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Pregnancy outcomes of women with untreated 'mild' gestational diabetes (gestational diabetes by the WHO 2013 but not by the WHO-1999 diagnostic criteria) – A population-based cohort study

Gergely Á. Visolyi [a,b,*], Attila Kun [c], Orsolya Szalai [d], Márk M. Svébis [a,b], Beatrix A. Domján [b], László Zsirai [e], Ádám G. Tabák [b,f,g]

[a] Károly Rácz School of PhD Studies, Semmelweis University, Budapest, Hungary
[b] Department of Internal Medicine and Oncology, Semmelweis University Faculty of Medicine, Budapest, Hungary
[c] Tolna County Balassa János Hospital, Department of Obstetrics and Gynaecology, Szekszárd, Hungary
[d] Bajcsy-Zsilinszky Teaching Hospital, Budapest, Hungary
[e] Department of Gynecology and Family Planning, Istenhegyi GeneDiagnostic Center, Hungary
[f] UCL Brain Sciences, University College London, London, United Kingdom
[g] Department of Public Health, Semmelweis University Faculty of Medicine, Budapest, Hungary

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ABSTRACT

Aims: We compared pregnancy outcomes of untreated 'mild' GDM (GDM by WHO 2013 but not by WHO-1999) to normal glucose tolerant women (NGT).
Methods: In a universal screening program 4333 pregnant women had a 3-point 75 g OGTT in Hungary in 2009–2013. By WHO-2013 untreated NGT was diagnosed in n = 3303, 'mild' GDM in n = 336 cases.
Results: 'Mild' GDM women were older (mean difference, SE: 1.4, 0.3 yrs), had higher fasting (1.0, 0.02), 60-minute (1.0, 0.09), and 120-minute (0.4, 0.06 mmol/l) blood glucose, and blood pressure (2.6, 0.5/2.0, 0.5 mmHg). Weight gain was similar in both groups (−0.3, 0.3 kg). GDM newborns were heavier (142, 50 g) and were more frequently macrosomic (>4000 g, OR 1.85, 95 %CI 1.35–2.54). Hypertension during pregnancy was more prevalent in the GDM group (OR 1.55, 95 %CI 1.05–2.28), as well as induced (OR 1.38, 95 %CI 1.10–1.74) and instrumental delivery (OR 1.34, 95 %CI 1.07–1.68), and acute caesarean section (OR 1.32, 95 %CI 1.04–1.64). Most of these differences substantially attenuated or became non-significant after adjustment for pre-pregnancy BMI.
Conclusions: Pregnancy outcomes of 'mild' GDM were worse compared to normal glucose tolerant women however these differences were explained by the pre-pregnancy BMI difference between groups.

1. Introduction

Gestational diabetes mellitus (GDM) is abnormal glucose tolerance first diagnosed during pregnancy [1]. During pregnancy, placental secretion of diabetogenic hormones (such as progesterone and growth hormone) leads to increasing insulin resistance. In women with normal glucose tolerance this is compensated by increased insulin secretion, while GDM women are unable to fully compensate and GDM develops that is associated with increased risks for both mother and offspring [2].

Randomised controlled trials (RCTs) support that the association between increased glucose values and adverse pregnancy outcomes is causal [3–12]. The largest RCTs and a meta-analysis showed lower mean

Abbreviations: BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; 'mild' GDM, gestational diabetes by the WHO 2013 but not by the WHO-1999 diagnostic criteria; HAPO, Hyperglycemia and Adverse Pregnancy Outcome; IADPSG, International Association of Diabetes and Pregnancy Study Groups; LGA, large for gestational age; MD, mean difference; OGTT, oral glucose tolerance test; SD, standard deviation; SGA, small for gestational age; WHO, World Health Organization; WHO-1999, diagnostic criteria of gestational diabetes according to the WHO introduced in 1999; WHO-2013, diagnostic criteria of gestational diabetes according to the WHO introduced in 2013.

* Corresponding author at: Department of Internal Medicine and Oncology, Semmelweis University Faculty of Medicine, 2/a Korányi Sándor Street, Budapest-1083, Hungary.
E-mail addresses: visolyi@gmail.com (G.Á. Visolyi), a.tabak@ucl.ac.uk (Á.G. Tabák).

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birth weight and neonatal fat mass, as well as decreased risk of LGA, macrosomia, and shoulder dystocia in the intensively treated GDM group [3–5,13].

The hypothesis that there is a continuous relationship between fasting, 1-hour, and 2-hour OGTT values with birth-weight percentile was finally confirmed with the publication of the large observational HAPO (Hyperglycemia and Adverse Pregnancy Outcome) study in 2008 [14]. Based on the HAPO results the IADPSG (International Association of Diabetes and Pregnancy Study Groups) and later the WHO proposed more stringent diagnostic thresholds (WHO-2013), although the committee acknowledged some drawbacks: the arbitrariness of these cut-offs and the huge increase in GDM prevalence [15]. Furthermore, the RCT evidence on the treatment of GDM uses different diagnostic criteria that only partly overlap and mostly less stringent than the proposed ones leading to equipoise regarding this important question [13].

