundal height reaches ~26 cm and it therefore represents abdominal fat deposition in pregnant individuals <26 weeks' gestation.[13] Maternal large WC[14] and short adult stature[15] have been demonstrated to be associated with an elevated risk of late-onset GDM. Evidence is scarce regarding the associations of maternal early-pregnancy WHtR with parameters of glucose metabolism across gestation. However, an older, small (n = 265) nested case–control study found WHtR measured 6–20 years before pregnancy to be associated with a hospital record of GDM .[16]

Most previous studies on early pregnancy glucose metabolism have focused on high-risk obstetric populations, with notable heterogeneity in the risk factors used to screen for early-onset hyperglycemia.[4] To our knowledge, maternal basic anthropometric characteristics have not been studied previously in a population-based setting in relation to early-pregnancy glucose tolerance test results. The aims of this study were to analyze the associations and interactions of maternal early-pregnancy WC and height with glucose concentrations during a 2-h 75-g oral glucose tolerance test at 12–16 weeks' gestation in a population-based cohort of Finnish pregnant women. Additionally, we compared the ability of WHtR

and BMI to predict fasting, 1- and 2-h glucose concentrations exceeding the 90th percentile at 12–16 weeks' gestation.

2 | MATERIAL AND METHODS

2.1 | Study design and population

The Early Diagnosis of Diabetes in Pregnancy (EDDIE) study is a population-based study conducted at South Karelia Central Hospital (SKCH), which is a secondary-level referral hospital in Lappeenranta, southeastern Finland, serving a population of ~133 000. SKCH is the only unit providing specialist antenatal, obstetric and neonatal care in the region and all deliveries (~1000/year) take place in this hospital.

In total, 2305 women who booked an early-pregnancy ultrasound examination at SKCH or at a small regional Honkaharju Hospital were assessed and recruited by a trained nurse from March 2013 to December 2016. Of these women, 527 (22.9%) declined to participate. Women with multiple pregnancies, diabetes diagnosed before pregnancy, oral glucocorticoid medication or inability to understand consent forms due to insufficient language skills were excluded. In addition, women with wrongly timed, incomplete or missing OGTT results at 12–16 weeks' gestation were excluded from the final study population (total excluded $n = 377$, 16.4%). The EDDIE cohort, sample collection and clinical follow-up have been described previously in detail.[6]

The formation of the study population for the present study is depicted in Figure 1. In total, 1361 women who had height and early-pregnancy WC information available were categorized into groups using the following cut-offs:

- The median maternal height in the EDDIE study population, 166 cm, which is also the mean height of Finnish women aged 25–44 years,[17] was used to categorize women into two groups of shorter and taller stature.
- WC 80 cm—included in the diagnostic criteria of the metabolic syndrome[7–9]—was used to define abdominal adiposity. The following four groups were created: (1) normal WC (<80 cm), short (<166 cm) (normal waist short [NWS]); (2) normal WC (<80 cm), tall (≥166 cm) (normal waist tall [NWT]); (3) large WC (≥80 cm), short (<166 cm) (large waist short [LWS]); and (4) large WC (≥80 cm), tall (≥166 cm) (large waist tall [LWT]); according to the maternal WC and height status.

2.2 | Collection of the clinical specimen and anthropometric data

Maternal height, weight, WC and blood pressure were measured, and venous blood samples were drawn for HbA_{1c} analysis at the recruitment visit at 8–14 weeks' gestation. Self-reported maternal pre-pregnancy weights were collected from antenatal care cards. These pre-pregnancy weights were checked by a clinician and compared with the early-pregnancy weights measured at the antenatal care booking visit and/or at the study recruitment visit, and corrected or deleted if the difference was implausible. WC was determined midway between the lowest ribs and the iliac crest. Body surface area (BSA) was calculated using the Mosteller–BSA formula. All women completed a 2-h 75-g OGTT between 11+4 weeks' gestation to 16+3 weeks' gestation (OGTT1). GDM was diagnosed if any of the glucose concentrations were abnormal, using the diagnostic thresholds recommended by the Finnish Current Care Guidelines, ie fasting plasma glucose ≥5.3 mmol/L, 1-h plasma glucose ≥10.0 mmol/L or 2-h plasma glucose ≥8.6 mmoL/L.[18] Women with normal OGTT1 results were recommended a repeat OGTT between 24 to 28 weeks' gestation. As a result, 1079 women underwent another OGTT at 22+3 to 34+0 weeks' gestation (OGTT2), 78 women had missing results. The same diagnostic thresholds were used to diagnose GDM at both OGTT1 and OGTT2, as currently recommended by the Finnish Current Care Guidelines.[18] Women diagnosed with GDM were given diet and exercise instructions and advised to measure capillary glucose from their fingertips. If abnormal glucose concentrations (ie ≥5.5 mmoL/L at fasting state or ≥7.8 mmoL/L 1 h after a meal) were recorded repeatedly,

