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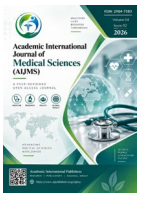

# Family History of Diabetes and Early-Life Exposures in Iraqi Children with Type 1 Diabetes: A Hospital-Based Case–Control Study

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## Abstract

**Background**: There is clear evidence for familial aggregation of childhood Type 1 Diabetes Mellitus (T1DM), but evidence of pregnancy, perinatal and childhood exposures is less consistent. Case–control comparisons in hospital settings also rely on control selection and similar exposure measurement.

**Objective**: We estimated the odds of T1DM in children based on parent-reported diabetes in first-degree relatives in Karbala, Iraq. We discussed limitations to interpret other exposure comparisons.

**Methods**: This hospital-based case–control study included 258 children with established T1DM, and 383 non-diabetic hospital controls recruited from the Karbala Teaching Hospital of Paediatrics between September 2014 and March 2015. We did not verify exposure records. Because the questionnaire did not reliably predict diabetes Type I in relatives, we used any reported diabetes in a first-degree relative as the main exposure. We performed the main analysis in children aged ≥12 months (n=254; n=196 controls) using Firth-penalised logistic regression adjusted for sex and age, fitted with a restricted cubic spline. Sensitivity analyses tested age restriction, recall period length, and sibling exclusion and parent-only family history. All other exposures were exploration.

**Results**: First-degree family history was reported for 57/254 cases (22.4%) and 16/196 controls (8.2%); adjusted OR 4.56 (95% CI 2.24–9.69). The sibling estimate was 15.39 (4.16–85.02), based on 35 exposed cases and two exposed controls; the parent estimate was 2.22 (0.98–5.11). We observed no

association between any relative family history and case status (OR 1.03, 0.64–1.67), and second-degree family history was more common among controls. Type-labelled family-history estimates were conflicting but unconfirmed due to the lack of verification for type. An age trend for cases was seen with gestational diabetes. The differences in early-life exposure clustered on variables that may depend on health care contact or diagnosis.

**Conclusions**: In this hospital sample, parent-reported diabetes in a first-degree relative was associated with T1DM case status with a more modest, though still fairly imprecise sibling-category estimate (based on two exposed controls). The results do not prove causation or a genetic cause. Comparability limitations include unverified and missing reporting versus negative coding, as well as the uncertain representativeness of hospital controls in terms of type and early life.

## 1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterised by insulin deficiency due to loss of pancreatic beta cells. Childhood incidence varies widely by population and has risen in many registries, suggesting that genetic susceptibility works alongside temporal and environmental effects [1–3,19]. Genetic susceptibility is polygenic, and HLA variation plays a significant role alongside many non-HLA loci [7,8]. Family studies have always shown familial aggregation, which is typically higher in the first degree than in more distant family members, but the majority of children who develop T1DM do not have an affected close relative [20–22].

Infections, early-life growth, perinatal events, and diet have been proposed as environmental contributors, but results vary by exposure and/or population and study design [7–11,19–27,36]. Observational studies cannot confirm that exposure causes or triggers T1DM. There is limited evidence from Iraq. A descriptive study in Karbala reported maternal, neonatal, and childhood exposures but did not include an appropriate non-diabetic control group [12]. Researchers have studied these factors in Kuwait and other settings, but results have not always been consistent [4–6,13–15,29,30].

A hospital-based case–control comparison is valid if two conditions are met [16]. First, controls should come from the population that controls should be sampled from, and the age distribution of the hospitalised children with acute illnesses may differ from the age distribution of children receiving ongoing specialist care, as may their healthcare access, and exposures may not be documented or distributed equally. Second, exposure data should use consistent definitions and be as precise as possible in both groups. Family history is particularly sensitive to the elicited term, “diabetes,” without specific clinical diagnosis of type. The current study thus aimed to estimate the relationship between parent-reported diabetes in first-degree relatives and T1DM case status, and to explore the interpretability of other family-history and early-life comparisons given the available information on measurements and recruitment. We conducted exploration analyses for the latter, but they were not designed to identify causal risk factors.

## 2. Methods

### 2.1 Design, setting and reporting.

We conducted a case–control study at Karbala Teaching Hospital of Paediatrics, the governorate's referral centre for children with diabetes, from 1 September 2014 to 1 March 2015. We used the STROBE case–control checklist to guide reporting [17,18]. We developed the analysis plan after collecting the data. It was not registered and should therefore be viewed as exploratory for analyses that

were not prespecified, with the primary exposure definition in the analysis plan generally the same as in the design.

### 2.2 Participants

Children with T1DM and a known diagnosis, who have been started on insulin since diagnosis and attend a diabetic clinic or are admitted with ketoacidosis or hyperglycaemia were included in the case group. The case group comprised children aged 4 months to 15 years, who had a known diagnosis of T1DM, had been commenced on insulin since diagnosis and attended the diabetic clinic, or were admitted with ketoacidosis or hyperglycaemia. Children with type 2, neonatal, monogenic or secondary diabetes, those aged over 15 years and those for whom parents did not provide a history were not included. We included no cases, only exposure history, because cases were prevalent rather than incident. Controls were children of the same age range admitted to the study during the same period as the children with diabetes, except that they were not admitted for a diagnosis of non-diabetic conditions. They were selected from hospital admission records, but the precise selection procedure and distribution of admission diagnoses could not be verified from the available documentation [16]. Children with a personal history of diabetes were excluded. We analysed 258 cases and 383 controls (Table 1; Figure 1).

### 2.3 Data collection

After obtaining verbal consent, the investigator interviewed the mother or other available parent using a structured questionnaire. Case and control forms were separate but included the same exposure items. The identity of the respondent is not kept on the dataset. We collected parent-reported exposure data and did not verify exposure through antenatal, delivery, neonatal, or paediatric records. We interviewed cases after T1DM diagnosis, while we interviewed controls when they were admitted for a non-diabetic condition. The item content was therefore identical, but the setting and perhaps the knowledge of the person answering the questions differed.

### 2.4 Exposure definitions

Family history. The questionnaire asked about diabetes (Type 1 or type 2) for eight relatives—father, mother, brother, sister, uncle, aunt, grandfather, and grandmother. First-degree relatives included parents and siblings; second-degree relatives were aunts, uncles and grandparents [21,30]. The major risk factor reported was any family member with diabetes in the first degree. We studied history from parents and siblings separately, and kept second-degree history separate. The study also used type-specific indicators (FH_T1DM and FH_T2DM), with one indicator per type. No medical verification was made for these labels, and the method for the respondent/investigator to designate the type of diabetes is not documented. The family-history burden is likely to be underestimated, as only one relative per type was retained and the number of affected relatives was not recorded. The data do not allow one to conclude whether family history ascertainment was equally accurate in cases and controls.

Other exposures and measurement. Only pregnancy, delivery, and neonatal and childhood exposures that were supported by the questionnaire and data set were analysed. Single-category variables include maternal habit and medication, neonatal condition and place/mode of delivery, but do not account for co-occurring exposures. Place and mode of delivery were collected as a composite variable, and therefore, caesarean delivery cannot be separated from delivery setting in all comparisons. We did not create a composite variable for childhood infection; we analysed individual infections separately. The interpretable feeding measure was feeding type (breast, bottle or mixed). The duration indicator was

limited to breast- and mixed-fed children only, so BF_6m should not be interpreted across all feeding groups; we analysed it only within this group. Supplementary Table S1 shows a summary of exposure sources, verification, exposure category and duration limitations.

