Association between maternal pregestational diabetes mellitus and spina bifida: A population-based case-control study, Finland, 2000-2014

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ABSTRACT

Background: Maternal pregestational diabetes mellitus (PGDM) is a known risk factor for neural tube defects. We examined the association between maternal PGDM and spina bifida in the offspring using PGDM status from medical records in Finland.

Methods: We conducted a nationally representative, multi-registry, population-based case-control study in Finland. Cases were included if they were live or stillborn infants and diagnosed with spina bifida and delivered between years 2000 and 2014 in Finland. Controls were Finnish infants without spina bifida or other major structural birth defects and delivered during the same time period as cases. Clinical and demographic data were obtained by linking multiple national health registers and census. Crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) for PGDM were estimated using logistic regression analysis. Interaction by maternal obesity was examined.

Results: Our study included 181 spina bifida cases (61% isolated) and 876,672 controls. Overall, 2.2% percent of all case, and 0.5% of control mothers, had PGDM during pregnancy. Maternal PGDM was significantly associated with an increased odds of spina bifida (adjusted OR 4.35; 95% CI 1.37, 13.82). A similar association was found in our sub-analysis on isolated spina bifida cases (adjusted OR 4.41; 95% CI 1.07, 18.24). There was no significant interaction by maternal obesity.

Conclusions: Maternal PGDM was positively associated with spina bifida in Finland, and maternal obesity did not modify this effect. We lacked information on maternal PGDM for electively terminated and spontaneously aborted cases; results should be interpreted with caution.

Keywords: diabetes mellitus; neural tube defects; pregnancy; risk factors; spina bifida

1 | INTRODUCTION

Spina bifida is a neural tube defect affecting the central nervous system, and occurs around 28 days after conception, a period during which most women are unaware of their pregnancies (Botto et al., 1999). Those born with spina bifida have varying degrees of morbidity, including paralysis, bowel and bladder dysfunction, and hydrocephalus (Liptak et al., 2015). Studies report additional impacts on the family including caregiver stress (Rofail et al., 2013), and high medical care costs (Grosse et al., 2016). It is also associated with an increased risk of stillbirths and mortality (Sutton et al., 2008; Oakeshott et al. 2009; Wang et al. 2011, Kancherla et al. 2014; Blencowe et al., 2018).

Type 1 pregestational diabetes mellitus is an autoimmune process with an early onset in life, and destroys the pancreatic b cells, needing insulin therapy, whereas, Type 2 diabetes mellitus, which can also be pregestational, occurs later in life, and is associated with peripheral insulin resistance, relative insulin deficiency, and obesity (American College of Gynaecology, 2018). Maternal diabetes, including pregestational diabetes mellitus (PGDM), has been identified as risk factors for several birth defects, including spina bifida. The exact mechanism of PGDM-induced spina bifida is unclear; however, hyperglycemia during organogenesis due to inadequate glucose control during the prepregnancy period is known to adversely impact embryos (Freinkel, 1988; Zhao & Reece, 2013; Baack et al., 2014; Ornoy et al., 2015). Animal models also show effects on gene expression leading to teratogenicity associated with PGDM (Liang et al., 2010; Zhao et al., 2016). There have been several large observational epidemiological studies that have shown similar findings of teratogenicity associated with PGDM and neural tube defects in humans, along with genetic susceptibility studies (Becerra et al., 1990; Correa 2008; Lupo et al., 2012). In addition, a recent study based on a very small sample size, reported that folic acid

supplementation (≥400 mcg/day) attenuated the association between PGDM and spina bifida, but did not completely eliminate the risk (Parker et al., 2013).

Maternal obesity is associated with the risk of neural tube defects (reviewed in Agopian et al., 2013; Rasmussen et al., 2008). Joint effects of maternal obesity and gestational diabetes for spina bifida were reported on a multiplicative scale in a population-based case-control study in Texas, and shared causal mechanisms between body mass index and diabetes were noted to contribute to the risk (Anderson et al., 2005). Additionally, a recent systematic review concluded that "The risk of congenital anomalies is increased in the offspring of obese women with diabetes" (Allen & Armson, 2007). There have been no previous studies that examined an interaction between pre-gestational diabetes and obesity and risk of spina bifida.

