



ADHD and ASD

# Association of maternal diabetes with neurodevelopmental disorders: autism spectrum disorders, attention-deficit/hyperactivity disorder and intellectual disability

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## Abstract

**Background:** Maternal diabetes has been associated with a risk of neurodevelopmental disorders (NDDs) in offspring, though the common co-occurrence of autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder (ADHD) and intellectual disability (ID) is rarely considered, nor is the potential for confounding by shared familial factors (e.g. genetics).

**Methods:** This population-based cohort study used data from Psychiatry Sweden, a linkage of Swedish national registers, to follow 2 369 680 individuals born from 1987 to 2010. We used population-averaged logit models to examine the association between exposure to maternal type 1 diabetes mellitus (T1DM), pre-gestational type 2 diabetes mellitus (T2DM) or gestational diabetes mellitus (GDM), and odds of NDDs in offspring. Subgroup analysis was then performed to investigate the timings of GDM diagnosis during pregnancy and its effect on the odds of NDDs in offspring. We compared these results to models considering paternal lifetime T1DM and T2DM as exposures.

**Results:** Overall, 45 678 individuals (1.93%) were diagnosed with ASD, 20 823 (0.88%) with ID and 102 018 (4.31%) with ADHD. All types of maternal diabetes were associated with odds of NDDs, with T2DM most strongly associated with any diagnosis of ASD (odds ratio<sub>adjusted</sub> 1.37, 95% confidence interval 1.03–1.84), ID (2.09, 1.53–2.87) and ADHD (1.43, 1.16–1.77). Considering common co-morbid groups, the associations were strongest between maternal diabetes and diagnostic combinations that included ID. Paternal T1DM and T2DM diagnoses were also associated with offspring NDDs, but these associations were weaker than those with maternal diabetes. Diagnosis of GDM between 27 and 30 weeks of gestation was generally associated with the greatest risk of NDDs in

offspring, with the strongest associations for outcomes that included ID.

**Conclusion:** The association of maternal diabetes with NDDs in offspring varies depending on the co-morbid presentation of the NDDs, with the greatest odds associated with outcomes that included ID. Results of paternal-comparison studies suggest that the above associations are likely to be partly confounded by shared familial factors, such as genetic liability.

**Key words:** Autism spectrum disorders, intellectual disability, attention-deficit hyperactivity disorder, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes mellitus

### Key Messages

- Maternal diabetes [i.e. type 1 diabetes mellitus, type 2 diabetes mellitus and gestational diabetes mellitus (GDM)] has been associated with an increased risk of neurodevelopmental disorders (NDDs) in offspring [i.e. autism spectrum disorders, intellectual disability (ID) and attention-deficit/hyperactivity disorder]. Though the co-occurrence of NDDs is common, previous studies have rarely taken this into account when exploring associations with maternal diabetes.
- This study presents evidence that associations of different types of maternal diabetes vary in relation to the co-occurrence of NDDs in offspring, with the strongest associations generally found for diagnostic groups that included ID.
- GDM diagnosed between 27 and 30 weeks of gestation was generally associated with the greatest risk of NDDs in offspring compared with GDM diagnosed earlier or later, especially for cases with co-occurring ID.

## Introduction

Autism spectrum disorders (ASD), intellectual disability (ID) and attention-deficit/hyperactivity disorder (ADHD) are common neurodevelopmental disorders (NDDs) with lifelong impacts on affected children and their families.<sup>1-3</sup> The co-occurrence of ASD, ADHD and ID is more common than would be expected by chance.<sup>1,2,4-9</sup> Clinically, the co-occurrence of NDDs indicates more severe impairment, different needs and poorer prognoses of the affected children compared with children with a single NDD diagnosis.<sup>4,7,8,10</sup>

Globally,  $\leq 15\%$  of pregnancies are complicated by diabetes, as gestational diabetes mellitus (GDM) or as pre-existing type 1 mellitus (T1DM) or type 2 diabetes mellitus (T2DM).<sup>11</sup> Multiple observational studies have reported that maternal diabetes is associated with an increased risk of NDDs in offspring.<sup>11-24</sup> Most studies have considered the NDDs individually without regard for their common co-occurrence, with few exceptions.<sup>15,25</sup> An adverse effect of a hyperglycaemic intrauterine environment on the developing nervous system has been proposed as one mechanism to explain these associations. Studies by Xiang *et al.* indicating that GDM diagnosed earlier than 26 weeks of gestation (wkGA) was associated with an increased risk of ASD

in offspring,<sup>14,26</sup> whereas GDM diagnosed after 26 wkGA was not, support the notion that hyperglycaemia during critical windows of development may impair the developing nervous system, though a similar pattern was not observed for ADHD.<sup>12</sup> However, ASD, ADHD and ID are disorders with high heritability estimates<sup>27,28</sup> and previous studies have reported that the relationship between maternal body mass index (BMI), a strong predictor for both GDM and T2DM, and offspring risk of ASD<sup>29,30</sup> and ADHD<sup>31,32</sup> is likely confounded by shared familial factors, such as genetic background. This is supported by studies indicating a genetic overlap between ADHD and body composition, particularly increased body-fat content.<sup>33</sup> It has also been suggested that psychiatric disorders may share common genetic loci with autoimmune disorders like T1DM.<sup>34</sup>

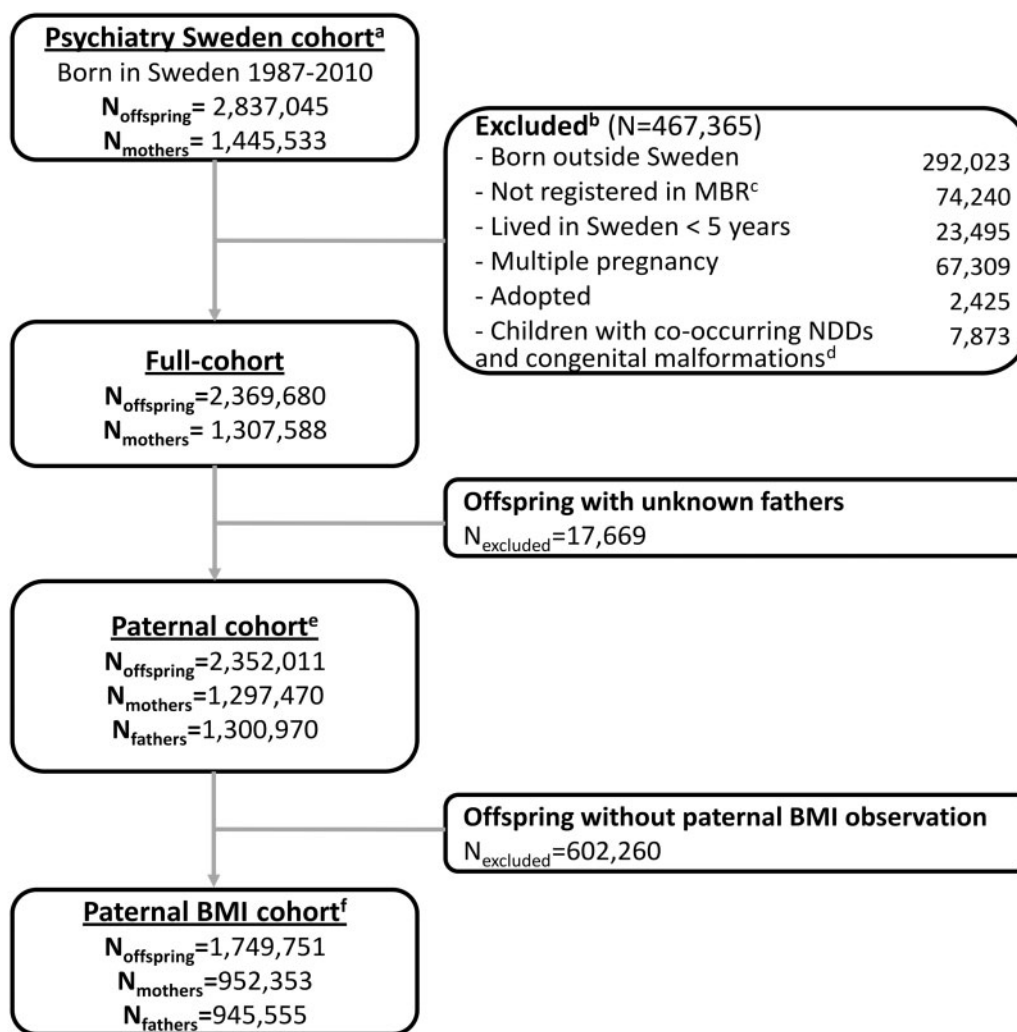
We aimed to evaluate the relationships between maternal diabetes (i.e. T1DM, pre-gestational T2DM and GDM) and risk of NDDs (i.e. ASD, ID and ADHD) in offspring, taking into account the co-occurrence of NDDs. In addition, we evaluated the timing of GDM diagnosis and used a family-based study design employing paternal-offspring comparisons to evaluate evidence for alternative mechanisms to explain the relationship between maternal diabetes and offspring risk of NDDs.