### 2.5 Missing data

The dataset has no blank exposure cells, and each exposure denominator is the group total. There are no special categories for "unknown", "not reported", or "not applicable" (except for the limited BF_6m analysis), and there is no "no exposure" category for the coding convention. This means that if someone has an exposure and it is not reported or recorded, it will not be distinguished from a true negative. Originally completed questionnaires and medical records were not available for this analysis, so we could not recover these distinctions. No values were imputed or recorded. The original coding was used. Timing (e.g., trimester) and duration were generally unavailable and therefore were not estimated. This missingness reflects a measurement limitation rather than conventional missingness and cannot be addressed with complete-case or multiple-imputation approaches using the provided data.

### 2.6 Statistical analysis

Because 187 controls and four cases were younger than 12 months, we conducted the primary analysis only in children aged ≥12 months (254 cases, 196 controls). This limit will decrease the maximum age non-overlap while omitting many controls and will not ensure that the controls used represent the source population of the cases. Crude odds ratios were generated using the Woolf method, and a 0.5 continuity correction was used only for the zero cells. We adjusted odds ratios using Firth penalised logistic regression [31,35]. We modelled age as a restricted cubic spline, with exposure and sex as categorical covariates with knots at the 10th, 50th, and 90th percentiles of the analysis sample [32]. We added sex and age because they varied between groups, along with additional covariates that we could not add due to limited numbers of exposed controls for some exposures. Profile penalised-likelihood 95% confidence intervals and penalised likelihood-ratio p-values are reported. We chose this definition of first-degree family history post hoc, based on data collection and inspection of the questionnaire structure and data. We also ran a secondary analysis using type-labelled family history for transparency. We fitted each of the 30 binary exposure models in Table 4 individually, and we corrected the p-values for multiple testing using the Benjamini–Hochberg procedure [34]. These tests are preliminary and do not estimate causal effects.

Sensitivity analyses were performed on the main family-history association over all ages, ages ≥5 years, ages 12–120 months, ages 12–60 months, using a five-stratum Mantel–Haenszel estimate, over all reported affected sibling cases (excluding children with an affected sibling report), and in a parent-only comparison (excluding sibling and second-degree history). These analyses use overlapping participants and are not replications. Comparability diagnostics included: age-specific patterns of exposure; unconditional comparisons between groups of cases and controls across age groups; and whether the process of recording particular exposures was affected by the medical contact. These diagnostics can show patterns that are consistent with bias but can't identify or quantify the cause.

### 2.7 Quantitative Exposure-Misclassification Analysis

Crude odds ratios (OR) were re-estimated for six exposure combinations of sensitivity (Se) and specificity (Sp) for the primary family-history exposure and six selected pregnancy, perinatal or childhood exposures. The number of unobserved cases and controls was estimated to be (observed − (1 − Sp) × group size) / (Se + Sp − 1) individually for cases and controls. We did not measure the assumed

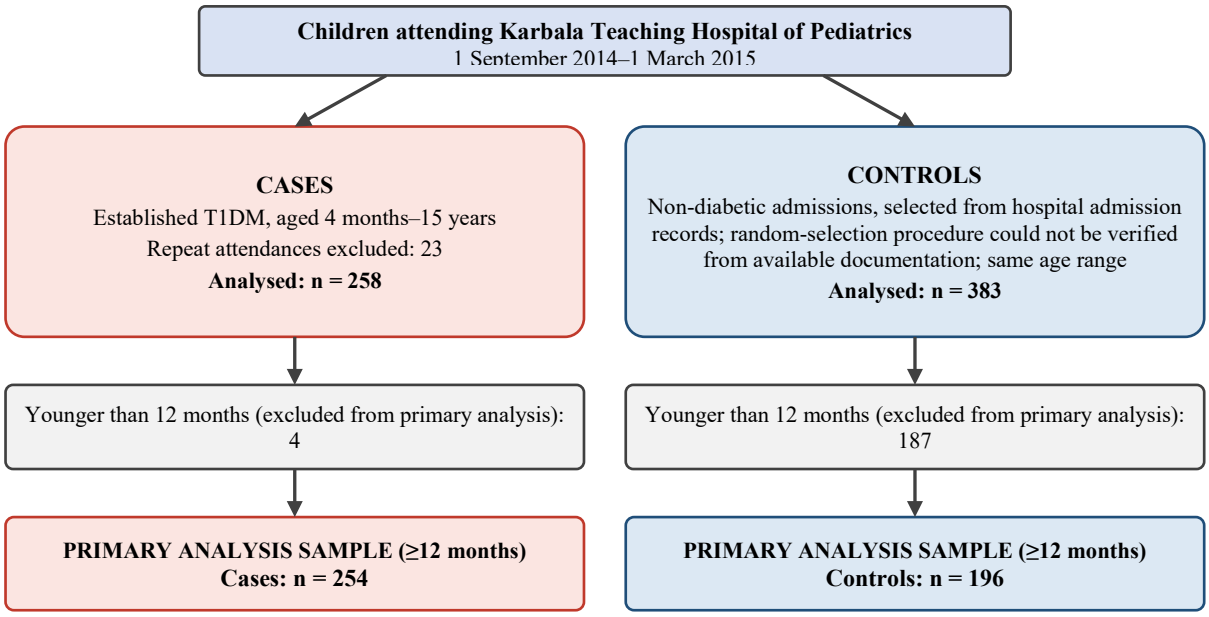
Se and Sp values; instead, we used them to demonstrate the potential impact of differential and non-differential misclassification on the crude estimates. In the cases where cells became negative after correction, the respective scenarios were considered not feasible; in the cases where the cells were few and extreme, they were flagged as unstable. We used tipping analysis to estimate the proportion of case sensitivity to control sensitivity needed to make the association disappear under perfect specificity. These analyses are illustrative quantitative bias analyses, not validation or correction for the true effect, and do not include control-selection bias.

### 2.8 Ethics

The study protocol received ethical approval from the Scientific Committee of Karbala Teaching Hospital of Pediatrics in March 2014, in accordance with the ethical standards and regulations of the Iraqi Ministry of Health.

## 3. Results

### 3.1 Study population




Sensitivity analysis samples (cases/controls): all ages 258/383; ≥5 years 228/67; age-overlap region (12–120 months) 86/177; cases diagnosed ≤24 months before interview vs all controls ≥12 months 67/196

Figure 1. Participant flow. The final analysed sample comprised of 258 cases and 383 controls. Records report 23 repeat attendances excluded; additional screening counts were not recorded, so no further screening totals are inferred.