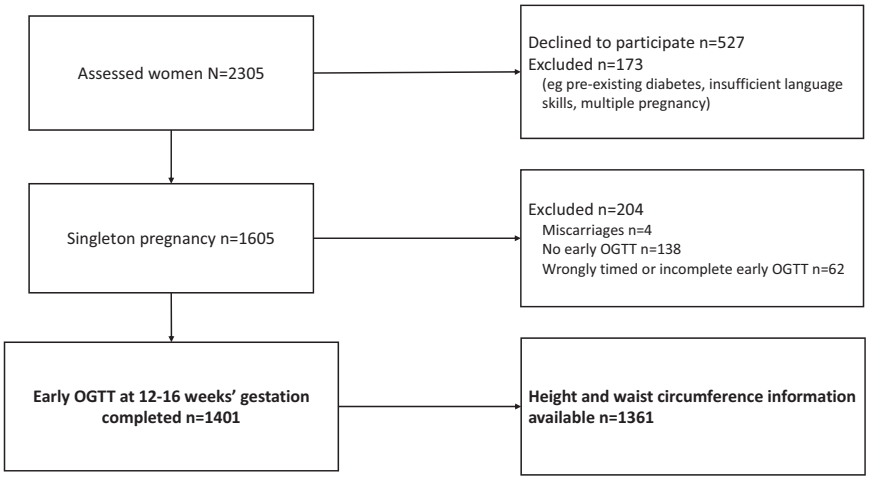

FIGURE 1 A flow chart depicting the formation of the study population.

metformin, Neutral Protamine Hagedorn insulin or both treatments were initiated. Taking into account the lack of evidence on how early GDM should be diagnosed,[4] and the international variation in clinical approaches as regards mild/diet-treated GDM, we only analyzed associations between maternal anthropometric parameters and "pharmacologically treated GDM" (n = 52), ie the GDM subtype likely to represent clinically significant impairments of glucose metabolism. These women not only exceeded the above-mentioned OGTT thresholds but also repeatedly exceeded 5.5 mol/L at fasting state or 7.8 mol/L 1 h postprandially in the home monitoring of blood glucose. Of the women with pharmacologically treated GDM, 39 women were diagnosed based on OGTT1 and 13 women were diagnosed based on OGTT2. All clinical diagnoses were confirmed from hospital and laboratory records by one research nurse and two physicians.

2.3 | Laboratory methods

Laboratory analyses were performed at the SKCH laboratory, except for fasting serum insulin, which was analyzed at Vita Laboratoriot Oy using an electrochemiluminescence immunoassay (ECLIA) method from frozen (−80°C) serum samples. A photometric hexokinase method was used to assess plasma glucose and a quantitative, latex agglutination inhibition method was used to determine HbA_{1c} concentrations. Insulin resistance index (HOMA-IR) was calculated with the formula fasting plasma glucose (mmol/L)×fasting serum insulin (mU/L) divided by 22.5.

2.4 | Statistical analyses

Data were presented as means with standard deviations or 95% confidence intervals (95% CI) or as frequencies with percentages. Statistical significance was evaluated using two-way factorial models (analysis of variance or logistic models). Models included the main effects (categorized WC and height) and their interaction effects. The possible non-linear associations between WHtR and plasma glucose values were modeled using restricted cubic spline regression models with four knots at the 5th, 35th, 65th and 95th percentiles. Knot locations were based on Harrell's recommended percentiles. Adjustments for maternal age, smoking during pregnancy, nulliparity and family history of type 2 diabetes were done when appropriate. Prediction of plasma glucose concentrations >90th percentile with WHtR and BMI was evaluated using the areas under the curve (AUC), sensitivity, specificity, positive and negative predictive values, and likelihood ratios; 95% CI were obtained by bias-corrected bootstrapping (5000 replications). Differences between the AUCs were evaluated using an algorithm by DeLong. We defined the best cut-off value as the value with the highest accuracy that maximizes Youden's index. In the case of violation of the assumptions (eg non-normality) for continuous variables, a bootstrap-type method or Monte Carlo p-values (small number of observations) for categorical variables were used. Hommel's adjustment (step-up method) was applied to correct levels of significance for multiple testing, if appropriate. Normality of data distribution was evaluated graphically and with the Shapiro–Wilk's W-test. STATA 16.1 (StataCorp LP) was used for all statistical analyses.

