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RESEARCH ARTICLE

Trends in the incidence of diabetes, its clinical sequelae, and associated costs in pregnancy

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Abstract

Background Increasing diabetes prevalence affects a substantial number of pregnant women in the United States. Our aims were to evaluate health outcomes, medical costs, risks and types of complications associated with diabetes in pregnancy for mothers and newborns.

Methods In this retrospective claims analysis, patients were identified from the Truven Health MarketScan® database (2004–2011 inclusive). Participants were aged 18–45 years, with ascertainable diabetes status [Yes/No], date of birth event >2005 and continuous health plan enrolment ≥21 months before and 3 months after the birth.

Results In total, 839 792 pregnancies were identified, and 66 041 (7.86%) were associated with diabetes mellitus [type 1 (T1DM), 0.13%; type 2 (T2DM), 1.21%; gestational (GDM), 6.29%; and GDM progressing to T2DM (patients without prior diabetes who had a T2DM diagnosis after the birth event), 0.23%]. Relative risk (RR) of stillbirth (2.51), miscarriage (1.28) and Caesarean section (C-section) (1.77) was significantly greater with T2DM *versus* non-diabetes. Risk of C-section was also significantly greater for other diabetes types [RR 1.92 (T1DM); 1.37 (GDM); 1.63 (GDM progressing to T2DM)]. Risk of overall major congenital (RR≥1.17), major congenital circulatory (RR≥1.19) or major congenital heart (RR≥1.18) complications was greater in newborns of mothers with diabetes *versus* without. Mothers with T2DM had significantly higher risk (RR≥1.36) of anaemia, depression, hypertension, infection, migraine, or cardiac, obstetrical or respiratory complications than non-diabetes patients. Mean medical costs were higher with all diabetes types, particularly T1DM ($27 531), than non-diabetes ($14 355).

Conclusions Complications and costs of healthcare were greater with diabetes, highlighting the need to optimize diabetes management in pregnancy. © 2015 The Authors. *Diabetes/Metabolism Research and Reviews* published by John Wiley & Sons, Ltd.

Keywords gestational diabetes; type 2 diabetes; type 1 diabetes; diabetes complications; pregnancy; cost-effectiveness

Introduction

The increasing prevalence of diabetes [currently 29 million individuals in the USA] affects a substantial number of pregnant women and approximately

5.5% of women of child-bearing age [1–4]. It is estimated that 7–18% of women develop gestational diabetes mellitus (GDM) during pregnancy [1,5], and up to 10% of United States (US) pregnancies are complicated by GDM, pre-existing type 1 diabetes mellitus (T1DM) or pre-existing type 2 diabetes mellitus (T2DM) [1,6]. Furthermore, undiagnosed diabetes affects an estimated 1.8–2.3% of the US adult population ≥20 years of age [7]. Although T2DM accounts for the majority of US diabetes cases overall, GDM is far more common during pregnancy [8–10]. According to recent epidemiological reports, the proportion of pregnancies complicated by diabetes of any type doubled from 1994 (3.5%) to 2008 (7.3%). The proportion of pregnant women with GDM rose from 2.9% to 5.4% during this time, and the proportion affected by pre-existing diabetes also doubled from 0.3% to 1.1%, primarily due to a 367% increase in T2DM [9,11,12].

Complications known to arise from the effects of maternal diabetes on early foetal development (i.e. during the first trimester) primarily include miscarriage and congenital malformation, while complications that arise during the second and third trimesters primarily include stillbirth and macrosomia [13]. Risk of neonatal complications is known to be greater with pre-existing diabetes than in non-diabetic pregnancies, that is, congenital malformation [odds ratio (OR) 2.7–8.6], stillbirth (OR 2.9) and pre-term delivery [19–25% (pre-existing diabetes); 10–17% (non-diabetes)] [14–17]. Risk is also greater with GDM *versus* non-diabetes, that is, congenital malformation (OR 1.2–1.5), stillbirth (OR 1.3) and pre-term delivery [13–19% (GDM) *versus* 10–17% (non-diabetes)] [15–19]. Maternal complications likewise occur more commonly in women with diabetes and include hypoglycaemia, gestational hypertension/preeclampsia and Caesarean delivery, among other comorbidities [8,11,14].

Although diabetes is occurring ever more frequently in women of child-bearing age, it can be effectively managed with ongoing advancements in lifestyle and drug therapy [20–22]. However, a literature search conducted to assess the number of trials examining the impact of diabetes in pregnancy produced limited results, particularly with regard to T2DM, and consisted mainly of small retrospective analyses. Hence, the aim of this study was to evaluate costs, risk and types of complications associated with diabetes in pregnancy via a large claims database analysis, to determine how these compare in pregnant patients with and without diabetes and their newborns and thereby identify potential areas for improvements in care. Therefore, the specific research objectives were to describe trends in the incidence of diabetes, perinatal morbidity and mortality, complications, and direct medical costs for (1) mothers with pre-existing diabetes or GDM and (2) infants of mothers with diabetes, with perinatal morbidity/mortality considered pre-term birth, miscarriage or stillbirth.

Materials and methods

Patients were identified from the Truven Health MarketScan® database (Truven Health Analytics, Ann Arbor, MI, USA). MarketScan is a medical insurance claims database containing adjudicated/paid claims for inpatient, outpatient and pharmacy visits, primarily sourced from self-insured employers across the US, along with regional health plans. A database encompassing the 2004–2011 time frame was selected so that data could be obtained for a large sample of patients for a sufficient length of time to capture significant differences in uncommon perinatal outcomes and determine whether descriptive trends emerged over time.

