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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.

Key words: Life course, register-based, prospective study, childhood adversities, adverse childhood experiences, life events, type 1 diabetes

Key Messages

- Previous studies have indicated a positive association between childhood adversities and type 1 diabetes but have been underpowered and limited by selection.
- 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.
- Females exposed to a very high degree of adversity may have a higher risk of developing 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 bereavement[10] 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 residents[25] 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) 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 Diabetes[28] (1980–95: 0–15 years, 1996–2015: 0–18 years), the Danish Adult Diabetes Registry[29] (2005–15: ≥18 years) and the Danish National Patient Registry[30] (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 Registry[31] (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 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).
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 graphs[32] (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

Table 1 Definitions and timing of the childhood adversities included in the DANish LIFE course (DANLIFE) cohort occurring when the child is between 0 and 18 years of age

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, alcohol 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[26] in the period 1980–93 or the ICD-10 codes included in the updated version of the Charlson comorbidity index[27] 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 by age in each state (illustrated in Supplementary Figure 2, available as Supplementary data at *IJE* online), assuming the effects of covariates are proportional. Due to small numbers, we combined the exposure to seven or more adversities into one state (7+). We used age as the underlying time scale since age is a strong predictor of developing type 1 diabetes.[22] Only the first occurrence of each specific adversity was considered, and we did not differentiate between which specific adversities (or their order) each individual experienced.

Hazard ratios (HRs) of developing type 1 diabetes were calculated for each adversity state using the state of no adverse experiences as reference. We estimated the linear effect of accumulation of childhood adversities from one adversity onwards and tested the appropriateness of the linearity assumption against both a categorical and a quadratic version of the adversity score using likelihood ratio tests. In addition, we investigated the effect of each specific childhood adversity on type 1 diabetes separately. Analyses were performed using packages Epi[33] and popEpi[34] in the statistical software R.

Results

The study population was followed for an average of 16.9 years during which 8335 (0.4%) persons developed type 1 diabetes. A total of 18 531 persons (0.9%) died and 151 630 persons (7%) emigrated. Of these, 2778 persons died or emigrated on their date of birth and, therefore, did not contribute to the analyses.

The characteristics of the study population by number of childhood adversities experienced before the age of 18 years are presented in Table 2. Since there was no difference when stratifying by sex, except for males having a slightly higher mean birth weight compared with females (data not shown), the background characteristics in Table 2 are presented for males and females combined. Almost half of the study population did not experience any adversities before the age of 18 years and 90% of the study population experienced between 0 and 2 adversities. There was a clear social gradient in the experience of childhood adversities since a larger proportion of children who experienced many adversities were born to parents with low education. Moreover, the proportions of children with parental type 1 diabetes increased with increasing number of adversities. Finally, those who experienced many adversities had a lower mean birth weight and were born to younger mothers compared with those who experienced fewer adversities.

The age-specific incidence rates of type 1 diabetes in DANLIFE for males and females respectively can be seen in Supplementary Figure 3, available as Supplementary data at *IJE* online. The incidence rates resemble the well-known age-specific incidence of type 1 diabetes,[22] with a peak in puberty at about 11 years of age for females and some years later for males, at about 14 years of age.

Figure 1 shows the unadjusted (left panel) and the adjusted (right panel) HRs of developing type 1 diabetes in each state of exposure to childhood adversities using no adversities as reference. The vertical blue and red lines in the left panel show the unadjusted linear trends from experiencing one adversity onwards for males and females, respectively. The slope of the linear trend is close to perpendicular for males 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: 1.10, 95% CI: 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		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	8214	0.4	4153	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	9922	47.7	3972	48.4	2002	48.2
Parental place of origin, *n*; %																		
European origin	2 038 677	94.7	954 624	96.0	599 016	94.4	292 720	92.5	114 739	91.8	45 907	93.1	19 758	95.0	7885	96.0	4028	97.0
Other	114 487	5.3	39 893	4.0	35 833	5.6	23 633	7.5	10 208	8.2	3428	6.9	1038	5.0	329	4.0	125	3.0
Parental education at birth, *n*; %																		
Low ≤9 years	295 034	13.7	65 637	6.6	87 081	13.7	69 142	21.9	37 679	30.2	19 074	38.7	9567	46.0	4407	53.7	2447	58.9
Middle 10–12 years	957 069	44.4	388 273	39.0	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	7967	16.1	2586	12.4	823	10.0	343	8.3
Parental type 1 diabetes, *n*; %	27 562	1.3	7839	0.8	8337	1.3	5795	1.8	3177	2.5	1367	2.8	652	3.1	262	3.2	133	3.2
Sibling type 1 diabetes, *n*; %	10 643	0.5	4033	0.4	3507	0.6	1860	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	8447	40.6	3235	39.4	1523	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	6851	32.9	2591	31.5	1319	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	3387	16.3	1455	17.7	793	19.1
4+	101 430	4.7	34 993	3.5	29 269	4.6	19 187	6.1	9929	7.9	4490	9.1	2111	10.2	933	11.4	518	12.5
Birth weight in grams, mean; SD	3457	597	3489	597	3465	589	3420	591	3370	600	3315	610	3263	623	3203	630	3126	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