The other important indirect (through an increased risk of GDM) and direct driver of LGA and its associated complications is maternal overweight and obesity [16–18]. Indeed some observations suggest an increasing role of obesity in the development of LGA with decreasing glucose intolerance [19–21].

Given this uncertainty, we aimed to compare maternal and foetal outcomes of untreated 'mild' GDM (GDM by WHO 2013 but not by WHO-1999) and normal glucose tolerant pregnancies in a population of all pregnancies in a Western region of Hungary where only women diagnosed with GDM based on the previous WHO criteria (WHO-1999) were offered treatment. Moreover, we investigated whether an increased risk associated with 'mild' GDM would be independent of pre-pregnancy BMI (body mass index).

2. Material and methods

2.1. Setting

We report results of a universal screening program from Hungary between 16 Jan 2009 and 10 Apr 2013. The screening program covers the whole of Tolna County that is located in the South-Western part of Hungary and has a population of approximately 240,000. All expectant women without known diabetes were routinely screened for GDM using a 3-point 75 g OGTT between 24 and 28 weeks of gestation. Selected risk factors, OGTT results, and pregnancy outcomes were recorded by district nurses. All women diagnosed as GDM according to the WHO-1999 criteria were offered treatment at the outpatient clinic of the county hospital [22].

All study related procedures have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Local ethical approval was obtained from the Ethics Committee of Szekszárd County Balassa János Hospital, Szekszárd, Hungary (Registration number: 13/2021 (XII. 7.)).

2.1.1. Diagnosis of gestational diabetes at screening

The screening test (75 g oral glucose tolerance test – OGTT) was performed according to WHO recommendation between 24 and 28 weeks of gestation. Venous blood samples were collected following an overnight fast (≥8 h) at fasting and 1 and 2 h after glucose ingestion [23].

GDM was diagnosed according to the WHO-1999 criteria (fasting glucose ≥ 7.0 mmol/l and/or 2-h glucose ≥ 7.8 mmol/l) [24].

2.1.2. Intervention

Women with a positive screening according to the WHO-1999 criteria were offered diabetes care at Tolna Country Diabetes Outpatient Clinic. Treatment was conducted according to the recommendations of the Hungarian Diabetes Association [22].

2.2. Study participants

Data of all pregnant women (n = 4830) delivering after 24 weeks of gestation living in Tolna County with a delivery between 16 Jan 2009 and 10 Apr 2013 were included. We excluded births of women with pregestational diabetes (n = 19), those with incomplete OGTTs (n = 411), and twin pregnancies (n = 67), leaving 4333 pregnancies. Finally, all women with WHO-1999 GDM were excluded (n = 342, of them n = 2 based on elevated fasting glucose, n = 5 based both on elevated fasting and postload glucose), leaving n = 3991 participants eligible for analysis. We further excluded n = 281 cases with missing covariates. There were n = 71 WHO-2013 GDM women who were labelled as normal glucose tolerant according to WHO-1999 criteria and received GDM treatment (1 insulin, the rest lifestyle treatment) against the treatment protocol applicable at the time. The exclusion of these women allows the investigation of the natural history of the effect of elevated blood glucose on outcomes and leads to a final analytical sample of n = 3724 pregnancies (93.3 % of eligible) (Fig. 1).

2.3. Diagnosis of gestational diabetes for analysis

We reclassified all included pregnancies based on the WHO-2013 GDM diagnostic criteria into (1) normal glucose tolerance or (2) GDM based on WHO-2013. Thus, GDM was diagnosed if the fasting glucose was ≥ 5.1 mmol/l, and/or the 1-hour postload glucose was ≥ 10.0 mmol/l, and/or the 2-hour glucose was ≥ 8.5 mmol/l [23]. For the present analysis we defined 'mild' GDM as GDM cases diagnosed by the WHO-2013 criteria but normal glucose tolerant by the WHO-1999 criteria. This also means that none of the 'mild' GDM cases were diagnosed by the 2-hour postload glucose.

2.4. Co-variables

Baseline characteristics including maternal age, pre-pregnancy hypertension (doctor diagnosis or blood pressure lowering drug use) anthropometric measures (reported pre-pregnancy weight and height measured at the first prenatal visit), as well as socioeconomic measures (marital status, highest level of education), and smoking history were recorded by district nurses on a standardized case report form at the time of the first prenatal visit. We stratified marital status in 3 group as married, living with partner, or single. Education was grouped as primary school, secondary school or university. Information on permanent residence was also collected (village, town, county capital or state capital). Smoking status was coded as never/ex- or current smoker (≥5 cigarettes/day).