## Methods

### Register linkage and study population

This national, population-based cohort study was based on ‘Psychiatry Sweden’, a comprehensive register linkage designed for studying the occurrence, determinants, and outcomes of psychiatric disorders (Supplementary Figure 1, available as Supplementary data at *IJE* online). The unique personal identification number assigned to each individual at birth (or upon arrival in Sweden for immigrant parents)<sup>35</sup> was replaced by a study identity number by Statistics Sweden. Individual-level data from national registers containing routinely collected health and socio-demographic data were linked using the study identity number by staff statisticians (Supplementary Figure 1,

available as Supplementary data at *IJE* online). We considered as eligible index persons all singleton children born in Sweden from 1 January 1987 to 31 December 2010 ( $n=2\,837\,045$ ), with follow-up to 31 December 2016 (Figure 1). Children who were born outside Sweden, not recorded in the Medical Birth Register (MBR), resident in Sweden for <5 years or adopted were excluded, as were children with both congenital malformations and diagnoses of ASD, ADHD or ID (Figure 1).<sup>36</sup> More than one index person could be born to the same mother in this study. Our final study population included 2 369 680 offspring born to 1 307 588 mothers. Ethics approval was obtained from the Stockholm regional ethical review committee (DNR 2010/1185-31/5). Informed consent was not required for the analysis of anonymized register data.



**Figure 1** Study-sample derivation. <sup>a</sup> Children born before 1987 were excluded from the study population since the date of gestational diabetes mellitus (GDM) diagnosis was only available from 1987. <sup>b</sup> Individuals were excluded stepwise. <sup>c</sup> Individuals without information from the Medical Birth Register (MBR) were excluded. <sup>d</sup> Children with co-morbidities of congenital malformations (or inborn error of metabolism) and neurodevelopmental disorders (NDDs), as NDDs may be attributable to the congenital condition. <sup>e</sup> Those whose biological fathers were unknown were excluded. <sup>f</sup> Those whose biological fathers were not registered in the conscription register, were unknown or who lacked body mass index (BMI) observations were excluded.

## Case ascertainment

ASD, ADHD and ID were identified using ICD-9 and ICD-10 codes in the National Patient Register (Supplementary Table 1, available as Supplementary data at *IJE* online),<sup>37–39</sup> supplemented with information from the Prescription Drug Register for ADHD case ascertainment (Supplementary Table 1, available as Supplementary data at *IJE* online).<sup>40,41</sup> We considered three potentially overlapping outcomes for comparability to previous studies (Supplementary Figure 2, available as Supplementary data at *IJE* online): any ASD diagnosis, any ADHD diagnosis and any ID diagnosis. In addition, five mutually exclusive outcomes were considered<sup>25,42</sup> (Supplementary Figure 2, available as Supplementary data at *IJE* online): ‘ASD only’ (without co-occurring ADHD and/or ID); ‘ADHD only’ (without co-occurring ASD and/or ID); ‘ASD + ADHD’ (ASD co-occurring with ADHD, without co-occurring ID); ‘ID + ASD’ (ID co-occurring with ASD, including those with co-occurring ADHD); and ‘ID without ASD’ (ID only or ID co-occurring with ADHD, excluding those with co-occurring ASD). The majority [9587 (70.7%)] of individuals included in the ‘ID without ASD’ group had only an ID diagnosis, with the remainder [3976 (29.3%)] diagnosed with ID with co-occurring ADHD.

## Parental diabetes

T1DM, pre-gestational T2DM or GDM were identified from the National Patient Register (Supplementary Table 1, available as Supplementary data at *IJE* online). If a mother’s diabetes diagnosis could not be clearly established as T1DM or T2DM, given the lack of distinction of these two diagnoses prior to ICD-10, the diagnosis was considered non-specified pre-gestational diabetes mellitus (PGDM-NOS). We classified offspring exposure to maternal diabetes into five mutually exclusive groups: ‘Unexposed’, ‘T1DM’, ‘Pre-gestational T2DM’, ‘GDM’ and ‘PGDM-NOS’ (Supplementary Table 1, available as Supplementary data at *IJE* online).

We calculated gestational weeks at GDM diagnosis using gestational week at delivery, GDM diagnostic date and birth date (0.11% individuals in the study population had missing values for gestational week at delivery and 13.94% of individuals with a diagnosis of GDM had missing values for date of GDM diagnosis). For the 0.11% of individuals with missing values for gestational week at delivery, we replaced these missing values with 40 wkGA. This resulted in 18 352 (86.06%) of GDM diagnoses with an estimated gestational week at diagnosis. We categorized GDM exposure according to gestational week at GDM diagnosis: ‘ $\leq 26$  wkGA’, ‘27–30 wkGA’ and ‘ $> 30$  wkGA’.<sup>12,14</sup>

For paternal-comparison analyses, paternal lifetime diagnoses of T1DM and T2DM were used. We classified offspring exposure to paternal diabetes into four mutually exclusive groups: ‘Unexposed’, ‘T1DM’, ‘T2DM’ and ‘DM-NOS’.

## Covariates

Parental covariates included parental age at delivery,<sup>43</sup> income quintile at birth,<sup>35</sup> immigration status,<sup>44</sup> education level (highest level achieved by either parent before birth of the index child)<sup>35</sup> and history of inpatient psychiatric care prior to the birth of the child (defined as neither parent, one parent or both parents with a psychiatric history); mothers’ diagnosis of Polycystic Ovarian Syndrome (PCOS)<sup>40</sup>; and paternal BMI measured at the time of conscription to the Swedish military (at age 18).<sup>29</sup> Obstetric covariates included parity, smoking during pregnancy, maternal hypertensive diseases, maternal early gestation BMI<sup>29,45</sup> and gestational weight gain (defined as ‘ideal’, ‘insufficient’ or ‘excessive’ according to the Institute of Medicine recommendations for each BMI category).<sup>46</sup> Offspring covariates include sex, birth year, gestational age at birth, Apgar score at 5 minutes, size for gestational age and population density of birthplace in Sweden (according to the European population-density index,<sup>47</sup> with additional categories for the three largest cities in Sweden: ‘Gothenburg and Malmö’, ‘Stockholm’ and ‘Stockholm Suburbs’).

Among these covariates, maternal hypertensive diseases, gestational age, size for gestational age and Apgar score were considered as being potentially on the causal pathways for the association between maternal diabetes and NDDs<sup>26</sup> and thus were not included in statistical models.

## Statistical analysis

Analyses were conducted using Stata/MP 14.0 (College Station, TX). We considered the neurodevelopmental outcomes to be dichotomous outcomes (i.e. present or absent). To account for clustering of multiple children born to the same mother and provide robust standard errors given this clustering, we used population average logit models, clustered on maternal identification number, to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the relationships between different forms of maternal diabetes (T1DM, T2DM, GDM and PGDM-NOS) and dates of GDM diagnosis ( $\leq 26$ , 27–30 and  $> 30$  wkGA) and each outcome.<sup>48</sup> In Model 1, we adjusted for children’s sex and birth year. In Model 2, we additionally adjusted for parental educational level, income, immigration status and history of inpatient psychiatric care; children’s birthplace in

Sweden; and maternal age, BMI, parity, smoking during pregnancy and PCOS.