There was a significant difference in age between cases and controls (Table 1, Figure 2): Median age of 145 months (IQR 95–161) in cases compared to 12 months (IQR 4–48) in controls ($p < 0.001$). When the full sample was analysed, 65.1% of cases, compared to 5.0% of controls, were aged> 10- 15 years (168 cases; 19 controls), while 48.8% of controls but only 1.6% of cases aged 4-11 months (187 controls and 4 cases). Median age was 145 months in the cases and 48 months in the controls of the primary sample (aged ≥12 months), with 66.1% of cases and 9.7% of controls aged 121–180 months. After restriction, there is still a significant amount of overlap. The limited number of older controls cannot be

completely matched by continuous age adjustment. There were more girls in both the cases (55.8%) and control (41.8%) groups ($p < 0.001$), and sex was added to the models. There was no difference in parental consanguinity (31.0% vs 26.9%) or preterm birth. Age at diagnosis of T1DM did not differ between cases with and without family history (49 months, median vs 57 months, median, $p = 0.55$).

Table 1. Characteristics of the study groups

| Characteristic | Cases (n = 258) | Controls (n =383) | p | Cases ≥12 mo (n = 254) | Controls ≥12 mo (n = 196) | p |
|---|---|---|---|---|---|---|
| Age, months, median (IQR) | 145 (95–161) | 12 (4–48) | <0.001 | 145 (99–162) | 48 (30–88) | <0.001 |
| 4–11 months, n (%) | 4 (1.6) | 187 (48.8) | | – | – | |
| 12–60 months, n (%) | 28 (10.9) | 131 (34.2) | <0.001 | 28 (11.0) | 131 (66.8) | <0.001 |
| 61–120 months, n (%) | 58 (22.5) | 46 (12.0) | <0.001 | 58 (22.8) | 46 (23.5) | 0.87 |
| 121–180 months, n (%) | 168 (65.1) | 19 (5.0) | <0.001 | 168 (66.1) | 19 (9.7) | <0.001 |
| Female, n (%) | 144 (55.8) | 160 (41.8) | <0.001 | 142 (55.9) | 90 (45.9) | 0.036 |
| Parental consanguinity, n (%) | 80 (31.0) | 103 (26.9) | 0.26 | 78 (30.7) | 55 (28.1) | 0.54 |
| Preterm birth, n (%) | 23 (8.9) | 31 (8.1) | 0.71 | 23 (9.1) | 15 (7.7) | 0.60 |
| Family history of T1DM (type-labelled), n (%) | 76 (29.5) | 35 (9.1) | <0.001 | 74 (29.1) | 19 (9.7) | <0.001 |
| Diabetes in a first-degree relative, any type, n (%) | 59 (22.9) | 29 (7.6) | <0.001 | 57 (22.4) | 16 (8.2) | <0.001 |
| Age at diagnosis, months, mean (SD) | 64.0 (45.8) | – | | 64.9 (45.6) | – | |
| Time since diagnosis at interview, months, median (IQR) | 59 (24–97) | – | | 60 (25–97) | – | |

Chi-square test (categorical) and Mann–Whitney test (age). IQR, interquartile range. The full-sample 4–11-month band comprises children younger than 12 months (4 cases and 187 controls). Children aged exactly 12 months are included in the primary sample (≥12 months), whose first age band is 12–60 months.

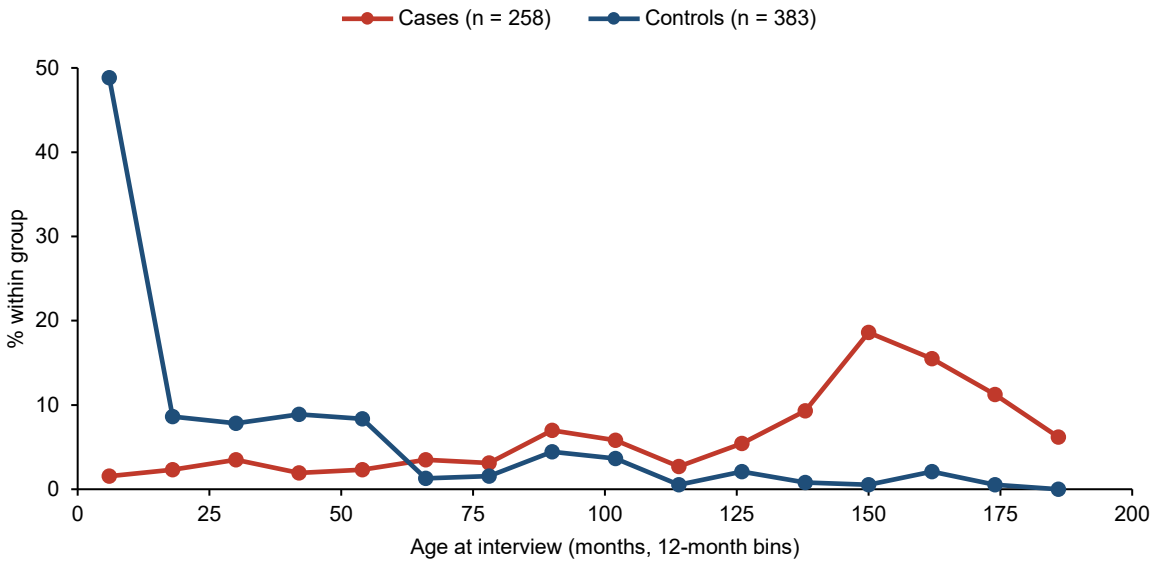



Figure 2. Age distribution of cases and controls (full sample, % within group). The groups overlap little, especially at older ages; only 19 controls were older than 10 years.

### 3.2 Reported diabetes in relatives (primary analysis)

For children ≥12 months, 57/254 (22.4%) and 16/196 (8.2%) reported having diabetes (any type) in a first-degree relative. The age- and sex-adjusted OR was 4.56 (95% CI 2.24–9.69) (Table 2; Figure 3). The sibling-category estimate was larger than the parent-category estimate (OR 15.39, 95% CI 4.16–85.02) because of the limited number of exposed cases (n = 35) and controls (n = 2). This was a smaller, statistically imprecise parent-category estimate (OR 2.22, 95% CI 0.98–5.11). Second-degree family history (OR 0.46, 0.27–0.78) and grandparents' family history (OR 0.35, 0.19–0.62) were associated with the control group, rather than with the case group. Any relative with T1DM was associated with an adjusted OR of 4.77 (2.49-9.49), while any relative with T2DM was associated with an OR of 0.39 (0.22-0.68). These estimates are not intended as type-specific familial effects. 57% of the controls' T1DM-labelled relatives were 2nd-degree relatives and 87% of controls' T2DM-labelled relatives were grandparents in the full sample. Because of the lack of clinical verification and documentation of how type was assigned, differential classification and type misclassification are of concern. We cannot rule out any explanation based on the dataset.

