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PhD Thesis

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Childhood adversities and type 1 diabetes risk

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List of papers

Study I: Bengtsson J, Dich N, Rieckmann A, Rod NH. Cohort profile: the DANish LIFE course (DANLIFE) cohort, a prospective register-based cohort of all children born in Denmark since 1980. *BMJ Open*. 2019 Sep 20;**9**(9):e027217.

Study II: Bengtsson J, Byberg S, Carstensen B, De Stavola BL, Svensson J, Jørgensen ME, Rod NH. Accumulation of childhood adversities and type 1 diabetes risk: a register-based cohort study of all children born in Denmark between 1980 and 2015. *Re-submitted after revision in International Journal of Epidemiology*.

Study III: Bengtsson J, Rieckmann A, Carstensen B, Svensson J, Jørgensen ME, Rod NH. Trajectories of childhood adversity and type 1 diabetes: a nationwide study of 1 million children. *Under review in Diabetes Care after the first submission*.

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List of abbreviations

HPA-axis	Hypothalamic-pituitary-adrenal axis
DANish LIFE course cohort	DANLIFE
CRS	Civil Registration System
CPR number	Civil Personal Registration number
MBR	Medical Birth Register
PY	Person-year
HR	Hazard ratio
CI	Confidence interval
IRR	Incidence rate ratio

English summary

Type 1 diabetes is a serious and burdensome condition that usually presents in childhood or young adulthood. Knowledge of the non-genetic risk factors of type 1 diabetes is sparse, but persons with type 1 diabetes and their relatives are often concerned that stressful adverse life events or circumstances have contributed to the development of the disease.

Childhood adversities cover a broad range of stressful adverse life events and circumstances from material deprivation to straining family dynamics. Studies, primarily from the US, have shown that exposure to childhood adversities is common and tends to cluster among socially deprived persons. Less is known about the prevalence and social clustering of childhood adversities in welfare states such as Denmark where the level of social security is high.

The overall objective of this thesis is to document the level of childhood adversities across age, sex, and social strata in Denmark and, based on this knowledge, thoroughly assess the effects of accumulation of adversities across childhood and adolescence on type 1 diabetes risk in males and females separately. The importance of timing of adversity exposure for the onset of type 1 diabetes in different age groups is also addressed. To do this, a large register-based cohort including all children born in Denmark since 1980 (N=2,223,927) was set up with annually registered information on exposure to social and family-related adversities such as death, severe illness, and alcohol abuse in the family across childhood and adolescence. The study population was followed for 16.8 years on average, during which 8335 persons developed type 1 diabetes.

The results showed that even in a welfare state like Denmark, exposure to childhood adversities is common; more than half of the study population experienced at least one childhood adversity, and one in 10 children experienced three or more adversities before the age of 18 years. Childhood adversities were experienced by males and females equally often, and a clear social gradient in exposure to accumulation of childhood adversities was observed.

Contrary to the expected, accumulation of childhood adversities was not associated with type 1 diabetes in the vast majority of the study population. A small group of children (3%) exposed to high and increasing annual rates of childhood adversities across childhood and adolescence had a higher risk of developing type 1 diabetes, but only among males who were diagnosed before 11

years of age and among females diagnosed after 16 years of age. These results are highly uncertain since very few of the persons who were highly exposed to childhood adversities also developed type 1 diabetes and these findings should, therefore, be interpreted with caution.

Thus, the overall finding of this thesis is that exposure to childhood adversities is not an important risk factor for type 1 diabetes, which may be reassuring to persons who are concerned that stressful adverse experiences have contributed to the development of the disease. However, exposure to childhood adversities have well-documented consequences for many other mental and physical health outcomes and, given their relatively high prevalence, should be considered a public health issue. Strategies to reduce the prevalence and effects of childhood adversities are, therefore, warranted.

Dansk resumé

Type 1 diabetes er en alvorlig sygdom, der ofte debuterer i barndommen. De ikke-genetiske årsager til type 1 diabetes er stort set ukendte, men personer med type 1 diabetes og deres pårørende er ofte bekymrede for, om stressende livsbegivenheder kan have bidraget til udviklingen af sygdommen.

Studier har vist, at stressende livsbegivenheder i barndommen, såsom dødsfald, alvorlig sygdom og alkoholmisbrug i familien, forekommer hyppigt og at socialt udsatte børn oplever flere stressende livsbegivenheder i løbet af barndommen og ungdomsårene end andre børn. Disse studier stammer primært fra USA og forekomsten af stressende livsbegivenheder blandt børn og unge i velfærdslande såsom Danmark, med et omfattende socialt sikkerhedsnet, er mindre kendt.

Formålet med denne ph.d.-afhandling er at kortlægge prævalensen af stressende livsbegivenheder i barndommen på tværs af alder, køn og sociale forhold og baseret på denne viden at undersøge, om akkumulering af stressende livsbegivenheder er en risikofaktor for udvikling af type 1 diabetes blandt drenge og piger i Danmark. Det undersøges også, om tidspunktet for eksponering for stressende livsbegivenheder kunne have en betydning for udvikling af type 1 diabetes i forskellige aldersgrupper. For at kunne gennemføre disse undersøgelser blev et stort registerbaseret studie etableret. Studiet indeholder information om stressende livsbegivenheder i barndommen blandt alle personer født i Danmark siden 1980 (N=2,223,927). Studiedeltagerne blev i gennemsnit fulgt i 16.8 år og 8335 personer udviklede type 1 diabetes i løbet af opfølgningstiden.

Resultaterne viste, at selv i et velfærdsland som Danmark, havde mere end halvdelen af studiedeltagerne været udsat for mindst én stressende livsbegivenhed, mens én ud af 10 havde været udsat for tre eller flere stressende livsbegivenheder før 18-årsalderen. De stressende livsbegivenheder ramte drenge og piger lige hyppigt, og der var en tydelig social ulighed i eksponeringen for akkumulering af stressende livsbegivenheder, hvor børn med lavt uddannede forældre oplevede langt flere stressende livsbegivenheder sammenlignet med børn af højt uddannede forældre.

I modsætning til forventningen, var akkumulering af stressende livsbegivenheder ikke forbundet med en øget risiko for at udvikle type 1 diabetes blandt langt størstedelen af studiedeltagerne. En lille gruppe af børn (3%), som havde været udsat for mange og gentagne stressende

livsbegivenheder i løbet af barndommen, havde en forøget risiko for at udvikle type 1 diabetes, men kun hvis sygdommen blev diagnosticeret før 11-årsalderen blandt drengene eller efter 16-årsalderen blandt pigerne. Disse resultater er behæftet med stor usikkerhed, fordi meget få af disse højt eksponerede børn udviklede type 1 diabetes, og de bør derfor fortolkes med forsigtighed.

Sammenfattende finder vi, at stressende livsbegivenheder i barndommen ikke er en vigtig risikofaktor for udviklingen af type 1 diabetes. Det er et betryggende resultat for dem, der er bekymret for om stressende livsbegivenheder har bidraget til udviklingen af type 1 diabetes. På baggrund af den relativt hyppige forekomst i befolkningen, bør stressende livsbegivenheder i barndommen dog stadig betragtes som et betydeligt folkesundhedsproblem, som følge af de påviste konsekvenser for en lang række andre psykiske og somatiske helbredstilstande. Forebyggelse af stressende livsbegivenheder i barndommen bør derfor prioriteres.

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1 Introduction

Type 1 diabetes is a serious condition that often presents in childhood or young adulthood.[1] The clinical onset of type 1 diabetes is usually preceded by an autoimmune destruction of the insulin-producing pancreatic beta cells, which ultimately leads to complete dependence on exogenous insulin for survival.[1] The aetiology of this destructive process is largely unknown.[2] Factors such as birth weight, caesarean section, dietary factors, and infections have been associated with type 1 diabetes risk, but the associations are weak and can explain only a fraction of the type 1 diabetes burden.[2–6] Further identification of potential risk factors for type 1 diabetes is, therefore, warranted to enhance the possibilities for future prevention.[5]

The limited knowledge of the aetiology of type 1 diabetes often leaves clinicians without an evidence-based answer when persons with type 1 diabetes ask them about possible non-genetic causes of the disease. A common concern among these often young and otherwise healthy individuals (and among their parents) is that stressful adverse life events or circumstances have contributed to the development of the disease. A workshop conducted in relation to this thesis with representatives from the type 1 diabetes community in Denmark confirmed that this is indeed a highly frequent concern that causes substantial worry and guilt.

Childhood adversities cover a broad range of stressful adverse life events or circumstances from material deprivation to straining family dynamics and have been identified as central sources of stress in children that tend to cluster among socially disadvantaged persons.[7] A recent review and meta-analysis including 37 studies primarily from the US demonstrated that exposure to childhood adversities is highly prevalent; 57% of the 250,000 participants across the studies had been exposed to at least one childhood adversity, and 13% had been exposed to more than four childhood adversities before the age of 18 years.[8] However, less is known about the prevalence and social clustering of childhood adversities in welfare states such as Denmark, with high levels of social security.

The beta cell stress hypothesis suggests that any factor that increases the workload of the beta cells should be regarded as a risk factor for type 1 diabetes.[6] The physiological stress response may lead to insulin resistance caused by increased peripheral levels of the stress hormone cortisol.[9] Excessive exposure to childhood adversities could, therefore, increase the workload of the beta cells and make them more susceptible to autoimmune attack.[3,6] There may also be specific periods where exposure

to childhood adversities is particularly detrimental for type 1 diabetes development. The physiological stress response system develops in infancy, and studies have shown that this development may be disrupted by excessive exposure to adversities, making the stress response hyper-sensitive to subsequent episodes of adversity exposure.[10–12] A disrupted stress response system may, in turn, affect the immunological balance leading to a higher risk of developing immune-mediated diseases,[10–12] including type 1 diabetes.[13] Also, the incidence of type 1 diabetes peaks in puberty where rapid physical growth and substantial hormone influence result in high insulin demand.[2] Puberty is, therefore, a potentially sensitive period in which excessive adversity exposure could increase the beta cells stress even further.[3,6] The onset of puberty, and the peak in type 1 diabetes incidence, occur earlier in females than in males.[14] There are also some indications that the perception of exposure to childhood adversities differs between males and females in adolescence.[15] Sex may, therefore, modify the effect of childhood adversities on type 1 diabetes development.

