Risk Factors for Insulin Resistance and Diabetes

Accumulation of childhood adversities and type 1 diabetes risk: a register-based cohort study of all children born in Denmark between 1980 and 2015

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Abstract

Background: Previous studies have indicated an association between childhood adversities and type 1 diabetes but have been underpowered and limited by selection. We aim to quantify the effect of accumulation of childhood adversities on type 1 diabetes risk, and to assess whether the effect differs between males and females in a large and unselected population sample.

Methods: We used register-based data covering all children born in Denmark between 1980 and 2015, totalling >2 million children. We specified a multi-state model to quantify the effect of accumulation of childhood adversities on type 1 diabetes risk. The effects of specific childhood adversities on type 1 diabetes were estimated using proportional hazards models.

Results: Accumulation of childhood adversities had a quantitatively small effect on type 1 diabetes risk among females [adjusted hazard ratio (HR) per adversity increase: 1.07; 95% confidence interval (CI): 1.02–1.11], but not among males (adjusted HR per adversity increase: 0.99; 95% CI: 0.97–1.03). Females exposed to extreme numbers (7+) of adversities had two times higher risk of type 1 diabetes compared with unexposed females (adjusted HR: 2.06; 95% CI: 1.10–3.86).

Conclusions: In an unselected total population sample, we generally find no or negligible effects of childhood adversities on type 1 diabetes risk, which may be reassuring to persons with type 1 diabetes who are concerned that personal trauma contributed to their disease. There is a very small group of females exposed to a high degree of adversity who may have a higher risk of type 1 diabetes and this group needs further attention.
Introduction

The aetiology of type 1 diabetes is largely unknown, but genetic, immune and environmental factors are likely involved. A common concern among persons with type 1 diabetes is that personal trauma or episodes of psychosocial stress have contributed to the development of the disease; a concern that has been supported by epidemiological studies.1–3 The beta cell stress hypothesis proposes that elevated levels of cortisol, which is one of the key mediators of the physiological stress response, increases insulin demands and may trigger autoimmune beta cell loss or promote progression from autoimmunity to overt type 1 diabetes in genetically susceptible individuals.4,5

Childhood adversities (i.e. a straining family environment, adverse life events and social disadvantage) have been defined as major sources of psychosocial stress in children.6,7 Previous studies have shown an association between childhood adversities and type 1 diabetes,1,3 with effect estimates indicating up to three times higher risk of type 1 diabetes after exposure to at least one adversity,2 although results are inconsistent.8,9

Previous studies on childhood adversity and type 1 diabetes have mainly focused on a specific adverse experience such as bereavement10 or have only had the statistical power to estimate the effect of (at least) one adversity occurrence on type 1 diabetes.2,3 However, adverse experiences tend to cluster within individuals living in adverse social circumstances,11 and evidence suggests that accumulation of adversities is more harmful for children’s health than any specific adversity in isolation.12–15 Case-control studies have found a higher frequency of adverse events in childhood among type 1 diabetes cases compared with controls,1,16–21 but prospective studies with objective measures of accumulation of childhood adversities are needed to bring this area of research forward.

Moreover, due to the age-specific differences in the incidence of type 1 diabetes between males and females,22 potential sex differences in the effect of childhood adversities on type 1 diabetes needs to be assessed. Most previous studies have also used retrospective self-reports of childhood adversities, which may induce recall bias. Prospective studies are few and are often based on birth cohorts, which are likely to be affected by selection since exposure to childhood adversities may be specifically associated with barriers for participation and loss to follow-up.23 We will add to the existing literature by quantifying the effect of accumulation of childhood adversities on type 1 diabetes risk in a large and unselected register-based cohort and by assessing whether the effect of childhood adversities on type 1 diabetes is different in males and females.