The study period was defined as 2005–2011 (inclusive), and patients with multiple pregnancies had all pregnancies included. For inclusion, female patients had to be 18–45 years old at the delivery date, with ascertainable diabetes status [Yes/No] and date of giving birth >2005. Continuous health plan enrolment, including prescription eligibility, was required of mothers from 21 months (630 days; i.e. 1 year plus gestation period) prior to their delivery date to 3 months (90 days) post-delivery. Individuals were excluded if they did not have insurance for at least 1 year prior to conception or if there were not at least 60 days of enrolment after delivery.

Pregnancies were defined by delivery date and identified by the International Classification of Diseases, 9th Revision (ICD-9) codes. Delivery could be inpatient or outpatient, and delivery dates closer than 90 days together were to be merged into the first date to account for potential coding errors. Pregnancy start dates were estimated based on the delivery diagnosis code. For most, this was 9×30 days $= 38.5$ weeks; early birth was considered 35 weeks; late birth was considered 42 weeks; miscarriage was considered 24 weeks. Mothers were linked to infants identified by an ICD-9 birth code by a unique 'family' identifier, indicating enrolment under the same plan, relationship status of dependent and year of the child's birth. Enrolment dates for the child did not necessarily cover delivery date; eligibility for children was thus considered to be enrolment starting within 30 days of delivery and lasting past 90 days post-delivery.

Diabetes definitions

Pregnancies were categorized as non-diabetes, GDM, progressing GDM (defined as GDM that progressed to

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T2DM within 3 months of delivery), or pre-existing T1DM or T2DM. The following criteria were used to categorize the subjects:

- Patients who were diagnosed with T1DM or T2DM prior to estimated start date of pregnancy *and not during another pregnancy* were categorized as pre-existing
  - T2DM: ≥2 diagnoses or 1 diagnosis + 1 oral anti-diabetic drug (OAD) claim, and ≤1 T1DM diagnosis
  - T1DM: ≥2 diagnoses or 1 diagnosis + insulin + no OAD, and ≤1 T2DM diagnosis
  - If diagnosis was not clear, patients were excluded
- Of the remaining patients, any diagnosed with any of the three types of diabetes during pregnancy are to be initially considered GDM
  - ≥2 of any diagnoses (T1DM, T2DM or GDM) during pregnancy period or 1 diagnosis + OAD or insulin
  - GDM changing to T1DM or T2DM in the 3 months after birth
  - If diagnosis was not clear, patients were excluded

The diagnoses of T1DM and T2DM had to have taken place prior to this pregnancy and not a previous one, and have been confirmed two separate times during the pregnancy period. Individuals who did not meet those criteria were excluded. Any diagnosis of T1DM or T2DM prior to the estimated pregnancy start and not during another pregnancy period was considered pre-existing; of the remaining patients, any diagnosis of diabetes during pregnancy was to be initially considered GDM. Of the GDM patients, those who had any further diagnosis of T1DM/T2DM within 3 months of follow-up after the delivery date were considered progressing GDM.

Cost definitions

All medical and prescription costs for the mother were tallied from the estimated pregnancy start date to 3 months post-delivery; costs were then broken down into pharmacy, inpatient and outpatient costs. Costs for matched children were from 3 months post-delivery.

Statistical analysis and coding

Statistical software used for data analysis was Unix SAS® v9.1.3 (SAS Institute, Cary, NC, USA). The analysis had two components: descriptive and comparative. The descriptive portion sought to determine the size of the relevant population, medical costs, complications and trends in diabetes prevalence over time. The comparative portion (unadjusted) examined the descriptive data and sought to determine how costs and complications compared in pregnant patients with and without diabetes. Complications were assessed as relative risk (RR) with 95% confidence intervals (CIs); an RR for which the lower bound of the 95% CI exceeded '1' was considered to be statistically significant.

Diagnosis codes used to identify pregnancy outcomes are detailed in Table S1. Patients with diabetes were identified using standard ICD-9 codes; these, plus codes used to identify maternal complications, are listed in Table S2, and codes for neonatal complications are listed in Table S3. The complications presented in this report were selected to encompass (1) frequently occurring and (2) serious complications of pregnancy, based on a MEDLINE literature search conducted of recent publications.

Results

Demographic characteristics and diabetes incidence

A total of 839 792 pregnancies met inclusion criteria as detailed earlier. Of these, 66 041 (7.9%) were associated with diabetes [1125 (0.1%) T1DM; 10 136 (1.2%) T2DM; 52 848 (6.3%) GDM; 1932 (0.2%) progressing GDM], and 773 751 were not associated with diabetes ('non-diabetes'). Mean age was slightly older among women with T2DM (34 years) and GDM (33 years) than among women with T1DM or non-diabetes (31 years). The majority of patients were located in the Southern USA (41–47%), followed by the Central (22–24%), Western (17-21%) and Northern (12–15%) regions of the USA. Diabetes incidence over time was plotted and revealed a modest increase in T2DM (Figure 1A) and GDM (Figure 1B) since 2005, with stabilization occurring around 2008. In agreement with previously published epidemiological data, incidence of GDM remained higher than T2DM, and pattern of incidence was comparable to that seen in other studies [8–10].