Childhood adversities have been associated with type 1 diabetes with effect estimates indicating an up to three times higher risk of developing type 1 diabetes after exposure to at least one adverse experience in childhood,[16] albeit not consistently.[17,18] Previous studies on childhood adversities and type 1 diabetes have been affected by a range of methodological shortcomings such as selection and recall bias, reverse causality, and lack of power (see also the literature review in Section 2.4). The conclusions that can be drawn from these studies are, therefore, limited. Also, the importance of accumulation and timing of childhood adversities for type 1 diabetes development has yet to be addressed in prospective studies. Finally, studies investigating potential sex differences in the effect of childhood adversities on type 1 diabetes are lacking.

This thesis contributes to the existing literature by setting up a large population-based cohort with prospective and objective information on childhood adversities in a total population sample and by thoroughly assessing the effects of accumulated exposure patterns of adversities across childhood and adolescence on type 1 diabetes development in males and females separately. Hopefully, this will increase our knowledge on the risk factors of type 1 diabetes and provide clinicians with more robust evidence to lean on in consultations with persons who are concerned that childhood adversities have contributed to the development of type 1 diabetes.

1.1 Objective and hypotheses

The overall objective of this thesis is to document the level of childhood adversities across age, sex, and social strata in Denmark and, based on this knowledge, thoroughly assess the effects of cumulative exposure to adversities across childhood and adolescence on type 1 diabetes risk in males and females. Such assessment requires large and prospective high-quality data with objective and repeated information on adversity across entire childhoods and a follow-up that stretches into young adulthood. The specific aims of this thesis are:

1. To assemble a register-based cohort of all children born in Denmark since 1980 and define and construct measures of repeated exposure to childhood adversities, providing an adequate data source for the investigation of the association between exposure to childhood adversities and type 1 diabetes.
2. To estimate the prevalence of specific and accumulated childhood adversities before 18 years of age among males and females in the Danish population and determine whether there is a social gradient in exposure to accumulation of childhood adversities.
3. To quantify the association between accumulation of childhood adversities and type 1 diabetes among males and females separately. Accumulation of childhood adversities will be measured both as a cumulative score and as five trajectory groups of adversity across three dimensions (family dynamics, loss or threat of loss in the family, and material deprivation).[19]
4. To investigate whether the association depends on timing of exposure to childhood adversities and age at onset of type 1 diabetes by describing the age-specific incidence of type 1 diabetes in the five trajectory groups of adversity and estimating the risk of developing type 1 diabetes in three age groups: childhood (0-10 years), puberty (11-15 years), and young adulthood (≥16 years) separately for males and females.

I address and present the first aim in a cohort profile (Study I). The second aim is also addressed in the cohort profile supplemented by background information from two scientific studies (Study II and Study III) and additional descriptive analyses performed specifically for this thesis. The second aim is based on the hypothesis that exposure to adversities is as prevalent in Denmark as in other high-income countries and that there is a social gradient in exposure to childhood adversities. I further hypothesise that the prevalence of childhood adversities is similar among males and females.

I address the third aim in both Study II and Study III. The specific hypotheses are that exposure to accumulation of childhood adversities is a risk factor for type 1 diabetes development and that the effect differs between males and females.

The fourth aim is addressed in Study III based on the specific hypotheses that the effect of childhood adversities on type 1 diabetes risk depends on the timing of exposure to adversities and age at onset of type 1 diabetes and that the effect differs between males and females.

1.2 Outline of the thesis

Including this introduction, this PhD thesis contains eight main sections. The background section introduces the theoretical background for this thesis and provides an overview of the current scientific literature and gaps in the evidence. Then the material and methods that were used in this thesis are described in detail, followed by a summary of the study results. In the discussion, the main findings are viewed in relation to previous studies and potential sources of bias in the included studies are discussed. The thesis ends with conclusions, suggestions for future research, and public health perspectives. Copies of the three studies can be found in the appendix.

2 Background

2.1 Childhood adversity

There is no consensus on what the concept of childhood adversity includes, and numerous studies have assessed the effect of childhood adversities on a wide range of health outcomes using various definitions.[7,8,20,21] The common notion across these studies is that childhood adversities impose substantial psychosocial stress that may have lasting consequences for physical and mental health and well-being.

In this thesis, childhood adversities cover a broad range of social and family-related adverse and stressful experiences with scientifically supported implications for health and well-being. In childhood, the family environment is an essential resource to thrive and develop. Consequently, straining family dynamics[22–28] and threatened or actual losses within the family[29,30] constitute important sources of stress in children. Material deprivation in the family is another central source of stress in children as it may affect the family environment and the availability of material and social resources to maintain mental and physical health.[31–34] Thus, the concept of childhood adversities is applied in this thesis to cover a broad range of stressful factors in childhood related to family dynamics (i.e., foster care, parental and 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 material deprivation (i.e., family poverty and parental long-term unemployment) with the objective to investigate whether patterns of accumulation of such adversities are important risk factors for type 1 diabetes development.

It has been argued that most children can handle single episodes of adversity without suffering enduring harm, while multiple exposures often have consequences for health.[35,36] This may be because exposure to multiple adverse experiences may exceed an individual's capacity to cope with the stress they induce[10,37] (further explained in Section 2.3). Exposure to one childhood adversity often leads to another adversity exposure, and then another.[20,38] Childhood adversities also tend to cluster among persons with low socioeconomic status.[38–40] On top of that, children who grow up in low socioeconomic households may be more vulnerable to the harmful effects of childhood adversities because they are more likely to lack the buffering support provided by responsive

caregivers.[37,40] Accumulation of childhood adversities may, therefore, have much more substantial health consequences than specific adversity exposures in isolation.[22]

Previous studies have indicated that the prevalence of childhood adversities is high. A recent review and meta-analysis of 37 studies predominantly conducted in the US found that 57% of the more than 250,000 participants across all studies had experienced at least one childhood adversity and 13% had experienced at least four adversities before the age of 18 years.[8] This underscores that exposure to accumulation of childhood adversities is frequent even in high-income countries. However, most studies on the health effects of accumulation and social clustering of childhood adversities originate from the US,[8,39] and therefore, less is known about the prevalence and clustering of childhood adversities in welfare states such as Denmark, with extensive social security systems in contrast to the US. The construction of a nationwide cohort of all children born in Denmark since 1980 with objective measures of childhood adversities will provide an estimate of the prevalence of childhood adversities and answer the question of whether the social gradient in exposure to childhood adversities is as strong in Denmark as it is in other high-income countries. Finally, it will provide an opportunity to elucidate the importance of accumulation of childhood adversities for the development of type 1 diabetes, and for health and well-being beyond type 1 diabetes in future studies.

2.2 Type 1 diabetes

Type 1 diabetes is one of the most common chronic diseases in children, and the highest incidence rates are found in populations of European origin, particularly in the Nordic countries.[41] It is estimated that more than 1 million children and adolescents aged 0-19 years are living with type 1 diabetes worldwide and that about 130,000 are diagnosed yearly.[41] The incidence of type 1 diabetes has increased substantially over the past 30 years with a shift toward younger age at onset.[2] This pattern is also recognised in Denmark where the prevalence has increased by 3% annually,[42] especially in the youngest age group (0-4 years),[43] with approximately 300 new cases aged 0-15 years reported in 2014.[44] The increasing incidence of type 1 diabetes is too rapid to be attributed to genetic changes in the population, suggesting influence from environmental and behavioural factors.[2]

Daily life with type 1 diabetes remains a great challenge and substantial burden for a child and the whole family as a fine balance between exercise, food intake, and insulin injections must be

maintained. This requires a structured self-management plan including administration of insulin, monitoring of blood glucose, physical activity, and diet.[41] Without exogenous insulin injection, hyperglycaemia (high blood glucose) occurs, which over time leads to diabetic ketoacidosis and ultimately death.[41] A natural reaction when confronted with such a serious, lifelong, and incurable illness is wanting to know what caused it, but the knowledge of the non-genetic risk factors of type 1 diabetes remains limited. Conversations with type 1 diabetes clinicians at Steno Diabetes Center Copenhagen, workshops with representatives from the type 1 diabetes community in Denmark (persons with type 1 diabetes and parents of children and adolescents with type 1 diabetes), and online forums[45] witness that exposure to childhood adversities is commonly suspected to contribute to type 1 diabetes development among affected persons and their relatives. Assessment of the role of childhood adversities in the development of type 1 diabetes is, therefore, highly warranted.

2.3 Potential mechanisms linking childhood adversities to type 1 diabetes

In this thesis, the concept of allostasis is used to explain how exposure to childhood adversities may affect type 1 diabetes risk. Allostasis is the process by which the body readjusts itself to maintain homeostatic balance in stressful situations.[46] The cumulative costs of allostasis to the body is referred to as allostatic load, and chronic allostatic overload is a state in which pathologies develop.[46] There are two types of allostatic overload. The first type refers to situations in which the demand for energy exceeds its availability.[46] The second type of allostatic overload is the one relevant for the hypothesis of this thesis. It refers to situations in which the energy supply is not inadequate, but allostatic overload occurs as a result of social conflict or social dysfunction that exceeds the individual's capacity to cope,[46] such as excessive exposure to childhood adversities.[10,37,47] The hypothalamic-pituitary-adrenal (HPA) axis is one of the key mediators of the physiological stress response.[13] The stress associated with exposure to childhood adversities can activate the HPA-axis, which ends with a release of glucocorticoid cortisol from the adrenal cortex.[13] Cortisol is central to the body's stress response as it helps fuel the body's 'fight-or-flight' instinct in a crisis.[12] However, cortisol also causes insulin resistance, and excessive or prolonged exposure to childhood adversities may lead to chronically elevated levels of peripheral cortisol[46] and constant pressure on the insulin-producing pancreatic beta cells.[2,6]

The beta cell stress hypothesis suggests that any factor that increases the workload of the beta cells should be regarded as a risk factor for type 1 diabetes.[6,9] The idea is that such factors may trigger or accelerate the autoimmune destruction of the pancreatic beta cells in genetically susceptible

individuals.[2] Since cortisol causes insulin resistance, exposure to childhood adversities contributes to beta cell stress and may be one of the factors that can trigger or accelerate the autoimmune process of type 1 diabetes (Figure 1).[9] The beta cell stress hypothesis is compatible with the accelerator hypothesis[48] and the overload hypothesis,[3] which also suggest that beta cell exhaustion caused by exogenous factors (e.g., weight gain, rapid growth, and puberty) is important in type 1 diabetes development.