The proportion of missing data for most of the covariates and the gestational week at delivery was low (<1%), except for smoking during pregnancy (5.15%), maternal pre-gestational BMI (24.63%) and gestational weight gain (65.62%). To address missing values, we used the missing-indicator method, replacing missing values (except in gestational-weight-gain observations) with a dummy category.<sup>49</sup>

We conducted several sensitivity analyses. To test for potential confounding by shared familial factors (e.g. genetic factors), we used paternal-comparison models, evaluating the associations of offspring NDDs in relation to paternal-diabetes diagnoses in a restricted population including individuals with an identified biological father (which was most of the population, as only 1.35% did not have an identified biological father). Models evaluating paternal DM as an exposure were adjusted analogously to models evaluating maternal diabetes (Models 1 and 2) and were further adjusted for maternal-diabetes exposure (Model 3). To test for potential biases introduced by the missing-indicator method, we repeated our analyses excluding subjects with missing values. We then adjusted estimates for gestational weight gain within the sub-cohort that had gestational-weight-gain observations. Finally, to investigate whether changes in GDM diagnostic criteria over time affected the odds of NDDs, we stratified GDM-exposed offspring into those born before (<1993) or after 1993 ( $\geq 1993$ ).

## Results

### Study sample

After being followed for 6–29 years, 45 678 (1.93%) individuals were diagnosed with ASD, 20 823 (0.88%) with ID and 102 018 (4.31%) with ADHD, with considerable overlap between the diagnoses (Supplementary Figure 2, available as Supplementary data at *IJE* online). Individuals exposed to different types of maternal diabetes differed with regard to all covariates ( $P < 0.001$ ) compared with the unexposed group, except offspring sex ( $P = 0.11$ , Table 1). This was also true for individuals exposed to different gestational weeks of GDM diagnosis (Supplementary Table 2, available as Supplementary data at *IJE* online;  $P < 0.001$  except for sex, where  $P = 0.049$ ) and paternal diabetes (Supplementary Table 3, available as Supplementary data at *IJE* online;  $P < 0.001$  except for sex, where  $P = 0.069$ ).

The number of pregnancies complicated by T2DM and GDM grew between 1987 and 2010, whereas the trend for

T1DM was relatively stable (Supplementary Figure 4A, available as Supplementary data at *IJE* online). Additionally, the prevalence of different types of maternal diabetes varied across regions in Sweden, especially for GDM (Supplementary Figure 4B and C, available as Supplementary data at *IJE* online). The incidence of ASD, ADHD and ID also increased from 1987 to 2016 (Supplementary Figure 4D, available as Supplementary data at *IJE* online). Women were diagnosed with GDM at every week from  $\leq 5$  to 43 wkGA (Supplementary Figure 3, available as Supplementary data at *IJE* online). Furthermore, whereas there were several peaks in gestational week at GDM diagnosis, GDM cases were generally more likely to be diagnosed near the end of pregnancy.

### Primary analysis

Maternal diabetes was associated with increased odds of ASD ('Any ASD'), ADHD ('Any ADHD') and ID ('Any ID'), with T2DM being associated with greater odds compared with GDM and T1DM (Table 2). Odds associated with all types of maternal diabetes were stronger in the 'Any ID' group compared with 'Any ASD' and 'Any ADHD'. Estimates across exposure categories and outcomes were generally attenuated in adjusted models compared with unadjusted models (Table 2).

Considering the mutually exclusive diagnostic categories containing individuals diagnosed with ASD (i.e. 'ASD only', 'ASD + ADHD' and 'ASD + ID') (Supplementary Figure 2, available as Supplementary data at *IJE* online), the odds of 'ASD only' (OR<sub>adjusted</sub> 1.25, 95% CI 1.08–1.45) and 'ASD + ADHD' (OR<sub>adjusted</sub> 1.23, 95% CI 1.06–1.42) among individuals exposed to T1DM were similar to each other (Table 2, Model 2) and compared with the odds of 'Any ASD' (OR<sub>adjusted</sub> 1.29, 95% CI 1.17–1.42, Table 2, Model 2). However, T1DM exposure was associated with somewhat higher odds of ASD co-occurring with ID ('ID + ASD') (OR<sub>adjusted</sub> 1.54, 95% CI 1.25–1.90). T2DM was associated with greater odds of 'ID + ASD' (OR<sub>adjusted</sub> 1.61, 95% CI 0.90–2.88) and 'ASD only' (OR<sub>adjusted</sub> 1.54, 95% CI 1.01–2.34) compared with 'ASD + ADHD' (OR<sub>adjusted</sub> 1.12, 95% CI 0.68–1.86). Odds associated with GDM were similar across the mutually exclusive outcome groups (Table 2) and comparable to estimates for 'Any ASD' (OR<sub>adjusted</sub> 1.30, 95% CI 1.20–1.42, Table 2).

Among the mutually exclusive categories containing individuals diagnosed with ID (i.e. 'ID without ASD' and 'ID + ASD') (Supplementary Figure 2, available as Supplementary data at *IJE* online), exposures to T1DM and GDM were associated with odds of 'ID without ASD' and 'ID + ASD' that were similar to each other and to 'Any ID' (T1DM: OR<sub>adjusted</sub> 1.58, 95% CI 1.40–1.79;

**Table 1** Characteristics of the cohort, born in 1987–2010, according to maternal-diabetes exposure during the index pregnancy