2.5 | Ethics statement

Our research protocol was approved by the Helsinki University Hospital Ethical Committee, with the latest amendment accepted on November 13, 2019 (HUS/1794/2016). Informed written consent was obtained from all participants included in the study.

3 | RESULTS

In the total cohort, 460/1361 (33.8%) of participants had a normal (<80 cm) WC, including 242/1361 (17.8%) short women (<166 cm, NWS) and 218/1361 (16.0%) tall women (≥166 cm, NWT). A large WC (≥80 cm) was recorded in 901/1361 (66.2%) participants, including 422/1361 (31.0%) short women (<166 cm, LWS) and 479/1361 (35.2%) tall women (≥166 cm, LWT).

Maternal characteristics of women categorized according to WC and height into the above-mentioned four groups (NWS; NWT; LWS; LWT) are presented in Table 1. There were no interactions between maternal WC and height regarding any of the maternal characteristics compared, ie differences between the characteristics of women with normal vs large WC were not explained by maternal height or vice versa. Women with a normal WC were younger, more often nulliparous, and less often had a family history of type 2 diabetes than did women with a large WC. Shorter women had a higher frequency of prior GDM, and the difference in prior GDM rates between shorter and taller women was more pronounced in the normal WC groups (NWS vs. NWT). Smoking during pregnancy was slightly more common among shorter women than taller women. Pre-gestational weight, BSA, BMI, HbA_{1c}, fasting insulin concentrations and HOMA-IR indices were higher in women with a large WC than in women with a normal WC. Similarly, rates of pharmacologically treated GDM, as well as systolic and diastolic blood pressure levels, were higher in the large WC groups than in the normal WC groups. Pre-gestational weight, BSA and systolic blood pressure were higher among taller women than shorter women, whereas pre-gestational BMI was slightly lower in tall than short women.

Figure 2 displays the mean plasma glucose concentrations during a 75 g 2-h OGTT at 12–16 weeks' gestation in women categorized according to their first-trimester WC (normal WC <80 cm; large WC ≥80 cm) and height (short <166 cm; tall ≥166 cm). Women with a large WC had increased fasting, 1- and 2-h post-load plasma glucose concentrations, compared with women with a normal WC, independent of maternal height. Shorter women, on the other hand, had increased 1- and 2-h post-load plasma glucose concentrations, compared with taller women, independent of maternal WC. The

TABLE 1 Comparison of maternal characteristics of 1361 Finnish women categorized based on waist circumference (normal WC <80 cm; large WC ≥80 cm) and height (short <166 cm; tall ≥166 cm).