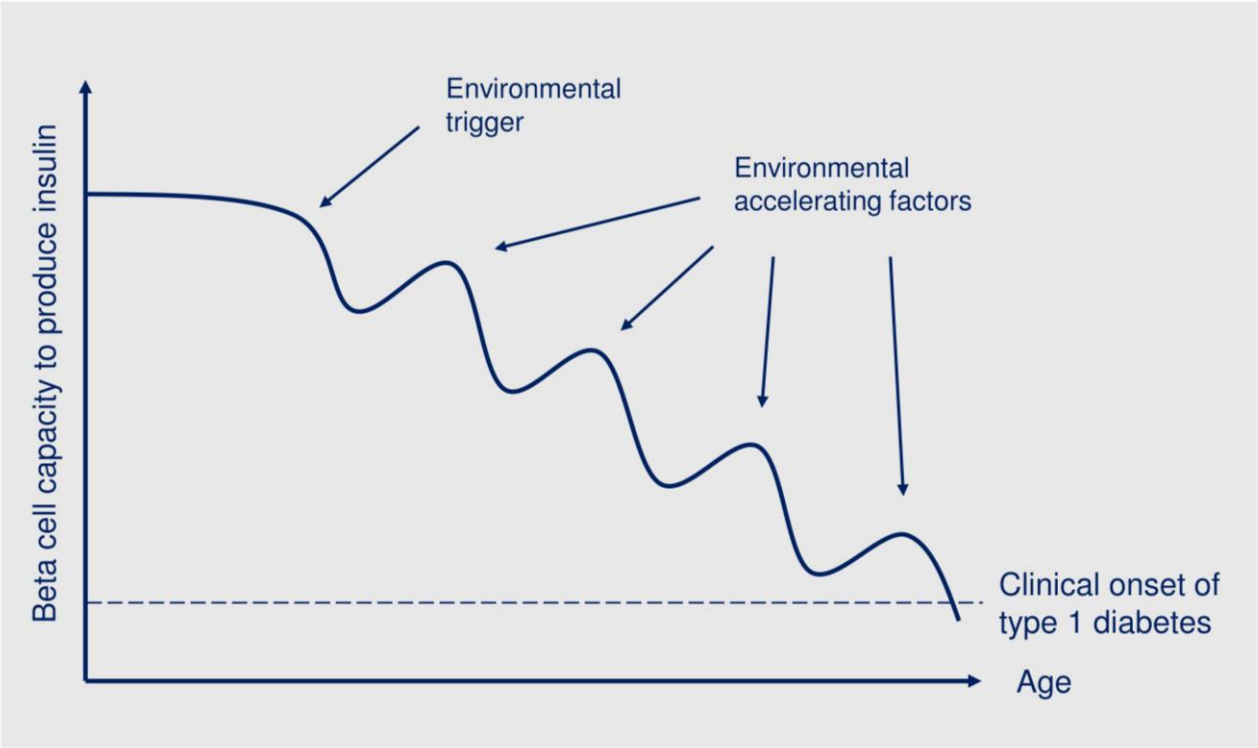

Figure 1 Model of the autoimmune process of type 1 diabetes in genetically susceptible individuals as described by Knip et al.[4] modified by Nygren.[49] A factor in the environment triggers the autoimmune destruction of the beta cells, a process that may be accelerated by other factors that cause beta cell stress. Childhood adversities may be one of these triggering or accelerating factors. Finally, the beta cells can no longer produce enough insulin, and the clinical onset of type 1 diabetes occurs.

2.3.1 Sex as a potential modifying factor

Sex may be a modifying factor of the effect of exposure to childhood adversities on type 1 diabetes development. Evidence suggests that relationships with family and friends are associated with higher levels of stress among females than among males, particularly in adolescence.[15] Females have also been shown to respond with increased and prolonged cortisol output when exposed to biological and physiological stress in adolescence.[50,51] The effects of childhood adversities on type 1 diabetes may, therefore, be stronger among females compared with males in adolescence. In addition, a prospective study by Dube et al. found that the risk of developing an autoimmune disease, including type 1 diabetes, increased more per adversity exposure among women than

among men.[52] Also, the incidence rate of type 1 diabetes is similar among males and females until it peaks in puberty at about 11 years of age among females and about 14 years of age among males.[14] Hereafter, males are known to have a higher type 1 diabetes incidence than females in most parts of the world.[14] These aspects highlight the importance of investigating the effect of childhood adversities on type 1 diabetes among males and females separately.

2.3.2 Timing of adversity exposure and type 1 diabetes risk

The timing of exposure to childhood adversities may be of importance for type 1 diabetes development. Within the life course framework of epidemiology, a distinction has been made between critical and sensitive periods where exposure to adversities may have more detrimental effects on future health outcomes.[38] Both concepts may be interpreted as qualitatively different interactions between time and exposure.[53] A critical period refers to a time window of rapid development of bodily functions or organ systems where exposure to adversity could cause irreversible changes that are not possible outside of this time window.[53] The physiological stress response system develops rapidly in infancy and may be disrupted by excessive or prolonged exposure to adversity.[10,12,37] Such disruption is permanent and may sensitise a person to subsequent exposure to adversities with exaggerated excretion of stress hormones, including cortisol, as a result.[10,12,37] However, some studies have also demonstrated that excessive exposure to adversities may lead to blunted cortisol reactivity.[11,37] In such cases, excessive adversity exposure would not contribute to beta cell stress. Alterations in the stress response system may, in turn, disrupt the immunological balance leading to a more inflammatory phenotype and a higher risk of developing immune-mediated diseases,[11,12] including type 1 diabetes.[13] Excessive exposure to adversities in infancy may, therefore, be important for type 1 diabetes development.

Sensitive periods occur during times of rapid behavioural development, and the effect of adversities during a sensitive period is not necessarily permanent.[38] Hence, during a sensitive period, exposure to childhood adversities would have a more pronounced effect on type 1 diabetes risk, but may also be associated with a higher risk outside of this time window, although to a lesser extent.[53] Puberty may be a sensitive period for excessive adversity exposure because increased cortisol levels may add to the beta cell stress that is already ongoing due to the rapid physical growth and substantial hormone influence that takes place during puberty.[3,6] There is also rapid brain development going on in puberty, and frequent or prolonged exposure to adversities may have lasting effects on HPA-reactivity.[37,54] In that sense, puberty may also be regarded as a critical period for adversity exposure.

The appearance of diabetes-related autoantibodies is the first sign of beta cell autoimmunity, and the time that elapses before the clinical onset of type 1 diabetes is highly individual and can last for months or more than 10 years.[4] Evidence suggests that beta cell autoimmunity can be triggered at any age by a factor in the environment in susceptible individuals. However, the majority of the processes seem to be initiated in early childhood.[4] Between the age of six months and three years, there is a burst of autoimmunity in genetically susceptible individuals, and more than 80% of those who develop manifest type 1 diabetes before adolescence develop beta cell autoimmunity at this age.[55] Excessive adversity exposure in infancy may thus either trigger or accelerate the autoimmune beta cell destruction. Since the beta cell autoimmunity is already likely to be ongoing in puberty, the role of exposure to childhood adversities on type 1 diabetes development in puberty would, therefore, be accelerating rather than triggering.[3] In sum, exposure to childhood adversities in the critical period of infancy and the sensitive/critical period of puberty may be particularly important for type 1 diabetes development.

2.4 Childhood adversities and type 1 diabetes: review of the literature

A comprehensive literature search was undertaken to gain an overview of the evidence base to which this thesis intends to contribute. The PubMed database was searched for articles published until 1 April 2020. The search terms: [family relations]; [family conflict]; [stress, psychological] [life change events]; [adverse childhood experiences]; “childhood adversities”; “life event*”; “psychosocial stress”; “child abuse”; “social environment”; or “stressor*” in combination with [diabetes mellitus, type 1]; “insulin dependent diabetes mellitus”; “IDDM”; “T1D”; or “type 1 diabetes” were applied. Words in square brackets indicate MeSH (Medical Subject Headings) terms and * truncates the search term allowing for variant spellings. In total, 27 studies specifically assessing childhood adversities (most often measured as stressful life events) as a potential risk factor of type 1 diabetes or type 1 diabetes-related autoimmunity were identified for review. Since this review was not undertaken systematically, it may not be an exhaustive presentation of all available evidence, but it reviews the key evidence that this thesis builds on. Table 1 presents an overview of the identified studies.

