Association of types of diabetes and insulin dependency on birth outcomes

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**Abstract**

**BACKGROUND**

Diabetes rates among pregnant women in the United States have been increasing and are associated with adverse pregnancy outcomes.

**AIM**

To investigate differences in birth outcomes (preterm birth, macrosomia, and neonatal death) by diabetes status.

**METHODS**

Cross-sectional design, using linked Missouri birth and death certificates (singleton births only), 2010 to 2012 (n = 204057). Exposure was diabetes (non-diabetic, pre-pregnancy diabetes-insulin dependent (PD-I), pre-pregnancy diabetes-non-insulin dependent (PD-NI), gestational diabetes-insulin dependent (GD-I), and gestational diabetes-non-insulin dependent (GD-NI)]. Outcomes
included preterm birth, macrosomia, and infant mortality. Confounders included demographic characteristics, adequacy of prenatal care, body mass index, smoking, hypertension, and previous preterm birth. Bivariate and multivariate logistic regression assessed differences in outcomes by diabetes status.

RESULTS
Women with PD-I, PD-NI, and GD-I remained at a significantly increased odds for preterm birth (aOR 2.87, aOR 1.77, and aOR 1.73, respectively) and having a very large baby [macrosomia] (aOR 3.01, aOR 2.12, and aOR 1.96, respectively); in reference to non-diabetic women. Women with GD-NI were at a significantly increased risk for macrosomia (aOR1.53), decreased risk for their baby to die before their first birthday (aOR 0.41) and no difference in risk for preterm birth in reference to non-diabetic women.

CONCLUSION
Diabetes is associated with the poor birth outcomes. Clinical management of diabetes during pregnancy and healthy lifestyle behaviors before pregnancy can reduce the risk for diabetes and poor birth outcomes.

Key Words: Epidemiology; Pregnancy; Health care delivery; Birth outcomes; Gestational diabetes; Insulin

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Core Tip: This study investigated the differences in birth outcomes by timing of diabetes (pre-gestational and gestational) status and insulin use. The odds for preterm birth (PTB) and macrosomia were the most increased (187% and 201%, respectively) among women with insulin-dependent pre-pregnancy diabetes, followed by non-insulin dependent pre-pregnancy diabetes (77% and 112%, respectively) in comparison with women without diabetes. Women with insulin dependent gestational diabetes were also at an increased risk for PTB and macrosomia (73% and 95%, respectively). Clinical management of diabetes during pregnancy and healthy lifestyle behaviors before pregnancy can reduce the risk for diabetes and poor birth outcomes.

INTRODUCTION
Diabetes mellitus (DM) rates in the United States have been increasing and women with diabetes in pregnancy have high rates of congenital anomalies, preeclampsia, preterm delivery, macrosomia, and perinatal mortality[1-7]. In the United States, approximately seven percent of pregnancies are affected by DM, a condition in which a woman’s blood glucose levels are above normal. Traditionally, DM has been classified into one of three categories: Type 1 diabetes, type 2 diabetes, and gestational diabetes (GDM)[8]. All three forms result in the body’s inability to produce enough insulin, the hormone responsible for cells taking in sugar from the bloodstream to be stored and later used as energy. Type 1 diabetes accounts for about 5% of all diabetes cases, mainly caused by the autoimmune system’s attack on beta cells that create insulin-dependence, the etiology of which involves both genetic and environmental risk factors. Type 2 diabetes is not an autoimmune condition, but rather a metabolic condition often related to obesity, a sedentary lifestyle and poor diet, where the body loses its ability to respond to insulin, creating insulin-resistance[9,10]. GDM is diabetes that is diagnosed in a woman during pregnancy and accounts for about 85% of diabetes cases among pregnant women, also associated with genetic and environmental factors, with incidence rates also rising[11-13]. As the prevalence of DM is increasing among women, so too grows the public health threat this health condition poses to pregnancy and birth outcomes[14,15].

