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Research: Pregnancy

Trends in pregnancy outcomes for women with gestational diabetes mellitus in Sweden 1998–2012: a nationwide cohort study

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Abstract

Aim To assess whether incidence of maternal and neonatal outcomes for women with or without gestational diabetes mellitus (GDM) have changed over time.

Methods Population-based cohort study in Sweden including all singleton pregnancies over the period 1998–2012. GDM was diagnosed following Diabetic Pregnancy Study Group 1991 criteria. Poisson regression or negative binomial regression was used to model yearly relative change in numbers of cases and incidence of the outcomes with 95% confidence intervals (CI), and yearly absolute change in birthweight *z*-score.

Results The study included 1 455 667 pregnancies. The number of pregnancies increased over time and the overall prevalence of GDM was 1%. For women with GDM there was a significantly decreasing trend in incidence per year for large for gestational age (LGA) (0.986, 95% CI 0.975 to 0.996), birthweight *z*-score (−0.012, 95% CI −0.017 to −0.007) and birth trauma (0.937, 95% CI 0.907 to 0.968). The trend for small for gestational age (SGA) among women with GDM increased by an odds ratio per year (1.016, 95% CI 1.002 to 1.029). No significant interaction tests for maternal characteristics were found. Trends in outcomes for women without diabetes were similar to those for women with GDM.

Conclusions This study shows that there were improvements in pregnancy outcomes for women with GDM between 1998 and 2012, although the incidence of SGA increased. Improvements followed similar trends in the background population. Inequalities in obstetric outcomes between women with GDM and those without have continued unchanged over 15 years, suggesting that new management strategies are required to reduce this gap.

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Introduction

Hyperglycaemia in pregnancy is an increasing problem worldwide. In Sweden, rates of type 1 and type 2 diabetes mellitus in pregnancy, as well as gestational diabetes mellitus (GDM) are increasing [1]. Women with GDM are at greater risk for maternal and neonatal complications, and in 1989, the St Vincent Declaration set the goal that the pregnancy outcomes for women with diabetes should be comparable with those for women without diabetes [2–4]. There are few studies of trends in pregnancy outcomes for women with GDM over time. There is one study by Feig *et al.* from Canada, focusing on uncommon outcomes such as perinatal mortality [5]. Another recent single-centre study from Denmark reported decreasing birthweight in offspring of women with GDM [6]. During the past few decades there have been improvements in the medical care of both pregnant women with and without GDM. For example, the use of ultrasound as a tool for evaluating fetal well-being and weight is now more reliable, and the quality of the examination is better [7,8]. Maternal health care has focused to a greater extent on improving weight gain and lifestyle, alongside a shift to more visits in early pregnancy [9]. The criteria for GDM in Sweden have remained largely unchanged over this period allowing an evaluation of outcomes over time.

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What's new?

- Women with gestational diabetes (GDM) have a higher incidence of adverse maternal and perinatal outcomes during pregnancy and labour.
- The trends for maternal and perinatal outcomes are similar for women with GDM and women without GDM.
- Among women with GDM and those without, birth trauma has declined in parallel with reductions in birthweight and rates of large for gestational age, and increases in rates of small for gestational age.
- The differential in outcomes between women with GDM and those without has persisted over 15 years.

The aim of this study was to assess whether incidence of maternal and neonatal outcomes for women with GDM have changed over the period 1998–2012 in Sweden. Because such outcomes would be affected by wider population changes and changes in care, we compared the trends for women with GDM and women without GDM.

Methods

This is a population-based cohort study including all singleton pregnancies resulting in a birth in Sweden over the period 1998–2012. Women with pregestational diabetes were excluded. Data were obtained from the Swedish Medical Birth Register (MBR), which is maintained by the National Board of Health and Welfare. The MBR contains data on 98% of all pregnancies, including anthropometric data and complications during pregnancy, delivery and the neonatal period. Data were collected prospectively during the pregnancy after obtaining oral consent from the pregnant women. The MBR does not have information on laboratory measures such as HbA_{1c}. The registry has been validated and the quality is regarded as high [10].