Immediately before the 75 g OGTT maternal blood pressure was recorded. During the 75 g OGTT venous samples were taken for the determination of fasting, 1-hour, and 2-hour postload blood glucose levels.

BMI was calculated by person's weight in kilograms divided by the square of height in meters.

Blood pressure was measured 3 times using a calibrated digital blood pressure meter (OMRON M2-4, Omron Electronics Kft., Budapest, Hungary) on the upper arm with adequate-sized cuff after 5-minute rest in sitting.

All glucose samples were analysed using a glucose oxidase method in the same central laboratory.

Gestational age was determined on the basis of the woman's last normal menstrual period if it coincided within 1 week of the date determined by ultrasound done between 10 and 13 weeks of gestation, otherwise we used the ultrasound estimates [25,26].

2.5. Outcomes

We divided the collected outcomes into maternal (hypertension during pregnancy, severe preeclampsia), delivery related (induced

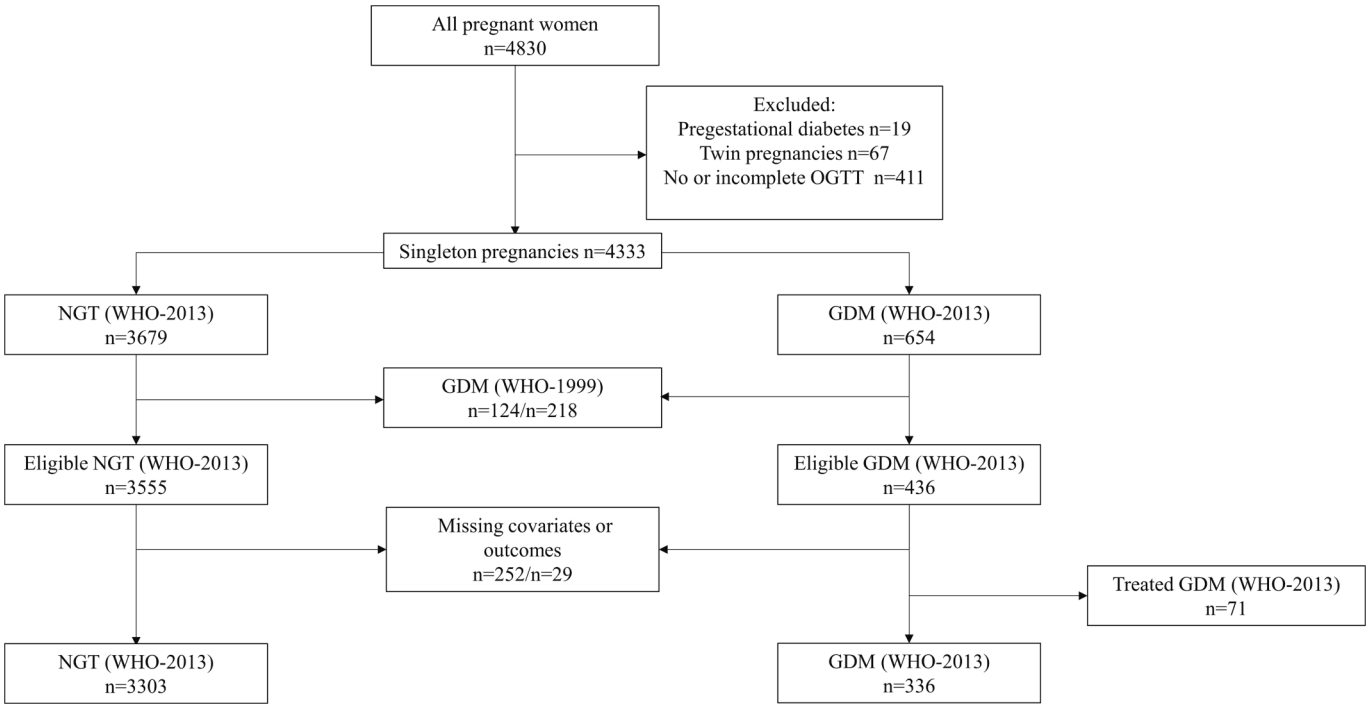

Fig. 1. Flow diagram of patient selection. GDM = gestational diabetes mellitus, NGT = normal glucose tolerance, OGTT = oral glucose tolerance test, WHO = World Health Organization, WHO-1999 = diagnostic criteria of gestational diabetes according to the WHO introduced in 1999, WHO-2013 = diagnostic criteria of gestational diabetes according to the WHO introduced in 2013.

births, instrumental delivery, and acute caesarean section), and foetal (birthweight, macrosomia, large for gestational age [LGA], small for gestational age [SGA], and congenital malformation) events.