The effect of insulin resistance on birth outcomes has been well documented. For example, Klemetti et al[16] analyzed hospital data from 881 pregnant patients with type 1 diabetes, over a ten-year span (1998-2008), and found that poor glycemic control was associated with increases in emergency caesarean sections, macrosomia, and Neonatal Intensive Care Unit (NICU) admission rates. One large population study in Denmark found that among women with type 1 diabetes, those with the greatest glycemic control before pregnancy had the lowest risk for poor birth outcomes, including perinatal mortality and
serious adverse outcomes[17]. Others report that when evaluating type 2 diabetes, those with preconception care had lower rates of fetal malformations than those without preconception care[18]. A large meta-analysis supports the claim that there is evidence of increased pre-eclampsia, cesarean delivery, and macrosomia for women with type 1 diabetes that have poor glycemic control[19]. Conversely, strong glucose control among type 1 diabetes has been associated with decreased risk for perinatal mortality, decreased maternal hypoglycemia, and normal fetal weight[20-22].

There is an important gap in the published literature, however, regarding population level studies of diabetes during pregnancy. For example, several large cohort studies of birth certificate data have reported an association between diabetes and birth outcomes, although differences in birth outcomes between diabetes types have rarely been reported[5,15,23,24]. Further, when types of DM have been compared, the results have been inconsistent[6]. For example, one study comparing type 1 diabetes to type 2 diabetes reported pregnant women with type 1 diabetes had an increased risk for preterm birth, large for gestational age, and hypertension[25]. Others have reported no differences between pregnant women with type 1 diabetes and type 2 diabetes as it relates to rates of congenital malformations and perinatal mortality[26,27]. Still another study found that still births and congenital anomalies were highest in the type 1 diabetes group with the lowest glycemic levels, although women with GDM were not included in that study[28]. One population-based study in France reported that preterm birth and macrosomia rates were significantly higher for women with type 1 diabetes (ORs 5.8 and 7.7, respectively), type 2 diabetes (ORs 3.1 and 3.8, respectively), and GDM (ORs 1.2 and 1.8, respectively). Further, in that study, there was 95% confidence that the odds of perinatal mortality for women with type 1 diabetes were comparable with non-diabetic women (OR 1.8, 95% CI: 1.0, 3.1), yet significantly higher for women with type 2 diabetes (OR 3.9, 95% CI: 2.1, 7.4) and significantly lower yet for women with GDM (OR 0.70, 95% CI: 0.60, 0.80)[29]. A major limitation to that population based study in France was that they did not have any data on body mass index, an important variable related to diabetes and strong potential confounder. Given the inconsistent results of these previous studies, additional research is needed to clarify the differential impact of each type of DM on birth outcomes.

Understanding the differential impact of prepgregnancy diabetes with and without insulin dependence and GDM can offer important clues to understanding the population impact of insulin dependence on birth outcomes in the United States. The newest United States standard birth certificate allows for the examination of DM as it is related to birth outcomes, based upon timing of DM (pregnancy DM or GDM) and pre-pregnancy DM insulin dependence (insulin dependent DM: PD-I and non-insulin dependent DM: PD-NI) and GDM insulin-dependence (GD-I) and non-insulin-dependence (GD-NI). This study will explore how birth outcomes vary for women exposed to different categories of DM, marked PD-I, PD-NI, GD-I, and GD-NI and build upon previous studies by including potentially important confounders like body mass index (BMI) (a reliable measure for population-based surveillance)[30,31].

MATERIALS AND METHODS

Study design
We conducted a population-based cross-sectional study of live, singleton births in Missouri from 2010-2012 inked with death certificate data. We removed implausible BMI categories (< 12 and > 70 BMI), resident zip codes outside the state of Missouri, and gestational age less than 20 wk, bringing our sample to 207511[32]. Cases were also removed when birth weight, race/ethnicity, marital status, smoking status, maternal education, and maternal age were missing (1.7%), resulting in a final sample of 204057. Listwise deletion was used, as there was sufficient sample size to support removing data that was missing at random and the percent of cases that were removed was less than 5% of the overall sample[33,34].