Methods

Study population

We used the DANish LIFE course (DANLIFE) cohort which includes all children born to a mother with residence in Denmark at the time of birth between 1 January 1980 and 31 December 2015, totalling 2 223 927 children.24 The unique civil personal registration number given to all Danish residents25 facilitated exact linkage of valid and continuously updated information from the nationwide registers on demographic, socioeconomic and health-related factors. The civil personal registration number also enabled linkage between child, parent and siblings for identification of family-related childhood adversities and covariates. We excluded persons with missing information on any of the potential confounders (n = 70 763, 3%). The excluded persons were more likely (16 vs 5%) to have a father with a nationality of non-European origin (nationalities outside of Europe, North America, Australia and New Zealand).
Zealand) but were otherwise similar to the complete records. The final study population included 2 153 164 children. A detailed description of the DANLIFE cohort has been reported elsewhere.24

Childhood adversities
DANLIFE includes information on 12 social and family-related childhood adversities with important psychosocial implications for health and well-being in childhood reflecting aspects of straining family dynamics (i.e. being placed in foster care, parental or sibling psychiatric illness, parental alcohol or drug abuse and parental separation), loss or threat of loss within the family (i.e. death of a parent or a sibling and parental or sibling somatic illness) and social disadvantage (i.e. family poverty and parental long-term unemployment). The specific childhood adversities in DANLIFE were selected based on the notion that they constitute important sources of stress in children with support from scientific literature.24 Direct information on other relevant childhood adversities like child abuse/neglect or domestic violence was unfortunately not available in the registers. Information on some of the childhood adversities (i.e. parental separation, family poverty and parental long-term unemployment) is reported in the registers only once a year and the time of occurrence for these adversities was, therefore, set to a fixed date within that year. Table 1 provides an overview of the adversities included in DANLIFE and defines the timing of their occurrence. A detailed description of the definitions of the adversities can be found in the DANLIFE cohort profile.24 All childhood adversities were recorded from 1980 onwards except family poverty, which was only available from 1987 onwards.

Type 1 diabetes
Date of diagnosis of type 1 diabetes was linked to DANLIFE from several nationwide registers: the Danish Registry of Childhood and Adolescent Diabetes28 (1980–95: 0–15 years, 1996–2015: 0–18 years), the Danish Adult Diabetes Registry29 (2005–15: ≥18 years) and the Danish National Prescription Registry30 (1980–2015: all age groups). Moreover, we supplemented the information in these registers with information on purchased prescriptions of oral antidiabetic drugs and insulin from the Danish National Prescription Registry31 (1995–2015: <15 and <30 years of age, respectively). The Danish Registry of Childhood and Adolescent Diabetes includes information on type 1 diabetes with nearly 100% completeness, and nearly 70% of the type 1 diabetes cases in DANLIFE could be identified using this register. The classification of diabetes type is inconsistent in the Danish Adult Diabetes Registry and even more so in the Danish National Patient Registry where many individuals have several records with different recordings of diabetes type. Due to these inconsistencies, persons were classified as having type 1 diabetes if they met one of the following criteria.

i. Type 1 diabetes diagnosis in the Danish Registry of Childhood and Adolescent Diabetes.

ii. More than half of the recordings of diabetes type in the Danish Adult Diabetes Registry for that person are type 1 diabetes and the person is not classified with another diabetes type in the Danish Registry of Childhood and Adolescent Diabetes.

iii. More than half of the recordings of diabetes type in the Danish National Patient Registry for that person are type 1 diabetes and the person is not classified with another diabetes type in the Danish Adult Diabetes Registry (i.e. more than half of the recordings of diabetes type in the Danish Adult Diabetes Registry for that person are type 2).

iv. Having purchased prescribed oral antidiabetic drugs twice before the age of 15 years or prescribed insulin twice before the age of 30 years recorded in the Danish National Prescription Registry and the person is not classified with another diabetes type in the Danish Registry of Childhood and Adolescent Diabetes or in the Danish Adult Diabetes Registry (i.e. more than half of the recordings of diabetes type in the Danish Adult Diabetes Registry for that person are type 2).