Screening and diagnoses of GDM

In Sweden during the study period, GDM screening was performed by four to six random, repeated capillary blood glucose measurements during pregnancy, in combination with screening using traditional risk factors in 87% of pregnancies. If the capillary plasma blood glucose was ≥ 9 mmol/l, an oral glucose tolerance test (OGTT) was performed with fasting and 2-h glucose measurements. If traditional risk factors were identified such as previous pregnancy affected by GDM, previous birth of a large for gestational age (LGA) or a macrosomic baby (> 4500 g), BMI (kg/m^2) > 30 or > 35 in early pregnancy and family history of diabetes mellitus, an OGTT was performed in gestational week 28–32. Criteria differed by region. Accelerated growth or polyhydramnios was also an indication for OGTT in most centres. If a woman had a high random glucose early in pregnancy and the subsequent OGTT was normal, a repeat OGTT was undertaken at 28–32 weeks' gestation. In the southern region of Sweden, screening was made by offering every woman a simplified OGTT in pregnancy at week 28–32 with measurement of 2-h value and no fasting value [11]. This region represented 13% of the population.

The diagnosis of GDM was made by undertaking a 75-g OGTT using capillary sampling: no region used venous sampling for the OGTT at any time. The main diagnostic criteria during 1998–2003 were fasting glucose ≥ 6.1 mmol/l or a 2-h value ≥ 9 mmol/l using capillary whole blood [12]. In 2004, there was a shift to measuring glucose in capillary plasma. The new 'converted' criteria for capillary plasma were: fasting value ≥ 7 mmol/l and 2-h value ≥ 10 mmol/l. In one region, which comprised ~ 20% of the population, only overt diabetes (fasting capillary plasma glucose ≥ 7 mmol/l or a 2-h value ≥ 12.2 mmol/l) was diagnosed during 1998–2010. After 2011, the region changed to the main diagnostic criteria described above. Women diagnosed with GDM were treated according to local protocols: all with dietary advice and insulin therapy if considered hyperglycaemic (usually if several fasting values during a week were > 6–6.5 mmol/l and/or post-meal values were > 8 mmol/l).

Definition of outcomes

Weight was registered at the first antenatal visit early in pregnancy (gestational week 12–14) without shoes in light clothes. Height was registered at recall. BMI was calculated as weight (kg)/length (m)^2. When adjusting for BMI, we used the categories defined by the World Health Organization (WHO): underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (≥ 25.0–29.9 kg/m^2), obese 1 (≥ 30.0–34.9 kg/m^2) and obese 2 (≥ 35 kg/m^2). Women with extreme values for weight and height were excluded (weight < 30 or > 200 kg, height < 100 or > 200 cm). Smoking was defined as smoking at first antenatal visit. Women were divided into two groups depending on country of birth, Nordic (Sweden, Denmark, Norway, Finland, Iceland) and non-Nordic. Pregnancy and neonatal outcomes were identified using codes in the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10). Chronic hypertensive disease was defined as blood pressure (BP) ≥ 140/90 mmHg before gestational week 20, ICD-code O10.0, O10.2, O10.4 or O10.9. GDM was defined as ICD-code O24.4A or O24.4B. Pre-eclampsia was defined as BP ≥ 140/90 mmHg and proteinuria > 0.3 g 24 h^{-1} l^{-1}, ICD-code O14, O14.0, O14.1A, O14.1B, O14.1C, O14.1X, O14.2, O14.9 after gestational week 20. Perinatal mortality was defined as stillbirth, ICD code O36.4, or neonatal death within 7 days from birth. In the study period before 2008, stillbirth included fetal death