	Normal WC <80 cm		Large WC ≥80 cm		*p*-value	
	Short	Tall	Short	Tall	Main effects[a]	
Maternal characteristic (outcome variable)	(NWS)	(NWT)	(LWS)	(LWT)	WC	Height
	n = 242	*n* = 218	*n* = 422	*n* = 479		
Waist circumference (cm), mean (SD)	74.7 (3.4)	75.3 (3.1)	90.1(9.0)	90.9 (9.9)	-	-
Height (cm), mean (SD)	161 (4)	170 (4)	161(3)	171 (4)	-	-
Age (years), mean (SD)	28 (5)	29 (5)	30 (5)	31 (5)	<0.001	0.089
Nulliparous, *n* (%)	144 (60)	126 (58)	196 (46)	223 (47)	<0.001	0.78
Previous history of GDM, *n* (%)	10 (4)	1 (0)	52 (12)	52 (11)	<0.001	0.027
Family history of type 2 diabetes, *n* (%)	94 (39)	84 (39)	191 (45)	214 (45)	0.027	0.88
Smoking during pregnancy, *n* (%)	29 (12)	14 (6)	46 (11)	47 (10)	0.40	0.043
Pre-gestational weight (kg), mean (SD)	55.9 (5.3)	60.7 (5.3)	73.0 (13.2)	79.0 (15.6)	<0.001	<0.001
Body surface area (m^2), mean (SD)	1.58 (0.08)	1.69 (0.08)	1.80 (0.16)	1.93 (0.19)	<0.001	<0.001
Pre-gestational BMI (kg/m^2), mean (SD)	21.6 (1.9)	21.0 (1.8)	28.1(4.9)	27.2 (5.2)	<0.001	0.001
Glycated hemoglobin (%; mmol/mol), mean (SD)	5.2 (0.5); 33.0 (3.1)	5.2 (0.5); 33.3 (3.4)	5.2 (0.5); 33.8 (3.5)	5.2 (0.5); 33.8 (3.5)	<0.001[b]	0.62[b]
Fasting insulin (mU/L), mean (SD)	7.2 (7.0)	6.3 (7.5)	10.1 (9.7)	9.6 (7.7)	<0.001	0.18
Insulin resistance index (HOMA-IR), mean (SD)	1.52 (1.48)	1.34 (1.57)	2.23 (2.27)	2.11 (1.73)	<0.001	0.18
Pharmacologically treated GDM	5 (2)	2 (1)	25 (6)	20 (4)	0.003	0.18
Systolic blood pressure (mmHg), mean (SD)	115 (11)	117 (11)	118 (11)	120 (11)	<0.001	<0.001
Diastolic blood pressure (mmHg), mean (SD)	73 (8)	73 (8)	76 (9)	76 (8)	<0.001	0.48

Note: Statistical significance was evaluated using two-way factorial models (ANOVA or logistic models). The models included the main effects (categorized WC and height) and their interaction effects.

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; GDM, gestational diabetes mellitus; NWS, normal waist short; NWT, normal waist tall; SD, standard deviation; WC, waist circumference.

[a]No interactions between the main effects were detected.

[b]Analyses were done using mmol/mol.

analyses were adjusted for maternal age, smoking during pregnancy, nulliparity and family history of type 2 diabetes.

The associations between maternal WHtR at 8–14 weeks' gestation and plasma glucose levels during a 2-h 75-g OGTT at 12–16 weeks' gestation are presented in Figure 3. The graphs demonstrate an inflection point at WHtR ~0.5, after which WHtR is positively associated with both fasting and post-load glucose concentrations. The data were adjusted for maternal age, smoking during pregnancy, nulliparity and family history of type 2 diabetes.

Considering the observed association of WHtR >0.5 with increased glucose levels at all timepoints of an early-pregnancy OGTT, we assessed the ability of WHtR and BMI to predict high glucose concentrations (>90th percentile) in an OGTT at 12–16 weeks' gestation. Table 2 presents the best cut-offs and their respective AUC, sensitivities, specificities, positive and negative predictive values, and likelihood ratios for WHtR and BMI with respect to predicting early-pregnancy OGTT glucose concentrations >90th percentile. Maternal early-pregnancy WHtR was a better predictor of 1- and 2-h post-glucose load results >90th percentile than maternal pre-pregnancy BMI.

4 | DISCUSSION

In this prospective population-based study, large maternal early-pregnancy WC (>80 cm) was positively associated with fasting and post-load plasma glucose concentrations in an OGTT at 12–16 weeks' gestation. Shorter maternal height (<166 cm), on the other hand, was positively associated with post-load glucose concentrations. Maternal early-pregnancy WHtR >0.5 was positively associated with both fasting and post-load glucose concentrations at 12–16 weeks' gestation. WHtR was a stronger predictor of post-load glucose concentrations exceeding the 90th percentile than pre-pregnancy BMI. Of note, in our study population of Finnish women of reproductive age, the frequency of large early-pregnancy WC ≥80 cm, suggesting abdominal adiposity, was alarmingly high. Moreover, women who entered pregnancy with a WC ≥80 cm displayed higher HbA_{1c}, fasting plasma glucose and insulin concentrations, post-load glucose concentrations and HOMA-IR indices suggesting insulin resistance. In line with this metabolic syndrome-like profile, women with early-pregnancy WC ≥80 cm were also characterized by higher blood pressure levels and higher frequencies of pharmacologically treated GDM, compared with women with a WC <80 cm.