We used the date of the first record of a diabetes diagnosis or the date of the second purchase of antidiabetic drugs or insulin as the date of diagnosis. The same registers and criteria were applied to identify parental and sibling type 1 diabetes.

Potential confounding factors
Identification of potential confounders was based on prior evidence and guided by the method of directed acyclic graphs32 (see Supplementary Figure 1, available as Supplementary data at IJE online). These were: age, sex, date of birth, parental education at birth (low: ≤9 years, middle: 10–12 years, high: >12 years), parental type 1 diabetes, sibling type 1 diabetes, birth order (1, 2, 3, 4+), birth weight, maternal age at birth and parental area of origin based on father’s (or in case of missing, mother’s) nationality [European origin (including Europe, North America, Australia and New Zealand), other]. Information recorded in the Danish nationwide registers (see the specific registers in the DANLIFE cohort profile)24 at the time of birth was used for all confounders except for parental
| Adversity                      | Definition                                                                                                                                                                                                 | Timing                                                                                      |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Foster care                   | Being placed in out-of-home care                                                                                                                                                                             | Date of first placement                                                                     |
| Parental psychiatric illness  | A parent’s admission for at least 1 day to a psychiatric hospital or ward with a primary diagnosis related to psychiatric illness (excluding primary diagnoses related to alcohol and drug abuse) | Date of first diagnosis among the parents                                                   |
| Sibling psychiatric illness   | A sibling’s admission for at least 1 day to a psychiatric hospital or ward with a primary diagnosis related to psychiatric illness                                                                        | Date of first diagnosis among the siblings                                                  |
| Parental alcohol abuse        | A parent diagnosed with one of the following illness related to alcohol abuse: alcoholic psychosis, alcoholism, alcoholic cirrhosis of the liver, alcoholic steatosis of the liver, alcoholic psychosis and abuse syndrome, alcoholic polyneuropathy, alcoholic cardiomyopathy, alcoholic-induced acute or chronic pancreatitis, alcoholic liver disease, alcoholic gastritis or purchasing a drug prescribed for treatment of alcohol dependence | Date of first diagnosis/purchase of prescription among the parents                           |
| Parental drug abuse           | A parent diagnosed with drug dependence or a mental or behavioural disorder due to use of opioids, cannabinoids, sedatives or hypnotics, cocaine, other stimulants, hallucinogens, volatile solvents, psychoactive substances, multiple drugs or purchasing a drug prescribed for treatment of drug dependence | Date of first diagnosis/purchase of prescription among the parents                           |
| Parental separation           | Separation of the parents defined as the parents no longer sharing address                                                                                                                                 | 30 June in the year of first separation between the parents                                  |
| Death of a parent             | Death of a parent                                                                                                                                                                                         | Date of the first death among the parents                                                   |
| Death of a sibling            | Death of a sibling                                                                                                                                                                                         | Date of the first death among the siblings                                                  |
| Parental somatic illness      | A parent diagnosed with one of the ICD-8 codes included in the Charlson comorbidity index in the period 1980–93 or the ICD-10 codes included in the updated version of the Charlson comorbidity index in the period 1994–2015 | Date of first diagnosis among the parents                                                   |
| Sibling somatic illness       | A sibling diagnosed with one of the following somatic illnesses related to mortality in children aged 0–18 years in Denmark: malignant neoplasm, congenital anomalies of the heart and circulatory system, congenital anomalies of the nervous system, cerebral palsy, epilepsy, cardiomyopathy and congenital disorders of lipid metabolism | Date of first diagnosis among the siblings                                                  |
| Family poverty                | Family income <50% of the median national family income in three consecutive years                                                                                                                        | 30 June in the second year of poverty in the first sequence of three consecutive years of poverty |
| Parental long-term unemployment| A parent being unemployed for at least 12 months within two consecutive years                                                                                                                              | 31 December in the first year of unemployment                                              |
type 1 diabetes and sibling type 1 diabetes, which was retrieved at the end of follow-up. Parental and sibling type 1 diabetes were used as proxies for genetic predisposition to type 1 diabetes and the timing of the family member’s diagnosis was, therefore, not important but merely an indication of genetic susceptibility to type 1 diabetes acquired at conception. Parental and sibling type 1 diabetes were, therefore, included in the analyses as time-fixed variables. Date of birth, birth weight and maternal age at birth were treated as continuous variables.