Hypertension during pregnancy included women with repeated blood pressure value ≥ 140/90 mmHg, doctor diagnosis of hypertension, or the use of any blood pressure-lowering medication.

Severe preeclampsia was defined as preeclampsia (blood pressure ≥ 140/90 mmHg that occurs > 20 weeks of gestation in a woman with normal blood pressure before and proteinuria ≥ 0.3 g/24 h) and at least one of the following criteria: blood pressure ≥ 160/110 mmHg on 2 occasions at least 6 h apart, proteinuria ≥ 5 g/24 h, proteinuria ≥ 3 + on 2 random samples collected ≥ 4 h apart, oliguria < 500 mL/24 h, cerebral or visual symptoms, pulmonary oedema or cyanosis, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia or foetal growth restriction [27].

Foetal outcomes were reported on the newborn discharge letter and included foetal weight (the first measure after delivery on a calibrated scale), and any congenital malformations.

Weight status of the newborn was described using the following derived variables: (1) macrosomia (newborn weight > 4000 g or 4500 g), (2) large for gestational age (birthweight > 90th centile taking newborn sex and gestational age at delivery into account), and (3) small for gestational age (birthweight < 10th centile). For the main analysis, we defined SGA and LGA based on locally derived centile charts, while for the sensitivity analysis, we used the INTERGROWTH-21st charts [28,29].

2.6. Statistical analysis

Descriptive data are reported as mean ± SD for continuous and n (%) for categorical variables. For the baseline comparison of continuous variables 2-sample t -tests, for categorical variables $\chi 2$ -tests were used.

For the analysis of each outcome, we ran two separate models. The first model was an unadjusted model (Model 1) with the given outcome as the independent and GDM status as the dependent variable. The second model (Model 2) was adjusted for maternal pre-pregnancy BMI. For categorical outcomes (such as hypertension, preeclampsia, induced birth, instrumental delivery, acute caesarean section, macrosomia, LGA, SGA and congenital malformation) logistic, for continuous outcomes (such as foetal weight) linear regression models were used. We adjusted for newborn sex and gestational week at delivery in both models when analysing birthweight differences between groups. Results are reported as odds ratios (categorical outcomes) or estimated mean differences (continuous outcomes) with their respective 95 % confidence intervals. We also estimated excess risk mediated by weight at delivery by calculating percentage attenuation in Model 1 β coefficient after inclusion of maternal weight in Model 2:

$$\text{Percentage of excess risk mediated by risk factors} = 100 \times (\beta_{\text{Model 1}} - \beta_{\text{Model 2}}) / (\beta_{\text{Model 1}})$$

We calculated 95 % confidence interval around the percentage attenuation by using a bootstrap method with 1000 re-samplings in Stata (version 15.1).

All other statistical analyses were done on SPSS for Windows version 26.0. The threshold of statistical significance was set at $p < 0.05$.

3. Results

3.1. Baseline characteristics of WHO-2013 GDM women by treatment

To exclude the potential that treatment of 'mild" GDM women was driven by any socioeconomic or other baseline characteristics, we compared treated and untreated 'mild' GDM women. The treated and untreated groups were similar in terms of weight, marital status, level of education, residence, ethnicity, and the frequency of smoking before pregnancy (all $p > 0.10$), while treated women were older, shorter, had higher systolic blood pressure and higher 1-hour and 2-hour postload glucose during the OGTT. As expected, treated women had a smaller weight gain during pregnancy (9.4 ± 5.0 vs 13.0 ± 5.0 kg, $p < 0.0001$). (**Supplemental Table S1**).

3.2. Pre-pregnancy maternal characteristics by GDM status

Untreated 'mild' GDM women (as expected) were older (mean difference [MD]: 1.4, 95 %CI: 0.8–2.0 years) and heavier (MD: 8.6, 95 %CI: 7.0–10.2 kg) compared to control women. We found no significant difference in height, the distribution of marital status, educational attainment, residence, ethnicity, and pre-pregnancy smoking status between the groups (all $p > 0.10$) (Table 1).

3.3. Maternal characteristics at the time of the diagnostic OGTT

Untreated 'mild' GDM women had higher fasting (MD: 1,0, 95 %CI: 1.0–1.1), 1-hour (MD: 1.0, 95 %CI: 0.8–1.2), and 2-hour (MD: 0.4, 95 % CI: 0.3–0.5 mmol/l) glucose levels as well as higher systolic and diastolic blood pressure (systolic MD: 2.6, 95 %CI: 1.6–3.7, diastolic MD: 2.0, 95 %CI: 1.0–2.9 mmHg) compared to the control group (all $p < 0.0001$) (Table 1).