Exposure
Diabetes categories were selected based upon diabetes status and insulin-dependence status identified on the birth certificate. Prepregnancy diabetes non-insulin dependent (PD-NI), or insulin dependent (PD-I), gestational diabetes-insulin dependent (GD-I) and non-insulin dependent (GD-NI) and nondiabetic. Birth certificate recorders gather DM information from prenatal records, and this data has been reported elsewhere as having moderate sensitivity[35].

Covariates
Demographic characteristics included: maternal age (< 19, 19-34, > 34), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and Other), education (less than high school, high school or GED, some college, college grad or more), adequacy of prenatal care (inadequate, intermediate, adequate, adequate plus, and unknown, based upon the Kotelchuck index), marital status, and Medicaid status. Maternal risk covariates included BMI category (< 18.5 (underweight), 18.5-24.9 (normal), 25-29.9 (overweight), ≥ 30 (obese)), smoking during pregnancy, preconception hypertension, gestational hypertension, preeclampsia, and previous preterm birth. Covariates often found to correlate with
adverse birth outcomes were selected.

**Outcomes**
Preterm birth (gestational age < 37 wk), macrosomia (birth weight > 4000 g), and infant mortality (death < 365 d of age).

**Statistical analysis**
Crude and multivariate logistic regressions were calculated to assess differences between diabetes groups in outcomes, with 99.8% confidence intervals calculated to measure precision. Bonferroni correction was used for the twenty-four 95% CIs to give a nominal confidence level of 99.8%. Chi-square tests were used to assess differences in selected covariates. Cramer’s V was used to assess the magnitude of the relationship between categorical variables where 0.1 indicates a weak relationship, 0.3 indicating a moderate relationship, and 0.5 indicating a strong relationship.

**RESULTS**
A larger proportion of non-diabetic women were under age 35, and white, non-Hispanic, when compared to diabetic women. In addition, non-diabetic women reported a higher proportion of women that received adequate prenatal care and lower proportion of women that received adequate-plus prenatal care, in comparison with diabetic women. In contrast, a significantly higher proportion of women with PD-I (51.4%), PD-NI (59.4%), GD-I (64.4%) and GD-NI (46.1%) reported 30+ BMI category (obese) and a lower proportion of normal weight gain during pregnancy (20.2%, 21.3%, 20.4%, and 25.8%, respectively) in comparison with non-diabetic women (22.5% and 28.2%, respectively) (Table 1).

Table 2 presents the crude and adjusted odds ratios for the relationship of diabetes status to each birth outcome. PD-I, PD-NI, GD-I, and GD-NI were significantly associated with an increased risk for preterm birth [cOR 4.15 (95% CI: 3.22, 5.34); cOR 2.45 (95% CI: 1.85, 3.24); cOR 2.54 (95% CI: 1.91, 3.39); and cOR 1.41 (95% CI: 1.27, 1.56); respectively]. PD-I, PD-NI, GD-I, and GD-NI were significantly associated with an increased risk for macrosomia [cOR 3.12 (95% CI: 2.19, 3.77); cOR 2.32 (95% CI: 1.74, 3.10); cOR 2.15 (95% CI: 1.58, 2.92); and cOR 1.57 (95% CI: 1.42, 1.74), respectively]. The risk for infant mortality was significantly decreased for women in the GD-NI category [PD-I: cOR 1.87 (95% CI: 0.66, 5.28); PD-NI: cOR 1.90 (95% CI: 0.71, 5.10); GD-I: cOR 1.62 (95% CI: 0.54, 4.88); and GD-NI: cOR 0.51 (95% CI: 0.29, 0.89)], in reference to non-diabetic women. There were significantly different crude odds between both the PD-I and GD-NI categories for preterm birth and macrosomia, in comparison to all other preterm birth categories, while the PD-NI and GD-I categories were non-significantly different from each other. Only women within the GD-NI category had significantly different infant mortality rate in reference to non-diabetic women.