after 28 completed weeks of gestation. In 2008, the definition changed to include fetal death after 22 completed weeks. Premature birth was defined as birth before 37 completed gestational weeks. Birth trauma included Erb's palsy, spinal cord injury, basal skull fracture, intracranial haemorrhage and fracture of long bones, ICD-codes P14.0-3, P11.5, P11.9, P13.0-1, P10.0-4, P10.8-9, P13.2-4 and P13.8-9 according to the definition of Feig *et al.* [13]. LGA was defined as birthweight over the 90th percentile within the data set, excluding stillbirths, major malformation and multiple pregnancies. Small for gestational age (SGA) was defined as birthweight lower than the10th percentile within the data set with the same exclusions as for LGA. The validity of these SGA and LGA cut-offs was confirmed by comparison with an older national data set derived from the MBR 1991–1997 [2]. The *z*-score for birthweight was calculated using national, standardized growth references [14] from 1990 to 1999, not necessarily reflecting the current population.

Statistical analysis

For categorical variables, χ^2-test for trend was used to analyse possible changes in maternal characteristics between the periods; for continuous variables, one-way analysis of variance (ANOVA) was used. Linear regression was used to evaluate trend for *z*-score for birthweight over the years. Yearly incidence during 1998 to 2012 of the outcomes: pre-eclampsia, caesarean section, perinatal mortality, premature birth, birth trauma, LGA and SGA was calculated by dividing number of cases by the number of pregnancies in the Swedish population. We used Poisson regression or negative binomial regression to model the yearly relative change in the number of cases and the incidence of the outcomes with 95% confidence intervals (CI). For example, an incidence change of 1.020 represents a 2.0% increase per year and a change of 0.980 represents a 2.0% decrease per year. The Poisson regression was evaluated by Pearson's goodness-of-fit test, and if the variation exceeded that of the Poisson distribution, negative binomial regression was used instead. The analyses were performed for the GDM population in total and stratification with interaction tests were performed on mother's BMI, categorized as above, country of birth (Nordic/non-Nordic), age (< 25, 25–34, ≥ 35 years), smoking status and chronic hypertension. Because the incidence of LGA indicated different trends over time, the analyses were performed in two periods, 1998–2007 and 2008–2012, and the yearly relative changes were compared between the periods using interaction tests. Analyses of SGA and LGA were repeated after exclusion of women with intercurrent disease during pregnancy to exclude potential effects on fetal size. Incidence trends for women without GDM were also reported. Intercurrent disease was defined as ICD code O10.0, O10.2, O10.4, O10.9, O98.0-2, O98.4 A-C, O98.4W-X, O98.7 and O99.0-8. A *P*-value of < 0.05 was considered significant. All statistical analyses were conducted using IBM SPSS version 22 (Armonk, NY, USA) or STATA release 14 (Stata Corp, College Station, TX, USA).

Ethical approval

The study was approved by the Regional Ethical Committee in Uppsala, Sweden (2009/187/1); date of approval 25 October 2017. The study followed the Declaration of Helsinki.