Table 1 Overview of observational studies examining the association between childhood adversities and type 1 diabetes or type 1 diabetes-related autoimmunity ordered by year of publication

Study	Design and population	Exposure	Outcome	Key findings
Stein & Charles (1971)[56] **USA**	Case-control study of 38 cases with type 1 diabetes aged 11–25 years and 38 unmatched controls aged 5–25 years.	Retrospective recall of parental loss and severe family disturbance measured by interview.	Type 1 diabetes	A larger proportion of cases had been exposed to parental loss and severe family disturbance compared with controls. Most had been exposed before type 1 diabetes onset.
Leaverton et al. (1980)[57] **USA**	Case-control study of 37 cases with type 1 diabetes and 37 controls aged 2–18 years matched on age, sex, race, geographic area, and socioeconomic status.	Retrospective recall of parental loss and severe family disturbance measured by interview.	Type 1 diabetes	A larger proportion of cases had been exposed to parental loss before type 1 diabetes onset compared with controls.
Robinson & Fuller (1985)[58] **UK**	Case-control study of 13 cases with type 1 diabetes and 26 controls aged 17–34 years matched on age and sex.	Retrospective recall of severe life events and severe difficulties experienced within 3 years before type 1 diabetes onset measured by interview using the Life Events and Difficulties Schedule.	Type 1 diabetes	A larger proportion of cases had been exposed to severe life events and severe difficulties compared with controls.
Kisch (1985)[59] **Israel**	Case-control study of 66 cases with type 1 diabetes and 62 controls aged 17–85 years matched on age and sex.	Retrospective recall of stressful life events experienced before type 1 diabetes onset measured by questionnaire.	Type 1 diabetes	The frequency of stressful life events was higher among cases compared with controls.
Robinson et al. (1989)[60] **UK**	Case-control study of 12 families with one person with type 1 diabetes each. Six case families with one ICA positive person and six control families without an ICA positive person.	Retrospective recall of sever life events and severe long-term difficulties experienced within 5 years before the second family member's type 1 diabetes onset measured by interview using the Life Events and Difficulties Schedule.	Type 1 diabetes	Case families had been exposed to a higher frequency of severe life events and long-term difficulties compared with control families.
Vialettes et al. (1989)[61] **France**	Case-control study of 32 cases with type 1 diabetes and 53 controls aged 15–40 years matched on age.	Retrospective recall of 37 life events and their emotional impact measured by interview using questionnaire.	Type 1 diabetes	A larger proportion of cases had been exposed to at least one stressful life event compared with controls.
Siemiatycki et al. (1989)[62] **Canada**	Case-control study of 161 cases with type 1 diabetes and 321 controls aged 0–17 years matched on age and sex.	Retrospective recall of stressful events within 1 year before type 1 diabetes onset measured by telephone interview using questionnaire.	Type 1 diabetes	The frequency of stressful events was higher among cases compared with controls.
Hägglöf et al. (1991)[63] **Sweden**	Case-control study of 339 cases with type 1 diabetes and 528 controls aged 0–14 years matched on age, sex, and geographic area.	Retrospective recall of 45 life events and their severity experienced within 1 year before type 1 diabetes onset measured by Coddington's questionnaire[64] and a self-esteem analogue scale.	Type 1 diabetes	The frequency of stressful life events related to actual or threatened losses within the family was higher among cases in the age-group 5–9 years compared with controls.

Study	Design and population	Exposure	Outcome	Key findings
Dahlquist et al. (1991)[65] **Sweden**	Case-control study using the same study population as Hägglöf et al. (1991).[63]	Retrospective recall of 45 stressful life events as in Hägglöf et al. (1991).[63]	Type 1 diabetes	Exposure to stressful life events was associated with a higher risk of type 1 diabetes in the age-group 5–9 years.
Soltész et al. (1994)[66] **Hungary**	Case-control study of 130 cases with type 1 diabetes and 175 controls aged 0–14 years matched on age, sex, and geographical area.	Retrospective recall of stressful life events experienced within 1 year before type 1 diabetes onset measured by a modified version of the questionnaire used by Hägglöf et al. (1991).[63]	Type 1 diabetes	The frequency of stressful life events was higher among cases aged 10–14 years compared with controls in the same age group.
Hägglöf et al. (1994)[67] **Sweden**	Case-control study of 67 cases with type 1 diabetes and 61 controls aged 0–14 years matched on age, sex, and geographical area.	Retrospective recall of 48 life events experienced from birth until type 1 diabetes onset measured by interview based on Coddington's questionnaire.[64]	Type 1 diabetes	The frequencies of negative life events and events with coping problems experienced within the first two years of life were higher among cases compared with controls.
Thernlund et al. (1995)[68] **Sweden**	Case-control study using the same study population as Hägglöf et al. (1994).[67]	Retrospective recall of 27 negative life events and 13 other events experienced from birth until type 1 diabetes onset measured by interview based on Coddington's questionnaire.[64]	Type 1 diabetes	Exposure to negative life events in the first two years of life was associated with a higher risk of type 1 diabetes.
Djarova & Dube (1998)[69] **Zimbabwe**	Case-control study of 19 cases with type 1 diabetes and 20 controls aged 9–18 years matched on age and geographical area.	Retrospective recall of 45 stressful life events experienced within 1 year before type 1 diabetes onset measured by interview based on Coddington's questionnaire.[64]	Type 1 diabetes	The frequency of stressful life events was higher among cases compared with controls.
Littorin et al. (2001)[18] **Sweden**	Case control study of 349 cases with type 1 diabetes and 979 controls aged 15–34 years matched on age and sex.	Retrospective recall of 26 life events experienced within 1 year before type 1 diabetes diagnosis measured by a modification of the Sarason's Life-Event Survey.[70]	Type 1 diabetes	The proportions exposed to life events did not differ between cases and controls.
Sepa et al. (2004)[71] **Sweden**	Case-control study of 18 GADA or IA-2A positive cases and 32 negative controls aged 1 year.	Maternal attachment insecurity was measured by the Adult Attachment Interview.	GADA and/or IA-2A positivity at age 1 year	A larger proportion of cases had insecure mothers compared with controls.
Sepa et al. (2005)[72] **Sweden**	Cohort study of 1845 children followed from 1 to 2.5 years of age. Cross-sectional study of 5986 children at 2.5 years of age. 291 persons tested positive to GADA, 304 to IA-2A, and 32 to both.	Divorce between the parents measured by questionnaire at age 1 year. Retrospective recall of life events experienced by the child's mother measured by questionnaire at age 2.5 years.	GADA and/or IA-2A positivity at age 1 and 2.5 years	Parents' divorce at age 1 and 2.5 years, and mother's experience of violence at age 2.5 years, were associated with a higher risk of diabetes-related autoantibodies in children at age 2.5 years.

Study	Design and population	Exposure	Outcome	Key findings
Sepa et al. (2005)[73] **Sweden**	Cohort study of 4400 children followed from birth until age 1 year. 221 persons tested positive to GADA, 220 to IA-2A, and 33 to both during follow-up.	Retrospective recall of a serious life event measured by a question covering exposure during the child's first year of life.	GADA and/or IA-2A positivity at age 1 year	Exposure to a serious life event was associated with a higher risk of diabetes-related autoantibodies at age 1 year.
Vlajinac et al. (2006)[74] **Serbia**	Case-control study of 68 cases with type 1 diabetes and 68 controls aged 0–16 years matched on age.	Retrospective recall of 13 stressful events experienced within 1 year before type 1 diabetes onset measured by interview using questionnaire.	Type 1 diabetes	The frequency of stressful life events was higher among cases compared with controls.
Sipetic et al. (2007)[75] **Serbia**	Case-control study of 105 cases with type 1 diabetes and 210 controls aged 0–16 matched on age, sex, and geographical area.	Retrospective recall of 26 stressful events experienced within 1 year before type 1 diabetes onset measured by questionnaire.	Type 1 diabetes	The frequency of stressful life events was higher among cases compared with controls.
Djarova et al. (2007)[76] **Zimbabwe**	Case-control study of 42 cases with type 1 diabetes and 49 controls aged 6–15 years matched on age.	Retrospective recall of 45 stressful life events experienced within 1 year before type 1 diabetes onset measured by interview based on Coddington's questionnaire.[64]	Type 1 diabetes	The frequency of stressful life events was higher among cases compared with controls.
Karavanaki et al. (2008)[77] **Greece**	Case-control study of 107 cases with type 1 diabetes and 153 controls aged 1–16 years matched on age and sex.	Retrospective recall of an unstated number of life events experienced in different time periods measured by Coddington's questionnaire.[64]	Type 1 diabetes	The frequency of life events experienced within 2 years before type 1 diabetes onset was higher among cases of low socioeconomic status compared with controls.
Zung et al. (2012)[78] **Israel**	All persons (n=1822) with type 1 diabetes aged 0–17 years diagnosed in the four years before, or the two years after the Second Lebanon War in 2006.	Living in the war-affected region during the Second Lebanon War.	Type 1 diabetes	The increase in type 1 diabetes incidence after the war was higher in the war-affected region compared with the war-skipped region.
Nygren et al. (2013)[17] **Sweden**	Cohort study of 8921 children followed from birth until 11–13 years of age. 42 persons were identified with type 1 diabetes during follow-up.	Retrospective recall of a serious life event measured by two questions covering exposure during pregnancy and the child's first year of life.	Type 1 diabetes	Exposure to a serious life event was not associated with type 1 diabetes.
Virk et al. (2016)[79] **Denmark**	Cohort study of all singleton births in Denmark in the period 1980–2005 (n=1,740,245) followed from age 5 years until 2010. 6110 persons were identified with type 1 diabetes during follow-up.	Register-based information on bereavement due to death of a parent or a sibling in different age groups from age 5 years onward.	Type 1 diabetes	Bereavement occurring after 11 years of age was associated with a higher risk of type 1 diabetes among children born to mothers with low educational attainment at the time of birth.
Nygren et al. (2015)[16] **Sweden**	Cohort study of 10,495 children aged 2–14 years. 58 persons were identified with type 1 diabetes during follow-up.	Retrospective recall of a serious life event measured by a question and an 8–14-item checklist inspired by Coddington[64] at age 2–3, 5–6, 8, and 10–13 years.	Type 1 diabetes	Exposure to a serious life event was associated with a higher risk of type 1 diabetes.

Study	Design and population	Exposure	Outcome	Key findings
Antonela et al. (2017)[80] **Croatia**	Case-control study of 249 cases with type 1 diabetes and 250 controls aged 1–21 years matched on age, sex, and geographical area.	Retrospective recall of 6 stressful life events before type 1 diabetes onset measured by questionnaire.	Type 1 diabetes	The frequency of stressful life events was higher among cases compared with controls.
Lundgren et al. (2018)[81] **Sweden**	Cohort study of 23,187 children participating at age 2 months and 3784 high-risk children also participating at age 2 years followed for an average of 15 years. 166 persons were identified with type 1 diabetes during follow-up.	Retrospective recall of severe life events measured by a question covering exposure during pregnancy or the child's first 2 months of life followed by an 8-item checklist. The same question was repeated in the high-risk group at age 2 years.	Type 1 diabetes	Exposure to severe life events before the age of 2 years was associated with a higher risk of developing type 1 diabetes both in the total cohort and in the high-risk group.