Pregnancy outcomes by diabetes status

The proportion of patients who experienced miscarriage was evaluated out of total pregnancies, and an RR [95% CI] was calculated for each diabetes type *versus* non-diabetes (Table 1). The proportion of patients with miscarriage was significantly higher with T2DM (25%) *versus*

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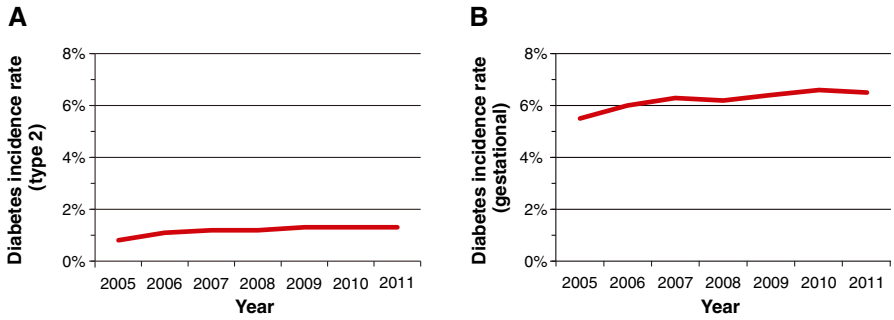

Figure 1. Incidence of type 2 diabetes (A) and gestational diabetes (B) among pregnant women in the United States, by year

Table 1. Pregnancy outcomes

Outcome *n*, % RR [95% CI]	Non-diabetes *n* = 773 751	T1DM *n* = 1125	T2DM *n* = 10 136	GDM *n* = 52 848	GDM (progressing) *n* = 1932
Miscarriage	152 185 (19.7%)	201 (17.9%) 0.91 [0.80, 1.03]	**2552 (25.2%)** **1.28 [1.24;1.32]**	450 (0.9%) 0.04 [0.04;0.05]	149 (7.7%) 0.39 [0.34;0.46]
Pregnancies that did not end in miscarriages (excluding unknown), *n*	586 875	783	6665	49 254	1618
Stillbirth	1745 (0.3%)	3 (0.4%) 1.47 [0.55;3.92]	**50 (0.8%)** **2.51 [1.94;3.26]**	57 (0.1%) 0.41 [0.32;0.52]	6 (0.4%) 1.07 [0.48;2.38]
C-section	160 762 (27.4%)	**411 (52.5%)** **1.92 [1.79;2.05]**	**3235 (48.5%)** **1.77 [1.73;1.82]**	**18 447 (37.5%)** **1.37 [1.35;1.38]**	**724 (44.7%)** **1.63 [1.55;1.72]**
Delivery timing					
Normal*	493 661 (84.1%)	657 (83.9%)	5638 (84.6%)	43 228 (87.8%)	1396 (86.3%)
Early	35 624 (6.1%)	121 (15.5%)	830 (12.5%)	4049 (8.2%)	196 (12.1%)
Late	57 590 (9.8%)	5 (0.6%)	197 (3.0%)	1977 (4.0%)	26 (1.6%)
Chi-square test of independence		<0.001	<0.001	<0.001	<0.001

n = total pregnancies within each diabetes category. Miscarriage rate is reported for total pregnancies. Stillbirth, C-section and delivery timing rates are reported for pregnancies that did not end in miscarriages, excluding unknown outcomes. Bolded text indicates statistical significance. T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; GDM; gestational diabetes mellitus; RR, relative risk; CI, confidence interval.
*Normal delivery indicates classification as neither early nor late in terms of delivery timing.

non-diabetes [20%; RR 1.28 (1.24, 1.32)], and no difference was seen with T1DM (18%) *versus* non-diabetes [RR 0.91 (0.80, 1.03)]. Rates of miscarriage were numerically lower with GDM (0.9% GDM; 7.7% progressing GDM) than non-diabetes; however, no significant difference was noted.

The proportion of patients experiencing stillbirth, Caesarean section (C-section), or early, normal or late delivery was evaluated in pregnancies that did not end in miscarriages, excluding unknown outcomes (*n* values in Table 1). The proportion of patients with stillbirth was significantly higher with T2DM (0.8%) *versus* non-diabetes [0.3%; RR 2.51 (1.94, 3.26)]. No difference was seen between the T1DM (0.4%) and non-diabetes groups [RR 1.47 (0.55, 3.92)]. The rate of stillbirth was numerically lower with GDM (0.1%) and numerically slightly higher with progressing GDM (0.4%) than with non-diabetes; however, these RR comparisons were not significantly different.

The risk of experiencing delivery by C-section was significantly greater with diabetes of any type (Table 1). Approximately 85% of patients across groups experienced 'normal' (neither early nor late) timing of delivery. However, more patients with diabetes of any type experienced early delivery, and late delivery was fairly uncommon among patients with diabetes. Patients with T1DM had the highest risk for C-section and for early delivery.

Maternal complications

The proportion of mothers experiencing complications ('any' and grouped by organ system) was evaluated in pregnancies that did not end in miscarriages, excluding unknown outcomes (*n* values in Table 2). Mothers with diabetes had a significantly higher risk of experiencing 'any' complication than non-diabetes patients (Table 2); this proportion ranged from 55.3% GDM [RR 1.22 (1.21, 1.23)]

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Table 2. Maternal complications