Results

After exclusions, the study cohort included 1 455 667 women; 1 440 834 without GDM and 14 833 with GDM. The prevalence of GDM increased significantly from 0.7% in 1998 to 1.2% in 2012. Changes in maternal characteristics were similar in the group without GDM and the group with GDM (Table 1). There was a significant increase in maternal age and maternal BMI at first visit to antenatal care. Being of non-Nordic descent and being primiparous also became significantly more common. Smoking decreased significantly over time and chronic hypertension increased significantly, although remaining a rare condition. Pregnancy duration became significantly shorter both in women with GDM and those without over time (Table 1). During the study period, the number of births increased significantly per year for both women with GDM (1.047, 95% CI 1.03 to 1.058) and the background population (1.021, 95% CI 1.018 to 1.024) (Fig. S1). For both women with and those without GDM, there was a significant declining trend per year for birthweight *z*-score (GDM: −0.012, 95% CI −0.017 to −0.007; no GDM: −0.006, 95% CI −0.006 to −0.005) (Fig. S2), LGA incidence (GDM: 0.986, 95% CI 0.975 to 0.996; no GDM: 0.987, 95% CI 0.983 to 0.992) (Table 2; Fig. 1) and birth trauma (GDM: 0.937, 95% CI 0.907 to 0.968; no GDM: 0.937, 95% CI 0.933 to 0.942) (Table 2; Fig. 2). However, there was an increase in absolute numbers with LGA over time due to the growing total number of pregnancies. There was an increasing trend in SGA incidence for both women with GDM and those without (GDM: 1.016, 95% CI 1.002 to 1.029; no GDM: 1.007, 95% CI 1.004 to 1.009) (Table 2, Fig. S3). For women with GDM there were no significant changes in trends in the incidence of pre-eclampsia, perinatal mortality and prematurity. For women without GDM, there was a significant decrease in incidence of pre-eclampsia (0.994, 95% CI 0.989 to 0.999), perinatal mortality (0.990, 95% CI 0.982 to 0.998) and premature birth (0.996, 95% CI 0.994 to 0.998), but an increase in caesarean section rates (1.024, 95% CI 1.017 to 1.031) (Table 2; Figs S1–S7). There were no significant reductions in pregnancy complications among women with GDM, but caesarean rates increased overall and LGA rates increased significantly among women with GDM from 2008. The overall rate of insulin-treated GDM was 38%. The frequency changed from 34% in 1998 to 41.5% in 2012.

Table 1 Maternal characteristics for women with and without gestational diabetes (GDM) over five periods.

	No GDM (N = 1 440 834)					GDM (N = 14 833)				
Period	1998–2000 n = 249 791	2001–2003 n = 270 874	2004–2006 n = 292 929	2007–2009 n = 307 487	2010–2012 n = 319 753	1998–2000 n = 2155	2001–2003 n = 2689	2004–2006 n = 2717	2007–2009 n = 3496	2010–2012 n = 3776
Age	29.4 ± 5.0	29.9 ± 5.0	30.2 ± 5.1	30.3 ± 5.3	30.2 ± 5.3	31.9 ± 5.1	31.9 ± 5.3	32.3 ± 5.4	32.4 ± 5.5	32.4 ± 5.6
BMI	24.2 ± 4.2	24.4 ± 4.3	24.5 ± 4.4	24.5 ± 4.5	24.7 ± 4.6	27.7 ± 6.0	28.7 ± 6.1	28.8 ± 6.2	28.7 ± 6.4	29.1 ± 6.4
Non-Nordic*	15.7	16.6	18.2	20.6	23.3	30.8	36.3	38.2	41.5	47.3
Multipara*	57.4	55.0	55.4	54.8	55.2	67.8	64.3	64.6	63.2	63.0
Smoking*	11.6	10.0	7.6	6.6	6.0	12.5	11.2	8.2	8.0	7.0
Chronic hypertension*	0.2	0.2	0.3	0.3	0.3	0.8	1.0	1.5	1.3	1.7
Gestational age (days)	279 ± 13	279 ± 13	279 ± 13	279 ± 13	279 ± 13	275 ± 14	274 ± 14	274 ± 14	274 ± 14	274 ± 14

Values are *rates (%) or ± SD for age, BMI and gestational age. Pre-gestational diabetes and multiple pregnancies excluded.
$P < 0.05$ for all characteristics over time in both women with and those without GDM.