None of the 27 identified studies called the exposure 'childhood adversities'. Instead, most studies used the term stressful or severe life events. However, all studies intended to assess psychosocial or psychological stress as a potential risk factor of type 1 diabetes or type 1 diabetes-related autoimmunity. Most studies used a case-control design and measured the exposure via retrospective recall of stressful/severe life events in different periods before type 1 diabetes onset using a checklist. Most studies were conducted in Europe, predominantly in Sweden.

The case-control studies generally found an association between stressful life events and type 1 diabetes (or type 1 diabetes-related autoimmunity).[56–63,65–69,72,74–77,80] While some of these studies measured only exposure to stressful life events in a specific period (i.e., the first years of life[72] or the year(s) preceding type 1 diabetes onset),[58,60,62,63,65,66,69,74–76] other studies measured life events at any time before type 1 diabetes onset.[56,57,59,61,67,68,77,80] Some of the latter studies found an association only when exposure to adverse events or type 1 diabetes onset occurred in specific, but highly varying, age groups.[63,65–68,77] Only one of the identified case-control studies concluded that they found no evidence of an association between stressful life events (measured in the year before onset) and type 1 diabetes.[18]

Seven studies using prospective information were identified. Nygren et al. conducted two cohort studies using the All Babies In southeast Sweden (ABIS) study where children born between 1997–1999 were followed from birth until 11–13 years of age.[16,17] The first study, including 8921 persons, measured exposure to 'something which you perceived as a serious life event during pregnancy' at birth and 'some serious or dramatic event' and age 1 year and found no association with type 1 diabetes development.[17] The second study by Nygren et al., including 10,495 persons,

measured serious life events at four time points using a checklist and found that those exposed to at least one serious life event had a three times higher risk of developing type 1 diabetes.[16] A total of 42 and 58 persons developed type 1 diabetes during follow-up in the two studies conducted by Nygren et al., respectively.[16,17] Lundgren et al. measured severe life events using a checklist during pregnancy and the first months of life among 23,187 study participants, and at age 2 years among a subsample of 3784 study participants deemed at high risk of developing type 1 diabetes and followed them for an average of 15 years.[81] The authors found an association with type 1 diabetes development, both in the total cohort and in the high-risk group.[81] Virk et al. examined the association between bereavement due to death of a parent or a sibling and type 1 diabetes from age 5 years onward using Danish register data.[79] They reported a small effect when the bereavement occurred after 11 years of age.[79] Zung et al. found a higher increase in type 1 diabetes incidence after the Second Lebanon War that took place in 2006 in a war-affected region compared with a war-skipped region using register data.[78] Finally, Sepa et al. found an association between divorce between the parents measured at age 1 year and diabetes-related autoimmunity at age 2.5 years,[72] and between a serious life event in the first year of life and diabetes-related autoimmunity at age 1 year.[73]

Thus, many studies have investigated aspects of childhood adversities as risk factors for type 1 diabetes during the past half-century, and most have found a positive association. However, these studies have several important limitations that should be noted. First, the identified studies have predominantly used retrospective recall of exposure to adverse events, and the case-control studies may have been affected by bias due to differential recall of adversities between type 1 diabetes cases and controls. Second, although the results of the few cohort studies point toward a positive association, low response rates and substantial loss to follow-up may have biased the results. Third, some of the case-control studies included few type 1 diabetes cases, and few persons developed type 1 diabetes during follow-up in some of the cohort studies. The results of these studies are, therefore, highly uncertain. Finally, the use of autoimmunity as a proxy for type 1 diabetes in some of the identified studies calls for caution in the interpretation because single positivity to type 1 diabetes autoantibodies is not a strong predictor of type 1 diabetes development, and many false positives in the blood sample measurements can be expected.[82,83]

Moreover, several gaps in the literature examining the association between childhood adversities and type 1 diabetes were identified during this review. While several of the case-control studies found a higher frequency of adverse experiences among cases compared with controls, none of the

prospective studies considered accumulation of adverse events. Also, exposure to adverse events have been measured in different periods, but the results do not provide a clear picture. Finally, none of the identified studies considered potential sex differences in the association between adverse experiences and type 1 diabetes. Thus, this thesis adds to the literature by investigating the effect of timing and accumulation of objectively measured exposure to childhood adversities across childhood and adolescence on type 1 diabetes among males and females separately using a large and unselected total population sample.

3 Material and methods

The two scientific studies on the effects of accumulation (Study II) and trajectories of childhood adversities (Study III) on type 1 diabetes in this thesis are based on the DANish LIFE course (DANLIFE) cohort including information from several Danish nationwide registers (Study I). Professor Naja Hulvej Rod is the principal investigator of DANLIFE, and the establishment of the cohort has been an ongoing and collaborative process in her research group. I was responsible for obtaining access to the administrative and health research registers that lay the foundation for DANLIFE. This task includes thorough preparations to gain insights into family linkage and changes in the available data registrations over time. After Statistics Denmark and the Danish Health Data Authorities had granted access to the data, I was responsible for all data management and linking of information on individual level from the many different registers to finalise the DANLIFE dataset.

In this section, I present the study populations, definitions of key variables, and applied statistical methods for Studies I, II, and III. Additional descriptive analyses were performed specifically for this thesis to elucidate whether exposure to specific and accumulated childhood adversities affects males and females equally often. The analytical strategy for these additional analyses is presented at the end of this section.

3.1 The DANish LIFE course (DANLIFE) cohort, Study I

3.1.1 Study population

The DANLIFE cohort was established to enable prospective investigation of complex life course mechanisms linking objective and repeated measures of childhood adversities to health and well-being in childhood, adolescence, and young adulthood. The Danish Civil Registration System[84] (CRS) is an electronic register established in 1968 for administrative purposes, such as tax collection, and provides every resident with a unique 10-digit Civil Personal Registration (CPR) number.[84] The CPR number is key in the individual-level linkage between nationwide registers in Denmark and essential in the establishment of DANLIFE.

Information from many nationwide registers is available and valid from 1980 onward. Therefore, all children born in Denmark since 1980 were successively included in DANLIFE until 31 December

2015. The cohort will continue to be updated as children are born and the registers are updated. The information from the CRS included in DANLIFE contained the population on 1 January each year. Children who were born alive but died or emigrated during the same calendar year were, therefore, not included in this information. These children were instead identified in the Danish Medical Birth Register (MBR) which contains all births taking place in Denmark by women residing in Denmark at the time of birth.[85] In total, 13,760 additional children were identified and included in DANLIFE using this method. Immigrants were not included in DANLIFE because no information would be available from before their immigration to Denmark. Figure 2 presents the inclusion and exclusion criteria for the DANLIFE study population.

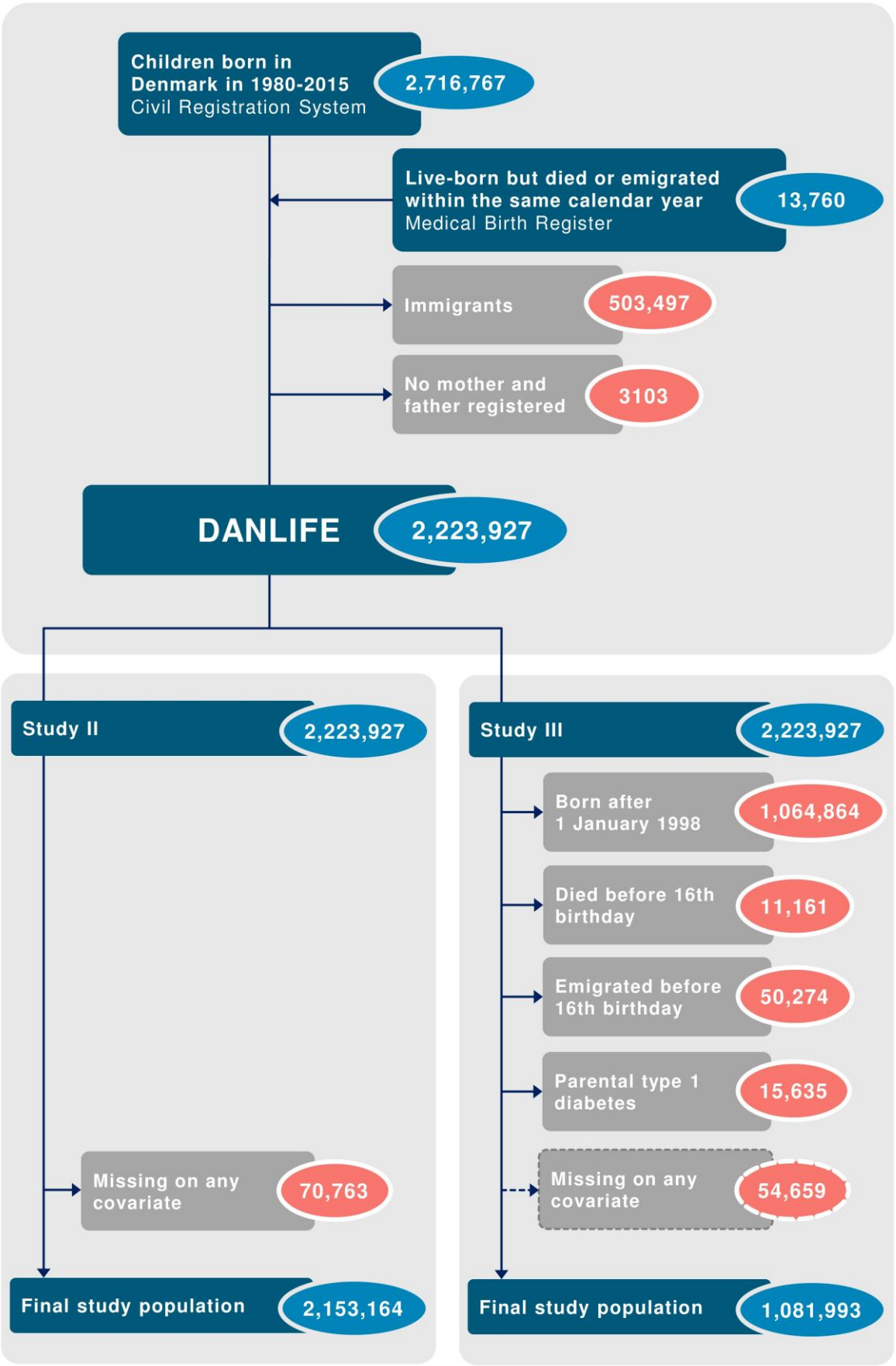

Figure 2 Flow chart of the study population in DANLIFE and the exclusion criteria that were used to define the study populations of Study II and Study III

The DANLIFE study participants have been followed from birth until emigration or death and as of 31 December 2015, the DANLIFE cohort includes 2,223,927 persons followed for an average of 16.8 years corresponding to 37 million person-years. Persons emigrating during follow-up (n=164,348, 7.4%) were censored at the date of emigration and were not re-entered into the cohort if ever returning to Denmark because there would be an information gap in the period that the person spent abroad. In total, 20,514 (0.9%) persons died during follow-up and were censored on their date of death. The characteristics of the DANLIFE cohort and follow-up period are shown in Figure 3.