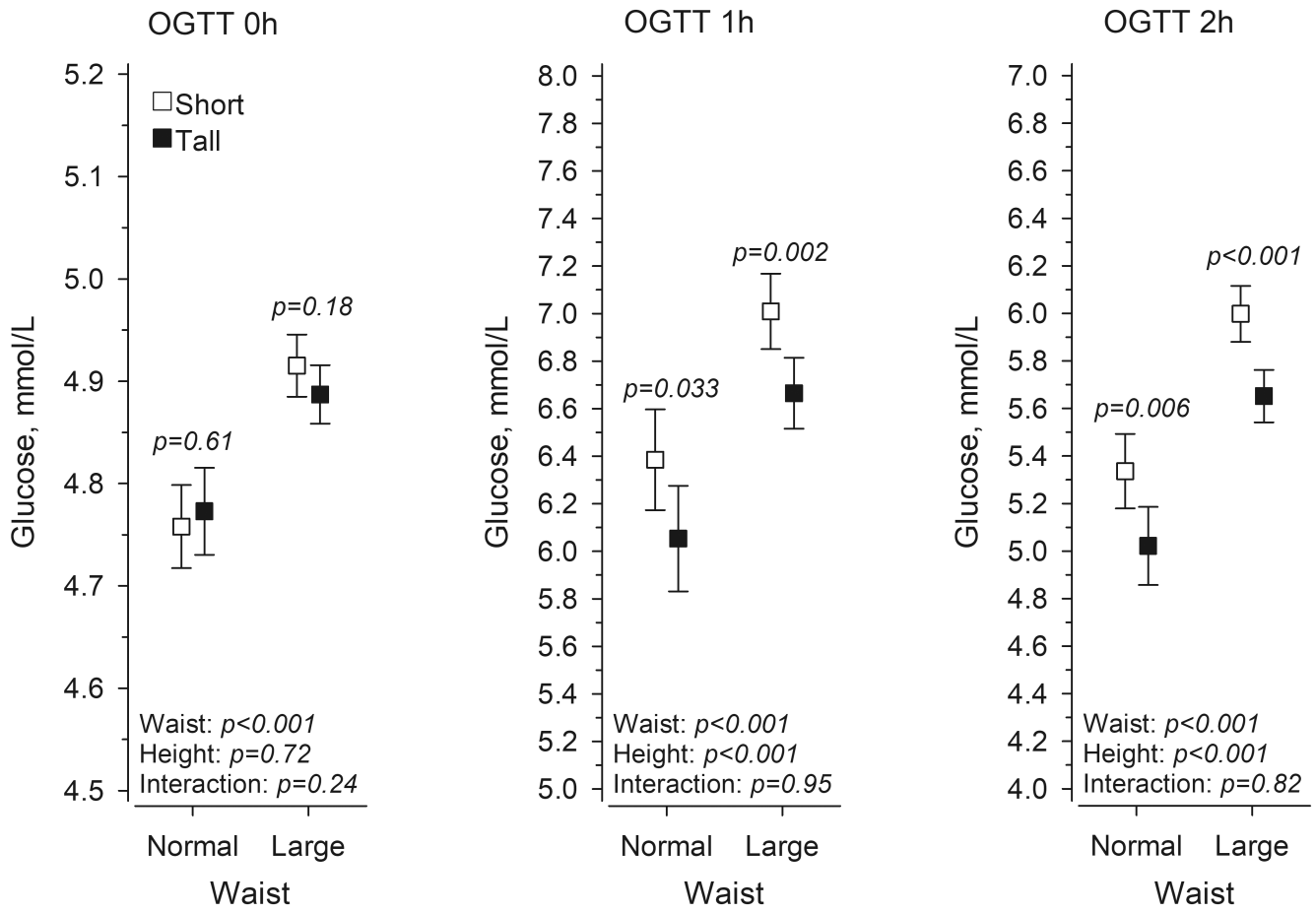

FIGURE 2 Mean plasma glucose concentrations and 95% CI at 0-, 1- and 2-h timepoints in a 75-g oral glucose tolerance test at 12–16 weeks' gestation in a population-based cohort of 1361 Finnish pregnant women categorized according to their first-trimester waist circumference (normal waist circumference <80 cm, large waist circumference ≥80 cm) and height (short <166 cm or tall ≥166 cm). The results were adjusted for maternal age, smoking during pregnancy, nulliparity and family history of type 2 diabetes. Statistical significance was evaluated using two-way factorial analysis of variance models. The models included the main effects (categorized waist circumference and height) and their interaction effects. *p*-values for the differences in 0-, 1- and 2-h mean plasma glucose concentrations between short vs tall women with normal or large waist circumferences are shown above the square symbols.