Complication *n*, % RR [95% CI]	Non-diabetes *n* = 773 751	T1DM *n* = 1125	T2DM *n* = 10 136	GDM *n* = 52 848	GDM (progressing) *n* = 1932
Pregnancies that did not end in miscarriages (excluding unknown), *n*	586 875	783	6665	49 254	1618
Any complication	265 460 (45.2%)	**495 (63.2%)** **1.40 [1.32;1.47]**	**4644 (69.7%)** **1.54 [1.52;1.57]**	**27 240 (55.3%)** **1.22 [1.21;1.23]**	**1097 (67.8%)** **1.50 [1.45;1.55]**
Anaemia	45 777 (7.8%)	59 (7.5%) 0.97 [0.76;1.23]	**871 (13.1%)** **1.68 [1.57;1.78]**	**4810 (9.8%)** **1.25 [1.22;1.29]**	**239 (14.8%)** **1.89 [1.68;2.13]**
Cardiac	2999 (0.5%)	5 (0.6%) 1.25 [0.52;3.00]	**79 (1.2%)** **2.32 [1.86;2.90]**	**438 (0.9%)** **1.74 [1.57;1.92]**	**23 (1.4%)** **2.78 [1.85;4.18]**
Depression	26 532 (4.5%)	41 (5.2%) 1.16 [0.86;1.56]	**555 (8.3%)** **1.84 [1.70;2.00]**	**2599 (5.3%)** **1.17 [1.12;1.21]**	**94 (5.8%)** **1.29 [1.06;1.56]**
Hypertension	165 350 (28.2%)	**371 (47.4%)** **1.68 [1.56;1.81]**	**3693 (55.4%)** **1.97 [1.92;2.01]**	**18 887 (38.3%)** **1.36 [1.34;1.38]**	**810 (50.1%)** **1.78 [1.69;1.87]**
Infection	32 698 (5.6%)	48 (6.1%) 1.10 [0.84;1.45]	**512 (7.7%)** **1.38 [1.27;1.50]**	**3136 (6.4%)** **1.14 [1.10;1.18]**	**131 (8.1%)** **1.45 [1.23;1.71]**
Migraine	5070 (0.9%)	11 (1.4%) 1.63 [0.90;2.93]	**81 (1.2%)** **1.41 [1.13;1.75]**	**490 (1.0%)** **1.15 [1.05;1.26]**	19 (1.2%) 1.36 [0.87;2.13]
Obstetrical	63 801 (10.9%)	**139 (17.8%)** **1.63 [1.40;1.90]**	**987 (14.8%)** **1.36 [1.29;1.44]**	**6302 (12.8%)** **1.18 [1.15;1.21]**	**259 (16.0%)** **1.47 [1.32;1.65]**
Respiratory	1779 (0.3%)	**6 (0.8%)** **2.53 [1.14;5.62]**	**68 (1.0%)** **3.37 [2.64;4.28]**	**188 (0.4%)** **1.26 [1.08;1.46]**	**18 (1.1%)** **3.67 [2.31;5.82]**

n = total pregnancies within each diabetes category. Complication rates are reported for pregnancies that did not end in miscarriages, excluding unknown outcomes. Bolded text indicates statistical significance. T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; GDM; gestational diabetes mellitus; RR, relative risk; CI, confidence interval.

to 69.7% T2DM [RR 1.54 (1.52, 1.57)], and was 45.2% in mothers without diabetes.

The most common maternal complications were hypertension, obstetrical complications and anaemia, and anaemia was more common both during pregnancy and up to 3 months post-partum. Mothers with T2DM had significantly greater risk for all categories of complications evaluated (anaemia, hypertension, depression, infection, migraine, and cardiac, respiratory or obstetrical complications) *versus* non-diabetes patients. Mothers with GDM likewise had statistically greater risk of complications than non-diabetes patients in almost all of the categories assessed, with the exception of migraine in progressing GDM. The proportions of mothers with T1DM who experienced hypertension (47.4%), obstetrical (17.8%) or respiratory (0.8%) complications were significantly greater than non-diabetes patients (RRs in Table 2); no other significant difference was seen with T1DM for the remaining complications evaluated.

Neonatal complications

The proportions of neonates experiencing infection, respiratory complications, macrosomia or congenital or 'major' congenital complications ('any' and grouped by organ system) were evaluated in all pregnancies, excluding unknown outcomes (*n* values in Table 3). Risk of infection-related complications ranged from 4.4% with T1DM [RR 2.06 (1.36, 3.13)] to 2.5% with GDM [RR 1.19 (1.10, 1.27)], and neonates of mothers of all diabetes types were at significantly greater risk *versus* non-diabetes (2.1%). Risk of respiratory complications was significantly greater with progressing GDM [5.6%; RR 1.45 (1.11, 1.88)] and T2DM [5.1%; RR 1.33 (1.16, 1.52)] *versus* non-diabetes (3.8%). Macrosomia was significantly more prevalent among neonates of mothers with T1DM or T2DM; risk was greatest with T1DM.

Congenital complications of 'any' type occurred in approximately 15–19% of neonates of mothers with diabetes and 13% of neonates of non-diabetes patients. Major congenital complications ('any') occurred in approximately 7-11% of neonates of mothers with diabetes and 6% of neonates of non-diabetes patients. Diagnosis codes for issues that were considered to be 'major' congenital complications are presented in Table S3. The most common types of congenital complications were heart or circulatory related (Table 3).

Risk was significantly elevated with T2DM for the following organ system congenital complications: circulatory (RR 2.58), cleft (RR 2.00), digestive (RR 1.79), face (RR 1.61), heart (RR 2.16), integument (RR 1.50), nervous system (RR 1.72) and 'other' (RR 2.41) congenital complications *versus* non-diabetes (Table 3). Risk was also significantly elevated with T2DM for major circulatory (RR 2.75), major cleft (RR 2.00), major digestive (RR 2.19), major heart (RR 2.17) and major nervous system (RR 1.89) congenital complications.