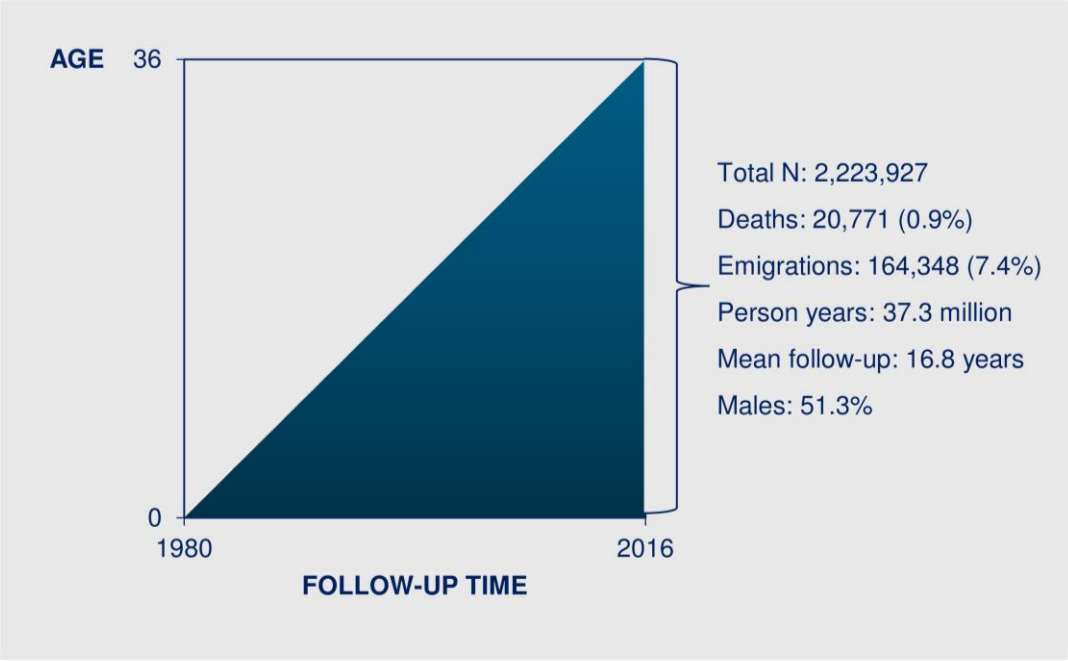

Figure 3 Characteristics of the DANLIFE study population and follow-up period

3.1.2 Family linkage

Identification of the parents of the DANLIFE study population was possible using the CRS as children are registered with information on the CPR numbers of their parents. It is not possible to distinguish between biological and adoptive parents in the CRS. However, the number of adopted children born in Denmark is low (1%).[86] The CPR numbers of the parents are also registered in the MBR. This information was used to identify the parents of children not appearing in the CRS (i.e., who died or emigrated in the same calendar year as their date of birth) and of those who had missing information on their mother's or father's CPR number in the CRS. Persons with missing information on both parents in both the CRS and the MBR were excluded (n=3103) because almost all definitions of the childhood adversities rely on this information (see Table 2 for definitions).

Full and half siblings can be identified using the CPR numbers of the parents registered in the CRS or the MBR. For Studies II and III, only full siblings (registered with the same mother and father) were considered.

3.1.3 Ethical aspects

Statistics Denmark and the Danish Health Data Authorities granted access to the registers included in DANLIFE. The data are securely stored on a server at Statistics Denmark and can be accessed only via secure remote access to this server. The CPR numbers are encrypted, and the data are, therefore, anonymous to the researcher. All data linkage is performed in accordance with Danish law, and DANLIFE is registered with the Danish Data Protection Agency (no. 514-0262/18-3000). Studies based on Danish registers do not require informed consent nor is an ethical approval required by the Danish National Committee on Health Research Ethics.

3.2 Study population in Study II

The entire birth cohort of DANLIFE was included in Study II. However, to be able to compare unadjusted estimates with adjusted estimates, persons with missing information on any of the covariates included in the adjusted analyses as potential confounders (see Section 3.4.3) were excluded (n=70,763), corresponding to 3% of the DANLIFE study population. Thus, the final study population in Study II included 2,153,164 children with complete information on all covariates (Figure 2). 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.

3.3 Study population in Study III

Study III builds on the five trajectory groups of childhood adversity identified in a previous study by Rod et al. using DANLIFE, which had follow-up time only until 2014 (introduced in Section 3.4.1).[19] The aim of this previous study was to cover trajectories of adversities from an entire childhood (0–16 years of age). Therefore, only children who could be followed for at least 16 years were eligible for analysis. Consequently, 1,064,864 children born after 1998 were excluded. Additionally, 50,274 children who emigrated before their 16th birthday and 11,161 children who

died before their 16th birthday were excluded. The remaining 1,097,628 persons with full information on trajectories of adversities from their entire childhood were eligible for inclusion in Study III. However, because parental type 1 diabetes was one of the somatic illnesses included in the measure of the childhood adversity 'parental somatic illness', another 15,635 persons with parental type 1 diabetes were excluded to avoid confusing the effect of genetic predisposition to type 1 diabetes with the effect of childhood adversities. Type 1 diabetes was not included in the measure of 'sibling type 1 diabetes' (see Table 2 for definitions), and persons with sibling type 1 diabetes were therefore kept in the study population. Thus, the final study population in Study III consisted of 1,081,993 persons without parental type 1 diabetes. Figure 2 presents a flow chart for the study population in Study III.

3.4 Measurement of key variables

3.4.1 Childhood adversities

DANLIFE cohort profile: Study I

DANLIFE includes 12 objectively measured social and family-related childhood adversities. The specific adversities were selected based on the notion that they constitute important sources of stress in children based on the scientific literature[23,24,26–33,36,87] (further elaborated in Section 2.1). Since the purpose of DANLIFE was to enable assessment of the effects of adversities experienced in childhood on type 1 diabetes (and other health outcomes), the exposure period was restricted to 0–18 years of age. Table 1 of the DANLIFE cohort profile (Study I) presents a thorough description of the definitions of the 12 childhood adversities in DANLIFE, including diagnostic and prescription codes.

Accumulation of childhood adversities and type 1 diabetes: Study II

Only the first experience of each of the 12 specific adversities occurring before the child turned 18 years old was considered in Study II. The statistical analyses required specifications of the exact timing of exposure to the adversities in DANLIFE. Many of the adversities were registered with a specific date, i.e., date of parental and sibling death, date of placement in foster care, date of the diagnosis of parental and sibling somatic and psychiatric illness, and parental alcohol and drug abuse. The information used to define parental separation, family poverty, and parental long-term unemployment was reported in the registers only once a year and the timing of these adversities were, therefore, set to a fixed date within that year. Table 2 presents the specific timing of each adversity exposure in Study II.

Table 2 Definitions and timing of childhood adversities in Study II and Study III

	Adversity	Study II	Study III	Registers
Family dynamics	**Foster care**	Date of first placement in out-of-home care	1 count each year of life where the child was registered as placed in out-of-home care	The Register of Support for Children and Adolescents
	Parental psychiatric illness	Date of the first parent being admitted for at least one day to a psychiatric hospital or ward with a primary diagnosis related to psychiatric illness (excluding primary diagnoses related to alcohol and drug abuse)	1 count each year of life for each parent	The Danish Psychiatric Central Research Register;[88] The Danish National Patient Registry[89]
	Sibling psychiatric illness	Date of the first sibling being admitted for at least one day to a psychiatric hospital or ward with a primary diagnosis related to psychiatric illness	1 count each year of life for each sibling aged less than 18 years	The Danish Psychiatric Central Research Register;[88] The Danish National Patient Registry[89]
	Parental alcohol abuse	Date of the first parent being diagnosed with a disease related to alcohol abuse or buying a prescribed drug used in treatment of alcohol dependence	1 count each year of life for each parent	The Danish Psychiatric Central Research Register;[88] The Danish National Patient Registry;[89] The Danish National Prescription Registry[90]
	Parental drug abuse	Date of the first parent being diagnosed with a disease related to drug abuse or buying a prescribed drug used in treatment of drug dependence	1 count each year of life for each parent	The Danish Psychiatric Central Research Register;[88] The Danish National Patient Registry;[89] The Danish National Prescription Registry[90]
	Parental/ maternal separation	30 June in the first year where the parents no longer share address	1 count each year of life where the mother no longer shares address with a partner	The Danish Civil Registration System[84]
Loss or threat of loss	**Death of a parent**	Date of the first death among the parents	1 count for each death of a parent	The Danish Civil Registration System[84]
	Death of a sibling	Date of the first death among the siblings	1 count for each death of a sibling	The Danish Civil Registration System[84]
	Parental somatic illness	Date of the first parent being diagnosed with one of the diseases included in the Charlson comorbidity index[91] in the period 1980–1993 or one of the diseases included in the updated version of the Charlson comorbidity index[92] in the period 1994–2015	1 count each year of life for each parent	The Danish National Patient Registry[89]
	Sibling somatic illness	Date of the first sibling being diagnosed with one of the seven somatic diagnoses most commonly related to mortality in children aged 0–18 years in Denmark (i.e., malignant neoplasm, congenital anomalies of the heart and circulatory system, congenital anomalies of the nervous system, cerebral palsy, epilepsy, cardiomyopathy, and congenital disorder of lipid metabolism)	1 count each year of life for each sibling aged less than 18 years	The Danish National Patient Registry[89]
Material deprivation	**Family poverty**	30 June in the second year in a sequence of three years where the family income was below 50% of the median national family income in that specific year	1 count each year of life when the family income was below 50% of the median national family income in that specific year	The Income Statistics Register[93]
	Parental long-term unemploy-ment	31 December in the first year a parent has been unemployed for at least 12 months within two consecutive years	1 count per parent each year of life at the second year of two calendar years where a parent had been unemployed for at least half of this period	The Integrated Database for Labour Market Affiliation[94]