Globally, it is estimated that one in every three women with diabetes is of reproductive age (International Diabetes Federation, 2017). About 1-2% of pregnancies worldwide are affected by PGDM (Lawrence et al., 2008; Agha et al., 2016; Britton et al., 2018). PGDM goes undiagnosed in about 30% of those with the condition (Correa et al., 2012). Finland has a high prevalence of diabetes, and is experiencing an upward trend in the prevalence of type 1 diabetes in the recent decades, especially in young women of reproductive age (Hakkarainen et al., 2017). Based on unpublished statistics from the National Institute for Health and Welfare's (THL) Medical Birth Register (MBR), prevalence of maternal PGDM in Finland ranged from 0.69% in 2006 to 1.09% for all deliveries in 2018 (Congenital Anomalies THL, 2019). Birth defects surveillance systems in Finland show that for the period between 2000 and 2014, the total prevalence of spina bifida (including live births, stillbirths and elective terminations, and excluding cases with known genetic causes) was 3.73 per 10,000 births, and that about 51% of all spina bifida cases were live births, 2% were stillbirths, and 47% were electively terminated

after prenatal diagnosis (EUROCAT, 2018). In the context of projected increases in diabetes in Europe (Guariguata et al., 2014), there have not been any recent studies in Finland, or other similar Nordic countries, that examined the association between maternal PGDM and spina bifida. The objective of this study was to contribute to the current understanding of spina bifida etiology by examining the association between maternal PGDM and spina bifida in Finland.

2 | METHODS

2.1 | Data Sources

We used linked data from multiple nationwide healthcare registries in Finland. Cases of spina bifida were ascertained from Finland's Register of Congenital Malformations (RCM). RCM collects data on congenital chromosomal and structural anomalies in live births and stillbirths throughout Finland (National Institute for Health and Welfare, 2015). Information on congenital anomalies includes verbal diagnosis, *International Classification of Diseases and Related Health Problems* – 10th version (ICD-10) codes, pattern of anomaly (isolated, multiple, syndrome), time of detection and a variety of other details. Although the RCM includes information on elective terminations of pregnancies for fetal anomalies, maternal diagnoses are not collected systematically. The second data source, the Finnish Hospital Discharge Register (FHDR), was used to obtain information on maternal inpatient care in hospitals and primary health care centers (National Institute for Health and Welfare, 2016). This database includes nationwide linkable data on all hospital discharges and identification codes. Data are recorded for date of birth, sex, area of residence, hospital identification code, admission and discharge days, patient diagnosis and surgical procedures. Diagnoses are coded using the ICD-10 coding scheme since 1996. The third data source included the Finnish Medical Birth Register (MBR), which includes data on

maternal demographic and health data (National Institute for Health and Welfare, 2019). The MBR, maintained by the National Institute for Health and Welfare, provide information on live birth and stillbirths from 1987. Lastly, Census data from Statistics Finland was used for information on income and educational attainment for each parturient (Official Statistics of Finland [OSF], n.d.).

Above data sources were linked using unique identification codes for the mother and the newborn who were characterized as citizens and permanent residents of Finland. Overall, 99.8% of women in Finland have valid identification code and are thus eligible for data linkages. For the current study, 99.9% of records were linked successfully between all data sources.

2.2 | Case and control selection

The study included all live births and stillbirths in Finland delivered between 2000 through 2014. Eligible cases were identified from the RCM using Centers for Disease Control and Prevention – British Pediatric Association (CDC-BPA) codes 741000-741999. Spina bifida cases that were electively terminated or spontaneously aborted were not included in the analysis due to lack of data on maternal PGDM status. We also excluded cases that presented as a part of known chromosomal or genetic syndrome. All cases in RCM were reviewed and validated by clinical geneticists and are classified into isolated and multiple defect categories. Isolated spina bifida was defined as a case with no other major malformations. A multiple case was defined as a case of spina bifida co-occurring with one or more additional major birth defects that are not related to spina bifida. Controls were live or stillborn infants and with no major congenital anomalies (e.g., congenital heart defects, oral clefts). Birth defects case definitions and classifications of major congenital anomalies are based on criteria defined by EUROCAT as mentioned in the RCM (Congenital anomalies – THL, n.d.).