As expected for an untreated GDM group, weight gain during the whole pregnancy was similar in the GDM and the control groups (13.2 ± 5.1 vs 13.0 ± 5.0 kg, $p = 0.36$).

Table 1
Baseline characteristics of the control and the untreated 'mild' GDM groups.

	Control	Untreated 'mild' GDM	p
n	3303	336	
Maternal baseline characteristics			
Marital status - n (%)			0.18
Married	1752 (53)	196 (58.3)	
Living with partner	1362 (41.2)	122 (36.3)	
Single/divorced	189 (5.7)	18 (5.4)	
Education - n (%)			0.64
Primary school	264 (8)	22 (6.5)	
Secondary school	2587 (78.3)	268 (79.8)	
College	452 (13.7)	46 (13.7)	
Residence - n (%)			0.17
Village	1547 (46.8)	149 (44.3)	
Town	992 (30)	95 (28.3)	
County capital	753 (22.8)	89 (26.5)	
State capital	11 (0.3)	3 (0.9)	
Caucasian - n (%)	2953 (89.4)	308 (91.7)	0.2
Smoker - n (%)	351 (10.6)	31 (9.2)	0.4
Age (years) - mean ± SD	29.3 ± 5.5	30.7 ± 5.2	<0.0001
Height (cm) - mean ± SD	165.2 ± 6.7	165.7 ± 6.8	0.16
Weight (kg) - mean ± SD	68.8 ± 14.0	77.4 ± 18	<0.0001
BMI (kg/m^2) - mean ± SD	23.9 ± 4.8	26.7 ± 6.1	<0.0001
Weight status			<0.0001
Underweight – n (%)	253 (7.7 %)	12 (3.6 %)	
Normal weight – n (%)	1985 (60.1 %)	146 (43.5 %)	
Overweight – n (%)	711 (21.5 %)	76 (22.6 %)	
Obesity – n (%)	354 (10.7 %)	102 (30.4 %)	
Physiological measures at time of OGTT mean ± SD			
Systolic blood pressure (mmHg)	119 ± 9	121 ± 10	<0.0001
Diastolic blood pressure (mmHg)	76 ± 8	78 ± 8	<0.0001
Fasting blood glucose (mmol/l)	4.3 ± 0.4	5.4 ± 0.4	<0.0001
1-h postload glucose (mmol/l)	6.3 ± 1.4	7.3 ± 1.6	<0.0001
2-h postload glucose (mmol/l)	5.3 ± 1.1	5.7 ± 1.0	<0.0001

For the comparison of continuous variables 2-sample t -tests, for categorical variables $\chi 2$ -tests were used. GDM = gestational diabetes mellitus. 'mild' GDM = gestational diabetes by the WHO 2013 but not by the WHO-1999 diagnostic criteria. OGTT = oral glucose tolerance test. Underweight – BMI < 18.5 kg/m^2. Normal weight – BMI 18.5–24.9 kg/m^2. Overweight – BMI 25–29.9 kg/m^2. Obesity – BMI > 30 kg/m^2.

3.4. Pregnancy and delivery outcomes

All pregnancy and delivery related outcomes (hypertension, induced birth, instrumental delivery, acute caesarean section) except for severe preeclampsia were significantly more frequent in the untreated GDM group compared to controls in the unadjusted models (ORs 1.09–1.55). When we adjusted the models for pre-pregnancy BMI, none of the odds ratios remained statistically significant. When we calculated the percentage of risk explained by pre-pregnancy BMI, the explained risk was between 40 and 91 % (all $p < 0.05$). The adjustment for pre-pregnancy BMI almost completely abolished the association of untreated GDM with pregnancy induced hypertension, while (based on the point estimates) around 20 % excess risk remained for the other outcomes (induced birth, instrumental delivery, acute caesarean delivery) (Table 2).

3.5. Foetal outcomes

Newborns of untreated GDM women were 142 g (95 %CI: 94–189 g) heavier compared to controls. This difference was significantly reduced by 39 % to 87 g (95 %CI: 39–134) after the effect of maternal weight at delivery was taken into account (Table 2, Fig. 2).

Newborns of untreated GDM women were more likely (ORs 1.9–3.5) to be of extreme high weight independent whether it was defined as a weight of 4000 or 4500 g or large for gestational age. Pre-pregnancy BMI explained a statistically significant proportion of this excess risk (25–51 %), although newborns of untreated GDM women still remained 2.55 times (95 %CI: 1.3–5.0) more likely to be heavier than 4500 g (Table 2, Fig. 2).

Our sensitivity analysis using LGA and SGA based on the INTERGROWTH-21st centile charts confirmed the results of our main analysis (data available on request) [29].

4. Discussion

4.1. Short summary

Untreated 'mild' GDM women (as expected) were older and had a worse cardiometabolic profile compared to the control group before

Table 2
Crude rates of pregnancy, delivery, and foetal outcomes in the control and 'mild' GDM groups.