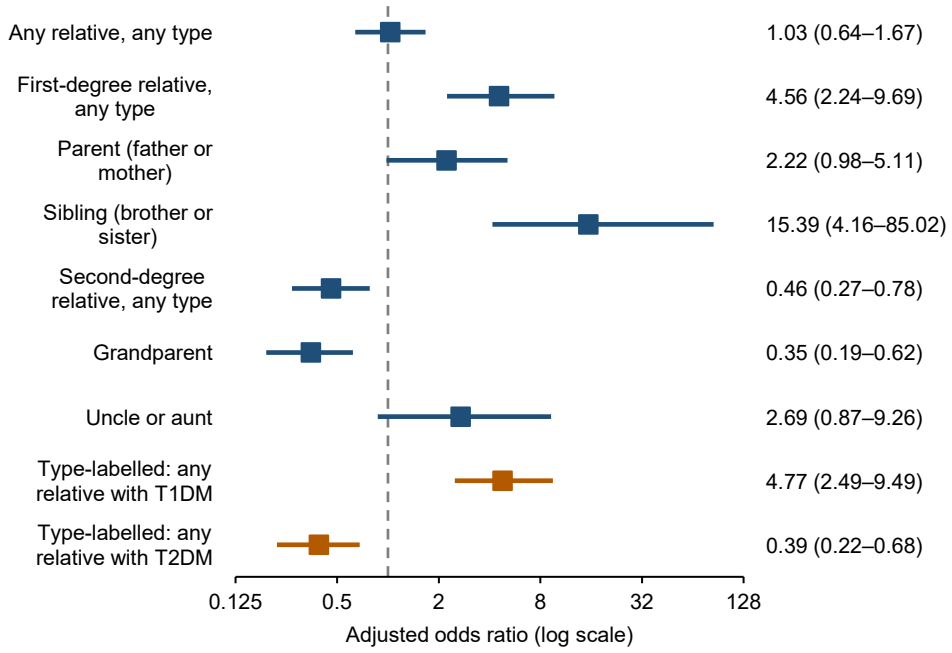



Figure 3. Association of reported diabetes in relatives with T1DM case status (age- and sex-adjusted OR, 95% CI; children aged ≥12 months; log scale). Blue: diabetes of any type. Orange: type-labelled variables as recorded.

Table 2. Reported diabetes in relatives and T1DM case status, children aged ≥12 months

| Exposure | Cases n/N (%) | Controls n/N (%) | Crude OR (95% CI) | Adjusted OR (95% CI) | p |
|---|---|---|---|---|---|
| Any relative, any type | 103/254 (40.6) | 85/196 (43.4) | 0.89 (0.61–1.30) | 1.03 (0.64–1.67) | 0.90 |
| **First-degree relative, any type** | **57/254 (22.4)** | **16/196 (8.2)** | **3.26 (1.80–5.87)** | **4.56 (2.24–9.69)** | **<0.001** |
| Parent (father or mother) | 25/254 (9.8) | 14/196 (7.1) | 1.42 (0.72–2.81) | 2.22 (0.98–5.11) | 0.057 |
| Sibling (brother or sister) | 35/254 (13.8) | 2/196 (1.0) | 15.50 (3.68–65.30) | 15.39 (4.16–85.02) | <0.001 |
| Second-degree relative, any type | 52/254 (20.5) | 72/196 (36.7) | 0.44 (0.29–0.68) | 0.46 (0.27–0.78) | 0.004 |
| Grandparent | 36/254 (14.2) | 67/196 (34.2) | 0.32 (0.20–0.50) | 0.35 (0.19–0.62) | <0.001 |
| Uncle or aunt | 18/254 (7.1) | 5/196 (2.6) | 2.91 (1.06–7.99) | 2.69 (0.87–9.26) | 0.087 |
| Type-labelled: any relative with T1DM | 74/254 (29.1) | 19/196 (9.7) | 3.83 (2.22–6.61) | 4.77 (2.49–9.49) | <0.001 |
| Type-labelled: any relative with T2DM | 43/254 (16.9) | 73/196 (37.2) | 0.34 (0.22–0.53) | 0.39 (0.22–0.68) | <0.001 |

Adjusted: Firth-penalised logistic regression age (restricted cubic spline) + sex; profile-likelihood CIs; no missing data (all 254 cases, 196 controls; see Section 2.5). The row numbers 8-9 are not diagnoses but reported types—primary exposure highlighted in bold. Categories overlap (children in any-relative row below; any-relative row can have multiple children). Relative-level analyses by relatives as originally labelled are in Supplementary Table S4.

### 3.3 Sensitivity analyses

Association at the first-degree family level was reported to be greater than the null level (Table 3), with estimates ranging from 2.49 to 5.62. It persisted in the 12–120-month age-overlap region (86 cases, 177 controls; OR 5.62, 2.63–12.50) and among cases diagnosed within 24 months before interview (OR 4.16, 1.80–9.69). These analyses indicate that the observed association was not driven by these restrictions; they do not demonstrate that age or recall-related bias has been eliminated. The estimate was attenuated after the exclusion of children with a reported affected sibling (OR 2.49, 1.06–5.94), and the comparison of the parent-only group was imprecise (OR 1.84, 0.73–4.75). Of particular concern is the large sibling estimate, as it relied on only two controls; exposure to a control varied by age and family structure, and family identifiers were unavailable.

Table 3. Sensitivity analyses for diabetes of any Type 1n a first-degree relative

| Analysis | Cases/controls | OR (95% CI) | Method |
|---|---|---|---|
| **Primary: age ≥12 months** | **254 / 196** | **4.56 (2.24–9.69)** | **Firth; age spline + sex** |
| All ages (4–180 months) | 258 / 383 | 5.42 (2.73–11.04) | Firth; age spline + sex |
| Age ≥5 years (≥60 months) | 228 / 67 | 3.40 (1.33–10.35) | Firth; age spline + sex |
| Age-overlap region, 12–120 months | 86 / 177 | 5.62 (2.63–12.50) | Firth; age spline + sex |
| Age 12–60 months only | 28 / 131 | 4.96 (1.79–13.71) | Firth; linear age + sex |
| Mantel–Haenszel, five age strata | 254 / 196 | 4.14 (1.97–8.69) | Mantel–Haenszel; strata 12–60, 61–90, 91–120, 121–150, 151–180 months |
| Cases diagnosed ≤24 months before interview vs all controls ≥12 months | 67 / 196 | 4.16 (1.80–9.69) | Firth; age spline + sex |
| Excluding children with an affected sibling | 219 / 194 | 2.49 (1.06–5.94) | Firth; age spline + sex |
| Affected parent vs no affected relative (siblings and second-degree excluded) | 170 / 123 | 1.84 (0.73–4.75) | Firth; age spline + sex |

The analysis of 12-60 months is adjusted for sex and linear age due to the smaller number of cases. Mantel–Haenszel is unadjusted for sex. Time since diagnosis = age at interview – age at diagnosis. These analyses are not independent replications; they use overlapping data.

### 3.4 Pregnancy, delivery, neonatal and childhood exposures (exploratory)

There were 30 exploratory binary exposure comparisons, summarised in Table 4. The Benjamini–Hochberg q-values were less than 0.05 for 12 of them. These differences between the recruited groups do not imply that the exposures prevented or caused T1DM. A few measures had fewer exposed controls and were less precise, such as gestational diabetes and cesarean delivery. For variables that have only two categories, the binary indicator is compared to all other categories recorded, rather than to a clinically defined "unexposed" category, and mutually exclusive category comparisons are presented in Supplementary Table S3 separately. Breastfeeding (at least 6 months) was reported in 60/183 (0.62,

0.36–1.07; p=0.09) breast- or mixed-fed children and 73/157 controls. This limited time comparison does not account for exclusive or partial breastfeeding.