Statistical analyses
The study population was followed from birth until the date of type 1 diabetes diagnosis, emigration, death or 31 December 2015, which marked the end of follow-up. Emigrated persons did not re-enter the study if returning to Denmark since there would be an information gap in the period spent outside of Denmark. We restricted the exposure period to 0–18 years of age since the purpose of this study was to investigate the effects of adversities experienced in childhood on type 1 diabetes. The analyses were conducted separately for males and females.

To investigate if accumulation of childhood adversities influences type 1 diabetes risk, we specified a multi-state model where we let the occurrence of each additional adverse experience represent a new state of exposure to childhood adversities and calculated the incidence rates of type 1 diabetes for males (HR per adversity increase: 1.01, 95% CI: 0.97–1.05) and, thus, experiencing more than one adversity does not seem to add to the risk of type 1 diabetes for males (HR per adversity increase: 1.01, 95% CI: 0.97–1.05). For females, there is a tendency towards a higher risk of developing type 1 diabetes with increasing number of adversities experienced (HR per adversity increase: 1.06–1.15). However, after adjusting for confounders, and especially after adjusting for parental type 1 diabetes (right panel), the linear effect seen among females was attenuated (adjusted HR per adversity increase: 1.07, 95% CI: 1.02–1.11), and only the effect of
### Table 2: Characteristics of the study population according to exposure to accumulation of childhood adversities experienced before the age of 18 years