Table 2 Unadjusted incidence trends per year (1998 to 2012) of outcomes among populations with gestational diabetes (GDM) and populations without GDM*

	GDM 1998–2012	Non GDM 1998–2012
Large for gestational age	0.986 (0.975–0.996)	0.987 (0.983–0.992)
Small for gestational age	1.016 (1.002–1.029)	1.007 (1.004–1.009)
Birth trauma	0.937 (0.907–0.968)	0.937 (0.933–0.942)
Pre-eclampsia	1.004 (0.989–1.020)	0.994 (0.989–0.999)
Caesarean section	1.016 (1.008–1.024)	1.024 (1.017–1.031)
Perinatal mortality	1.022 (0.996–1.080)	0.990 (0.982–0.998)
Prematurity	1.004 (0.992–1.016)	0.996 (0.994–0.998)

Incidence change per year with 95% CI estimated by Poisson or negative binomial regression (see statistics for details).

Table S1 shows that the trends were comparable within strata (BMI, non-Nordic descent, smoking, parity and age of the women) with no significant interaction tests. Excluding women with intercurrent disease did not change the trends in outcomes.

Discussion

In this large, population-based cohort study we show that there have been improvements in some outcomes for women with GDM. Birthweight, incidence of LGA and birth trauma have decreased, but SGA and caesarean section incidence have increased. The same trends are also seen in the general population. Pre-eclampsia, perinatal mortality and prematurity did not show a significant change in trend for women with GDM, but in women without GDM there was a decrease in pre-eclampsia, prematurity and perinatal mortality.

The strength of the study is that it is nationwide, based on a validated register with prospectively collected data on almost all pregnancies in Sweden during the study period [10]. The study incorporates a long period, which diminishes the possibility of misinterpreting minor changes in trends. The large data set allows sub-analyses to further evaluate the results. Limitations include the higher diagnostic plasma glucose criteria for GDM in Sweden compared with several other countries. This would result in the inclusion of some women in the non-GDM group that have GDM by other criteria, and probably dilutes the differences between the groups. However, it includes women with indisputable GDM by any criteria globally. Although there was no abrupt shift in incidence with the change of capillary testing method, this was introduced gradually over several years and any impact could have been obscured by wider secular changes. Another drawback is the regional differences in screening methods and variations in diagnostic criteria across the study population. These variations affect the number of women

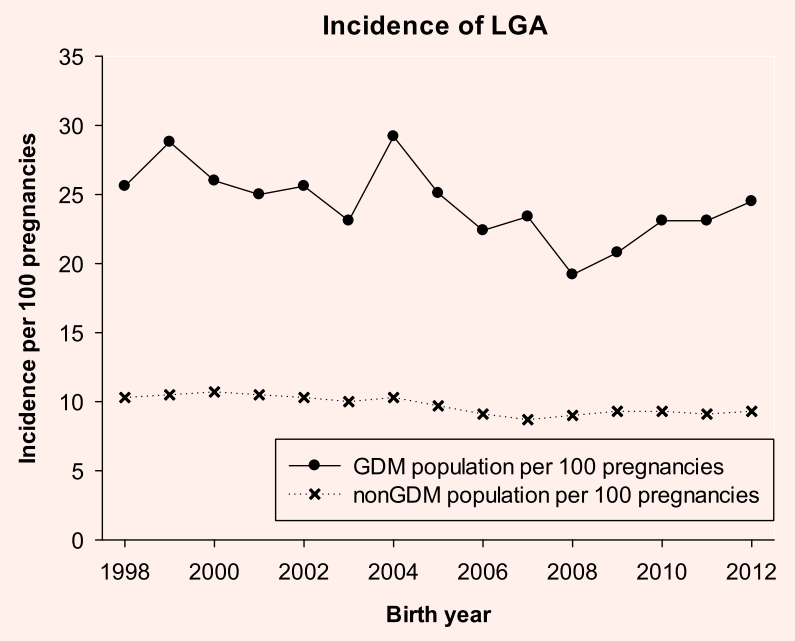

FIGURE 1 Trend in incidence per year for LGA for women with GDM 0.986 (0.975-0.996) and women without GDM 0.987 (0.983-0.992).