2.3 | Exposure Assessment

The Finnish MBR provided detailed information including maternal diagnoses during pregnancy and delivery. Maternal PGDM, the primary exposure variable, were ascertained from MBR, and defined using ICD-10 codes O24.0-O24.3 including insulin-dependent, non-insulin dependent, malnutrition-related and unspecified type of diabetes prior to the index pregnancy. We also examined maternal gestational diabetes using ICD-10 codes O24.4 and O24.9 relating to diabetes mellitus arising in pregnancy and diabetes in pregnancy that is unspecified; pre-existing hypertension using ICD-10 codes O10.0-O10.4, O10.9 for unspecified pre-existing hypertension, O11 for pre-existing hypertensive disorder, and gestational hypertension using ICD-10 code O13 to identify women with gestational hypertension without significant proteinuria.

2.4 | Co-Variables

A list of potential co-variables was selected based on the review of previous studies. Co-variables related to the infant included sex (male / female); gestational age (weeks) (<37 / ≥37); birth weight (grams) (≤2499 / 2500-3999 / ≥4000); and co-occurring birth defects (isolated / multiple). Maternal co-variables consisted of age at delivery (years) (<20 / 20-34 / ≥35); highest attained education (basic or no education / upper secondary, pre-bachelors education / bachelors or greater); parity (1 / ≥1); income level (percentile) (<20 / 20-80 / >80); nativity (Finnish background, born in Finland / other); maternal body mass index (kg/m^2) (<18.5 / 18.5-24.9 / 25-29.9 / ≥30); gestational diabetes (no / yes); pre-existing hypertension (no / yes); gestational hypertension (no / yes); and cigarette smoking status history (never smoker / smoked during pregnancy)

2.5 | Statistical Analyses

Descriptive analyses were conducted to compare infant and maternal co-variables for cases and controls. We estimated crude and adjusted odds ratios (OR) and 95% confidence intervals (CIs) for the associations between maternal PGDM and all cases of spina bifida combined and for isolated spina bifida cases. Isolated cases are considered to be etiologically homogenous compared to multiple and syndromic cases, and hence, we conducted an additional sub-analysis that examined isolated cases separately.

For unadjusted analysis, exact estimates were calculated when one of the cell sizes was less than 5. For multivariable logistic regression analysis, co-variables were identified based on literature review, and those that were included in the model selection process were identified based on bivariate analysis examining each variable's association with the main exposure variable (PGDM) and the outcome (spina bifida), The significance for these associations was set at $P<0.05$. Co-variables that altered the main effect by more than 10% when they were entered into the model were retained in the final model. We used exact logistic regression analysis for our multivariable analysis due to small number of cases. We assessed effect modification of PGDM and spina bifida by maternal obesity among all cases and isolated cases.

All analyses were performed using the Statistical Analysis System (SAS) version 9.4 statistical software (SAS Institute, Cary, NC). The study has been approved by the Finnish National Institute for Health and Welfare and Statistics Finland.

3 | RESULTS

A total of 181 cases of spina bifida, and 876,672 controls were eligible for our analysis. There were 181 live born cases, of which 111 (61%) were classified as 'isolated', i.e., without other co-occurring major congenital malformations. In addition, 29% of all cases had multiple

birth defects and information on the remaining 10% of cases was not available. For both groups of cases (i.e., all cases and isolated cases), there was a slightly higher preponderance of spina bifida among males compared to females. Among all cases of spina bifida combined, a greater proportion were preterm (<37 weeks gestation) and normal birth weight (2500-3999 g) compared to controls infants, and these differences were significant. Further, among all cases combined, about 80% were born to mothers aged 20-34 years, 45% to mothers with no education after the basic level that was below upper secondary schooling or pre-bachelors level, and 11% to mothers with income level below 20th percentile. About 13% of case mothers were smokers, who either stopped during their 1st trimester or continued after their 1st trimester (Table 1).