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Table 3. Neonatal complications

Complication *n*, % RR [95% CI]	Non-diabetes *n* = 353 599	T1DM *n* = 482	T2DM *n* = 4166	GDM *n* = 31 700	GDM (progressing) *n* = 935
Infection	7474 (2.1%)	**21** (**4.4%**) **2.06** [**1.36;3.13**]	**162** (**3.9%**) **1.84** [**1.58;2.14**]	**794** (**2.5%**) **1.19** [**1.10;1.27**]	**29** (**3.1%**) **1.47** [**1.02;2.10**]
Respiratory	13 604 (3.8%)	16 (3.3%) 0.86 [0.53;1.40]	**213** (**5.1%**) **1.33** [**1.16;1.52**]	1239 (3.9%) 1.02 [0.96;1.08]	**52** (**5.6%**) **1.45** [**1.11;1.88**]
Macrosomia	16 316 (4.6%)	**53** (**11.0%**) **2.38** [**1.85;3.07**]	**275** (**6.6%**) **1.43** [**1.27;1.61**]	1490 (4.7%) 1.02 [0.97;1.07]	38 (4.1%) 0.88 [0.64;1.20]
Congenital complications, 'any'	47 228 (13.4%)	**89** (**18.5%**) **1.38** [**1.15;1.67**]	**791** (**19.0%**) **1.42** [**1.33;1.51**]	**4670** (**14.7%**) **1.10** [**1.07;1.13**]	**165** (**17.6%**) **1.32** [**1.15;1.52**]
Alimentary	6429 (1.8%)	9 (1.9%) 1.03 [0.54;1.96]	74 (1.8%) 0.98 [0.78;1.23]	622 (2.0%) 1.08 [0.99;1.17]	12 (1.3%) 0.71 [0.40;1.24]
Chromosomal	971 (0.3%)	—	18 (0.4%) 1.57 [0.99;2.51]	**126** (**0.4%**) **1.45** [**1.20;1.74**]	2 (0.2%) 0.78 [0.19;3.11]
Circulatory	7305 (2.1%)	**25** (**5.2%**) **2.51** [**1.71;3.68**]	**222** (**5.3%**) **2.58** [**2.27;2.94**]	**800** (**2.5%**) **1.22** [**1.14;1.31**]	**37** (**4.0%**) **1.92** [**1.40;2.63**]
Cleft	510 (0.1%)	—	**12** (**0.3%**) **2.00** [**1.13;3.54**]	49 (0.2%) 1.07 [0.80;1.44]	2 (0.2%) 1.48 [0.37;5.94]
Digestive	998 (0.3%)	—	**21** (**0.5%**) **1.79** [**1.16;2.75**]	107 (0.3%) 1.20 [0.98;1.46]	2 (0.2%) 0.76 [0.19;3.03]
Eye	2631 (0.7%)	4 (0.8%) 1.12 [0.42;2.96]	33 (0.8%) 1.06 [0.76;1.50]	263 (0.8%) 1.12 [0.98;1.27]	8 (0.9%) 1.15 [0.58;2.29]
Face	1216 (0.3%)	1 (0.2%) 0.60 [0.09;4.28]	**23** (**0.6%**) **1.61** [**1.06;2.42**]	107 (0.3%) 0.98 [0.81;1.20]	**7** (**0.7%**) **2.18** [**1.04;4.56**]
Genital	5353 (1.5%)	11 (2.3%) 1.51 [0.84;2.71]	69 (1.7%) 1.09 [0.86;1.38]	516 (1.6%) 1.08 [0.98;1.18]	13 (1.4%) 0.92 [0.53;1.58]
Heart	11 261 (3.2%)	**43** (**8.9%**) **2.80** [**2.10;3.73**]	**286** (**6.9%**) **2.16** [**1.92;2.41**]	**1200** (**3.8%**) **1.19** [**1.12;1.26**]	**58** (**6.2%**) **1.95** [**1.52;2.50**]
Integument	4074 (1.2%)	5 (1.0%) 0.90 [0.38;2.15]	**72** (**1.7%**) **1.50** [**1.19;1.89**]	**413** (**1.3%**) **1.13** [**1.02;1.25**]	**18** (**1.9%**) **1.67** [**1.06;2.64**]
Musculoskeletal	11 336 (3.2%)	11 (2.3%) 0.71 [0.40;1.28]	136 (3.3%) 1.02 [0.86;1.20]	**1087** (**3.4%**) **1.07** [**1.01;1.14**]	35 (3.7%) 1.17 [0.84;1.62]
Nervous	1231 (0.3%)	2 (0.4%) 1.19 [0.30;4.76]	**25** (**0.6%**) **1.72** [**1.16;2.56**]	129 (0.4%) 1.17 [0.98;1.40]	**7** (**0.7%**) **2.15** [**1.03;4.51**]
Respiratory	1743 (0.5%)	5 (1.0%) 2.10 [0.88;5.04]	26 (0.6%) 1.27 [0.86;1.86]	179 (0.6%) 1.15 [0.98;1.34]	6 (0.6%) 1.30 [0.59;2.89]
Urinary	3093 (0.9%)	5 (1.0%) 1.19 [0.50;2.84]	46 (1.1%) 1.26 [0.95;1.69]	357 (1.1%) 1.29 [1.15;1.44]	12 (1.3%) 1.47 [0.84;2.58]
Other	1163 (0.3%)	1 (0.2%) 0.63 [0.09;4.47]	**33** (**0.8%**) **2.41** [**1.71;3.40**]	114 (0.4%) 1.09 [0.90;1.32]	3 (0.3%) 0.98 [0.31;3.02]
Major congenital complications, 'any'	20 977 (5.9%)	**55** (**11.4%**) **1.92** [**1.50;2.47**]	**454** (**10.9%**) **1.84** [**1.68;2.01**]	**2203** (**6.9%**) **1.17** [**1.12;1.22**]	**89** (**9.5%**) **1.60** [**1.32;1.96**]
Major alimentary	1086 (0.3%)	1 (0.2%) 0.68 [0.10;4.79]	16 (0.4%) 1.25 [0.76;2.05]	114 (0.4%) 1.17 [0.97;1.42]	2 (0.2%) 0.70 [0.17;2.78]
Major circulatory	5314 (1.5%)	**17** (**3.5%**) **2.35** [**1.47;3.75**]	**172** (**4.1%**) **2.75** [**2.37;3.19**]	**569** (**1.8%**) **1.19** [**1.10;1.30**]	**29** (**3.1%**) **2.06** [**1.44;2.96**]
Major cleft	510 (0.1%)	—	**12** (**0.3%**) **2.00** [**1.13;3.54**]	49 (0.2%) 1.07 [0.80;1.44]	2 (0.2%) 1.48 [0.37;5.94]