	Unexposed <sup>b</sup>	T1DM <sup>b</sup>	T2DM <sup>b</sup>	GDM <sup>b</sup>	PGDM-NOS <sup>b</sup>
Total <sup>a</sup>	2 326 033	17 444	1679	21 325	3199
Children's characteristics					
NDDs diagnosis ( <i>n</i> , %)					
Unaffected	2 193 432 (94.3%)	16 024 (91.9%)	1523 (90.7%)	19 808 (92.9%)	2961 (92.6%)
Any ASD	44 493(2.0%)	482 (2.9%)	51 (3.2%)	577 (2.8%)	75 (2.5%)
Any ID	20 151 (0.9%)	277 (1.7%)	43 (2.7%)	306 (1.5%)	46 (1.5%)
Any ADHD	99 665 (4.3%)	1038 (6.1%)	102 (6.3%)	1035 (5.0%)	178 (5.7%)
ASD only	19 029 (0.9%)	191 (1.2%)	23 (1.5%)	256 (1.3%)	27 (0.9%)
ADHD only	74 982 (3.3%)	753 (4.5%)	74 (4.6%)	750 (3.6%)	132 (4.3%)
ASD + ADHD	18 439 (0.8%)	199 (1.2%)	16 (1.0%)	205 (1.0%)	33 (1.1%)
ID without ASD <sup>c</sup>	13 126 (0.6%)	185 (1.1%)	31 (2.0%)	190 (1.0%)	31 (1.0%)
ID + ASD <sup>d</sup>	7025 (0.3%)	92 (0.6%)	12 (0.8%)	116 (0.6%)	15 (0.5%)
Male sex ( <i>n</i> , %)	1 194 408 (51.3%)	8924 (51.2%)	826 (49.2%)	11 096 (52.0%)	1658 (51.8%)
Birth year ( <i>n</i> , %)					
1987–1991	542 753 (23.3%)	3813 (21.9%)	238 (14.2%)	4292 (20.1%)	978 (30.6%)
1992–1996	508 881 (21.9%)	3701 (21.2%)	124 (7.4%)	4880 (22.9%)	1065 (33.3%)
1997–2001	408 397 (17.6%)	3205 (18.4%)	227 (13.5%)	3505 (16.4%)	294 (9.2%)
2002–2006	461 388 (19.8%)	3714 (21.3%)	474 (28.2%)	4155 (19.5%)	485 (15.2%)
2007–2010	404 614 (17.4%)	3011 (17.3%)	616 (36.7%)	4493 (21.1%)	377 (11.8%)
Birthplace in Sweden ( <i>n</i> , %)					
Stockholm	213 925 (9.2%)	1584 (9.1%)	186 (11.1%)	1432 (6.7%)	359 (11.2%)
Stockholm Suburbs	264 836 (11.4%)	1981 (11.4%)	217 (12.9%)	1766 (8.3%)	362 (11.3%)
Gothenburg and Malmö	201 673 (8.7%)	1413 (8.1%)	192 (11.4%)	2686 (12.6%)	305 (9.5%)
Other cities	329 077 (14.1%)	2395 (13.7%)	199 (11.9%)	3656 (17.1%)	414 (12.9%)
Other towns and suburbs	630 402 (27.1%)	4839 (27.7%)	422 (25.1%)	5648 (26.5%)	719 (22.5%)
Rural areas	675 646 (29.0%)	5098 (29.2%)	448 (26.7%)	6058 (28.4%)	1016 (31.8%)
Missing data	10 474 (0.5%)	134 (0.8%)	15 (0.9%)	79 (0.4%)	24 (0.8%)
Parental characteristics					
Maternal age at birth ( <i>n</i> , %)					
<25	442 481 (19.0%)	3370 (19.3%)	99 (5.9%)	2124 (10.0%)	398 (12.4%)
25–29	792 177 (34.1%)	5756 (33.0%)	315 (18.8%)	5401 (25.3%)	916 (28.6%)
30–34	719 640 (30.9%)	5223 (29.9%)	546 (32.5%)	7083 (33.2%)	1087 (34.0%)
35–39	311 475 (13.4%)	2557 (14.7%)	505 (30.1%)	5083 (23.8%)	620 (19.4%)
≥40	60 122 (2.6%)	538 (3.1%)	214 (12.7%)	1633 (7.7%)	178 (5.6%)
Missing data	138 (0.01%)	0 (0.0%)	0 (0.0%)	1 (<0.01%)	0 (0.0%)
The highest educational level (either parent) ( <i>n</i> , %)					
<9 years	75 775 (3.3%)	772 (4.4%)	141 (8.4%)	1146 (5.4%)	187 (5.8%)
9–12 years	964 083 (41.4%)	8123 (46.6%)	825 (49.1%)	9838 (46.1%)	1568 (49.0%)
>12 years	1 284 664 (55.2%)	8546 (49.0%)	708 (42.2%)	10 311 (48.4%)	1442 (45.1%)
Missing data	1511 (0.1%)	3 (0.02%)	5 (0.3%)	30 (0.1%)	2 (0.1%)
Parental income quintile at birth ( <i>n</i> , %)					
1 (lowest)	322 599 (13.9%)	2411 (13.8%)	389 (23.2%)	4199 (19.7%)	674 (21.1%)
2	473 313 (20.3%)	3797 (21.8%)	488 (29.1%)	5249 (24.6%)	851 (26.6%)
3	496 273 (21.3%)	3876 (22.2%)	362 (21.6%)	4381 (20.5%)	648 (20.3%)
4	507 830 (21.8%)	3896 (22.3%)	263 (15.7%)	3988 (18.7%)	539 (16.8%)
5 (highest)	509 785 (21.9%)	3328 (19.1%)	162 (9.6%)	3362 (15.8%)	443 (13.8%)
Missing data	16 233 (0.7%)	136 (0.8%)	15 (0.9%)	146 (0.7%)	44 (1.4%)
Parents born in Sweden ( <i>n</i> , %)					
Only mother	152 039 (6.5%)	1141 (6.5%)	134 (8.0%)	1163 (5.5%)	230 (7.2%)
Only father	124 902 (5.4%)	636 (3.6%)	121 (7.2%)	1754 (8.2%)	184 (5.8%)
Both born in Sweden	1 790 854 (77.0%)	13 692 (78.5%)	908 (54.1%)	13 340 (62.6%)	2264 (70.8%)
Both born outside Sweden	258 238 (11.1%)	1975 (11.3%)	516 (30.7%)	5068 (23.8%)	521 (16.3%)

(Continued)

Table 1 Continued

	Unexposed <sup>b</sup>	T1DM <sup>b</sup>	T2DM <sup>b</sup>	GDM <sup>b</sup>	PGDM-NOS <sup>b</sup>
Total <sup>a</sup>	2 326 033	17 444	1679	21 325	3199
Parental history of inpatient psychiatric care ( <i>n</i> , %)					
Neither	1 959 617 (84.2%)	13 457 (77.1%)	1209 (72.0%)	17 296 (81.1%)	2544 (79.5%)
One parent	318 642 (13.7%)	3394 (19.5%)	394 (23.5%)	3513 (16.5%)	566 (17.7%)
Both parents	33 198 (1.4%)	481 (2.8%)	48 (2.9%)	361 (1.7%)	65 (2.0%)
Missing data	14 576 (0.6%)	112 (0.6%)	28 (1.7%)	155 (0.7%)	24 (0.8%)
Mothers with PCOS ( <i>n</i> , %)	14 618 (0.6%)	296 (1.7%)	103 (6.1%)	409 (1.9%)	42 (1.3%)
Paternal diabetes ( <i>n</i> , %)					
Unexposed	224 9630 (96.7%)	16 631 (95.3)	1560 (92.9)	20 258 (95)	3028 (94.7)
T1DM	19 167 (0.8%)	201 (1.2%)	7 (0.4%)	171 (0.8%)	34 (1.1%)
T2DM	32 543 (1.4%)	386 (2.2%)	70 (4.2%)	596 (2.8%)	84 (2.6%)
DM-NOS	7418 (0.3%)	78 (0.5%)	9 (0.5%)	116 (0.5%)	24 (0.8%)
With unknown fathers	17 275 (0.7%)	148 (0.9%)	33 (2.0%)	184 (0.9%)	29 (0.9%)
Maternal obstetric characteristics					
Pre-gestational body mass index ( <i>n</i> , %)					
Normal weight	1 153 118 (49.6%)	6483 (37.2%)	276 (16.4%)	5944 (27.9%)	1146 (35.8%)
Underweight	58 613 (2.5%)	195 (1.1%)	10 (0.6%)	271 (1.3%)	45 (1.4%)
Overweight	391 062 (16.8%)	3740 (21.4%)	368 (21.9%)	4839 (22.7%)	623 (19.5%)
Obese	150 831 (6.5%)	2293 (13.1%)	672 (40.0%)	5073 (23.8%)	424 (13.3%)
Missing during 1990–1991	230 970 (9.9%)	1646 (9.4%)	82 (4.9%)	1799 (8.4%)	389 (12.2%)
Otherwise missing	341 439 (14.7%)	3087 (17.7%)	271 (16.1%)	3399 (15.9%)	572 (17.9%)
Gestational weight gain ( <i>n</i> , %)					
Ideal	309 229 (13.3%)	1827 (10.5%)	173 (10.3%)	2478 (11.6%)	401 (12.5%)
Inadequate	197 679 (8.5%)	1279 (7.3%)	152 (9.1%)	2540 (11.9%)	271 (8.5%)
Excessive	293 373 (12.6%)	2348 (13.5%)	210 (12.5%)	2369 (11.1%)	398 (12.4%)
Missing during 1990–1993	352 596 (15.2%)	2616 (15.0%)	126 (7.5%)	3107 (14.6%)	709 (22.2%)
Otherwise missing	1 173 156 (50.4%)	9374 (53.7%)	1018 (60.6%)	10 831 (50.8%)	1420 (44.4%)
Smoking during pregnancy ( <i>n</i> , %)					
No	1 857 941 (79.9%)	13 039 (74.7%)	1253 (74.6%)	17 236 (80.8%)	2420 (75.6%)
Yes	348 790 (15.0%)	3050 (17.5%)	323 (19.2%)	3022 (14.2%)	637 (19.9%)
Missing data	119 302 (5.1%)	1355 (7.8%)	103 (6.1%)	1067 (5.0%)	142 (4.4%)
Maternal hypertensive diseases ( <i>n</i> , %)					
Neither	2 218 576 (95.4%)	14 426 (82.7%)	1370 (81.6%)	19 302 (90.5%)	2854 (89.2%)
Pre-gestational hypertension	15 684 (0.7%)	639 (3.7%)	111 (6.6%)	423 (2.0%)	173 (5.4%)
Pre-eclampsia	67 759 (2.9%)	1908 (10.9%)	137 (8.2%)	1268 (5.9%)	99 (3.1%)
Both	5234 (0.2%)	316 (1.8%)	45 (2.7%)	170 (0.8%)	25 (0.8%)
Missing data	18 780 (0.8%)	155 (0.9%)	16 (1.0%)	162 (0.8%)	48 (1.5%)
Parity ( <i>n</i> , %)					
1	1 000 242 (43.0%)	7546 (43.3%)	408 (24.3%)	7233 (33.9%)	658 (20.6%)
2	842 920 (36.2%)	6105 (35.0%)	523 (31.1%)	7130 (33.4%)	1218 (38.1%)
≥3	482 871 (20.8%)	3793 (21.7%)	748 (44.6%)	6962 (32.6%)	1323 (41.4%)
Neonatal characteristics					
Maturity at birth ( <i>n</i> , %)					
Preterm	111 937 (4.8%)	2879 (16.5%)	227 (13.5%)	1761 (8.3%)	212 (6.6%)
Term	2 043 315 (87.8%)	14 135 (81.0%)	1405 (83.7%)	18 671 (87.6%)	2772 (86.7%)
Post-term	168 224 (7.2%)	389 (2.2%)	47 (2.8%)	880 (4.1%)	210 (6.6%)
Missing data	2557 (0.1%)	41 (0.2%)	0 (0.0%)	13 (0.1%)	5 (0.2%)
Size for gestational age ( <i>n</i> , %)					
AGA	1 121 277 (48.2%)	6564 (37.6%)	652 (38.8%)	9429 (44.2%)	1462 (45.7%)
SGA	1 158 209 (49.8%)	8703 (49.9%)	879 (52.4%)	10 428 (48.9%)	1565 (48.9%)
LGA	38 724 (1.7%)	1873 (10.7%)	126 (7.5%)	1345 (6.3%)	151 (4.7%)
Missing data	7823 (0.3%)	304 (1.7%)	22 (1.3%)	123 (0.6%)	21 (0.7%)