Table 4. Parent-reported pregnancy, delivery, neonatal and childhood exposures in children aged ≥12 months (254 cases, 196 controls): crude and age- and sex-adjusted odds ratios (exploratory; see Section 3.5)

| Exposure | Cases n/N (%) | Controls n/N (%) | Crude OR (95% CI) | Adjusted OR (95% CI) | p | FDR q |
|---|---|---|---|---|---|---|
| **Family history** | | | | | | |
| Family history of T2DM, any relative | 43/254 (16.9) | 73/196 (37.2) | 0.34 (0.22–0.53) | 0.39 (0.22–0.68) | <0.001 | 0.004 |
| Family history of celiac disease | 9/254 (3.5) | 2/196 (1.0) | 3.56 (0.76–16.68) | 1.22 (0.26–8.10) | 0.81 | 0.841 |
| Family history of asthma | 37/254 (14.6) | 10/196 (5.1) | 3.17 (1.54–6.55) | 2.99 (1.33–7.14) | 0.008 | 0.023 |
| Family history of rhinitis | 51/254 (20.1) | 10/196 (5.1) | 4.67 (2.31–9.47) | 4.55 (2.03–10.90) | <0.001 | 0.002 |
| Family history of eczema | 21/254 (8.3) | 10/196 (5.1) | 1.68 (0.77–3.65) | 1.71 (0.66–4.59) | 0.27 | 0.468 |
| Family history of thyroid disease | 2/254 (0.8) | 3/196 (1.5) | 0.51 (0.08–3.09) | 0.29 (0.03–2.75) | 0.28 | 0.468 |
| Parental consanguinity | 78/254 (30.7) | 55/196 (28.1) | 1.14 (0.75–1.71) | 1.26 (0.75–2.13) | 0.39 | 0.585 |
| **Pregnancy** | | | | | | |
| Maternal pre-eclampsia | 48/254 (18.9) | 11/196 (5.6) | 3.92 (1.98–7.77) | 4.19 (1.93–9.68) | <0.001 | 0.002 |
| Maternal gestational diabetes | 20/254 (7.9) | 4/196 (2.0) | 4.10 (1.38–12.21) | 7.32 (2.38–26.70) | <0.001 | 0.002 |
| Maternal infection in pregnancy | 36/254 (14.2) | 36/196 (18.4) | 0.73 (0.44–1.22) | 0.74 (0.38–1.43) | 0.38 | 0.585 |
| Antihypertensive in pregnancy | 39/254 (15.4) | 10/196 (5.1) | 3.37 (1.64–6.94) | 3.08 (1.33–7.57) | 0.008 | 0.023 |
| Anti-emetic in pregnancy | 42/254 (16.5) | 31/196 (15.8) | 1.05 (0.64–1.75) | 0.98 (0.52–1.86) | 0.95 | 0.947 |
| Antibiotic in pregnancy | 19/254 (7.5) | 37/196 (18.9) | 0.35 (0.19–0.63) | 0.30 (0.14–0.63) | 0.001 | 0.005 |
| Maternal tea | 80/254 (31.5) | 112/196 (57.1) | 0.34 (0.23–0.51) | 0.38 (0.23–0.63) | <0.001 | 0.002 |
| Maternal coffee | 37/254 (14.6) | 15/196 (7.7) | 2.06 (1.09–3.87) | 1.82 (0.85–4.02) | 0.12 | 0.249 |
| **Birth and neonatal** | | | | | | |
| Pre-term birth | 23/254 (9.1) | 15/196 (7.7) | 1.20 (0.61–2.37) | 1.24 (0.54–2.89) | 0.61 | 0.795 |
| Caesarean section | 38/254 (15.0) | 7/196 (3.6) | 4.75 (2.07–10.89) | 4.74 (1.97–12.62) | <0.001 | 0.002 |
| Home delivery | 49/254 (19.3) | 75/196 (38.3) | 0.39 (0.25–0.59) | 0.45 (0.26–0.77) | 0.003 | 0.011 |
| Neonatal respiratory disease | 60/254 (23.6) | 10/196 (5.1) | 5.75 (2.86–11.57) | 6.22 (2.83–14.81) | <0.001 | <0.001 |
| Neonatal jaundice | 79/254 (31.1) | 52/196 (26.5) | 1.25 (0.83–1.89) | 1.07 (0.64–1.82) | 0.79 | 0.841 |
| Neonatal infection | 31/254 (12.2) | 19/196 (9.7) | 1.30 (0.71–2.37) | 1.27 (0.60–2.70) | 0.54 | 0.731 |
| **Childhood** | | | | | | |

| Exposure | Cases n/N (%) | Controls n/N (%) | Crude OR (95% CI) | Adjusted OR (95% CI) | p | FDR q |
|---|---|---|---|---|---|---|
| Measles | 73/254 (28.7) | 29/196 (14.8) | 2.32 (1.44–3.75) | 2.11 (1.18–3.84) | 0.012 | 0.030 |
| Varicella | 65/254 (25.6) | 35/196 (17.9) | 1.58 (1.00–2.51) | 1.67 (0.93–3.03) | 0.085 | 0.190 |
| Rubella | 12/254 (4.7) | 7/196 (3.6) | 1.34 (0.52–3.47) | 0.63 (0.19–2.26) | 0.46 | 0.664 |
| Pertussis | 9/254 (3.5) | 4/196 (2.0) | 1.76 (0.53–5.81) | 1.22 (0.31–5.43) | 0.78 | 0.841 |
| Mumps | 14/254 (5.5) | 8/196 (4.1) | 1.37 (0.56–3.34) | 1.19 (0.39–3.76) | 0.76 | 0.841 |
| Conjunctivitis in infancy | 40/254 (15.7) | 27/196 (13.8) | 1.17 (0.69–1.98) | 0.87 (0.44–1.72) | 0.69 | 0.824 |
| Bottle feeding (vs breast or mixed) | 71/254 (28.0) | 39/196 (19.9) | 1.56 (1.00–2.44) | 1.51 (0.86–2.64) | 0.15 | 0.278 |
| Breast-feeding ≥6 months (breast- or mixed-fed children only) | 60/183 (32.8) | 73/157 (46.5) | 0.56 (0.36–0.87) | 0.62 (0.36–1.07) | 0.089 | 0.190 |
| Incomplete vaccination | 17/254 (6.7) | 14/196 (7.1) | 0.93 (0.45–1.94) | 0.80 (0.31–2.03) | 0.64 | 0.795 |

Adjusted: Firth-penalised logistic regression, one exposure at a time, with age (restricted cubic spline) and sex; p are penalised likelihood-ratio tests; q are Benjamini–Hochberg values across these 30 tests. Multi-level models with explicit reference categories are in Supplementary Table S3, while binary indicators for single-category variables (tea, coffee, drug classes, neonatal disease, delivery) compare each category with the rest of the children (including those in other categories). BF_6m is displayed only for children who are breast- or mixed-milk fed. Some rows have very wide intervals because they include few exposed controls.