(Continues)

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Table 3. (Continued)

Complication *n*, % RR [95% CI]	Non-diabetes *n* = 353 599	T1DM *n* = 482	T2DM *n* = 4166	GDM *n* = 31 700	GDM (progressing) *n* = 935
Major digestive	426 (0.1%)	—	**11 (0.3%)**	50 (0.2%)	1 (0.1%)
			2.19 [1.21;3.98]	1.31 [0.98;1.75]	0.89 [0.12;6.31]
Major eye	165 (0.0%)	—	—	14 (0.0%)	—
				0.95 [0.55;1.63]	
Major face	54 (0.0)%	—	1 (0.0%)	8 (0.0%)	**2 (0.2%)**
			1.57 [0.22;11.4]	1.65 [0.79;3.47]	**14.0 [3.42;57.4]**
Major genital	1713 (0.5%)	4 (0.8%)	24 (0.6%)	**185 (0.6%)**	4 (0.4%)
		1.71 [0.64;4.55]	1.19 [0.80;1.78]	**1.20 [1.04;1.40]**	0.88 [0.33;2.35]
Major heart	10 661 (3.0%)	**38 (7.9%)**	**272 (6.5%)**	**1129 (3.6%)**	**51 (5.5%)**
		2.61 [1.93;3.55]	**2.17 [1.93;2.43]**	**1.18 [1.11;1.25]**	**1.81 [1.38;2.36]**
Major musculoskeletal	2370 (0.7%)	1 (0.2%)	31 (0.7%)	231 (0.7%)	8 (0.9%)
		0.31 [0.04;2.19]	1.11 [0.78;1.58]	1.09 [0.95;1.24]	1.28 [0.64;2.55]
Major nervous	585 (0.2%)	1 (0.2%)	**13 (0.3%)**	64 (0.2%)	**5 (0.5%)**
		1.25 [0.18;8.90]	**1.89 [1.09;3.27]**	1.22 [0.94;1.58]	**3.23 [1.34;7.78]**
Major respiratory	86 (0.0%)	—	2 (0.0%)	6 (0.0%)	—
			1.97 [0.49;8.02]	0.78 [0.34;1.78]	
Major urinary	2257 (0.6%)	3 (0.6%)	28 (0.7%)	260 (0.8%)	9 (1.0%)
		0.98 [0.32;3.02]	1.05 [0.73;1.53]	1.28 [1.13;1.46]	1.51 [0.79;2.89]

n = neonates from all pregnancies within each diabetes category. Complication rates are reported for all neonates from all pregnancies. Bolded text indicates statistical significance. T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; GDM; gestational diabetes mellitus; RR, relative risk; CI, confidence interval.

Pregnancy costs

Medical costs were evaluated in pregnancies that did not end in miscarriages, excluding unknown outcomes; see *n* values in Table 4. Costs presented were not adjusted for inflation; inflation-adjusted results did not change materially. Mean medical costs (pharmacy, inpatient, outpatient and total) were higher in patients with diabetes than without diabetes, with the highest total cost seen in T1DM patients. The largest cost difference was for mean outpatient costs in T1DM ($10 226) *versus* non-diabetes ($3964). Mean pharmacy costs ($3604) were also highest with T1DM. Women with GDM had the lowest mean costs of the diabetes patients. Costs for women with GDM remained higher than mean costs for women without diabetes.

Discussion

In this study, we aimed to evaluate health outcomes and medical costs associated with diabetes in pregnancy. Adverse pregnancy outcomes, rates of complications and costs were higher for mothers with diabetes and their newborns, particularly in association with T2DM. In line with recent epidemiological reports, a gradual increase in T2DM and GDM prevalence was observed over time in this retrospective cohort analysis. The proportions of women with T1DM, T2DM or GDM were likewise in accord with those expected in a typical US sample of women of child-bearing age [1,9,11,12], and the exploration of 'progressing GDM' may provide unique data to the literature on the impact of diabetes post-pregnancy. The extremely large population included within this study, along with the relative homogeneity of the patient population and the strength of the methods used to confirm their type of diabetes, validates the results.

Pregnancy complications known to occur more frequently in diabetes patients include miscarriage, Caesarean delivery, birth trauma, foetal death and congenital malformations [13–19]. These adverse outcomes are reported to occur up to three to nine times more frequently in infants of mothers with diabetes *versus* infants of mothers without diabetes [23]. In the present study, T2DM was associated with a significantly higher risk of adverse delivery outcomes and all types of maternal complications assessed, as well as a number of serious neonatal complications. While a significant difference *versus* non-diabetes was observed for fewer maternal and neonatal complications with T1DM than for T2DM, patients with T1DM showed the highest risk for C-section and early delivery. GDM appeared to be