Table 2 also presents the adjusted odds ratios for the relationship of diabetes status to each birth outcome, adjusted for maternal age, race/ethnicity, maternal education, marital status, BMI. In the adjusted model, preterm birth remained significantly associated in three of the four categories: PD-I (2.87, 95% CI: 2.19, 3.77), PD-NI (1.77, 95% CI: 1.31, 2.39), GD-I (1.73, 95% CI: 1.27, 2.35), while there was no significant difference in the GD-NI category (1.07, 95% CI: 0.96, 1.19). Macrosomia also remained significantly associated with all four categories: PD-I (3.01, 95% CI: 2.26, 4.01), PD-NI (2.12, 95% CI: 1.57, 2.86), GD-I (1.96, 95% CI: 1.42, 2.70), and GD-NI (1.53, 95% CI: 1.39, 1.70). Women with GD-NI were found to have a significantly lower risk for infant mortality [aOR 0.41 (0.23, 0.72)] in reference to non-diabetic women. There were significantly different adjusted odds between both the PD-I and GD-NI categories for preterm birth and macrosomia, in comparison to all other preterm birth categories, while the PD-NI and GD-I categories were non-significantly different from each other.

**DISCUSSION**
This large population-based study found that women with pregestational DM had the highest increased risk for preterm birth and macrosomia, with the highest risk for women with insulin dependent pre-pregnancy diabetes, in reference to non-diabetic women. Statistically, there was no significant difference between the risks for preterm birth and macrosomia among women with PD-NI and GD-I. Interestingly, women with gestational diabetes that had no insulin-dependence were at a 59% reduced risk for infant mortality in comparison with women without diabetes. These findings are fairly comparable to the large population-based study in France, although our odds are slightly lower perhaps due to our ability to include BMI in our adjusted model[33]. With the growing prevalence of DM, the differential impact of type of diabetes on birth outcomes is important to identify so evidence-based plans can be implemented to reduce the deleterious impact of this growing public health crisis.

Interestingly, differences in risks between types of DM seem to reflect differences in timing of DM (pre-pregnancy vs gestational) and insulin use. For example, the odds for preterm birth and macrosomia
Table 1 Distribution of demographic factors and birth outcomes by diabetes status (n = 203222)