In our unadjusted analysis examining all cases of spina bifida combined and controls, we found that preterm gestation, low birth weight, having multiple birth defects, having family income level over 80th percentile, and maternal obesity, and maternal PGDM were all associated with an increased odds of spina bifida (Table 1). However, these associations were not significant when we restricted our analysis to isolated spina bifida cases alone, except for the association with maternal obesity, which persisted at the same magnitude and direction as it did for all spina bifida cases combined (Table 1).

Maternal PGDM was reported in only 4 out of 181 cases of spina bifida, with a prevalence of 2.2% among mothers of all spina bifida cases combined. Among isolated spina bifida cases, only 2 out of 111 cases (1.8%) had maternal PGDM. PGDM prevalence was 0.5% among controls (Table 1). The crude odds ratio for the association between maternal PGDM and spina bifida was elevated for all spina bifida cases combined as well as isolated cases; however, for isolated cases, the 95% CI included the null (cOR 4.80; 95% CI 1.29, 12.52 and cOR 3.90; 95% CI 0.47, 14.43, respectively) (Table 1). We did not find interaction by obesity to be

significant for either all cases (p=0.24) or isolated cases (p=0.97), and therefore did not further stratify our analyses by obesity.

Results from our multivariable analysis showed that maternal PGDM was positively associated with all spina bifida cases combined, after controlling for maternal age, education, income and body mass index (aOR 4.35; 95% CI 1.37, 13.82). This association was also positive in for isolated spina bifida cases (aOR 4.41; 95% CI 1.07, 18.24) (Table 2).

4 | DISCUSSION

This study is based on a nationally representative, multi-registry, population-based case-control study of infants with and without spina bifida in Finland using latest data available for birth years 2000-2014. The case selection criteria included both live and stillborn infants, although there were no stillbirths identified through our data linkages for spina bifida cases during the study period. We lacked information on maternal PGDM for electively terminated and spontaneously aborted cases, and hence these birth outcomes were not examined in our analysis. There is almost a four-fold increased risk of spina bifida among live born offspring of mothers with PGDM compared to those without. We found a similar association when the analysis was restricted to isolated spina bifida cases only that were live born. We did not see a significant interaction between PGDM and maternal obesity in our study.

It is estimated that about 1-2% of pregnancies are affected by PGDM (Lawrence et al., 2008; Agha et al., 2016; Britton et al., 2018). The overall prevalence of PGDM in Finland during our study period was slightly lower than that in above referred studies. However, population-based data from the United States reported a similar prevalence of PGDM (0.5%) among mothers that delivered non-malformed live born infants, consistent with what was noted among

control mothers in the current study (Correa et al., 2008). Additionally, the Slone Epidemiology Center Birth Defects Study in multiple sites from United States and Canada reported the prevalence of pre-existing diabetes as 0.7% among case mothers and 0.4% among control mothers, consistent with our study (Parker et al., 2013).

The magnitude and direction of association between PGDM and spina bifida in Finland is consistent with some but not other studies in the past. Findings from population-based National Birth Defects Prevention Study in the US for births between 1997-2003 showed a positive association between PGDM and spina bifida cases co-occurring with other major birth defects (OR=8.0; 95% CI 1.6, 39.7); however, the association was not significant when the analysis was restricted to isolated spina bifida cases (OR=0.8; 95% CI 0.2, 3.2) (Correa et al., 2008). It is important to note that aforementioned findings from the US were based on a small number of PGDM-affected case mothers (2 out of 444 for isolated spina bifida and 2 out of 43 for multiple spina bifida). Our study was not consistent with another large population-based study, where the association between preexisting diabetes and spina bifida was positive, but the confidence interval around the effect estimates included the null, for both isolated and multiple spina bifida case groups, with aORs of 1.84 and 2.56, respectively (Parker et al., 2013).