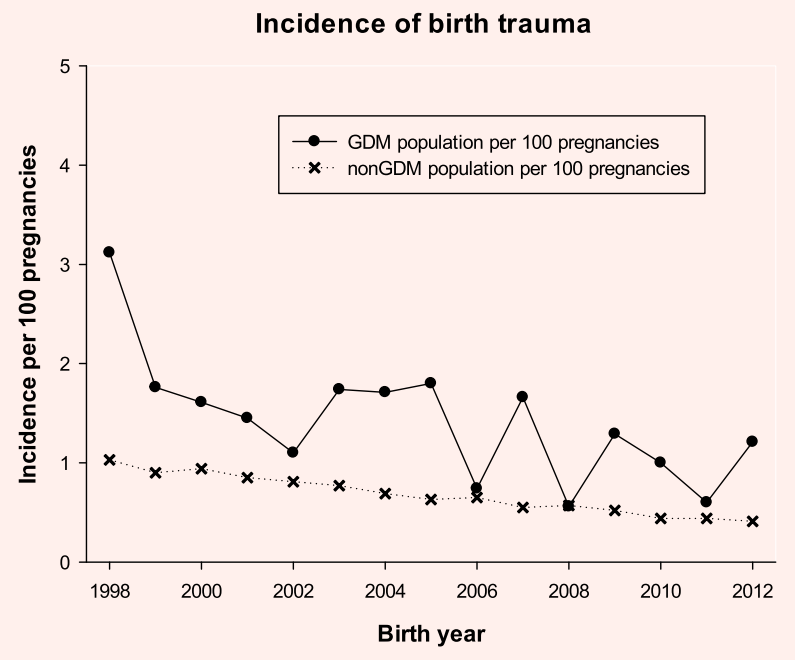

FIGURE 2 Trends in incidence per year for birth trauma, in women with and without GDM. GDM 0.937 (0.907-0.968), no GDM 0.937 (0.933-0.942).

diagnosed with GDM, but during the study period the variations were between the regions and no major changes were undertaken in the regions during this time. Compared with other Nordic countries, Sweden has the most restrictive screening for GDM, resulting in a very low prevalence. It cannot be ruled out that the results could be different if the prevalence of GDM was higher, resulting in a healthier background population and possibly a lower rate of

complications in the group with GDM. Although only 1% of the population had GDM, and this could have limited our ability to show a statistical difference over time, these are data are across the whole of Sweden and hence the overall numbers are large. We cannot rule out that there have been minor changes in diagnostic criteria over the period of study. Possible changes could affect results and in part explain the decrease in LGA. Another limitation is lack of data on compliance with offered treatment.

No significant trend in perinatal mortality was seen for women with treated GDM. In the background population, there was a significant decrease, although small. This is in line with the findings of Feig *et al.* [5], although they also showed that women with GDM were at less risk of perinatal death than women without diabetes. Compared with that study, the Swedish incidence of perinatal mortality was lower.

Birth trauma decreased by ~ 50% both in the GDM group and the background population. The decrease in birth trauma could be due to reduction in fetal size since the results show a decrease in absolute birthweight but also a decrease in LGA with an increase in SGA babies. The rate of caesarean section is increased and this could contribute to reduced birth trauma [15]. Obstetric education and management in Sweden has changed over the period of study with a focus on team-based training for adverse, obstetrical situations, and this could have an impact on the decreasing rate of birth trauma [16]. The finding of reduced incidence of birth trauma is of clinical importance and needs further analysis.

There is no obvious reason for a decrease in the rate of LGA babies. However, an unexplained increase in incidence of LGA for women with GDM after 2008, needs to be recognized. The number of cases are too small to be able to draw conclusions about trends, but these results need to be followed up. Decreasing birthweight has previously been shown from the late 1990s onwards [17]. A large American study reported decreasing birthweight in term singletons and the changes could not be explained by changes in the pregnant population or obstetric care [18]. Ovesen *et al.* [6] also showed a decreasing trend in birthweight and LGA for women with GDM but they did not present data for the general population. Contradictory results are reported in England and Wales, where there was an increase in birthweight during the period 1986–2012 [19].