|                        | Overall | Non-diabetic | PD-I | PD-NI | GD-I | GD-NI | Chi-Square | Cramer's V |
|------------------------|---------|--------------|------|-------|------|-------|-------------|------------|
| **n**                  | 204057  | 192329       | 733  | 0.40% | 798  | 0.40% | 742         | 0.40%      | 9455       | 4.60%      |
| **%**                  | 100.00% | 94.40%       | 4.20%| 3.10% | 7.90%| 5.40% | 3.70%       | 2.70%      | 4.10%      |
| **Age**                |         |              |      |       |      |       |             |            |            |
| ≤ 19                   | 19374   | 18915        | 31   | 4.20% | 25   | 3.10% | 20          | 2.70%      | 383        | 4.10%      |
| 20-34                  | 163515  | 154633       | 553  | 74.90%| 598  | 75.90%| 563         | 75.90%     | 7168       | 75.80%     |
| ≥ 35                   | 21168   | 18781        | 149  | 20.30%| 175  | 21.90%| 159         | 21.40%     | 1904       | 20.10%     |
| **Race**               |         |              |      |       |      |       |             |            |            |
| White Non-Hispanic     | 157144  | 148434       | 532  | 72.60%| 539  | 67.50%| 492         | 66.30%     | 7147       | 75.60%     |
| Black Non-Hispanic     | 30053   | 28420        | 139  | 19.00%| 182  | 22.80%| 161         | 21.70%     | 1151       | 12.20%     |
| Hispanic               | 10638   | 9813         | 41   | 5.60% | 50   | 6.30% | 60          | 8.10%      | 674        | 7.10%      |
| Other Non-Hispanic     | 6222    | 5662         | 21   | 2.90% | 27   | 3.40% | 29          | 3.90%      | 483        | 5.10%      |
| **Education**          |         |              |      |       |      |       |             |            |            |
| Less than HS           | 32650   | 30970        | 134  | 18.30%| 118  | 14.80%| 106         | 14.30%     | 1322       | 14.00%     |
| HS or GED              | 49222   | 46356        | 188  | 25.60%| 216  | 27.10%| 203         | 27.40%     | 2259       | 23.90%     |
| Some college           | 64878   | 60666        | 282  | 36.50%| 274  | 34.30%| 298         | 40.20%     | 3358       | 35.50%     |
| College grad or more   | 57307   | 54337        | 129  | 17.60%| 190  | 23.80%| 135         | 18.20%     | 2516       | 26.60%     |
| **Married/paternity**  |         |              |      |       |      |       |             |            |            |
| Married paternity      | 121764  | 114191       | 430  | 38.30%| 490  | 49.40%| 444         | 59.80%     | 6209       | 65.70%     |
| Not married            | 54920   | 52032        | 191  | 26.10%| 202  | 25.30%| 184         | 24.80%     | 2311       | 24.40%     |
| Paternity not acknowledged | 27373 | 26106       | 112  | 15.30%| 106  | 13.30%| 114         | 15.40%     | 935        | 9.90%      |
| **Adequacy of prenatal care** |     |              |      |       |      |       |             |            |            |
| Inadequate             | 26633   | 75618        | 122  | 16.60%| 187  | 23.40%| 134         | 18.10%     | 2769       | 29.30%     |
| Intermediate           | 14269   | 25365        | 57   | 7.80% | 89   | 11.20%| 89          | 12.00%     | 1033       | 10.90%     |
| Adequate               | 78830   | 15762        | 24   | 3.30% | 35   | 4.40% | 34          | 4.60%      | 414        | 4.40%      |
| Adequate plus          | 64277   | 58787        | 410  | 55.90%| 390  | 48.90%| 395         | 53.20%     | 4295       | 45.40%     |
| Unknown                | 20048   | 18797        | 97   | 12.20%| 90   | 12.10%| 944         | 10.00%     |            |            |
| Medicaid | Medicaid | < 0.0001 | 0.01 |
|----------|----------|----------|------|
| Medicaid | 96861    | 47.50%   | 91165 | 47.40% | 300 | 40.90% | 362 | 45.40% | 319 | 43.00% | 4715 | 49.90% |
| Private  | 88330    | 43.30%   | 83149 | 43.20% | 378 | 51.60% | 375 | 47.00% | 387 | 52.20% | 4041 | 42.70% |
| Other    | 9697     | 4.80%    | 9244  | 4.80%  | 23  | 3.10%  | 27  | 3.40%  | 20  | 2.70%  | 383  | 4.10%  |
| Missing  | 9169     | 4.50%    | 8771  | 4.60%  | 32  | 4.40%  | 34  | 4.30%  | 16  | 2.20%  | 316  | 3.30%  |
| Smoking during pregnancy | 0.002 | 0.01 |
| No       | 153347   | 75.10%   | 144659| 75.20% | 506 | 69.00% | 585 | 73.30% | 539 | 72.60% | 7058 | 74.60% |
| Yes      | 50710    | 24.90%   | 47670 | 24.80% | 227 | 31.00% | 213 | 26.70% | 203 | 27.40% | 2397 | 25.40% |
| Hypertension (prepregnancy gestational eclampsia) | < 0.0001 | 0.06 |
| Yes      | 10862    | 5.30%    | 182744| 95.00% | 639 | 87.20% | 712 | 89.20% | 628 | 84.60% | 8472 | 89.60% |
| No       | 193195   | 94.70%   | 9585  | 5.00%  | 94  | 12.80% | 86  | 10.80% | 114 | 15.40% | 983  | 10.40% |
| Sexually transmitted infection | 0.004 | 0.01 |
| Yes      | 2055     | 1.00%    | 1911  | 1.00%  | 5   | 0.70%  | 16  | 2.00%  | 13  | 1.80%  | 110  | 1.20%  |
| No       | 202002   | 99.00%   | 190418| 99.00% | 728 | 99.30% | 782 | 98.00% | 729 | 98.20% | 9345 | 98.80% |
| Previous preterm birth | < 0.0001 | 0.04 |
| Yes      | 6321     | 3.10%    | 5697  | 3.00%  | 66  | 9.00%  | 59  | 7.40%  | 50  | 6.70%  | 449  | 4.70%  |
| No       | 197736   | 96.90%   | 186632| 97.00% | 667 | 91.00% | 739 | 92.60% | 692 | 93.30% | 9006 | 95.30% |
| BMI category | < 0.0001 | 0.08 |
| Underweight | 9037  | 4.40%   | 8812  | 4.60%  | 6   | 0.80%  | 5   | 0.60%  | 5   | 0.70%  | 209  | 2.20%  |
| Normal weight | 97666 | 47.90%  | 94641 | 49.20% | 177 | 24.10% | 163 | 20.40% | 100 | 13.50% | 2585 | 27.30% |
| Overweight | 48393 | 23.70%  | 45603 | 23.70% | 173 | 23.60% | 156 | 19.50% | 159 | 21.40% | 2302 | 24.30% |
| Obese    | 48961    | 24.00%   | 43273 | 22.50% | 377 | 51.40% | 474 | 59.40% | 478 | 64.40% | 4359 | 46.10% |
| Weight gain | < 0.0001 | 0.03 |
| Normal gain | 57096 | 28.00%  | 54188 | 28.20% | 148 | 20.20% | 170 | 21.30% | 151 | 20.40% | 2439 | 25.80% |
| Under gain | 36867 | 18.10%  | 34032 | 17.70% | 117 | 16.00% | 172 | 21.60% | 157 | 21.20% | 2389 | 25.30% |
| Over gain | 103203  | 50.60%   | 97568 | 50.70% | 444 | 60.60% | 417 | 52.30% | 413 | 55.70% | 4361 | 46.10% |
| Missing  | 6891     | 3.40%    | 6541  | 3.40%  | 24  | 3.30%  | 39  | 4.90%  | 21  | 2.80%  | 266  | 2.80%  |
| Preterm birth | < 0.0001 | 0.06 |
Table 2 Crude and adjusted relationship of diabetes status with birth outcomes