We found a positive association between pre-pregnancy obesity and spina bifida. The association between maternal BMI and spina bifida has been noted previously in a study in the United States, independent of maternal PGDM. A two-fold risk of spina bifida was reported among obese mothers compared to mothers within normal weight range in a population-based study in the US (Parker et al., 2013). We found one previous study that reported a significant effect-modification between gestational diabetes and central nervous system defects (Anderson et al., 2005). Our study was the first to examine the interaction between PGDM and obesity for

spina bifida risk. Future studies should consider the interaction between PGDM and obesity in the causal analysis for spina bifida while including all pregnancy outcomes (i.e., live births, stillbirths, and elective termination of pregnancy for congenital anomalies). Similarly, future studies should examine the role of folic acid supplementation as an effect modifier for the association between PGDM and spina bifida, which has been examined in populations elsewhere (Parker et al., 2013). We were unable to examine the role of folic acid supplementation in our analysis due to lack of reliable folic acid intake data among Finnish women.

Howards et al. (2015) developed methods to quantify potential selection bias in studies where data are lacking non-live born cases (i.e., stillbirths, elective termination) with spina bifida. We did not have any stillborn spina bifida cases in our analysis. Because of lack of information on the status of PGDM in women who terminated their pregnancy, we could not apply the methods proposed for analyzing selection bias associated with not examining elective terminations in the current study.

There are some limitations in our study, and findings should be interpreted with caution. Most important limitation is that we did not have data on elective terminations. In addition, prenatal diagnosis is an important consideration as it can influence elective termination rates; however, as noted in the US, prenatal diagnosis is more likely to lead to termination of anencephaly than spina bifida (Cragan et al., 1995). Another limitation is lack of information on pre- and post-conception folic acid supplement intake. The MBR implemented data collection on folic acid supplement use beginning in 2017, a period not captured in our study period. However, a recent study in the US showed very modest effect modification by folic acid supplement intake (≥400 mcg/day) on the association between PGDM and spina bifida (Parker et al., 2013). Given very low prevalence and adherence (<30% women of reproductive age report taking prenatal

supplements) of preconception folic acid supplement use (Toivonen et al., 2018) and lack of fortification of staple foods with folic acid (Food Fortification Initiative, 2019) in European countries, including Finland, the association noted in our study is reasonably valid, and will not change greatly if we were to avail information on supplementation use. We were unable to examine the role of glucose control due to lack of data on contemporary medication use among case and control mothers with PGDM to treat and control the condition. Also, given a large proportion of women in the population whose PGDM remains undiagnosed, our study, like similar other studies that are conducted in scenarios with regular health screenings for women of reproductive age for PGDM, is subject to potential exposure misclassification.

There are also several strengths in our study. We used nationally-representative, population-based datasets on births linking multiple well-established data sources to abstract data on important infant and maternal characteristics for a comprehensive analysis of the association between PGDM and spina bifida. The study timespan covered a recent time period, including births from over 15 years. Data quality, reliability, completeness, and validity of linkages of registers have been well established, and the datasets have been regularly used for conducting nationally representative epidemiological studies in the past and present (Teperi, 1993; Gissler et al., 1995; Gissler & Shelley, 2002; Sund, 2012; Haikonen, Lunetta, Lillsunde, & Sund, 2013). Since each permanent resident in Finland is given a unique identification number used to link between various data sources, linkage errors are minimized (Sund, 2012). Finnish registers employ standardized procedures to define spina bifida and PGDM using ICD-10 codes. Finland, among other Nordic countries, has a comprehensive population-based medical birth register that details information on newborns. In addition, registries on congenital anomalies include

information on children until one year of age (Arbour et al., 2009; National Institute for Health and Welfare, 2016).