Trajectories of childhood adversity and type 1 diabetes: Study III

Study III added an extra layer of complexity to the investigation of the effect of accumulation of childhood adversities on type 1 diabetes by applying the five trajectory groups of adversity identified by Rod et al.[19] as the exposure measure of childhood adversities. A distinction was made between three dimensions of adversity reflecting family dynamics (i.e., foster care, parental or sibling psychiatric illness, parental alcohol or drug abuse, and maternal separation), loss or threat of loss within the family (parental or sibling death and parental or sibling somatic illness), and material deprivation (i.e., family poverty and parental long-term unemployment). The number of childhood adversities within the three dimensions were summed annually for each person. Hence, each of the 12 adversities in DANLIFE could count once (for each parent or sibling) in each year of life until the age of 16 years and the effects of the adversities were allowed to vary between dimensions and across time. Table 2 describes how the childhood adversities were counted across the three dimensions. Five distinct trajectory groups of adversities were identified using a group-based multi-trajectory model reflecting:

1) L*ow adversity* (54%): a very low annual rate of adversity across all three dimensions before 16 years of age,
2) *Early life material deprivation* (20%): a high annual rate of material deprivation in the first 4–5 years of life,
3) *Persistent material deprivation* (13%): a high annual rate of material deprivation before 16 years of age,
4) *Loss or threat of loss* (10%): a high and increasing annual rate of severe somatic illness or death within the family before 16 years of age,
5) *High adversity* (3%): a high and increasing annual rate of adversity across all three dimensions before 16 years of age.

Figure 4 illustrates the characteristics of the five trajectory groups of childhood adversities across the three dimensions. Further details of the identification of the five trajectory groups of adversity can be found in Rod et al.[19]

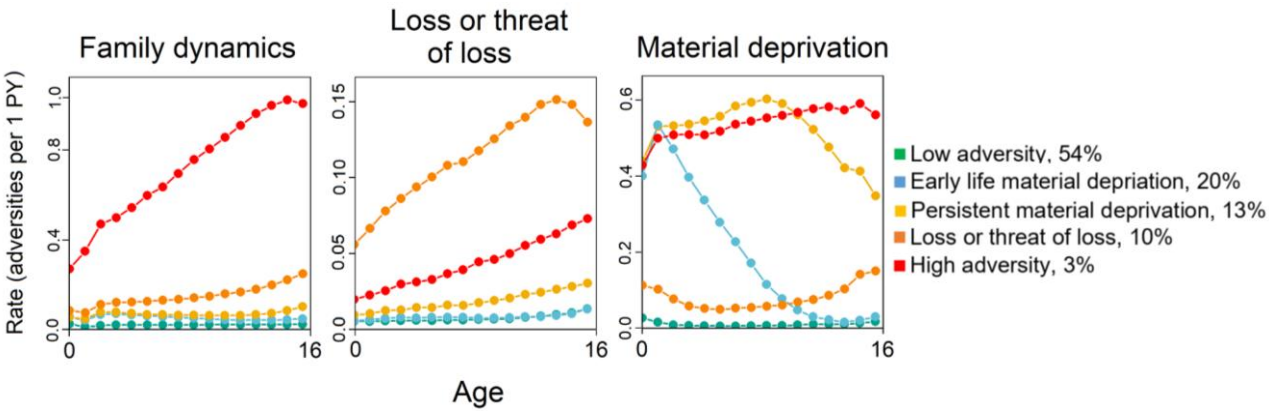

Figure 4 Trajectories of childhood adversity across dimensions of family dynamics, loss or threat of loss, and material deprivation as defined by Rod et al. 2020[19] presented as rates of adversities per 1 person-year (PY)

3.4.2 Type 1 diabetes

Type 1 diabetes was the outcome of interest in both Study II and Study III. Date of diagnosis of type 1 diabetes was linked to DANLIFE from several nationwide registers: the Danish Registry of Childhood and Adolescent Diabetes[44] (1980–1995: 0-15 years; 1996–2015: 0-18 years), the Danish Adult Diabetes Registry[95] (2005–2015: 18 years and older), and the Danish National Patient Registry[89] (1980–2015: all age groups). The information from these registers was supplemented by information on purchased prescriptions of oral antidiabetic drugs and insulin from the Danish National Prescription Registry[90] (1995–2015: before 15 and 30 years of age, respectively).

There were some substantial inconsistencies in terms of classification of diabetes type between the registers. Based on the level of data quality, registrations of type 1 diabetes in the Danish Registry of Childhood and Adolescent Diabetes were prioritised, followed by information from the Danish Adult Diabetes Registry, and then the Danish National Patient Registry. Purchased prescriptions of oral antidiabetic drugs and insulin from the Danish National Prescription Registry had the lowest priority. The methods section of Study II presents in detail the criteria for being classified as having type 1 diabetes using these registers. Table 3 presents a brief overview of the definitions of type 1 diabetes applied for each register.

Using these registers, 8335 persons were identified with type 1 diabetes among the 2,153,164 individuals with complete information on all covariates in Study II. In Study III, 5619 persons were identified with type 1 diabetes among the 1,081,993 persons born in the period 1980–1998 who were alive and residing in Denmark until their 16th birthday who did not have a parent with type 1 diabetes. Table 3 shows an overview of how many persons with type 1 diabetes each register contributed with in Study II.

Table 3 Identification of the 8335 persons with type 1 diabetes among the 2,153,164 persons included in Study II

Register	Definition of type 1 diabetes	Period	Age at diagnosis	Type 1 diabetes	
				n	%
Danish Registry of Childhood and Adolescent Diabetes[44]	Persons registered with type 1 diabetes	1980–1995 1996–2015	0–15 years 0–18 years	5574	67
Danish Adult Diabetes Registry[95]	Persons registered with type 1 diabetes in more than half of the records for that specific person	2005–2015	18+ years	1867	22
Danish National Patient Registry[89]	Persons registered with type 1 diabetes in more than half of the records for that specific person	1980–2015	All ages	733	9
Danish National Prescription Registry[90]	At least two purchases of oral antidiabetic drugs prescribed to that specific person before the age of 15 years	1995–2015	<15 years	89	1
Danish National Prescription Registry[90]	At least two purchases of insulin prescribed to that specific person before the age of 30 years	1995–2015	<30 years	72	1
Total				8335	100

3.4.3 Potential confounders

Identification of potential confounders for Study II and Study III was based on prior evidence and guided by the method of directed acyclic graphs[96] (Figure 5). The identified potential confounders were age, sex, date of birth, family type 1 diabetes (parents and siblings), parental education at the time of birth, birth order, birth weight, maternal age at birth, and parental area of origin. Table 4 presents the definitions of the potential confounders and the registers that provided the information.

In Study III, we described the age-specific incidence of type 1 diabetes in the five trajectory groups of adversity (introduced in Section 3.4.1). These analyses were not adjusted for confounders, but all persons with parental type 1 diabetes were excluded from the study population in order to not confuse the effect of the adversity 'parental somatic illness', including type 1 diabetes, with the effect of genetic predisposition to type 1 diabetes (further explained in Section 3.3). Type 1 diabetes was not one of the diagnoses defining 'sibling somatic illness' (see Table 2 for definitions) and persons with sibling type 1 diabetes were, therefore, kept in the study population. The subsequent adjusted analyses in Study III (described in Section 3.5.3) were, therefore, adjusted only for sibling type 1 diabetes since persons with parental type 1 diabetes were excluded from the study population altogether. All analyses in Study II were adjusted for both parental and sibling type 1 diabetes.

Information on all potential confounders was retrieved at the time of birth except for information on parental and sibling type 1 diabetes, which was retrieved at the end of follow-up. This was because family type 1 diabetes was used as a proxy for genetic predisposition to type 1 diabetes acquired at

conception, and the timing of the family member's diagnosis was, therefore, not important. All potential confounders were included in the analyses as time-fixed variables except for age, which was used as the underlying time scale. Date of birth, birth weight, and maternal age at birth were included in the analyses as continuous variables. All analyses in Study II and Study III were stratified by sex.