|                     | Preterm birth | Macrosomia | Infant mortality |
|---------------------|---------------|------------|-----------------|
|                     | cOR 95%CI     | aOR 95%CI  | cOR 95%CI       | aOR 95%CI        | cOR 95%CI | aOR 95%CI |
| Non-diabetic        | ref           | ref        | ref             | ref              | ref       | ref       |
| PD-I                | 4.15          | 3.22, 5.34 | 2.87            | 3.21, 3.77       | 3.12      | 2.37, 4.11 |
| PD-NI               | 2.45          | 1.85, 3.24 | 1.77            | 1.31, 2.39       | 2.32      | 1.74, 3.10 |
| GD-I                | 2.54          | 1.91, 3.39 | 1.73            | 1.27, 2.35       | 2.15      | 1.58, 2.92 |
| GD-NI               | 1.41          | 1.27, 1.56 | 1.07            | 0.96, 1.19       | 1.57      | 1.42, 1.74 |

PD-I: Pre-pregnancy diabetes-insulin dependent; PD-NI: Pre-pregnancy diabetes-non-insulin dependent; GD-I: Gestational diabetes-insulin dependent; GD-NI: Gestational diabetes-non-insulin dependent.

were higher when there was insulin-dependence, among women with pre-pregnancy diabetes (PTB: 187% vs 77%; Macrosomia: 126% vs 57%) and among women with gestational diabetes (PTB: 73% vs 9%; Macrosomia: 96% vs 53%) in comparison with women without diabetes. The risks were significantly higher when comparing insulin dependence within the gestational categories, because the 99.8% confidence intervals did not overlap between gestational categories, and further, there was no difference in risk for preterm birth between women without diabetes and women with non-insulin dependent gestational diabetes. These results reflect similar findings among other published studies, that is, more severe adverse birth outcomes are associated with worsening glycemic control. While measures of glycemic control are not provided in the birth certificate data used for this study, glycemic control is often harder to achieve in women with absolute insulin resistance, perhaps explaining the difference in...
poor birth outcomes among insulin use in comparison with non-insulin dependent women[36].