To the authors' knowledge, our study is the first to examine maternal WC and WHtR in a population-based cohort, and the associations and interactions between basic maternal anthropometric variables and maternal glucose concentrations in an early-pregnancy OGTT. The sample size of EDDIE is relatively robust and the number of women who declined to participate, were excluded, or were lost to follow-up was modest. Preexisting diabetes was reliably excluded with the HbA_{1c} testing and OGTTs that were completed by all participants. All maternal height and WC measurements in early pregnancy were measured by two trained research nurses. Similarly, OGTTs were executed applying standard subject preparation and test protocols in the same laboratory throughout the study period. Pre-pregnancy BMI values were calculated using self-reported pre-pregnancy weight, which may be subject to some underestimation. However, the bias caused by this reporting error associated with pregnancy-related weight in obstetric studies has been estimated to be minor.[19] Finally, among the limitations of our study is the homogeneous population of mainly white origin, which may limit the applicability of our results to other ethnic groups.

Short adult height has been shown to be associated with an elevated risk of GDM after 20 weeks' gestation in various populations utilizing different GDM screening approaches and criteria.[15] In a previous Finnish study, Laine et al. reported that in risk factor-based, nearly comprehensive OGTT screening at 12–16 and/or 24–28 weeks' gestation, GDM is more common among women with a short stature.[20] Data from several studies on late pregnancy OGTTs[21–25] and the study by Laine et al. mixing early- and late-pregnancy OGTT results,[20] suggest that maternal height correlates negatively with post-glucose load glucose concentrations, but not with fasting glucose concentrations, in agreement with our present results concerning early pregnancy. It is possible that in some cases, short maternal stature results from inadequate intrauterine nutrition, which can predispose to impaired beta cell function and/or insulin resistance in later life through fetal programming mechanisms.[26] Also, in short women, the amount of metabolically active