In summary, we found a relatively high magnitude positive association between PGDM and spina bifida in Finland, and maternal obesity did not modify this association. With an increasing trend in the incidence and prevalence of PGDM in young women of reproductive age in Finland, and with several studies, including ours, indicating potential positive association between PGDM and spina bifida, regular screenings and treatment protocols for PGDM should be implemented to reach all women of reproductive age before and during pregnancy. Any intervention to prevent spina bifida should reach the expectant mother during the periconceptional period, a critical time for the development of spina bifida. Thus, women who have PGDM or are at risk for it, should be treated and counseled to prepare for potential adverse pregnancy outcomes. Future studies in Finland should include all birth outcomes associated with spina bifida (i.e., stillbirths, elective terminations, spontaneous abortion), as well as examine the roles of maternal obesity, folic acid supplementation, and treatment status for PGDM, to further elaborate the association between PGDM and spina bifida.

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Table 1. Infant and maternal characteristics of infants with and without spina bifida, Finland, 2000-2014

	Controls (n=876,672)	All Spina Bifida (n=181)		Isolated Spina Bifida (n=111)	
Characteristics	**n (%)**	**n (%)**	**cOR (95% CI)[a]**	**n (%)**	**cOR (95% CI)[a]**
Infant Characteristics					
Sex					
Male	448,535 (51.16)	100 (55.25)	Referent	66 (59.46)	Referent
Female	428,098 (48.83)	81 (44.75)	0.85 (0.63, 1.14)	45 (40.54)	0.71 (0.49, 1.04)
Gestational age (weeks)					
≥37	823,153 (93.90)	142 (78.45)	Referent	100 (90.09)	Referent
<37	50,963 (5.81)	39 (21.55)	4.44 (3.11, 6.32)	11 (9.91)	1.78 (0.95, 3.31)
Birthweight (grams)					
≤2499	38,449 (4.39)	37 (20.44)	5.27 (3.55, 7.66)	8 (7.21)	1.66 (0.69 3.41)
2500-3999	684,505 (78.08)	125 (69.06)	Referent	86 (77.48)	Referent
≥4000	152,943 (17.45)	18 (9.94)	0.64 (0.37, 1.06)	17 (15.32)	0.89 (0.49, 1.50)
Co-ocurring birth defects					
Isolated	28,916 (3.30)	111 (61.33)	Referent	--	--
Multiple	2,936 (0.33)	52 (28.73)	4.61 (3.31, 6.43)	--	--
Maternal Characteristics					
Age at delivery (years)					
<20	22,074 (2.52)	6 (3.31)	1.30 (0.58, 2.94)	4 (3.60)	1.37 (0.50, 3.73)
20-34	688,008 (78.48)	144 (79.56)	Referent	91 (81.98)	Referent
≥35	166,590 (19.00)	31 (17.13)	0.89 (0.60, 1.31)	16 (14.41)	0.73 (0.43, 1.24)
Education					
Basic or no education	378,506 (43.18)	82 (45.30)	1.12 (0.82, 1.53)	52 (46.85)	1.18 (0.80, 1.75)
Upper secondary, Pre-Bachelors	403,502 (46.03)	78 (43.09)	Referent	47 (42.34)	Referent
Bachelors or greater	94,664 (10.80)	21 (11.60)	1.15 (0.71, 1.86)	12 (10.81)	1.09 (0.58, 2.05)
Parity					
0	365,255 (41.66)	68 (37.57)	Referent	44 (39.64)	Referent
≥1	510,671 (58.25)	113 (63.43)	0.81 (0.62, 1.05)	67 (60.36)	0.92 (0.63, 1.34)
Income level (percentile)					
<20	77,098 (8.79)	19 (10.50)	1.32 (0.81, 2.15)	11 (9.91)	1.17 (0.62, 2.20)
20-80	606,664 (69.20)	113 (62.43)	Referent	74 (66.67)	Referent
>80	76,836 (8.76)	25 (13.81)	1.75 (1.13, 2.69)	12 (10.81)	1.28 (0.70, 2.36)
Nativity					
Finnish background/born in Finland	795,004 (90.68)	158 (87.29)	Referent	99 (89.19)	Referent
Other	73,727 (8.41)	21 (11.60)	1.43 (0.90, 2.26)	11 (9.91)	1.20 (0.64, 2.23)
Body mass index (kg/m^2)					
<18.5	23,165 (2.64)	2 (1.10)	0.59 (0.07, 2.25)	2 (1.80)	1.07 (0.13, 4.22)
18.5-24.9	385,521 (43.98)	56 (30.94)	Referent	31 (27.93)	Referent
25-29.9	134,930 (15.39)	24 (13.26)	1.23 (0.73, 2.01)	14 (12.61)	1.29 (0.63, 2.50)
≥30	73,913 (8.43)	24 (13.26)	2.24 (1.33, 3.67)	17 (15.32)	2.86 (1.49, 5.33)
Pregestational diabetes					
No	872,564 (99.53)	177 (97.79)	Referent	109 (98.20)	Referent
Yes	4,108 (0.47)	4 (2.21)	4.80 (1.29, 12.52)	2 (1.80)	3.90 (0.47, 14.43)
Gestational diabetes (1st trimester)					
No	825,519 (94.17)	174 (96.13)	Referent	106 (95.50)	Referent
Yes	51,153 (5.83)	7 (3.87)	0.65 (0.31, 1.38)	5 (4.50)	0.76 (0.31, 1.87)
Pre-existing hypertension					
No	870,978 (99.35)	180 (99.45)	Referent	110 (99.10)	Referent
Yes	5,694 (0.65)	1 (0.55)	0.85 (0.02, 4.80)	1 (0.90)	1.39 (0.04, 7.91)
Gestational hypertension					
No	859,963 (98.09)	179 (98.90)	Referent	109 (98.20)	Referent