It is notable that women with GD-NI were found to be at a 59% significantly decreased odds for infant death in comparison with non-diabetic women, even after adjusting for socio-demographic, behavioral, and biological differences. This finding is consistent with a study in France, that found a 30% reduction in perinatal mortality among women with GDM in comparison with non-diabetic women[33]. Diagnosis of GDM is usually based upon results from oral glucose tolerance tests often conducted between the 24th and 28th week of gestation. Treatment is designed to lower glucose concentrations and typically involves high-risk obstetric management, including behavioral changes, nutritional plans, or insulin, as needed[37]. In the large population-based study from France discussed earlier, when their sample was limited to full-term deliveries that excluded cases of undiagnosed pregestational diabetes, the odds of perinatal mortality reversed from being decreased to being increased when compared with non-diabetic women. This led the authors to speculate that the timing and delivery of treatment may play a pivotal role in reducing risks for infant mortality. We similarly speculate that timing and intensity of GDM treatment play an important role in infant mortality among our study participants in the United States.

There are a number of limitations to this study, which include the possible misclassification of diabetes. First, women with PD-I or PD-NI may have first been diagnosed during pregnancy, and thus their DM status was wrongly classified as gestational. While extremely unlikely for women with PD-I, given the significant symptoms and typical younger age at onset associated with this condition, it is possible that women with PD-NI were undiagnosed before pregnancy and thus classified as GDM. In addition, it is possible that there are some women in the non-diabetic group who were diabetic. Prediabetes is also a growing population-level concern (women with prediabetes have higher blood glucose levels than normal, but not high enough to be medically diagnosed with diabetes[38]), but that data is not provided on birth certificates. Women with prediabetes are at increased risk for developing both GD and non-insulin dependent diabetes mellitus (PD-NI) later in life; this may distort the risk in the non-diabetic group, as individuals labeled as non-diabetic could be pre-diabetic (with increased risk for adverse birth outcomes). In addition, while the result for infant mortality was not significant in the PD-I, PD-NI, and GD-I categories, the point estimates were higher when compared to non-diabetic women and this may be due to the small number of people in those categories. Furthermore, there is potential for residual confounding within the data due to unmeasured behavioral risk factors, income levels, as well as other unmeasured c, that may impact the overall outcomes for these women and their babies. Also, due to the sample only coming from the state of Missouri, there is limited generalizability. Because the data set includes all Missouri births from 2010-2012, this study has strong internal validity with respect to risks of adverse birth outcomes by category of DM for women in Missouri.

CONCLUSION

As categories of diabetes differed, so too did risk for poor birth outcomes, with having insulin use among women with pre-pregnancy diabetes putting women at the highest risk for the poorest birth outcomes. Clinical management of DM and healthy lifestyle behaviors before pregnancy have been shown to improve birth outcomes, suggesting that access to preconceptional care plays an important role in reducing risks for poor birth outcomes. Clinical implications from these findings should recognize the increased risk for adverse birth outcomes for all categories of diabetes, especially for preterm birth and macrosomia. The classification schema of insulin-dependent, non-insulin dependent, and gestational diabetes may be outdated[6], yet the risks for poor birth outcomes were significantly increased based upon timing of DM onset (i.e., prepregnancy or gestational) and insulin use. We now have a better understanding of the spectrum of factors associated with different forms of DM, including age, weight, metabolic syndrome, autoimmune disease, inflammation, and c-peptide[39]. Future research should focus on maintaining proper glycemic control before pregnancy and throughout pregnancy to help reduce the risk for adverse birth outcomes. Further, findings from a large systematic review found that a diet high in fruits and vegetables, legume, nuts, whole grains, and fish before pregnancy may reduce one’s risk for developing GDM during pregnancy[40]. Future research should consider how non-pregnant women of childbearing age are assessed and provided education on management and prevention of DM, specifically as it relates to pregnancy. Increased knowledge and implementation of evidence-based standards of care during the preconceptional period could result in reduced rates of DM among women, and in turn, healthier moms and babies.
ARTICLE HIGHLIGHTS