	Control	Untreated 'mild' GDM	p
N	**3303**	**336**	
Pregnancy outcomes - n (%)			
Hypertension	217 (6.6)	33 (9.8)	0.025
Severe preeclampsia	36 (1.1)	4 (1.2)	0.87
Delivery Outcomes - n (%)			
Induced birth	1099 (33.3)	137 (40.8)	0.006
Instrumental delivery	1287 (39.0)	155 (46.1)	0.01
Acute caesarean section	969 (29.3)	119 (35.4)	0.02
Foetal outcomes - n (%)			
Foetal weight (g)	3335 ± 504	3465 ± 554	<0.0001
Macrosomia			
>4000 g	303 (9.2)	53 (15.8)	<0.0001
>4500 g	35(1.1)	12 (3.6)	<0.0001
LGA	648 (19.6)	95 (28.3)	<0.0001
SGA	181 (5.5)	17 (5.1)	0.75
Congenital malformation	25 (0.8)	1 (0.3)	0.3

Data are reported as mean ± SD for continuous and n (%) for categorical variables. For the comparison of continuous variables 2-sample t -tests, for categorical variables $\chi 2$ -tests were used. GDM = gestational diabetes mellitus. 'mild' GDM = gestational diabetes by the WHO 2013 but not by the WHO-1999 diagnostic criteria. LGA = large for gestational age. OGTT = oral glucose tolerance test. SGA = small for gestational age.