| Number of childhood adversities | Total, n; % | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7+ |
|---------------------------------|-------------|---|---|---|---|---|---|---|---|---|
| **Total, n** | 2,153,164 | 100 | 994,517 | 46.2 | 634,849 | 29.5 | 316,353 | 14.7 | 124,947 | 5.8 | 49,335 | 2.3 | 20,796 | 1.0 | 8,214 | 0.4 | 4,153 | 0.2 |
| **Females, n; %** | 1,048,279 | 48.7 | 483,321 | 48.6 | 309,443 | 48.7 | 154,419 | 48.8 | 61,360 | 49.1 | 23,840 | 48.3 | 9,922 | 47.7 | 3,972 | 48.4 | 2,002 | 48.2 |
| **Parental place of origin, n; %** | | | | | | | | | | | | | | | | | | | | |
| European origin | 2,038,677 | 94.7 | 954,624 | 96.0 | 399,016 | 94.4 | 292,720 | 92.5 | 114,739 | 91.8 | 45,907 | 93.1 | 19,758 | 95.0 | 7,885 | 96.0 | 4,028 | 97.0 |
| Other | 114,487 | 5.3 | 39,893 | 4.0 | 35,833 | 5.6 | 23,633 | 7.5 | 10,208 | 8.2 | 3,428 | 6.9 | 1,038 | 5.0 | 329 | 4.0 | 125 | 3.0 |
| **Parental education at birth, n; %** | | | | | | | | | | | | | | | | | | | | |
| Low ≤9 years | 295,034 | 13.7 | 65,637 | 6.8 | 87,081 | 13.7 | 69,142 | 21.9 | 37,679 | 30.2 | 19,074 | 38.7 | 9,567 | 46.0 | 4,407 | 53.7 | 2,447 | 58.9 |
| Middle 10–12 years | 957,069 | 44.4 | 388,273 | 43.9 | 309,434 | 48.7 | 162,298 | 51.3 | 61,544 | 49.3 | 22,458 | 45.5 | 8,681 | 41.7 | 3,008 | 36.6 | 1,373 | 33.1 |
| High >12 years | 901,061 | 41.8 | 553,713 | 55.7 | 243,718 | 38.4 | 86,769 | 27.4 | 26,282 | 21.0 | 7,967 | 16.1 | 2,586 | 12.4 | 823 | 10.0 | 343 | 8.3 |
| **Parental type 1 diabetes, n; %** | | | | | | | | | | | | | | | | | | | | |
| 27,662 | 1.3 | 7,839 | 0.8 | 8,337 | 1.3 | 5,795 | 1.8 | 3,177 | 2.5 | 1,367 | 2.8 | 652 | 3.1 | 262 | 3.2 | 133 | 3.2 |
| **Sibling type 1 diabetes, n; %** | 10,643 | 0.5 | 4,033 | 0.4 | 3,507 | 0.6 | 1,860 | 0.6 | 788 | 0.6 | 274 | 0.6 | 118 | 0.6 | 40 | 0.5 | 23 | 0.6 |
| **Birth order, n; %** | | | | | | | | | | | | | | | | | | | | |
| 1 | 974,488 | 45.3 | 450,486 | 45.3 | 291,159 | 45.9 | 144,623 | 45.7 | 54,220 | 43.4 | 20,795 | 42.2 | 8,447 | 40.6 | 3,235 | 39.4 | 1,523 | 36.7 |
| 2 | 789,415 | 36.7 | 378,653 | 38.1 | 231,478 | 36.5 | 109,828 | 34.7 | 42,360 | 33.9 | 16,335 | 33.1 | 6,851 | 32.9 | 2,591 | 31.5 | 1,319 | 31.8 |
| 3 | 287,831 | 13.4 | 130,385 | 13.1 | 82,943 | 13.1 | 42,715 | 13.5 | 18,438 | 14.8 | 7715 | 15.6 | 3,337 | 16.3 | 1,455 | 17.7 | 793 | 19.1 |
| 4+ | 101,430 | 4.7 | 34,993 | 3.5 | 29,269 | 4.6 | 19,187 | 6.1 | 9,929 | 7.9 | 4,490 | 9.1 | 2,111 | 10.2 | 933 | 11.4 | 518 | 12.5 |
| **Birth weight in grams, mean; SD** | 3,457 | 597 | 3,489 | 597 | 3,465 | 589 | 3,420 | 591 | 3,370 | 600 | 3,315 | 610 | 3,263 | 623 | 3,203 | 630 | 3,126 | 628 |
| **Maternal age at birth in years, mean; SD** | 28.9 | 5.0 | 29.9 | 4.6 | 28.6 | 4.9 | 27.7 | 5.2 | 27.3 | 5.4 | 27 | 5.5 | 26.8 | 5.6 | 26.8 | 5.6 | 26.8 | 5.6 |
Table 3 Total number of the study population experiencing each specific childhood adversity before the age of 18 years and the hazard ratios (HR) and 95% confidence intervals (CI) for developing type 1 diabetes after exposure to each specific childhood adversity presented for males and females separately.