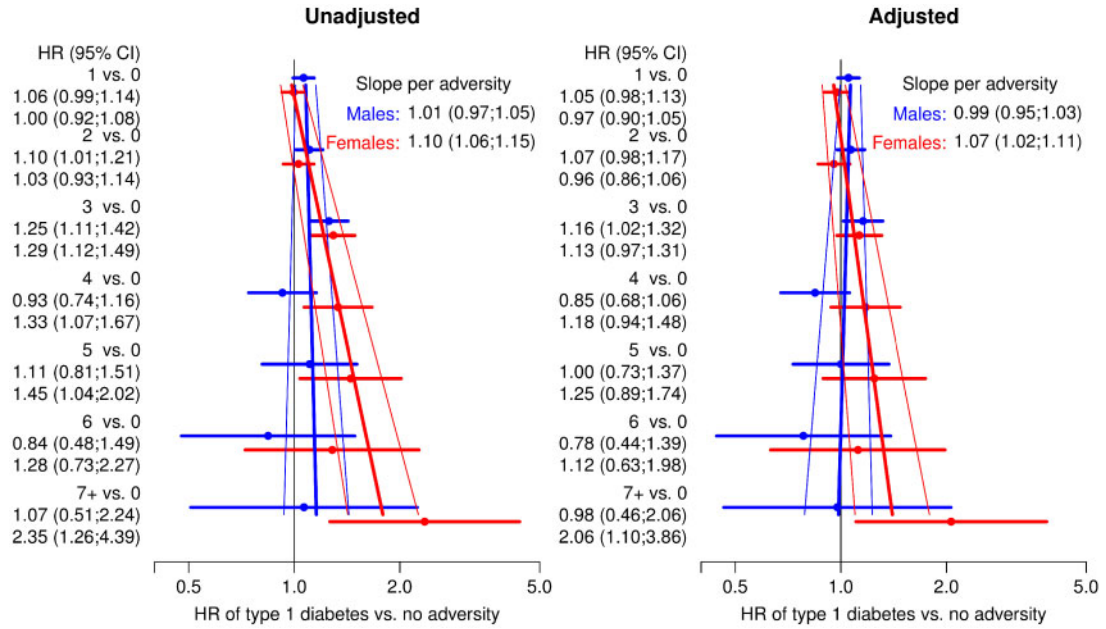

Figure 1 Hazard ratios (HR) and 95% confidence intervals (CI) of type 1 diabetes in each state of adversity exposure compared with no adversities, and the linear trend and 95% CI from experiencing one adversity onwards for males and females, respectively. The HRs and linear trend in the right-hand panel are adjusted 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 and maternal age at birth

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

	Total		Type 1 diabetes		Males		Females	
Childhood adversities	*n*	%[a]	*n*	%[b]	HR[c]	(95% CI)	HR[c]	(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 poverty[d]	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				

[a]Percentage of all children.

[b]Percentage of those exposed to that specific adversity.

[c]Adjusted 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.

[d]Only 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.[35] 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,[36] and sex-specific immune mechanisms[37] 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.[3,8] 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.*[2] 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.*[2] 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.[7,38] 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.[5,39] 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 Astra Zeneca, Amgen, Sanofi Aventis and Boehringer Ingelheim. All other authors declare no conflicts of interest.

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