(Continued)

Table 1 Continued

	Unexposed <sup>b</sup>	T1DM <sup>b</sup>	T2DM <sup>b</sup>	GDM <sup>b</sup>	PGDM-NOS <sup>b</sup>
Total <sup>a</sup>	2 326 033	17 444	1679	21 325	3199
Apgar score at 5 minutes ( <i>n</i> , %)					
<7	23 618 (1.0%)	426 (2.4%)	42 (2.5%)	295 (1.4%)	34 (1.1%)
≥7	2 280 141 (98.0%)	16 770 (96.1%)	1630 (97.1%)	20 797 (97.5%)	3116 (97.4%)
Missing data	22 274 (1.0%)	248 (1.4%)	7 (0.4%)	233 (1.1%)	49 (1.5%)

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; GDM, gestational diabetes mellitus; PGDM-NOS, pre-gestational diabetes mellitus-not specified; ASD, autism spectrum disorder; ID, intellectual disability; ADHD, attention-deficit hyperactivity disorder; NDD, neurodevelopmental disorders; PCOS, polycystic ovary syndrome; AGA, appropriate for gestational age; SGA, small for gestational age; LGA, large for gestational age.

<sup>a</sup>Table 1 includes 2 369 680 children born to 1 307 588 mothers. Results are presented as either numbers and percentages (*n*, %) or median.

<sup>b</sup>We applied the  $\chi^2$  test for proportions to compare NDD diagnoses and the parental, obstetric and neonatal and children's characteristics among the unexposed, T1DM, pre-gestational T2DM, GDM and PGDM-NOS. *P*-values were <0.001 for all covariates except *P* = 0.11 for children's sex.

<sup>c</sup>Includes individuals diagnosed with ID and ADHD.

<sup>d</sup>Includes individuals diagnosed with ASD, ID and ADHD.

GDM: OR<sub>adjusted</sub> 1.30, 95% CI 1.15–1.46). However, exposure to T2DM was associated with somewhat higher odds of 'ID without ASD' (OR<sub>adjusted</sub> 2.42, 95% CI 1.67–3.49) compared with 'ID + ASD' (OR<sub>adjusted</sub> 1.61, 95% CI 0.90–2.88) and 'Any ID' (OR<sub>adjusted</sub> 2.09, 95% CI 1.53–2.87) (Table 2).

Among the mutually exclusive categories containing individuals diagnosed with ADHD ('ADHD only', 'ASD + ADHD', 'ID without ASD' and 'ID + ASD') (Supplementary Figure 2, available as Supplementary data at *IJE* online), exposure to T1DM was associated with similar odds between the 'ADHD only' (OR<sub>adjusted</sub> 1.17, 95% CI 1.08–1.26) and 'ASD + ADHD' groups (which contain no cases of co-occurring ID) and to 'Any ADHD' (OR<sub>adjusted</sub> 1.21, 95% CI 1.13–1.29). However, exposure to T1DM was associated with greater odds of 'ID without ASD' and 'ID + ASD' (groups that contain individuals with co-occurring ADHD and ID). Similar patterns were observed for groups exposed to both T2DM and GDM (Table 2).

### Timing of GDM

After stratifying exposure to GDM by gestational week of diagnosis, we found that GDM diagnosed at 27–30 wkGA was associated with the greatest odds of 'Any ASD', 'Any ID' and 'Any ADHD' compared with diagnosis at ≤26 and >30 wkGA (Table 3, Supplementary Figure 5, available as Supplementary data at *IJE* online), with the highest odds associated with the outcome of 'Any ID'. Considering mutually exclusive groups, we found that, for all groups except 'ASD + ADHD', the highest odds were also associated with GDM between 27 and 30 wkGA (Table 3). Of these, the greatest odds were associated with outcomes including ID compared with outcomes without ID.

### Sensitivity analysis

After excluding those with missing values in confounders (Supplementary Tables 4 and 5, available as Supplementary data at *IJE* online), the magnitude and direction of point estimates were largely similar in crude and adjusted models comparing the results of the sensitivity analysis with the main analysis, though CIs tended to be wider. The greatest variability in the point estimates in the sensitivity analysis compared with the main analysis occurred for the exposure of PGDM-NOS. Among individuals with gestational-weight-gain information, associations with maternal diabetes were similar after additionally adjusting for gestational weight gain (Supplementary Tables 6 and 7, Model 3, available as Supplementary data at *IJE* online) compared with adjusting for maternal BMI and other confounders only (Supplementary Tables 6 and 7, Model 2, available as Supplementary data at *IJE* online).

Paternal T2DM was associated with most NDD outcomes (Supplementary Table 8, available as Supplementary data at *IJE* online; Figure 2). However, the odds associated with paternal T1DM and T2DM were generally lower than the odds associated with maternal T1DM and T2DM. Adjusting for paternal T1DM or T2DM had no material effect on the association between maternal T1DM or T2DM and NDDs. Results were similar after excluding individuals whose biological fathers were not in the conscription register or were otherwise missing BMI information (Supplementary Table 9, available as Supplementary data at *IJE* online).

After stratifying GDM-exposed offspring into those born <1993 and ≥1993, we found that, although the odds of NDDs in the <1993 group were generally slightly higher compared with those in the ≥1993 group, no drastic differences in the patterns of associations were observed (Supplementary Figure 6, available as Supplementary data at *IJE* online).