### 3.5 Are the case–control comparisons valid?

There was no relief for comparability worries from age-related diagnostics. The distribution of exposure prevalence was fairly consistent across age within groups for all 12 exposures analysed, with the exception of gestational diabetes for cases (Table 5). Crude case–control contrasts were also found for neonatal respiratory disease (OR 8.39), pre-eclampsia (5.90) and first-degree family history (5.17) in stratum 12–60 months, which had only 28 cases and were imprecise. The observed differences do not necessarily reflect age differences; they do not rule out age-related selection or residual confounding. There is a concern for differences in association with healthcare and ascertainment. Exposures were more common among cases, such as pre-eclampsia, gestational diabetes, antihypertensive treatment, cesarean delivery and neonatal respiratory disease, which may require access to health care services to detect or be reported if detected. Other exposures not as strongly associated with the formal diagnosis, such as consanguinity and preterm birth, did not vary significantly among the groups. This pattern may reflect access to health care or providers' recruitment or retrospective reporting into hospitals, but it cannot distinguish between these two mechanisms. Do not interpret this as evidence of selection or differential reporting bias driving the observed associations. Recall interval and common support.

The contrasts with controls were similar in cases diagnosed within 24 months of the interview (n = 67) and those diagnosed more than 24 months earlier (all Fisher $p \geq 0.24$), and exposure prevalence did not differ between the two groups. In the age-overlap region (12–120 months), estimates were likewise similar (pre-eclampsia 3.56 (1.53–8.53); caesarean section 4.30 (1.70–11.74); neonatal respiratory disease 7.77 (3.23–20.34)). There was also a similar distribution of enrolment dates for the two groups

(chi-square p = 0.13). The differences were not removed by restricting to the age-overlap range, or by examining shorter recall intervals, or by a focus on the timing of enrolment. These analyses indicate that the observed differences cannot be attributed to the measured factors alone. However, because they are hospital-based, they cannot rule out residual confounding, differential reporting, or selection bias within the hospital.

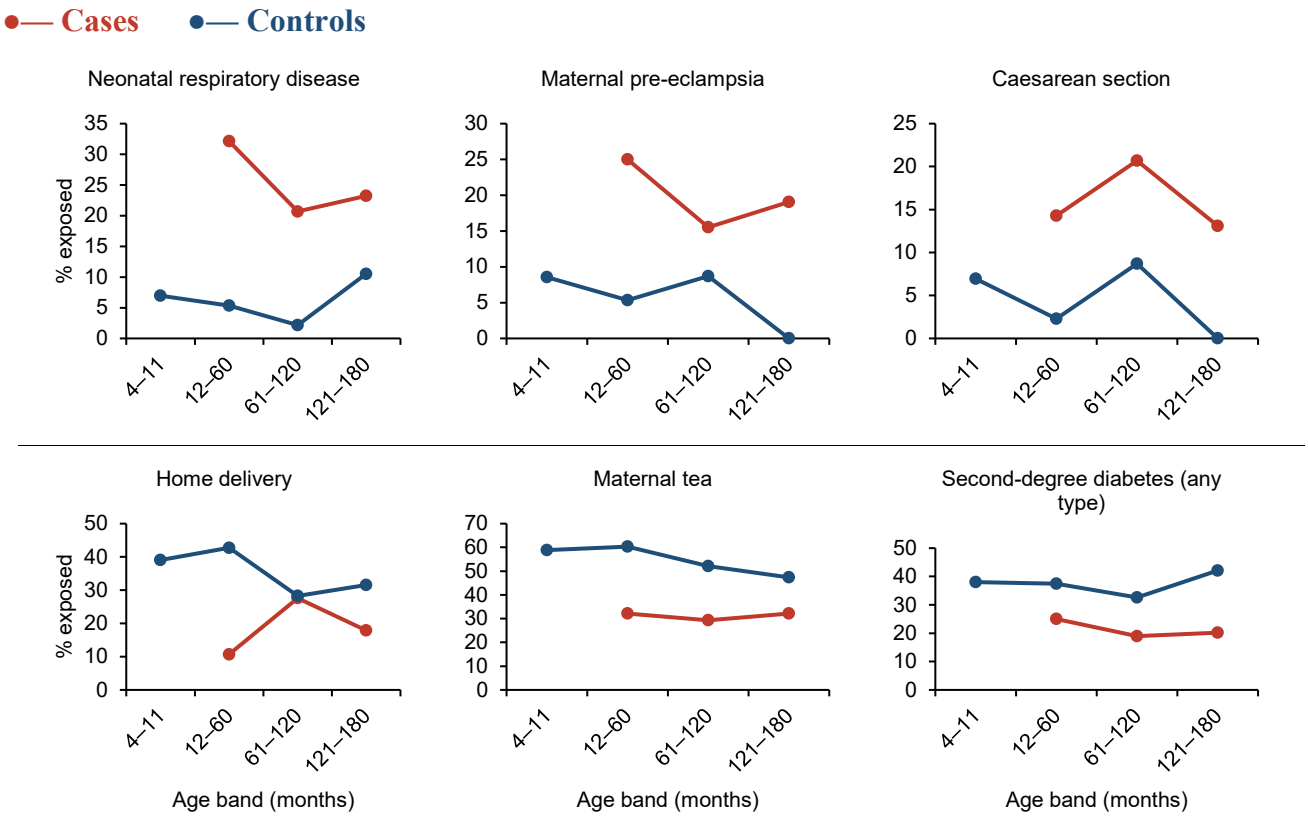



Figure 4. Prevalence (%) of selected exposures by age band, within cases and within controls (full sample; bands with fewer than 10 children not plotted, so cases aged 4–11 months, n = 4, are omitted). Lines show that differences between groups persist within age bands and that prevalence within each group is largely flat across age.

Table 5. Comparability diagnostics: crude case–control ORs by age stratum and change in exposure prevalence with age within each group

| Exposure | Crude OR, 12–60 months (28 cases / 131 controls) [exposed cases/controls] | Crude OR, >60 months (226 / 65) [exposed cases/controls] | Age trend in controls: OR per 10 years (p) | Age trend in cases: OR per 10 years (p) |
|---|---|---|---|---|
| First-degree diabetes, any type | 5.17 (1.89–14.12) [9/11] | 3.24 (1.23–8.51) [48/5] | 1.10 (0.86) | 0.54 (0.093) |
| Second-degree diabetes, any type | 0.56 (0.22–1.41) [7/49] | 0.45 (0.25–0.83) [45/23] | 0.99 (0.97) | 0.88 (0.75) |
| Family history of rhinitis | 7.09 (2.31–21.69) [8/7] | 4.86 (1.45–16.21) [43/3] | 1.31 (0.69) | 1.23 (0.61) |
| Maternal pre-eclampsia | 5.90 (1.88–18.56) [7/7] | 3.38 (1.16–9.82) [41/4] | 0.52 (0.36) | 1.08 (0.86) |
| Maternal gestational diabetes | 14.02 (2.56–76.66) [5/2] | 2.24 (0.50–10.06) [15/2] | 1.05 (0.96) | 0.31 (0.027) |

| Exposure | Crude OR, 12–60 months (28 cases / 131 controls) [exposed cases/controls] | Crude OR, >60 months (226 / 65) [exposed cases/controls] | Age trend in controls: OR per 10 years (p) | Age trend in cases: OR per 10 years (p) |
|---|---|---|---|---|
| Caesarean section | 7.11 (1.50–33.81) [4/3] | 2.70 (0.92–7.92) [34/4] | 0.64 (0.56) | 0.78 (0.56) |
| Neonatal respiratory disease | 8.39 (2.79–25.19) [9/7] | 6.02 (1.81–19.99) [51/3] | 0.74 (0.66) | 0.99 (0.98) |
| Home delivery | 0.16 (0.05–0.56) [3/56] | 0.62 (0.33–1.16) [46/19] | 0.77 (0.43) | 0.98 (0.95) |
| Maternal tea in pregnancy | 0.31 (0.13–0.74) [9/79] | 0.44 (0.25–0.78) [71/33] | 0.69 (0.23) | 1.04 (0.92) |
| Antibiotic in pregnancy | 0.63 (0.17–2.27) [3/21] | 0.23 (0.11–0.50) [16/16] | 1.11 (0.78) | 0.53 (0.23) |
| Measles | 3.40 (1.32–8.80) [9/16] | 1.58 (0.81–3.10) [64/13] | 1.36 (0.44) | 0.82 (0.58) |
| Parental consanguinity | 1.25 (0.52–3.02) [9/36] | 1.06 (0.58–1.95) [69/19] | 0.96 (0.90) | 0.84 (0.61) |