During the studied period, numbers with GDM increased significantly. There is evidence of a change in diet within the Swedish population [20]. Johansson *et al.* [21] showed that total consumption of fat and unsaturated fat increased significantly during the study period. At the same time, carbohydrate intake decreased. A diet with less carbohydrate could lead to a decreased glycaemic load, with potentially less circulating glucose passing through the placenta to the fetus, thereby reducing fetal growth. Szilcz *et al.* [22,23] showed a slight increase in physical activity during the studied period but there are also contradicting results that physical activity has decreased and will continue to do so. Although this study focused on changes in obstetric outcomes, the best way to prevent GDM complications would be to prevent GDM overall, something that has been largely difficult to achieve to date [24].

There are well-known risk factors for being born SGA including smoking [25] and pre-eclampsia [26,27], but the incidence for both smoking and pre-eclampsia decreased in all women during the studied years in Sweden. This change would have predicted a decrease in SGA, which did not occur. A further risk factor for SGA could be intense insulin treatment in women with GDM [28]. There have been no national guidelines on treatment goals for GDM in Sweden and we had no data on the extent of insulin treatment, or on specific dietary or other management provided to the women with GDM. Since the trends in outcomes are similar between women with and without GDM, this is probably not the explanation.

Indeed, the trends for fetal size (i.e. birthweight, SGA and LGA) are similar for both women with and without GDM. This suggests that improved care focused on women with GDM does not explain our findings. There have not been any major changes, except development in ultrasound diagnostics, in general obstetric care during these years in Sweden that would affect estimation of fetal size and concomitant possible interventions. Changes seen in trends are probably more related to factors on a population level, such as diet, exercise and basic maternal care. There was a one day difference in mean gestational age in the GDM group; so we think it unlikely that the general increase in induction rates have had an impact on the results. However, this needs to analysed further in future studies.

There have been changes in the composition of the group of pregnant women when analysing BMI, age, ethnic origin and smoking habits. Stratification by these factors did not change our findings in relation to trends in outcomes, which makes it less likely that our results originate from a change in composition of the pregnant group.

There have been changes in maternal health care or antenatal care during the study period. Women entered pregnancy earlier by the end of the study period, which provided an opportunity for earlier interventions during pregnancy, e.g. restricting weight gain, dietary advice, and advice on physical activity. However, to date, randomized controlled trials have not suggested that birth outcomes are influenced by lifestyle interventions [29,30].

When analysing the absolute numbers of cases for pre-eclampsia, caesarean section, prematurity and LGA it is evident that although there is a decreasing or insignificant trend for the outcome, absolute numbers of cases are rising due to increasing numbers of pregnancies. This means that the overall burden on public health care is increasing despite decreasing trends in incidence.

Conclusion

This study shows that there have been improvements in fetal outcomes for women with GDM between 1998 and 2012, although the incidence of SGA increased. Because the improvements are similar to or less than the background population this is probably not due to better medical care for women with GDM alone. Inequalities in obstetrical outcomes between women with and without GDM have continued unchanged, or even worsened, over 15 years in Sweden. New management strategies, such as screening, diagnosis and treatment of GDM, may be required to reduce this gap while we await strategies such as reducing pre-pregnancy obesity that prevent GDM development.

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Competing interests

None declared.

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Author contributions

KH, UH, DS and HF conceived the study. KH, AM, UH, DS and HF planned, performed, analysed and wrote the study.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Number of pregnancies.
Figure S2. Birth weight score.
Figure S3. Incidence of SGA.
Figure S4. Incidence of pre-eclampsia.
Figure S5. Incidence of caesarean section.
Figure S6. Incidence of premature birth.
Figure S7. Incidence of perinatal mortality.
Table S1. Unadjusted incidence trends per year (1998 to 2012) of outcomes among GDM and non-GDM populations.