**Table 2** Odds ratios and 95% confidence intervals for the association between maternal diabetes and neurodevelopmental disorders for children born in Sweden in 1987–2010 (N = 2 369 680)

	Unexposed			T1DM			T2DM			GDM			PGDM+NOS					
	No. cases (%)	No. cases (%)	Ref.	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	No. cases (%)	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	No. cases (%)	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	No. cases (%)	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	No. cases (%)	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Ref.
Unaffected	2 193 432	16 024	Ref.	Ref.	Ref.	1523	Ref.	Ref.	Ref.	Ref.	Ref.	2961	Ref.	Ref.	2961	Ref.	Ref.	Ref.
Any ASD	44 493 (1.99)	482 (2.92)	1.48 (1.35, 1.63)	1.29 (1.17, 1.42)	1.37 (1.03, 1.84)	51 (3.24)	1.85 (1.39, 2.48)	1.37 (1.03, 1.84)	577 (2.83)	1.43 (1.32, 1.56)	1.30 (1.20, 1.42)	75 (2.47)	1.21 (0.96, 1.53)	1.13 (0.90, 1.43)	75 (2.47)	1.21 (0.96, 1.53)	1.13 (0.90, 1.43)	1.13
Any ID	20 151 (0.91)	277 (1.70)	1.91 (1.69, 2.16)	1.58 (1.40, 1.79)	2.09 (1.53, 2.87)	43 (2.75)	3.57 (2.59, 4.92)	2.09 (1.53, 2.87)	306 (1.52)	1.68 (1.50, 1.89)	1.30 (1.15, 1.46)	46 (1.53)	1.49 (1.10, 2.02)	1.24 (0.92, 1.67)	46 (1.53)	1.49 (1.10, 2.02)	1.24 (0.92, 1.67)	1.24
Any ADHD	99 665 (4.35)	1038 (6.08)	1.42 (1.33, 1.53)	1.21 (1.13, 1.29)	1.43 (1.16, 1.77)	102 (6.28)	1.78 (1.44, 2.19)	1.43 (1.16, 1.77)	1035 (4.97)	1.17 (1.10, 1.25)	1.16 (1.08, 1.23)	178 (5.67)	1.22 (1.04, 1.43)	1.14 (0.97, 1.34)	178 (5.67)	1.22 (1.04, 1.43)	1.14 (0.97, 1.34)	1.14
ASD only	19 029 (0.86)	191 (1.18)	1.38 (1.20, 1.60)	1.25 (1.08, 1.45)	1.54 (1.01, 2.34)	23 (1.49)	2.00 (1.31, 3.03)	1.54 (1.01, 2.34)	256 (1.28)	1.49 (1.32, 1.69)	1.37 (1.21, 1.56)	27 (0.90)	1.02 (0.70, 1.49)	0.97 (0.66, 1.42)	27 (0.90)	1.02 (0.70, 1.49)	0.97 (0.66, 1.42)	0.97
ADHD only	74 982 (3.31)	753 (4.49)	1.37 (1.27, 1.49)	1.17 (1.08, 1.26)	1.43 (1.12, 1.82)	74 (4.63)	1.74 (1.37, 2.22)	1.43 (1.12, 1.82)	750 (3.65)	1.13 (1.05, 1.22)	1.14 (1.06, 1.23)	132 (4.27)	1.22 (1.02, 1.47)	1.15 (0.96, 1.38)	132 (4.27)	1.22 (1.02, 1.47)	1.15 (0.96, 1.38)	1.15
ASD + ADHD	18 439 (0.83)	199 (1.23)	1.46 (1.26, 1.69)	1.23 (1.06, 1.42)	1.12 (0.68, 1.86)	16 (1.04)	1.46 (0.88, 2.42)	1.12 (0.68, 1.86)	205 (1.02)	1.26 (1.09, 1.44)	1.20 (1.04, 1.38)	33 (1.10)	1.33 (0.94, 1.88)	1.27 (0.89, 1.80)	33 (1.10)	1.33 (0.94, 1.88)	1.27 (0.89, 1.80)	1.27
ID without ASD <sup>c</sup>	13 126 (0.59)	185 (1.14)	1.96 (1.68, 2.28)	1.59 (1.37, 1.85)	2.42 (1.67, 3.49)	31 (1.99)	4.22 (2.91, 6.12)	2.42 (1.67, 3.49)	190 (0.95)	1.62 (1.40, 1.88)	1.25 (1.08, 1.45)	31 (1.04)	1.50 (1.04, 2.17)	1.22 (0.85, 1.76)	31 (1.04)	1.50 (1.04, 2.17)	1.22 (0.85, 1.76)	1.22
ID + ASD <sup>d</sup>	7025 (0.32)	92 (0.57)	1.81 (1.46, 2.23)	1.54 (1.25, 1.90)	1.61 (0.90, 2.88)	12 (0.78)	2.74 (1.53, 4.90)	1.61 (0.90, 2.88)	116 (0.58)	1.82 (1.51, 2.19)	1.38 (1.14, 1.66)	15 (0.50)	1.54 (0.92, 2.57)	1.28 (0.77, 2.14)	15 (0.50)	1.54 (0.92, 2.57)	1.28 (0.77, 2.14)	1.28

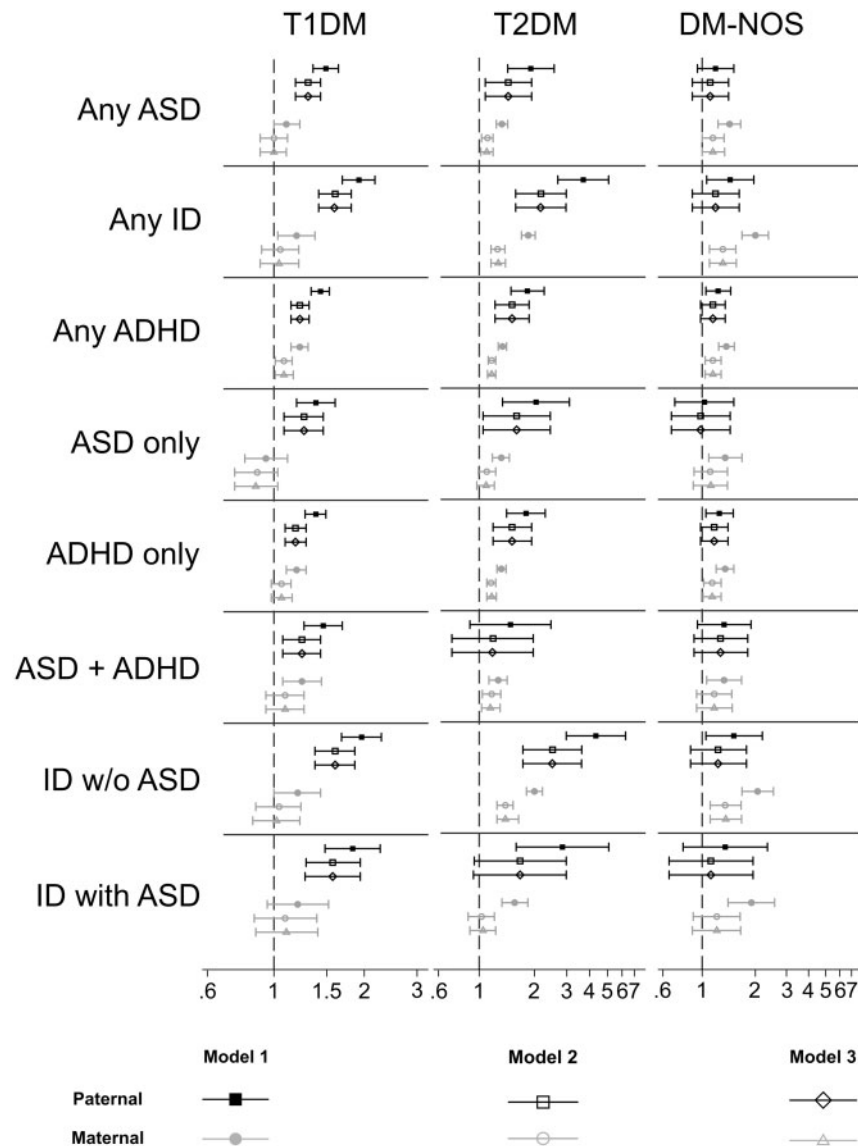
T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; GDM, gestational diabetes mellitus; PGDM+NOS, pre-gestational diabetes mellitus-not specified; ASD, autism spectrum disorder; ID, intellectual disability; ADHD, attention-deficit hyperactivity disorder.

<sup>a</sup>Model 1: adjusted for birth year and children's sex.

<sup>b</sup>Model 2: adjusted for birth year, children's sex, maternal age, parity, the highest parental educational level, parental income quintile at birth, children's birthplace in Sweden, parental immigration status, parental history of inpatient psychiatric care, smoking during pregnancy, PCOS and pre-gestational BMI. Missing values were replaced with dummy categories and a complete data set was used for this analysis.

<sup>c</sup>Includes individuals diagnosed with ID and ADHD.

<sup>d</sup>Includes individuals diagnosed with ASD, ID and ADHD.