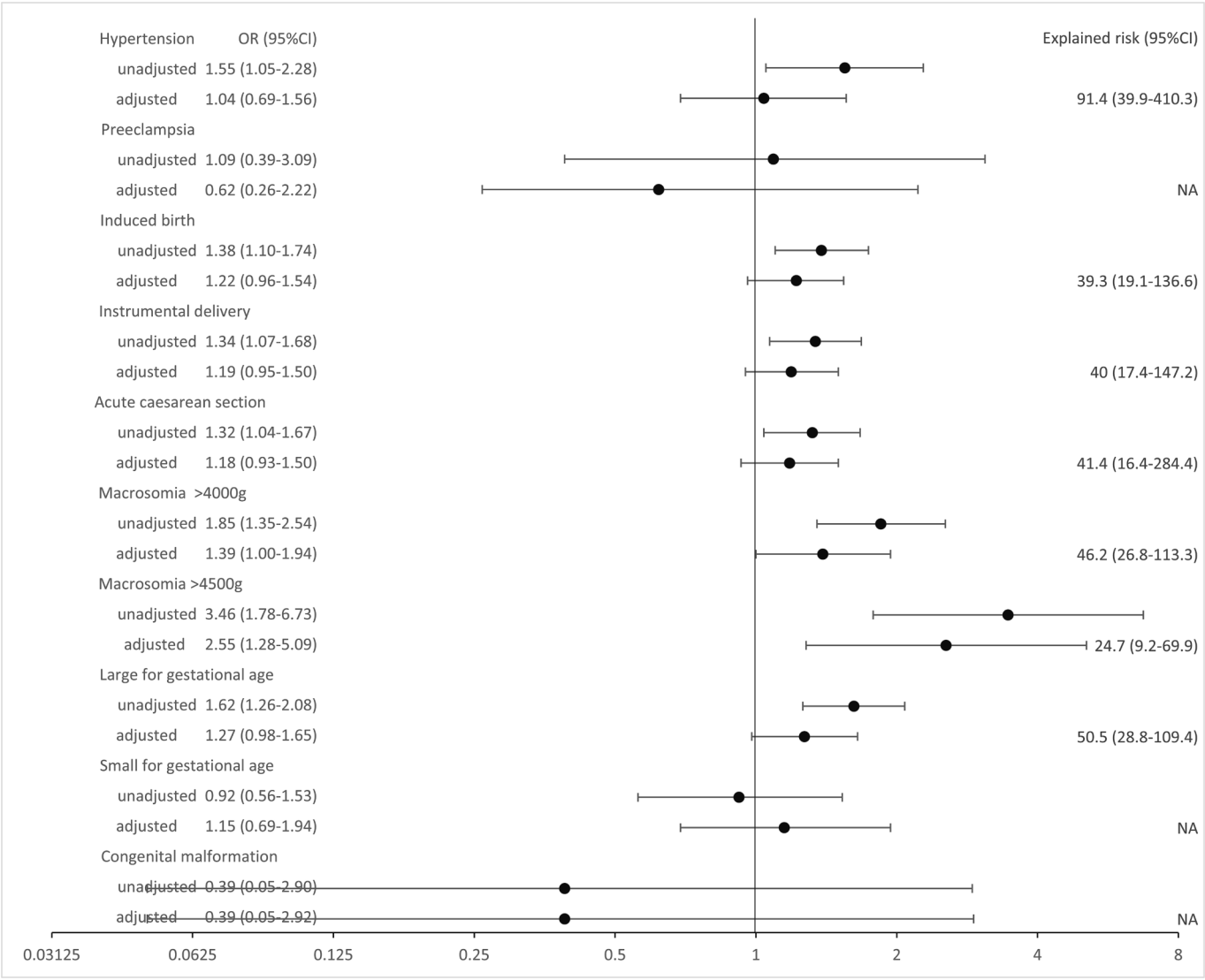

Fig. 2. Forest plot showing the association between untreated 'mild' GDM status and pregnancy, delivery, and foetal outcomes in unadjusted models and after adjustment for pre-pregnancy BMI. Results are reported as odds ratios and 95 % confidence intervals., Explained risk = Excess risk mediated by modifiable risk factors. 95 % confidence interval was calculated around the percentage attenuation by using a bootstrap method with 1000 re-samplings. Further details can be found in the Statistical analysis section., OR = odds ratio, CI = confidence interval, GDM = gestational diabetes mellitus.

pregnancy and at the time of the diagnostic OGTT, while their socio-economic characteristics were similar to controls. Regarding pregnancy and delivery related complications, we found that hypertension during pregnancy (either chronic or pregnancy induced hypertension), induced delivery, instrumental delivery, and acute caesarean section were all 32–55 % more frequent among untreated 'mild' GDM pregnancies compared to controls. Regarding foetal outcomes, risk of macrosomia and LGA was increased by 62–246 % among newborns of untreated 'mild' GDM mothers compared to controls, while no difference in the risk of severe preeclampsia and congenital malformations were found (although event numbers were low for these outcomes). Most of the observed differences substantially attenuated and became non-significant after adjustment for pre-pregnancy BMI. Newborn weight in the untreated 'mild' GDM group was significantly higher (by 142 g) compared to controls. Forty percent of this difference was explained by maternal pre-pregnancy BMI.

4.2. Maternal characteristics

It is well accepted that women diagnosed with GDM (based on older diagnostic criteria) are older, heavier [16,30,31], have a worse cardio-metabolic profile [32,33], and an increased risk of cardiovascular diseases compared to controls.[34] Furthermore, there is some support from the literature that women with 'mild' gestational diabetes (GDM based on the WHO-2013 but not on the WHO-1999 diagnostic criteria) are more likely than those with NGT to be obese and hypertensive [35]. In line with the latter notion, we found that untreated 'mild' GDM women (GDM by the WHO 2013 but not by the WHO-1999 diagnostic criteria) were older, more obese, had evidently higher glucose levels during the diagnostic OGTT, as well as higher systolic and diastolic blood pressure compared to the control group.

4.3. Pregnancy and delivery outcomes

Although the optimal glucose threshold to define GDM is not known, any level of hyperglycaemia during pregnancy is clearly associated with an increased risk of adverse pregnancy outcomes [14,16,30,31]. Furthermore, a Danish study of pregnant women with 'mild' glucose intolerance (without GDM) found a linear association between maternal 2-h glucose and caesarean delivery, spontaneous preterm delivery,

shoulder dystocia, and macrosomia after adjustment for potential confounders [36]. Indeed, women in our study classified as untreated 'mild' GDM had higher rates of adverse maternal outcomes, including hypertensive disorders during pregnancy, acute caesarean section and induced and instrumental delivery compared with women with NGT.

Most studies report increased rates of adverse maternal outcomes in obese and overweight women without GDM compared to controls [19,21,37]. Moreover, a population-based analysis from Canada found that after adjusting for maternal characteristics (including weight) and obstetrical history, the effect of GDM on pregnancy and delivery related outcomes substantially attenuated [38]. The above evidence overall suggests that obesity and glycaemia both increase the risk of adverse pregnancy outcomes. However, the individual weight of these risk factors requires further clarification. Our results extend the current literature by showing that over 90 % of the risk of hypertension and approximately 40 % of delivery related outcomes are attributable to pre-pregnancy BMI among women with 'mild' GDM.

4.4. Foetal outcomes

In general, foetal macrosomia or large for gestational age are more prevalent in GDM compared to controls [3–6]. Furthermore, the association between birthweight, macrosomia and glycaemia (based on a 50 g challenge test) extend to those women who had no gestational diabetes according to the Carpenter-Coustan diagnostic criteria even after adjustment for pre-gravid BMI [39]. Our results confirm the association between foetal weight and maternal glycaemia in women with 'mild' GDM based on the WHO-2013 criteria. Furthermore, our results suggest that a large proportion (25 to 50 %) of the excess risk or excess weight is explained by pre-pregnancy BMI.