Yes	16,709 (1.91)	2 (1.10)	0.58 (0.09, 2.11)	2 (1.80)	0.94 (0.11, 3.50)
Cigarette smoking status					
Never smoker	722,785 (82.45)	150 (82.87)	Referent	96 (86.49)	Referent
Smoker	131,700 (15.02)	24 (13.26)	0.89 (0.55, 1.36)	11 (9.91)	0.63 (0.30, 1.18)

[a]Exact odds ratios and 95% confidence intervals are reported where cell size was less than 5

Table 2. Multivariable analysis for the association between maternal pregestational diabetes mellitus and spina bifida in the offspring, Finland, 2000-2014

Maternal Characteristics	All Spina Bifida Adjusted Odds Ratio[a,b] (95% Confidence Interval)	Isolated Spina Bifida Adjusted Odds Ratio[a,b] (95% Confidence Interval)
Pregestational diabetes		
No	Referent	Referent
Yes	4.35 (1.37, 13.82)	4.41 (1.07, 18.24)
Age at delivery (years)		
<20	0.98 (0.24, 4.06)	0.74 (0.10, 5.50)
20-34	Referent	Referent
≥35	0.97 (0.55, 1.71)	1.09 (0.54, 2.21)
Education		
No education or basic	1.31 (0.83, 2.07)	1.50 (0.84, 2.68)
Upper secondary - Pre-Bachelors	Referent	Referent
Bachelors or greater	1.23 (0.59, 2.58)	1.17 (0.44, 3.13)
Income level (percentile)		
<20	1.53 (0.84, 2.79)	1.22 (0.54, 2.73)
20-80	Referent	Referent
>80	2.05 (1.15, 3.66)	1.44 (0.64, 3.28)
Body mass index (kg/m^2)		
<18.5	0.70 (0.17, 2.90)	1.26 (0.30, 5.30)
18.5-24.9	Referent	Referent
25-29.9	1.20 (0.72, 2.00)	1.34 (0.69, 2.60)
≥30	2.02 (1.19, 3.41)	2.69 (1.42, 5.09)

[a]Due to small number of cases, adjusted odds ratios and 95% confidence intervals are generated from exact logistic regression analysis.

[b]Each variable was adjusted for all other variables in the models presented for all spina bifida, and isolated spina bifida groups.