**Figure 2** Odds ratios (log-scale) and 95% confidence intervals for the associations between maternal/paternal diabetes and neurodevelopmental disorders in the offspring (see also [Supplementary Table 8](#), available as [Supplementary data](#) at *IJE* online)

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; GDM, gestational diabetes mellitus; PGDM-NOS, pre-gestational diabetes mellitus not specified; ASD, autism spectrum disorder; ID, intellectual disability; ADHD, attention-deficit hyperactivity disorder.

## Discussion

In this large population-based cohort study, we found that exposure to maternal diabetes was associated with an increased risk of ASD, ID and ADHD in offspring. Exposure to T2DM was associated with a greater risk of all three NDDs in offspring compared with T1DM and GDM. After categorizing the NDD outcomes into mutually exclusive diagnostic groups, we found that T2DM was still associated with the greatest risks for most outcomes. The associations with T1DM and T2DM were strongest for outcomes that included a diagnosis of ID. Paternal lifetime history of T1DM and T2DM was also associated with offspring risk of NDDs, though the associations were weaker

compared with associations with maternal T1DM and T2DM. Finally, considering the timing of GDM onset, we found that diagnosis of GDM between 27 and 30 wkGA was generally associated with the greatest risk of NDDs in offspring, with the strongest associations for outcomes including diagnoses of ID.

## Strengths and limitations

Our study has several strengths. By considering the co-occurrence of ASD, ID and ADHD, we were able to compare and contrast the magnitude of associations between diagnostic groups—something few other studies have done

**Table 3** Odds ratios and 95% confidence intervals for the association between gestational diabetes mellitus and neurodevelopmental disorders, according to gestational week at diagnosis, in children born in Sweden in 1987–2010 (N = 2347358)

	≤26 wkGA			27–30 wkGA			>30 wkGA			Unknown date		
	No. cases (%)	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	No. cases (%)	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	No. cases (%)	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	No. cases (%)	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>
Unaffected	2 193 432	Ref.	Ref.	2 117	Ref.	Ref.	12 547	Ref.	Ref.	2 773	Ref.	Ref.
Any ASD	44 493 (1.99)	1.55 (1.22, 1.97)	1.35 (1.06, 1.72)	70 (3.20)	1.78 (1.41, 2.26)	1.59 (1.25, 2.02)	355 (2.75)	1.37 (1.23, 1.53)	1.25 (1.12, 1.39)	82 (2.87)	1.38 (1.11, 1.72)	1.30 (1.04, 1.63)
Any ID	20 151 (0.91)	1.50 (1.04, 2.16)	0.98 (0.68, 1.40)	51 (2.35)	2.90 (2.19, 3.84)	2.12 (1.60, 2.81)	192 (1.51)	1.65 (1.43, 1.91)	1.32 (1.14, 1.52)	32 (1.14)	1.16 (0.82, 1.65)	0.92 (0.65, 1.31)
Any ADHD	99 665 (4.35)	1.33 (1.11, 1.59)	1.25 (1.04, 1.51)	110 (4.94)	1.24 (1.03, 1.51)	1.23 (1.01, 1.50)	668 (5.05)	1.18 (1.09, 1.27)	1.16 (1.07, 1.26)	130 (4.48)	0.99 (0.83, 1.18)	1.00 (0.84, 1.20)
ASD only	19 029 (0.86)	1.62 (1.13, 2.31)	1.47 (1.03, 2.10)	29 (1.35)	1.74 (1.21, 2.51)	1.58 (1.10, 2.29)	153 (1.20)	1.39 (1.18, 1.63)	1.27 (1.08, 1.50)	43 (1.53)	1.68 (1.24, 2.28)	1.58 (1.17, 2.14)
ADHD only	74 982 (3.31)	1.26 (1.02, 1.56)	1.22 (0.98, 1.51)	83 (3.77)	1.25 (1.00, 1.56)	1.29 (1.03, 1.61)	483 (3.71)	1.13 (1.03, 1.24)	1.14 (1.04, 1.26)	95 (3.31)	0.96 (0.78, 1.17)	0.99 (0.80, 1.21)
ASD + ADHD	18 439 (0.83)	1.45 (0.98, 2.13)	1.34 (0.91, 1.98)	21 (0.98)	1.27 (0.82, 1.96)	1.19 (0.77, 1.84)	128 (1.01)	1.23 (1.03, 1.46)	1.17 (0.98, 1.39)	30 (1.07)	1.23 (0.86, 1.77)	1.24 (0.86, 1.78)
ID without ASD <sup>c</sup>	13 126 (0.59)	1.40 (0.87, 2.25)	0.88 (0.55, 1.41)	31 (1.44)	2.76 (1.92, 3.96)	2.01 (1.40, 2.89)	118 (0.93)	1.58 (1.31, 1.90)	1.26 (1.05, 1.51)	23 (0.82)	1.26 (0.84, 1.91)	1.01 (0.67, 1.52)
ID + ASD <sup>d</sup>	7025 (0.32)	1.77 (1.01, 3.08)	1.16 (0.67, 2.02)	20 (0.94)	3.18 (2.05, 4.93)	2.29 (1.47, 3.56)	74 (0.59)	1.82 (1.45, 2.29)	1.41 (1.12, 1.78)	9 (0.32)	0.97 (0.50, 1.86)	0.76 (0.39, 1.46)

ASD, autism spectrum disorder; ID, intellectual disability; ADHD, attention-deficit hyperactivity disorder; GDM, gestational diabetes mellitus; wkGA, weeks of gestation.

<sup>a</sup>Model 1: adjusted for birth year and children's sex.

<sup>b</sup>Model 2: adjusted for birth year, children's sex, maternal age, parity, the highest parental educational level, parental income quintile at birth, children's birthplace in Sweden, parental immigration status, parental history of inpatient psychiatric care, smoking during pregnancy, PCOS and pre-gestational BMI. Missing values were replaced with dummy categories and a complete data set was used for this analysis. Missing values in gestational week at delivery (Percentage missing = 0.11%) were replaced by 40 wkGA (280 days) for calculating the gestational week of exposure to GDM.

<sup>c</sup>Includes individuals diagnosed with ID and ADHD.

<sup>d</sup>Includes individuals diagnosed with ASD, ID and ADHD.

despite the common co-occurrence of these disorders. Use of clinically diagnosed maternal diabetes to define exposure and clinically diagnosed outcomes recorded in population-based registers reduced biases in the ascertainment of both exposures and outcomes. We used a family-based study design to evaluate the potential for confounding of the relationship between maternal diabetes and offspring risk for NDDs by shared familial factors. We considered any diagnosis of each NDD as well as mutually exclusive groups reflecting commonly co-occurring diagnostic groups. This approach allowed us to question whether the relationships between maternal diabetes and neurodevelopmental disorders were unique to the individual diagnostic group. We observe that some relationships that were more apparent when we considered the mutually exclusive groups (e.g. the association between T2DM and ID without ASD) were somewhat attenuated compared with the analyses that considered overlapping diagnostic groups (e.g. T2DM and Any ID).

Our results ought to be interpreted in light of several limitations. The register data we used are generally considered to be of high quality.<sup>38</sup> For example, in the Swedish National Patient Register, the positive predictive value is over 99% for diabetes and 94.3% for ASD.<sup>38,39</sup> However, the ability of the registers to distinguish between the different types of maternal diabetes has not been validated.

Whereas records for most individuals were largely complete, we did have a large number of missing observations for two variables that are important in this context: BMI and gestational weight gain. Pre-gestational BMI is likely to be a strong modulating factor for the risks associated with T2DM<sup>50</sup> and GDM.<sup>51</sup> Although we generally found the same pattern of associations in the sensitivity analysis after excluding those with missing values in BMI and other confounders, variability in the point estimates and CIs suggests that there may be some residual confounding from individuals whose BMI could not be correctly classified in our main analysis. In addition, there is still the possibility for residual confounding by other factors not adequately captured by our analysis, particularly with regard to socio-demographic factors.

Sample sizes for different exposure groups varied, leading to a difference in statistical power across these groups. Additionally, when comparing results for different types of maternal diabetes, we have emphasized point estimates, though it is important to note that the 95% CIs between these groups sometimes overlap, so caution is necessary when interpreting differences between exposure groups relative to each other.