| Childhood adversities | Total | Type 1 diabetes | Males | Females |
|-----------------------|-------|-----------------|-------|---------|
|                       | $n$   | %a             | $n$   | %a     | HRc (95% CI) | HRc (95% CI) |
| Foster care           | 63,634| 3.0            | 234   | 0.4    | 1.04 (0.86; 1.27) | 1.18 (0.95; 1.47) |
| Parental psychiatric illness | 86,566| 4.0            | 278   | 0.3    | 0.92 (0.77; 1.09) | 0.99 (0.83; 1.19) |
| Sibling psychiatric illness | 17,763| 0.8            | 50    | 0.3    | 0.92 (0.62; 1.35) | 1.21 (0.81; 1.82) |
| Parental alcohol abuse | 142,720| 6.6           | 502   | 0.4    | 0.91 (0.80; 1.04) | 1.01 (0.87; 1.16) |
| Parental drug abuse   | 39,069| 1.8            | 121   | 0.3    | 0.87 (0.66; 1.14) | 1.19 (0.92; 1.54) |
| Parental separation   | 623,731| 29.0          | 2220  | 0.4    | 0.99 (0.93; 1.07) | 1.03 (0.95; 1.11) |
| Death of a parent     | 54,465| 2.5            | 188   | 0.3    | 1.01 (0.83; 1.23) | 0.90 (0.71; 1.14) |
| Death of a sibling    | 10,235| 0.5            | 33    | 0.3    | 0.83 (0.51; 1.34) | 0.99 (0.60; 1.62) |
| Parental somatic illness | 263,717| 12.2         | 1217  | 0.5    | 1.17 (1.07; 1.28) | 1.17 (1.06; 1.29) |
| Sibling somatic illness | 55,633| 2.6            | 200   | 0.4    | 0.98 (0.81; 1.18) | 0.99 (0.80; 1.23) |
| Family povertyd       | 118,765| 5.5           | 407   | 0.3    | 0.97 (0.84; 1.13) | 1.04 (0.89; 1.22) |
| Parental long-term unemployment | 547,049| 25.4          | 2635  | 0.5    | 1.05 (0.98; 1.13) | 0.94 (0.87; 1.02) |
| No adversities        | 994,517| 46.2          | 3609  | 0.4    |               |               |
| Total                 | 2,153,164| 100          | 8335  | 0.4    |               |               |

*aPercentage of all children.
bPercentage of those exposed to that specific adversity.
cAdjusted for: current age, date of birth, parental area of origin, parental education at birth, parental type 1 diabetes, sibling type 1 diabetes, birth order, birth weight, maternal age at birth and all other adversities.
dOnly available from 1987 onwards.
experiencing 7+ adversities remained pronounced when examined separately (adjusted HR: 2.06, 95% CI: 1.10–3.86). We assessed the appropriateness of the linearity specification of the effect of the adversity score but found no evidence of important differences.

In addition, we calculated the proportion of the study population that experienced each specific childhood adversity as well as how many of these persons developed type 1 diabetes during follow-up (Table 3). By far, the most common childhood adversities experienced by the study population were parental separation (29%), parental long-term unemployment (25%) and parental somatic illness (12%). Parental somatic illness was the only specific adversity associated with type 1 diabetes in both males (adjusted HR: 1.17, 95% CI: 1.07–1.28) and females (adjusted HR: 1.17, 95% CI: 1.06–1.29).

Discussion

In a nationwide study including all children born in Denmark since 1980, we generally find no or negligible effects of childhood adversities on the risk of type 1 diabetes, which may be reassuring to persons with type 1 diabetes who are concerned that personal trauma contributed to their disease. Only a small proportion of females experienced many adversities (10% had experienced ≥3 adversities) and those who experienced 7+ adversities (0.2%) had twice the risk of developing type 1 diabetes compared with those who experienced no childhood adversities, even after adjustment for confounders. This group may, thus, have a higher risk of developing type 1 diabetes and needs further attention. It should be noted that only 10 of the females exposed to 7+ adversities developed type 1 diabetes, which makes this estimate highly uncertain.

Parental somatic illness was the only specific adversity associated with a higher risk of developing type 1 diabetes. Parental somatic illness was defined as having a parent diagnosed with one of the diseases included in the Charlson comorbidity index, which includes type 1 diabetes and a few other autoimmune diseases (e.g. connective tissue disease). The association between parental somatic illness and type 1 diabetes found in this study may, therefore, be biased by residual confounding of underlying genetic predisposition to autoimmune disease, even after adjustment for parental type 1 diabetes, and should, therefore, be interpreted with caution.