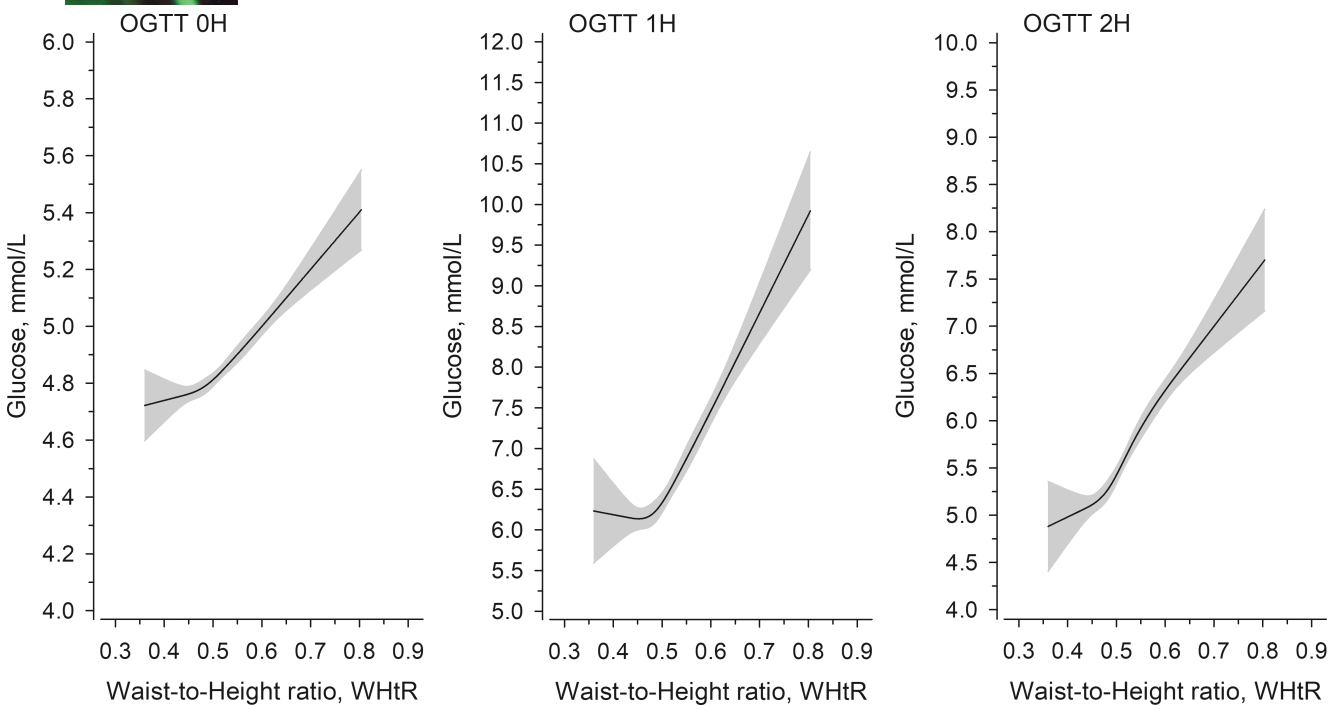

FIGURE 3 Waist-to-height ratio (WHtR) in relation to plasma glucose concentrations (0, 1 and 2 h) in a 75-g 2-h oral glucose tolerance test (OGTT) at 12–16 weeks' gestation in a population-based cohort of 1361 pregnant Finnish women. The curves were derived from a 4-knot-restricted cubic spline regression model. The models were adjusted for maternal age, smoking during pregnancy, nulliparity and family history of type 2 diabetes. Gray area represents 95% CI.

fat-free (muscle) mass may be lower than in tall women which might lead to higher plasma glucose levels after the standard glucose load.[27] Despite the observed inverse association of maternal height ≥166 cm with early-pregnancy post-load glucose levels, we did not find associations with pharmacologically treated GDM, in line with the study by Ogonowski et al.[25]

In computed tomography studies, WC has been demonstrated to be among the best simple anthropometric indices of abdominal adipose tissue accumulation.[28] Due to its strong association with cardiometabolic risk factors and morbidity across different ethnicities, large WC (eg ≥80 cm in white European women and ≥94 in white European men) is one of the diagnostic criteria of the metabolic syndrome.[7–9] In concordance with these data in non-pregnant populations, a systematic review and meta-analysis showed that maternal central obesity in the first or second trimester, as indicated by increased WC, waist-to-hip ratio, subcutaneous fat thickness or visceral adipose tissue depth, predisposes to GDM diagnosed after 20 weeks' gestation, independent of maternal BMI.[14] Our findings support a metabolic syndrome-like profile in women with a WC ≥80 cm, showing higher fasting and post-load glucose concentrations at 12–16 week' gestation, higher fasting insulin concentrations, and HOMA-IR indices suggesting insulin resistance, more frequent need for pharmacological GDM treatment, as well as higher blood pressure levels, than in women with WC <80 cm. In addition to prolonged hyperglycemia across gestation, the other characteristics of the metabolic milieu in central obesity—including early-pregnancy hyperinsulinemia—may also have unfavorable effects on the feto-placental unit.[29] Approximately two-thirds (66%) of the women in our population-based cohort had an early-pregnancy WC ≥80 cm, indicating a high prevalence of harmful abdominal adiposity and emphasizing the need to allocate public health resources to preventing cardiometabolic diseases in women of reproductive age.

Adding maternal height into the equation by using WHtR provides an even better estimate of body fat distribution. In our unselected obstetric cohort, maternal early-pregnancy WHtR >0.5 was strongly associated with both fasting and post-load glucose concentrations at 12–16 weeks' gestation, and WHtR superseded BMI in predicting post-load glucose concentrations >90th percentile. Our data are in accordance with the systematic review and meta-analysis by Ashwell et al.[30] which suggested that the screening potential of WHtR for cardiometabolic risks in non-pregnant populations is superior to WC and BMI in both sexes and in various ethnic groups. Likewise, a small case–control study of aboriginal Australian women reported that maternal WHtR measured 6–20 years before pregnancy predicts a hospital record of GDM later in life better than WC, height, hip circumference, waist-to-hip ratio or BMI.[16] The fact that WHtR performed better than BMI as an anthropometric predictor of high early-pregnancy glucose levels is not surprising, considering the limitations of BMI as an indicator of metabolic risks: it does not reliably reflect body fat percentage or adipose tissue distribution and does not work equally in all demographic groups or within extremities of height.[31] Furthermore, as already discussed above, pre-pregnancy BMI values based on self-reported weight and/or height may be associated with some degree of reporting or recall bias.[19] As can be expected for single risk factors, the AUC for the best cut-offs of both WHtR and BMI were modest in our unselected cohort, reflecting the

TABLE 2 Comparison of maternal first-trimester waist-to-height ratio (WHtR) and pre-gestational BMI in the prediction of plasma glucose (PG) concentrations >90th percentile at 0-, 1- and 2-h timepoints of an oral glucose tolerance test (OGTT) at 12–16 weeks' gestation in a population-based cohort of 1361 pregnant Finnish women.