Given that individuals in Sweden have universal access to comprehensive healthcare, we assume that most of the GDM cases were detected and recorded promptly. Using

the registered dates of diagnoses as a proxy for the onset of GDM may lead to misclassification if the true time of onset did not correspond to the registered date of diagnosis. Moreover, there was no information available regarding the methods and criteria used for diagnosing GDM, which have changed over time.<sup>52</sup> We did not have information on the efficacy of treatment of hyperglycaemia, nor do we have any information regarding biomarkers of glycaemic control, which is a key limitation as the risks associated with maternal diabetes may well differ with the degree of control of diabetes. Similarly, we lacked any information regarding subclinical disease or pre-diabetes, as we relied on clinical diagnosis of overt diabetes in this study.

Another limitation is the generalizability of the study. The prevalence of different types of maternal diabetes varies across ethnicities and countries.<sup>53</sup> Sweden has the second highest annual incidence of T1DM in the world next to Finland.<sup>54</sup> The prevalence of overweight and obesity, however, and the corresponding prevalence of T2DM and GDM are considerably lower in Sweden compared with those in other parts of the developed world.<sup>13</sup> Despite these differences, multiple other studies have reported similar patterns of associations,<sup>13,14,24,26</sup> indicating that our results may well be applicable to other populations.

### Comparison with previous studies

In accordance with previous studies, we showed that PGDM is associated with an increased risk of ASD in offspring.<sup>13,14,24,26</sup> Xiang *et al.* observed an association between GDM and risk of ASD after stratification by gestational week at diagnosis and observed that exposure at  $\leq 26$  wkGA was associated with the greatest risk of ASD.<sup>14,26</sup> Conversely, we found that exposure to cases diagnosed between 27 and 30 wkGA was associated with the greatest risk for ASD, though this difference may relate to the strategies for GDM screening in the two different healthcare settings. Few previous studies have investigated the association between maternal diabetes and ID in offspring.<sup>16,17</sup> Mann *et al.* found a stronger association between PGDM and ID in offspring compared with GDM,<sup>16</sup> consistently with our results for ID. A handful of studies have previously investigated the association between maternal diabetes and ADHD,<sup>12,25,55,56</sup> with results largely consistent with our own, though Xiang *et al.* reported no associations between GDM and ADHD, even after the timing of exposure was considered.<sup>12</sup>

While investigating the association between maternal diabetes and ASD, ID and/or ADHD in offspring, few studies have accounted for the frequent co-occurrence of these three conditions.<sup>15,25</sup> Li *et al.* reported that the risk of ASD associated with PGDM and GDM could mainly be

explained by the co-occurrence of ASD and ID, suggesting that ASD with ID formed an etiologically distinct group.<sup>25</sup> Our results support the idea that co-occurring ASD and ID may be etiologically distinct from ASD, though we observed the strongest associations with outcomes including ID regardless of other co-occurring NDDs. In another Swedish registered-based study, Ji *et al.* excluded ADHD cases with a secondary diagnosis of ID, ASD or Tourette syndrome and report an increased risk of ADHD in offspring whose mothers had T1DM,<sup>15</sup> consistently with our findings when considering ADHD without ASD and/or ID.

### Potential mechanisms and interpretation

ASD, ID and ADHD are complex NDDs with high estimated heritabilities.<sup>28</sup> Both T1DM and T2DM are polygenic disorders<sup>57,58</sup> and genes related to increased risks of both forms of diabetes may also be involved in the aetiology of NDDs.<sup>34,59–61</sup> Shared genetic liability may therefore contribute to the associations between maternal T1DM and T2DM and offspring risk of NDDs reported here, given the elevated risk for NDDs in offspring in relation to paternal lifetime T1DM and T2DM diagnoses. However, maternal diabetes was more strongly associated with NDDs compared with paternal diabetes, indicating that genetic factors or other shared familial factors do not completely explain the associations between maternal diabetes and offspring risk of NDDs. Genetic studies have provided mixed evidence as to whether genetic correlations exist between neurodevelopmental disorders and diabetes. A study using polygenic risk scores found no evidence that shared genetic liability contributed significantly towards the association between maternal diabetes and NDDs in offspring, though the authors noted that the study may not have been adequately powered to detect such associations.<sup>62</sup> Another study using data from genome-wide association studies showed a negative genetic association between T1DM and ADHD in the same individuals, and no association between T1DM and ASD.<sup>34</sup> However, genetic correlations have been noted between ADHD and indicators of obesity (high body-fat percentage, fat mass and fat-free mass, which are risk factors for T2DM and GDM) and Mendelian randomization subsequently indicated that the relationship between fat mass and ADHD may be causal.<sup>33</sup> The genetic overlap between body-fat composition and ADHD may support the idea for some cross-generational genetic liability<sup>33</sup> in that mothers at greater risk of obesity (and thus T2DM and GDM) also have greater genetic liability for ADHD, and may therefore transmit a higher risk of ADHD to their children.

Besides genetic liability, multiple plausible mechanisms to link maternal diabetes and NDDs have been proposed.

These mechanisms include oxidative stress, hypoxia, apoptosis, epigenetic changes and increased risk of pregnancy complications induced by the immunologic and metabolic disturbances associated with maternal diabetes.<sup>12–15,25,63–70</sup> While plausible, our study provides no direct evidence for the involvement of any of these mechanisms. Our study design also does not allow conclusions to be drawn regarding direct causality in the associations we observed, which would need to be explored further in future studies.

We found that PGDM was associated with a greater risk of NDDs in offspring compared with GDM. The timing of environmental exposures may lead to different phenotypic outcomes with regard to neurodevelopment.<sup>28</sup> Hyperglycemia due to PGDM may have a greater influence over gross development of the brain in the first trimester,<sup>63,71</sup> whereas GDM usually occurs during the second half of pregnancy when the major developmental events for the cerebral cortex occur<sup>72</sup> and may thus have a greater influence over the development of higher cognitive functions.<sup>63,64,73</sup>

We also observed that T1DM and T2DM were most strongly associated with outcomes including ID. Though we do not have direct evidence to suggest underlying mechanism for this observation, we speculate that it may be related to late-pregnancy fetal exposure to hyperglycaemia being associated with complications such as preterm birth, macrosomia and neonatal hyperinsulinaemia; which can occur with all forms of diabetes. These can subsequently lead to neonatal complications such as hypoxia/asphyxia.<sup>74</sup>

Whereas differences in risk for NDDs with regard to the timing of exposure lend plausibility to the notion that glycaemic control during distinct periods of pregnancy may influence the neurodevelopment of the offspring,<sup>75</sup> it is important to note that the observations regarding timing of GDM are not entirely consistent between our study and the only other setting in which the timing of GDM diagnosis has been considered.<sup>12,14</sup> The duration of diabetes exposure also did not have a large influence on the risk of NDDs in offspring, in the sense that risks associated with GDM diagnosed at earlier dates were not necessarily associated with higher risks of NDDs compared with GDM diagnosed at later dates.

### Conclusion

Our results suggest that differences in the association between maternal diabetes and risk of NDDs in offspring depend on the type and timing of maternal diabetes and the co-occurring presentation of NDDs, with the strongest associations observed for outcomes including ID. These associations remained when parental genetic factors were

accounted for. The underlying mechanisms of our findings remain unclear, thus future studies are needed to further explore whether neurodevelopmental disorders in children exposed to diabetic pregnancies may to some extent be related to exposure to hyperglycaemia during pregnancy.

## Supplementary data

Supplementary data are available at *IJE* online.

## Author Contributions

R.G. and C.D. proposed the research idea. S.C. conducted the statistical analysis and all authors participated in the interpretation of the statistical reports. S.C. and S.Z. wrote the first and subsequent drafts of the paper with important intellectual input and revision from all co-authors. Full access to the data, statistical reports and tables arising from the data analysis was granted to all authors, and all authors take responsibility for the integrity of the data and accuracy of the data analysis. All authors have approved the final version of the manuscript submitted for publication. R.G. and C.D. act as guarantors and assure that this manuscript is an honest, accurate and transparent account of the analysis undertaken.

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## Conflict of interest

None declared.

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