Cohort studies on accumulation of childhood adversities and type 1 diabetes are lacking, but a positive association has been observed between accumulation of adversities and autoimmune disease, including type 1 diabetes, in a retrospective cohort study. A test for linear trend revealed a 20% higher risk of developing an autoimmune disease per adversity in females and a 10% higher risk per adversity in males. Biological sex-differences in timing of hormonal factors influencing insulin sensitivity, and thereby pressure on the beta cell function, and sex-specific immune mechanisms might provide some explanation for the stronger association between childhood adversities and autoimmune disease found among females in the above-mentioned study and between childhood adversities and type 1 diabetes found among females in our study.

Most studies investigating the association between (at least) one adverse experience in childhood and type 1 diabetes have found a positive association. Most of them are case-control studies and have collected information on exposure to adversity in retrospect using questionnaires, which may cause recall bias and an overestimation of the association. Prospective studies only looking at exposure to adversities occurring during the first years of life have found mixed results. The only (to our knowledge) prospective study that has looked at the effect of exposure to at least one serious life event across childhood and development of type 1 diabetes was conducted by Nygren et al. The study found that exposure to at least one serious life event increased the risk of developing type 1 diabetes 3-fold. More than 10,000 children were followed for an average of 6.5 years but only 58 of them developed type 1 diabetes and the loss to follow-up was substantial. Approximately 90% of our study population experienced between 0 and 2 adversities during follow-up, but exposure to a few adversities did not have any effect of importance on type 1 diabetes risk, which is in contrast with the results of Nygren et al. Our study provides results derived from objectively measured exposure to childhood adversities in an unselected study population and the statistical power needed to assess the effect of accumulation of childhood adversities on type 1 diabetes in males and females separately.

Using register data also comes with limitations. First, exposure to adversity is likely to be underreported in registers. For example, parental alcohol abuse was measured using diagnostic codes related to alcohol abuse and prescriptions of medications used in treatment of alcohol addiction. Thus, we only detected those who sought help for their alcohol addiction or were detected in the healthcare system by other means, which we expect to be only a fraction of the total cases of parental alcohol abuse. Second, when using register data, we fail to take the perceived severity of the adverse experience into account, which could have been possible using self-reported information. Information bias in the measure of childhood adversities may provide some explanation as to why we find a smaller
effect of childhood adversities on type 1 diabetes compared with previous studies.

Finally, there may be sensitive time periods where exposure to childhood adversities is of importance for type 1 diabetes development. The human stress-response system is developed in infancy and may be disrupted by excessive or prolonged exposure to adversity. Exposure to stressful adversities may also add to the increased pressure on the beta cells that is caused by the rapid physical growth and substantial hormonal influence that takes place during puberty. The importance of timing of exposure to childhood adversities was beyond the scope of this study and we can, therefore, not rule out that childhood adversities may affect type 1 diabetes risk when experienced in particularly sensitive periods of development.

Conclusion
In an unselected total population sample, we generally find no or negligible effects of childhood adversities on the risk of type 1 diabetes, which may be reassuring to persons with type 1 diabetes who are concerned that personal trauma contributed to their disease. There is a very small group of females exposed to a high degree of adversity who may have a higher risk of developing type 1 diabetes, and this group needs further attention. Future studies should consider the importance of timing of exposure to childhood adversities for type 1 diabetes development.

Supplementary data
Supplementary data are available at IJE online.

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Conflict of interest
B.C., J.S. and M.E.J. own shares in Novo Nordisk A/S. J.S. serves as an adviser to Medtronic, Janssen and Novo Nordisk. J.S. has received fees for speaking on behalf of Medtronic, Sanofi, Novo Nordisk and Bayer AG. M.E.J. has received research grants from AstraZeneca, Amgen, Sanofi Aventis and Boehringer Ingelheim. All other authors declare no conflicts of interest.

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