Our results on pregnancy, delivery as well as on foetal outcomes are compatible with the hypothesis that pre-pregnancy BMI per se could be a more important determinant of pregnancy outcomes than hyperglycaemia in 'mild' GDM. This hypothesis is further supported by a large cohort study from Spain that reported that the upper quartile of maternal BMI accounted for 23 % of macrosomia, 50 % of pregnancy induced hypertension, and 17.6 % of LGA, while the population-attributable risks were much smaller for (treated) GDM based on the Carpenter-Coustan criteria [40]. Another line of supportive evidence comes from those randomized controlled trials that compared the effect of the use of the WHO-2013 GDM diagnostic criteria with either the Carpenter-Coustan or the Australasian Diabetes in Pregnancy Society cut-offs on pregnancy, delivery, and foetal outcomes and reported null findings [41,42].

4.5. Strengths and weaknesses

Some limitations of our study have to be acknowledged. Unfortunately, no data was obtained on the glucose tolerance status of <10 % of pregnant women that may have introduced selection bias into our estimates. It should be noted that 62 % of these women had a fasting glucose measurement suggesting that most of these women participated in antenatal care and thus the role of selection bias is limited. Our sample mostly included Caucasian women (90 %), while most of the remaining population was of Roma ethnicity. While we found no ethnic differences in the unadjusted risk of GDM or of its treatment suggesting good internal validity, the external validity to other racial or ethnic groups is limited. Unfortunately, no weight measurement was available on our main predictor (pre-pregnancy BMI) and thus we had to use self-reported weight for the BMI calculation. However, there was a strong correlation (r = 0.996) between measured booking and self-reported pre-pregnancy weight, supporting the robustness of our findings.

An important limitation of our study relates to the fact that we had to exclude 17.4 % (n = 71/407) of WHO-2013 GDM women, as they were treated for GDM against the recommendation of the Hungarian Diabetes Association. As these women had higher 1-hour glucose compared to the included women, it is likely that treatment initiation was driven by glycemia. While this selection bias limits the external validity of our findings, it should be noted that only 1 of these pregnant women required insulin treatment for glycemic control. Furthermore, as the health care providers were not blinded to the OGTT results, it is conceivable that women with the highest (but nondiagnostic) glucose values received more intensive prenatal care that may have led to information bias: more frequent diagnosis of hypertensive disorders and more frequent caesarean deliveries.

While our study has good external validity for those healthcare settings that previously used the WHO-1999 criteria for the diagnosis of GDM, it has limited external validity to settings that used other definitions (i.e. the Carpenter-Coustan criteria) for the diagnosis of GDM. This is related to the fact that the 2-hour postload diagnostic cutoff of the WHO-1999 criteria is lower than the WHO-2013 cutoff.

The relatively low number of participants with rare outcomes (severe preeclampsia, congenital malformation) precluded drawing any firm conclusions on these outcomes. Unfortunately, we do not have data on the more frequent outcome, preeclampsia that would improve statistical power. Even for the more frequent outcomes, we have somewhat imprecise estimates given the wide confidence intervals. Given the observational nature of our study, it is impossible to entangle cause-effect relationships. Furthermore, the role of unmeasured confounders could also bias our findings.

The strengths of our study include its population-based nature. Additionally, the OGTTs were done according to a standardized protocol and blood glucose values were analysed in the same central laboratory throughout the study. Another strength is related to the fact that most participants had 3-point OGTTs but the diagnosis and treatment of GDM was based on the WHO-1999 diagnostic criteria. This is further supported by the fact that we found no selection bias when comparing treated and untreated GDM women (**Supplemental Table S1**). The fact that the results of our main and sensitivity analyses show very similar results lend support for the robustness and the external validity of our conclusions.

5. Conclusion

According to our data, pregnancy outcomes of untreated 'mild' GDM pregnancies (GDM by the WHO 2013 but not by the WHO-1999 diagnostic criteria) were worse compared to NGT pregnancies. Most of these differences were explained by differences in pre-pregnancy BMI. Since the treatment of GDM leads to a decreased weight gain after diagnosis compared to control pregnancies but this does not result in improved outcomes in these 'mild GDM cases' [41,42], our results suggest that weight management starting before pregnancy or at the first prenatal visit could be required to improve pregnancy outcomes of these 'mild' GDM women. However, randomized controlled trials are required to prove this hypothesis.

CRediT authorship contribution statement

Ggely Á. Verisolyi: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Orsolya Szalai:** Methodology, Validation, Writing – original draft, Writing – review & editing. **Márk M. Svébis:** Methodology, Validation, Writing – review & editing. **Beatrix A. Domján:** Methodology, Validation, Writing – review & editing. **László Zsirai:** Methodology, Validation, Writing – review & editing. **Ádám G. Tabák:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110874.

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