Research background
Diabetes mellitus (DM) rates in the United States have been increasing and women with diabetes in pregnancy have high rates of congenital anomalies, preeclampsia, preterm delivery, macrosomia, and perinatal mortality. In the United States, approximately seven percent of pregnancies are affected by DM, a condition in which a woman’s blood glucose levels are above normal. The effect of insulin resistance on birth outcomes has been well documented. There is an important gap in the published literature, however, regarding population level studies of diabetes during pregnancy. For example, several large cohort studies of birth certificate data have reported an association between diabetes and birth outcomes, although differences in birth outcomes between diabetes types have rarely been reported.

Research motivation
Understanding the differential impact of pre-pregnancy diabetes with and without insulin dependence and GDM can offer important clues to understanding the population impact of insulin dependence on birth outcomes in the United States. This study explores how birth outcomes vary for women exposed based upon timing of diabetes (pre-gestational or gestational) and insulin-dependence, building upon previous studies by including potentially important confounders like BMI (a reliable measure for population-based surveillance).

Research objectives
To investigate differences in birth outcomes (preterm birth, macrosomia, and infant mortality/) by diabetes status.

Research methods
Cross-sectional design, using linked Missouri birth and death certificates [singleton births only], 2010 to 2012 (n = 204057). Exposure was diabetes (non-diabetic, pre-pregnancy diabetes-insulin dependent (PD-I), pre-pregnancy diabetes-non-insulin dependent (PD-NI), gestational diabetes-insulin dependent (GD-I), and gestational diabetes-non-insulin dependent (GD-NI)]. Outcomes included preterm birth, macrosomia, and neonatal death. Confounders included demographic characteristics, adequacy of prenatal care, BMI, smoking, hypertension, and previous preterm birth. Bivariate and multivariate logistic regression assessed differences in outcomes by diabetes status.

Research results
Women with PD-I, PD-NI, and GD-I remained at a significantly increased odds for preterm birth (aOR 2.87; aOR 1.77; and aOR 1.73, respectively) and having a very large baby (macrosomia) (aOR 3.01, aOR 2.12; aOR and 1.96; respectively); in reference to non-diabetic women. Women with GD-NI were at a significantly increased risk for macrosomia (aOR1.53), decreased risk for their baby to die before their first birthday (aOR 0.41) and no difference in risk for preterm birth in reference to non-diabetic women.

Research conclusions
As categories of diabetes differed, so too did risk for poor birth outcomes, with having insulin use among women with pre-pregnancy diabetes putting women at the highest risk for the poorest birth outcomes.

Research perspectives
Diabetes is associated with the poor birth outcomes. Clinical management of diabetes during pregnancy and healthy lifestyle behaviors before pregnancy can reduce the risk for diabetes and poor birth outcomes.

ACKNOWLEDGEMENTS
This project was completed in the epidemiology capstone course as part of the MPH degree requirements at Saint Louis University, College for Public Health and Social Justice, a course co-instructed by Pamela K Xaverius, PhD, MBA and Joanne Salas, MPH.
FOOTNOTES

Author contributions: Xaverius PK oversaw all aspects of this project including developing the research question, collecting and analyzing the data, and writing the overall manuscript; Xaverius PK and Kiel D designed the research study; Wankum E, Carter C, Fang C, and Carriere R analyzed the data; and Xaverius PK, Howard SW, and Thurman JE wrote the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: This study has been granted an exemption by the Institutional Review Board at Saint Louis University.

Conflict-of-interest statement: The authors have no financial or non-financial competing interests or conflicts of interests associated with this manuscript.

Data sharing statement: The data used in this manuscript were acquired from the Missouri Department of Health and Senior Services (MODHSS) and are not available for public access due to MODHSS guidelines. The contents of this document including data analysis, interpretation or conclusions are solely the responsibility of the authors and do not represent the official views of DHSS.

STROBE statement: The authors have read the STROBE Statement, and the manuscript was prepared and revised according to the STROBE Statement.

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

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