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Table 4. Pregnancy costs

	Non-diabetes $n = 773\,751$	T1DM $n = 1125$	T2DM $n = 10\,136$	GDM $n = 52\,848$	GDM (progressing) $n = 1932$
Pregnancies that did not end in miscarriages (excluding unknown), *n*	586 875	783	6665	49 254	1618
Mean total medical cost, $ (SD)	14 355 (14 544)	27 531 (16 296)	22 739 (20 435)	17 778 (14 738)	23 055 (20 587)
p value		<0.0001	<0.0001	<0.0001	<0.0001
Pharmacy	481 (1453)	3604 (2718)	1742 (2804)	842 (1744)	1257 (1842)
p value		<0.0001	<0.0001	<0.0001	<0.0001
Inpatient	9909 (12 442)	13 701 (12 820)	13 014 (16 826)	11 178 (11 881)	14 023 (18 665)
p value		<0.0001	<0.0001	<0.0001	<0.0001
Outpatient	3964 (5566)	10 226 (6447)	7983 (7822)	5758 (6173)	7776 (5917)
p value		<0.0001	<0.0001	<0.0001	<0.0001

p value is *versus* non-diabetes for each cost category (total, pharmacy, inpatient and outpatient). *n* = total pregnancies within each diabetes category. Data are reported for pregnancies that did not end in miscarriages, excluding unknown outcomes. Total cost = sum of pharmacy, inpatient and outpatient costs, tallied from estimated pregnancy start date to 3 months after delivery; sum may not equal total due to rounding. SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; GDM; gestational diabetes mellitus.

less clearly associated with adverse outcomes than T2DM or T1DM, although C-section and early delivery occurred more commonly than for women without diabetes. Rates of adverse pregnancy outcomes were comparable to those previously reported [14–19]; however, it is difficult to make precise comparisons, because outcome classification may differ slightly from study to study, and unlike here, pre-existing diabetes is often reported in the literature as a single category, meaning that it is not always possible to distinguish T1DM from T2DM data. The low observed rate for GDM in this study may have resulted because miscarriage might occur earlier in pregnancy than the time point at which GDM would normally be detected.

Most maternal complications were significantly higher with all diabetes types, again confirming the available literature [10,24,25]. Proportions of maternal and neonatal complications appeared similar for the progressing GDM and T2DM groups, which is perhaps as expected, because in many cases, patients with GDM are eventually diagnosed with T2DM (it is estimated that up to 60% of women with a pregnancy affected by GDM will develop T2DM within 5–10 years) [24]. Rates of congenital complications were comparable to results previously reported, and major circulatory, major heart and infection-related neonatal complications were significantly more common in all diabetes types than in non-diabetes. It is also important to note that approximately 28% of the individuals without diabetes had hypertension, and this exceeds the estimated 3–10% reported in other studies [26]. This may be the result of a greater proportion of individuals filing insurance claims, but further research would be required to confirm this hypothesis.

In this analysis, costs were elevated in women with diabetes, as expected. Perhaps due in large part to drug costs, patients with T1DM had the highest total mean costs, followed by patients with T2DM and then by progressing GDM. GDM patients had the lowest overall costs of patients with diabetes, but their costs were still approximately 25% greater than for those without diabetes, in accord with previous reports [27]. That fact was potentially related to the shorter length of time in which drug therapy is indicated (as GDM tends to be diagnosed later in pregnancy) and perhaps associated with the generally lower rates of complications observed for this group in this study.

Limitations

There are few similar long-term observational database studies with which to compare the outcomes investigated in this study, and relatively little data exist regarding outcomes in pregnancies affected by T2DM. This study was a non-randomized observational study (thus, data collected were descriptive in nature) and was not designed to assess glycaemic control; however, it is presumed that the patients in this population had access to standard medical care throughout pregnancy, as enrolment in a health plan with prescription coverage was requisite for inclusion. In terms of delivery outcomes, Truven MarketScan states that diagnosis codes for the child are sometimes instead assigned to the mother and no record for the child is ever created. This mostly happens for uneventful deliveries, but it is unclear how or to what extent this may bias results derived from infant data. A notable percentage (5–15%) of patients had coded deliveries with unclear status.

Codes for the various complications and pregnancy outcomes reported here were selected based on a literature search for common and serious complications of pregnancy and are not intended to be all-encompassing; these codes were selected for clinical relevance and may not

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capture all possible differences between the populations studied. Limited data on patients' medical history and concomitant medications during the study period restrict the ability to identify possible deficiencies in therapy or to design improved treatment strategies; however, trends were noted in terms of the impact of diabetes during pregnancy.

The only data included in this analysis were obtained from individuals who have insurance and therefore do not represent the entire US population. In addition, the reported miscarriage rates may not be accurate because all of them may not have been entered into the records. It is also important to note that race/ethnicity and BMI data, both of which can have an effect on perinatal outcomes, were not included.

Conclusions

Adverse pregnancy outcomes, maternal complications and neonatal complications appear significantly more frequently in association with diabetes. Costs of healthcare, including pharmacy, inpatient and outpatient expenses, are also higher in pregnancies complicated by diabetes. These data highlight a public health concern and call for optimizing diabetes management in pregnancy. Diabetes (particularly T2DM and GDM) has increased in prevalence and may in turn affect more women at younger ages; therefore, increased efforts are necessary for good access to prenatal care and improved glycaemic control throughout pregnancy, so that complications and costs may be minimized.

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Author contributions

N. W., W. W. and Y. L. were involved in the design of the study, and Y. L. provided the statistical analysis. L. J., Y. L., W. W., M. H., L. C. and N. W. contributed to the interpretation of the data. All authors gave input on, reviewed and approved the final manuscript.

Conflict of interest

L. J. is a member of an international scientific advisory board for Novo Nordisk Inc. M. H., W. W. and N. W. are employees of Novo Nordisk Inc. L. C. was an employee of Novo Nordisk Inc. at the time the analysis was performed and the manuscript was developed. Y. L. is an employee of Kelly Services, sponsored by Novo Nordisk Inc.