The Woolf method of crude ORs with 0.5 continuity correction. Age trend: logistic regression of each exposure by age within each group, using the entire sample. The multiplicities of the case-control differences are not adjusted; the other rows in the table are provided as illustrations of such differences that exist in both strata.

### 3.6 Exposure-misclassification sensitivity analysis

Table 6 shows the hypothetical scenarios. When possible, non-differential misclassification (S1) yielded corrected ORs that were higher than the crude ORs. The corrected ORs were lower than the crude ORs for first-degree diabetes (S3: 2.79 vs crude: 3.26), measles (S3: 1.71 vs crude: 2.32) and varicella (S3: 1.09 vs crude: 1.58), but were not below 1. Several scenarios (marked NF) were not viable because they assumed high specificity, resulting in more false positives than exposed controls. They corrected ORs for exposures with very few exposed controls (gestational diabetes, S3–S4) are unstable and should not be interpreted as estimates. The sensitivity of cases for varicella and for measles would have to be 1.4 and 1.9, respectively, times the sensitivity of controls, respectively, to remove the infection associations, which would compare with 2.7 (first-degree diabetes), 3.4 (pre-eclampsia), 3.9 (gestational diabetes), 4.2 (caesarean section) and 4.6 (neonatal respiratory disease). This analysis does not account for selection bias, as Section 3.5 indicates it could also affect infection associations; modest differences in reporting could suffice, whereas several-fold differences would be required for the others.

Table 6. Hypothetical exposure-misclassification scenarios (crude ORs, children aged ≥12 months)

| Exposure | Exposed cases/N; controls/N | Crude OR | S1 | S2 | S3 | S4 | S5 | S6 | Tipping: required Se ratio |
|---|---|---|---|---|---|---|---|---|---|
| First-degree diabetes, any type | 57/254; 16/196 | 3.26 | 6.77 | NF | 2.79 | 6.38 | 2.48 | NF | 2.7 |
| Maternal pre-eclampsia | 48/254; 11/196 | 3.92 | 27.26 | NF | 3.91 | 8.56 | 2.96 | NF | 3.4 |
| Maternal gestational diabetes | 20/254; 4/196 | 4.10 | NF | NF | >50 | >50 | NF | NF | 3.9 |
| Caesarean section | 38/254; 7/196 | 4.75 | NF | NF | 6.75 | 14.25 | 3.67 | NF | 4.2 |
| Neonatal respiratory disease | 60/254; 10/196 | 5.75 | >50 | NF | 6.29 | 14.30 | 5.72 | NF | 4.6 |
| Measles | 73/254; 29/196 | 2.32 | 3.02 | 5.23 | 1.71 | 4.33 | 1.83 | 6.96 | 1.9 |
| Varicella | 65/254; 35/196 | 1.58 | 1.81 | 2.33 | 1.09 | 2.72 | 1.11 | 3.39 | 1.4 |

S1: non-differential, Se 0.85 and Sp 0.95. S2: non-differential, Se 0.70 and Sp 0.90. S3: Se 0.90 in cases and 0.65 in controls, Sp 0.98. S4: Se 0.65 in cases and 0.90 in controls, Sp 0.98. S5: Se 0.85, Sp 0.90 in cases and 0.98 in controls. S6: Se 0.85, Sp 0.98 in cases and 0.90 in controls. All values are assumed, not measured, for validity. With corrected cell: NF: not feasible (>50). Sensitivity of cases relative to controls (Sp = 1): the fold difference that must be achieved in cases' sensitivity compared to controls for the true OR to be 1 (observed prevalence ratio).

## 4. Discussion

### 4.1 Principal's findings

The main result was that the prevalence of parent-reported diabetes in at least one first-degree relative was higher in children with T1DM than in hospital controls (OR 4.56; 95% CI 2.24–9.69; adjusted for age and sex) [20–22,30]. This is the most interpretable association, since it is not dependent on the distinction between relatives with T1DM and relatives with T2DM that was not verified by the questionnaire. However, this association is based on reported family history among the recruited children, not a population risk estimate. The larger sibling estimate was derived from only 2 exposed controls and is therefore subject to greater uncertainty. Pregnancy, perinatal, and childhood comparisons offer exploratory signals [4–6,13–15]. Still, they are limited in their ability to be interpreted due to retrospective reporting, limited exposure definitions, and control selection that may be uncertain.

### 4.2 Family history

The first-degree family-history finding matches the directionality of familial aggregation of T1DM reported by family and register-based studies [7,20–22]. Its magnitude should not be compared directly to familial recurrence risk from population cohorts [20,22]: this study used parent-reported exposure in a hospital-based case–control design and did not attempt to demonstrate that the controls were from the same population as the cases. Nor can this association be specifically attributed to inherited susceptibility [7,8]. The study did not record genetic markers or the extent of shared environmental factors, and first-degree relatives share behaviours, household environments, and genes [8,19].

The sibling and parent point estimates differ, but this does not establish that sibling history is more strongly associated with T1DM. With only two exposed controls, the sibling estimate (OR 15.39, 95% CI 4.16–85.02) is based on 35 exposed cases. The classification and sampling are so limited that few exposed controls are available to inform the estimate. There is also no information included on the number, age and full diabetes history of siblings or family identifiers to evaluate clustering or overlapping. Siblings are different ages and thus had different opportunities to develop T1DM by the time of the interview [20]. The parent-only estimate was smaller and not statistically precise [21,22]. These findings suggest that parent history and sibling history should be reported separately in subsequent research; however, it does not provide a reliable order of their relative contribution.

The family-history results with the type of label are not as reliable as the family-history results with the any-type label. Questionnaire items included diabetes and diabetes type; however, the dataset did not record the basis for the diabetes type or provide clinical confirmation. We kept a single family member of each type. Type attribution and relative classification are significant sources of uncertainty, because of the opposition of the two associations of T1DM- and T2DM-labelled histories and the clustering of controls' T1DM-labelled relatives within the second-degree relative's association. Therefore, the main analysis is suitable for including diabetes of any Type 1n first-degree family members; type-specific results should be limited to descriptive and hypothesis-generating interpretations.