OGTT parameter	WHtR	BMI	*p*-value
Fasting PG >90th percentile (≥5.3 mmoL/L)			
Best cut-off	0.53	26.2	
AUC (95% CI)	0.73 (0.68–0.79)	0.72 (0.67–0.78)	0.28
Sensitivity (95% CI)	0.70 (0.59–0.79)	0.68 (0.58–0.78)	
Specificity (95% CI)	0.69 (0.66–0.71)	0.68 (0.65–0.71)	
Predictive value (95% CI)			
Positive	0.14 (0.11–0.17)	0.13 (0.10–0.17)	
Negative	0.97 (0.95–0.98)	0.97 (0.95–0.98)	
Likelihood ratio (95% CI)	2.22 (1.90–2.60)	2.14 (1.82–2.51)	
1-h PG >90th percentile (≥8.9 mmoL/L)			
Best cut-off	0.58	28.1	
AUC (95% CI)	0.73 (0.68–0.79)	0.68 (0.63–0.74)	<0.001
Sensitivity (95% CI)	0.50 (0.41–0.59)	0.52 (0.43–0.61)	
Specificity (95% CI)	0.86 (0.84–0.88)	0.79 (0.76–0.81)	
Predictive value (95% CI)			
Positive	0.27 (0.22–0.33)	0.20 (0.16–0.25)	
Negative	0.94 (0.93–0.96)	0.94 (0.92–0.95)	
Likelihood ratio (95% CI)	3.62 (2.89–4.53)	2.44 (2.00–2.97)	
2-h PG >90th percentile (≥7.3 mmoL/L)			
Best cut-off	0.54	26.6	
AUC (95% CI)	0.73 (0.69–0.77)	0.69 (0.65–0.74)	<0.001
Sensitivity (95% CI)	0.61 (0.52–0.69)	0.59 (0.51–0.68)	
Specificity (95% CI)	0.75 (0.72–0.77)	0.71 (0.68–0.74)	
Predictive value (95% CI)			
Positive	0.21 (0.17–0.25)	0.18 (0.15–0.22)	
Negative	0.95 (0.93–0.96)	0.94 (0.92–0.96)	
Likelihood ratio (95% CI)	2.44 (2.06–2.88)	2.05 (1.74–2.42)	

Note: Differences between the area under the curve (AUCs) were evaluated using an algorithm by DeLong. *p*-values are for the differences between AUCs of WHtR and BMI.

Abbreviations: BMI, body mass index; CI, confidence interval.

multifactorial nature of diabetes pathogenesis. Altogether, however, our data support the inclusion of WHtR as one part of the metabolic risk assessment of reproductive-age women, of whom an increasing proportion are overweight or obese. Although interventions should ideally be started in the pre-conceptional period,[29] early pregnancy may be a fruitful time to motivate long-term lifestyle changes that potentially benefit the whole family.

5 | CONCLUSION

In our population-based study, early-pregnancy WHtR >0.5 predicted post-load glucose concentrations >90th percentile in an OGTT at 12–16 weeks' gestation better than the more commonly used parameter, self-reported pre-gestational BMI. Overall, women with a large early-pregnancy WC, especially when combined with a shorter stature, were characterized by an adverse metabolic profile and could benefit from early assessment of glucose metabolism, lifestyle counseling and obstetric follow-up to control perinatal risks and improve inter- and post-pregnancy health outcomes.

AUTHOR CONTRIBUTIONS

MJ wrote the first draft of the paper and participated in data management. MMK initiated the study and was re the design and planning of the study in collaboration with BS-L and KT. MMK and BS-L implemented the study, participating in data acquisition and management. AN was responsible for laboratory analyses and storage of samples. HK performed the statistical analyses in collaboration with MJ and MMK. All authors contributed toward data interpretation and critically revising the paper. MJ and MMK wrote the final version of the article, which was accepted by all authors.

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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