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References

1. US Centers for Disease Control and Prevention. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed April 30, 2015.
2. US Centers for Disease Control and Prevention. Diabetes report card 2012. http://www.cdc.gov/diabetes/pubs/pdf/diabetesreportcard.pdf. Accessed March 31, 2014.
3. Martin JA, Hamilton BE, Ventura SJ, Osterman MJK, Mathews TJ. Births: final data for 2011. *Natl Vital Stat Rep* 2013; **62**. http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_01.pdf. Accessed March 31, 2014.
4. US Centers for Disease Control and Prevention. More than 29 million Americans have diabetes; 1 in 4 doesn't know [press release]. June 10, 2014. http://www.cdc.gov/media/releases/2014/p0610-diabetes-report.html. Accessed June 16, 2014.
5. Coustan DR, Lowe LP, Metzger BE, Dyer AR. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. *Am J Obstet Gynecol* 2010; **202**: 654–656.
6. Lenhard MJ, Kinsley BT. Insulin therapy for the treatment of type 1 diabetes during pregnancy. *J Matern Fetal Neonatal Med* 2014; **27**: 1270–1275.
7. Razzaghi H, Marcinkevage J, Peterson C. Prevalence of undiagnosed diabetes among non-pregnant women of reproductive age in the United States, 1999–2010. *Prim Care Diabetes* 2013; **9**: 71–73.
8. American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care* 2013; **36**(suppl 1): S11–S66.
9. Wier LM, Witt E, Burgess J, Elixhauser A. Hospitalizations related to diabetes in pregnancy, 2008. Healthcare cost and utilization project statistical brief #102, December 2010. https://www.hcup-us.

ahrq.gov/reports/statbriefs/sb102.pdf. Accessed March 31, 2014.
10. Getahun D, Nath C, Ananth CV, Chavez MR, Smulian JC. Gestational diabetes in the United States: temporal trends 1989 through 2004. *Am J Obstet Gynecol* 2008; **198**: 525.
11. Albrecht SS, Kuklina EV, Bansil P, *et al*. Diabetes trends among delivery hospitalizations in the U.S., 1994–2004. *Diabetes Care* 2010; **33**: 768–773.
12. Bell R, Bailey K, Cresswell T, Hawthorne G, Critchley J, Lewis-Barned N. Trends in prevalence and outcomes of pregnancy in women with pre-existing type I and type II diabetes. *BJOG* 2008; **115**: 445–452.
13. Buchanan T. Pregnancy in preexisting diabetes. In: *Diabetes in America*, *2nd Edn* US National Institutes of Health, National Diabetes Information Clearinghouse: Bethesda, MD, 1995; 719–734. http://diabetes.niddk.nih.gov/dm/pubs/america/pdf/chapter36.pdf. Accessed March 31, 2014.
14. Balsells M, Garcia-Patterson A, Gich I, Corcoy R. Maternal and fetal outcome in women with type 2 versus type 1 diabetes mellitus: a systematic review and metaanalysis. *J Clin Endocrinol Metab* 2009; **94**: 4284–4291.
15. Correa A, Gilboa SM, Besser LM, *et al.* Diabetes mellitus and birth defects. *Am J Obstet Gynecol* 2008; **199**: 237–239.
16. Flenady V, Koopmans L, Middleton P, *et al*. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011; **377**: 1331–1340.
17. Hunt KJ, Marlow NM, Gebregziabher M, *et al*. Impact of maternal diabetes on birthweight is greater in non-Hispanic Blacks than in non-Hispanic Whites. *Diabetologia* 2012; **55**: 971–980.
18. Balsells M, Garcia-Patterson A, Gich I, Corcoy R. Major congenital malformations in women with gestational diabetes mellitus: a systematic review and meta-analysis. *Diabetes Metab Res Rev* 2012; **28**: 252–257.
19. Rosenstein MG, Cheng YW, Snowden JM, Nicholson JM, Doss AE, Caughey AB. The risk of stillbirth and infant death stratified by gestational age in women with gestational diabetes. *Am J Obstet Gynecol* 2012; **206**: 309.e1–309.e7.
20. American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care* 2014; **37**(suppl 1): S14–S80.
21. Rodbard HW, Blonde L, Braithwaite SS, *et al*. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract* 2007; **13**(suppl 1): 1–68.
22. American Diabetes Association. Management of diabetes in pregnancy. Sec 12. *In* Standards of Medical Care in Diabetes—2015. *Diabetes Care* 2015; **38**(Supplement 1): S77–S79.
23. Yang J, Cummings EA, O'Connell C, Jangaard K. Fetal and neonatal outcomes of diabetic pregnancies. *Obstet Gynecol* 2006; **108**: 644–650.
24. Katon J, Williams MA, Reiber G, Miller E. Antepartum A1C, maternal diabetes outcomes, and selected offspring outcomes: an epidemiological review. *Paediatr Perinat Epidemiol* 2011; **25**: 265–276.
25. Negrato CA, Mattar R, Gomes MB. Adverse pregnancy outcomes in women with diabetes. *Diabetol Metab Syndr* 2012; **4**: 41.
26. Rajagambeeram R, Abu RS, Ghosh S, Basu S, Ramasamy R, Murugaiyan SB. Diagnostic utility of heat stable alkaline phosphatase in hypertensive disorders of pregnancy. *J Clin Diagn Res* 2014; **8**: CC10–CC13.
27. Kolu P, Raitanen J, Rissanen P, Luoto R. Health care costs associated with gestational diabetes mellitus among high-risk women–results from a randomised trial. *BMC Pregnancy Childbirth* 2012; **12**: 71.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site.

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