### 4.3 Retrospective reporting and differential misclassification

There is the potential for nondifferential and differential exposure misclassification from retrospective parent report [18]. The same exposure items were used on both the case and control forms. Still, the cases were interviewed after the diagnosis of T1DM, and controls were interviewed as they were admitted for diagnoses other than T1DM. These varying contexts could impact recall, awareness of medical language, exposure to healthcare providers, and the chances of a pregnancy or neonatal event being considered a diagnosis. The respondent can be the mother or any available parent, but the respondent identity was not retained in the dataset, and this was not evaluated for differences in responses. Illustrative misclassification scenarios illustrate how the crude associations change with changing assumptions about sensitivity and specificity. No subsample of the exposures is available for validation or comparison with medical records to estimate exposure accuracy. In particular, the scenarios cannot determine whether reporting was more sensitive in cases or controls and do not account for selection bias. The lack of clear differences between recently diagnosed and longer-standing cases reduces the likelihood that differences reflect differential recall or interview context, but it does not control for elapsed time since diagnosis. The most defensible conclusion is thus that there is a possibility of differential ascertainment, and possibly a significant effect, although not necessarily in one direction.

### 4.4 Control selection and comparability

One of the most significant challenges to interpretation is the lack of reliability in comparing the hospital control group [16,18]. The prevalence of cases was found in children receiving specialist diabetes care or in those with metabolic complications presenting to hospital, and controls were children presenting to hospital for non-diabetic reasons. The authors do not document the control sampling procedure or the distribution of control admission diagnoses. It is therefore not possible to confirm that controls are truly representative of the distribution of exposure of the population from which the cases were drawn [16]. Case–control contrasts might be distorted by conditioning on hospital admission [16]if admission to this hospital was associated with an exposure or with other determinants of case recruitment.

Age adjustment and restriction to overlapping age ranges only correct measured age differences and do not correct an inappropriate control sampling frame [16]. Many young controls were also excluded, and the comparison group composition changed because of the primary age restriction. Selected contrasts in limited analyses can provide helpful descriptive evidence, but they cannot rule out selection bias. The differences in exposures that could be associated with healthcare recognition are consistent with differences in healthcare contact, selection, or reporting. Still, these exposures cannot be separated from the measured exposures. Other factors that may have affected some comparisons included socioeconomic factors, maternal age, birth weight, and pre-gestational diabetes in the mother [5,6,11,13,33]. Such restrictions should be taken into consideration when interpreting any odds ratio, adjusted or not, as an unbiased estimation of an etiological association.

### 4.5 Pregnancy, perinatal and childhood exposures

Analyses of pregnancy, perinatal and childhood exposures should be viewed as exploratory comparisons used to generate research questions that can be addressed by more well-designed studies that can inform the association between specific exposures and development or prevention of T1DM. Pre-eclampsia, gestational diabetes and caesarean delivery, as well as neonatal respiratory disease, are difficult to differentiate from differences in contact and diagnosis with health services [4,6,14]. Additionally, the combined place/mode of delivery variable cannot be used to calculate a valid caesarean delivery rate

independent of place of delivery, and the single-category maternal medication variable cannot be used to report co-occurring maternal medicines, timing, or indication. For example: antihypertensive medication use may be a proxy for maternal hypertension or another exposure, and not an exposure in its own right. The findings on the infection of children are limited [10,24,28,36]. Infection status was reported as yes or no; age at infection and the specific infection category were not consistently recorded. Children's ages when they have had the opportunity to experience an infection being recognised are diverse. Therefore, the reported links between measles and varicella are not considered to be a source of a viral trigger [10,36]. Inverse associations with tea, antibiotics or home delivery should NOT be called protective: this may be due to category construction, access to health care, reporting, or the selection of controls. The length of time indicator for bottle-fed children (BF_6m) is not interpretable, as it is not defined for bottle-fed children and cannot be compared between the feeding groups [9,23]. The biological interpretation of these data, without taking into account the gestational weeks, birth weight, exposure timing, medication indications and validated infection histories [11,25,33], would be outside the scope of the data.

### 4.6 Limitations

The study's limitations are interrelated and affect the evidence in different ways. Firstly, it is a single-hospital study conducted in 2014–2015, and source population comparability of controls has not been determined [16]. A control-sampling frame and an admission-diagnosis distribution were not adequately described. Second, all exposures were parent-reported and not validated [18]; interview settings varied across groups, the identity of all interviewees was not recorded, and the coding system did not distinguish a true negative from an exposure that was not reported or unknown. Third, family-history type was not clinically established, nor was there more than one member per Type 1n each case, and there were no family identifiers and no information about the number and age of family members with the disease. Fourth, some early-life variables were not timed, lasted only a short period, were not confirmed by clinical diagnosis or could record only one category of co-occurring variables. Fifth, the analysis plan had been written after data collection, multiple exploratory comparisons had been made [34], and some subgroup estimates were sparse. Last, the hypothetical misclassification analysis relies on assumed parameters and does not account for selection bias. The use of Firth penalisation [31, 35] does not eliminate these design limitations or measurement errors from small samples and separation. Therefore, the association of first-degree family history is the primary finding, and the associations of the other exposures should be considered as provisional.

### 4.7 Recommendations for future studies

Future studies could address the specific weaknesses listed here. Controls should be sampled from the population from which cases are drawn and should be taken from a sample frame; eligibility criteria should be documented, and the reasons for hospital admission and the dates of sampling should be documented. Ideally, recruit incident cases and controls simultaneously from the same geographic area using the same ascertainment methods [16]. Family history should be taken with a structured relationship-by-relationship tool which should include information about each family member's age, diabetes type, age of diagnosis and source of confirmation [21,22]. If possible, reported diagnoses should be confirmed from clinical records, and if they are not certain, they should be reported as such and not be classified as T1DM/T2DM.

Exposures during pregnancy and childhood should be asked as yes, no, unknown, not asked, not applicable and should allow multiple answers if there is a possibility of exposure occurring concurrently.

Documentation of dates, gestational weeks, birth weight, indication and time of medication, age of infection and diagnosis should be recorded. If available, maternal and neonatal records should be examined; and cases and controls should be treated equally in processing. The context of the response or interview should be documented, and interviewers should ensure that they use a standardised set of prompts. Family identifiers should be secure, so family members can be identified, and within-family dependence can be analysed. Lastly, investigators should decide before examining associations with the outcome what their main exposure of interest is, which confounders they wish to use, and any preconceived analysis or multiplicity approach [17,18,34].

## 5. Conclusions

When parents reported diabetes of any Type 1n a first-degree relative, this was associated with case status for children in this hospital-based sample after adjustment for age and sex. This is the study's main finding, but it does not reflect population recurrence risk or provide evidence of a genetic mechanism. The large sibling estimate also depends heavily on the number of controls reporting an affected sibling, which was 2 out of 196 controls. Type-specific family-history findings and comparisons of pregnancy, perinatal, and childhood exposures are less reliable because of unverified diagnoses, the inability to distinguish between negative and unreported exposures, and the unrepresentativeness of the hospital controls. Thus, the contribution of this study is dual: it adds hospital-based paediatrics data from Karbala, Iraq and demonstrates the need for a proper classification of exposures and choice of controls prior to interpreting associations of exposures with early life outcomes etiologically.

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