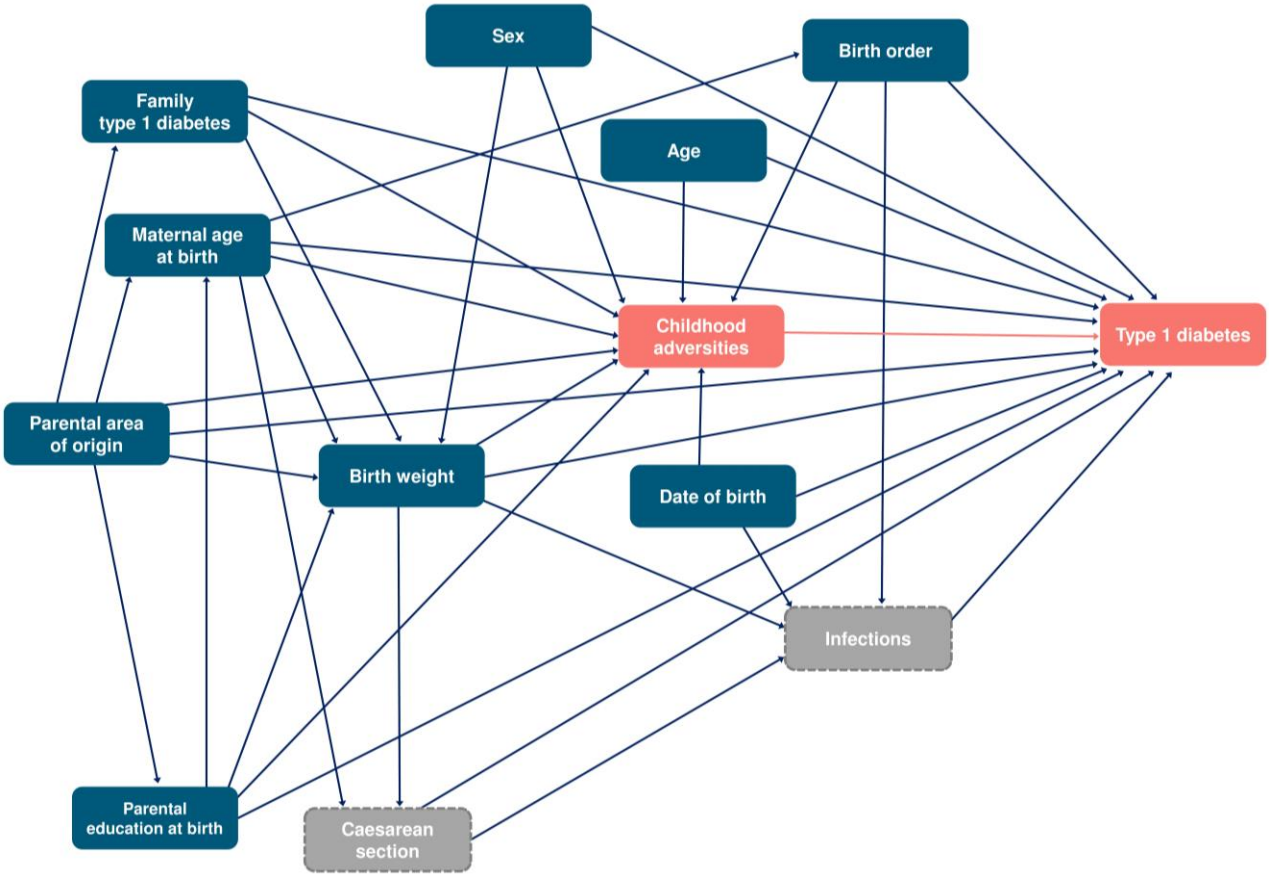

Figure 5 Directed acyclic graph applied to identify potential confounders of the association between childhood adversities and type 1 diabetes in Study II and Study III. The identified confounders were age, sex, date of birth, family type 1 diabetes, parental education at the time of birth, birth order, birth weight, maternal age at birth, and parental area of origin. The analyses were not adjusted for caesarean section and infections because the confounding paths through these nodes were blocked by adjustment for other variables.

Table 4 Definitions and registers providing information on potential confounders

Potential confounder	Definition	Register
Age	Time since date of birth	Danish Civil Registration System[84]
Sex	**Male**/**Female**	Danish Civil Registration System[84]
Date of birth	Date of birth	Danish Civil Registration System[84]
Parental education at birth	**Low**: ≤9 years **Middle**: 10–12 years **High**: >12 years	The Population Education Register[97]
Parental type 1 diabetes	**Yes**/**No**	Danish Registry of Childhood and Adolescent Diabetes;[44] Danish Adult Diabetes Registry;[95] Danish National Patient Registry;[89] Danish National Prescription Registry[90]
Sibling type 1 diabetes	**Yes**/**No**	Danish Registry of Childhood and Adolescent Diabetes;[44] Danish Adult Diabetes Registry;[95] Danish National Patient Registry;[89] Danish National Prescription Registry[90]
Birth order	Number of completed pregnancies by the mother at the time of birth: **1**, **2**, **3**, **4+**	Danish Medical Birth Register[85]
Birth weight	In grams	Danish Medical Birth Register[85]
Maternal age at birth	In years	Danish Civil Registration System[84]
Parental area of origin	Based on father's or, if missing, mother's nationality at the time of birth: **European origin**: Europe, North America, Australia, New Zealand **Other**: All other areas	Danish Civil Registration System[84]

3.5 Statistical analyses

3.5.1 DANLIFE cohort profile: Study I

Because Study I is a cohort profile, only descriptive analyses were performed. We calculated the proportions exposed to the 12 adversities included in DANLIFE in the total study population and across levels of maternal education at the time of birth measured as low (≤9 years of education), middle (10–12 years of education) and high (>12 years of education). We also assessed whether there was a social gradient in the exposure to accumulation of childhood adversities across the three levels of maternal education. Accumulation of childhood adversities was assessed both as a graded scale from 0 to 3 or more adversities and as a mean number of adversities experienced in each level of maternal education. The educational level of the mother was used as an indicator of socioeconomic status because the majority (85%) of Danish children live with their mothers.[98] Some individuals (3%) had missing information on maternal education and were, therefore, not included in the analyses. Missing information on maternal education in DANLIFE can occur if the mother completed her education abroad, for example, before immigration to Denmark. The analyses in Study I were performed using SAS 9.4 statistical software (SAS Institute, Inc., Cary, North Carolina).

3.5.2 Accumulation of childhood adversities and type 1 diabetes risk: Study II

In Study II, we followed the study population from birth until the date of type 1 diabetes diagnosis, emigration, death, or 31 December 2015. We specified a multi-state model[99] to quantify the effect of accumulation of childhood adversities on type 1 diabetes development. Each additional occurrence of an adverse event represented a new state of exposure to childhood adversities taking the risk time spent in each state of exposure to adversities into account. Due to small numbers, exposure to seven or more adversities was combined into one state of exposure. The incidence rates of type 1 diabetes by age were then calculated in each exposure state, assuming that the effects of the covariates were identical across states. Figure 6 illustrates the multi-state model.

Hazard ratios (HRs) and 95% confidence intervals (CI) of developing type 1 diabetes were estimated for each state of adversity exposure using the state of no adversity exposure as the reference. We estimated the linear effect of accumulation of childhood adversities on type 1 diabetes from one adversity onward, assuming that each extra adversity conveyed the same extra rate ratio. Likelihood ratio tests were used to test the appropriateness of the linearity assumption against both a categorical and a quadratic version of the adversity score. Also, we estimated the

effect of each specific childhood adversity on type 1 diabetes adjusted for the other childhood adversities and the potential confounders presented in Section 3.4.3. All analyses were conducted separately for males and females and were performed using packages Epi[100] and popEpi[101] in the statistical software R.

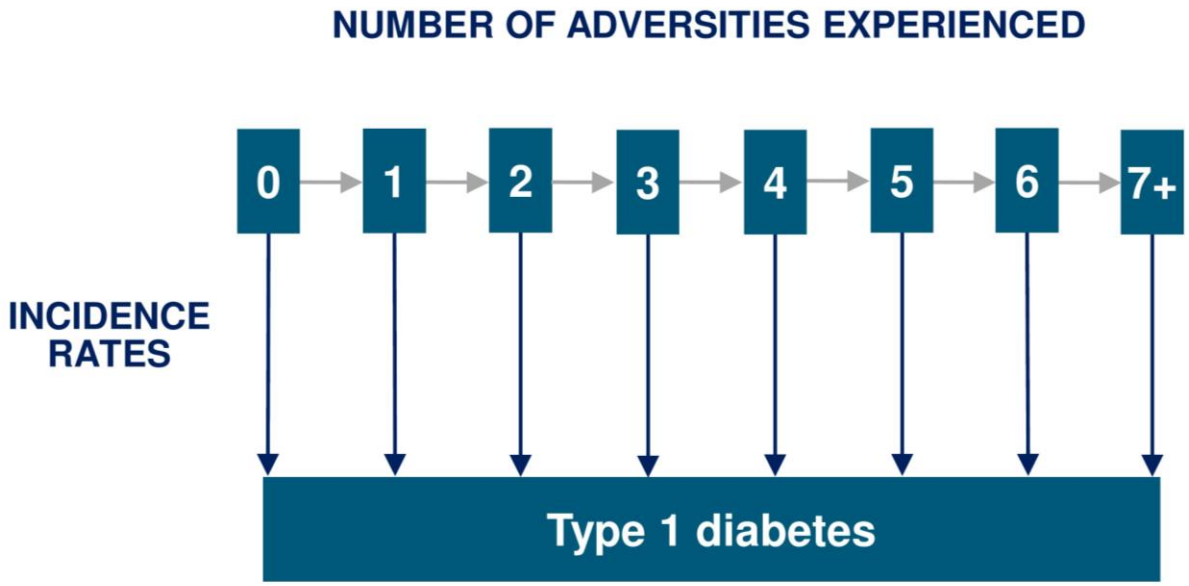

Figure 6 Illustration of the multi-state model applied to estimate incidence rates of type 1 diabetes in each state of exposure to childhood adversities in Study II. The boxes represent the number of adversities experienced, and the blue arrows represent incidence rates of type 1 diabetes. The grey arrows between the states represent incidence of adversity experience and were not modelled.

3.5.3 Trajectories of childhood adversities and type 1 diabetes: Study III

In Study III, we took advantage of the prospective and repeatedly registered information on exposure to childhood adversities in the Danish registers by using the allocation of each person to one of the five trajectory groups of adversity identified by Rod et al.[19] (introduced in Section 3.4.1) as the exposure variable. We specified a Poisson regression model with age as the underlying time scale split up in yearly intervals to describe the age-specific incidence rates of type 1 diabetes in each of the five trajectory groups. We also assessed the rate ratio between the age-specific incidence rates of type 1 diabetes in each trajectory group relative to the incidence rate in the low adversity group. In a subsample of the study population with complete information on all potential confounders presented in Section 3.4.3 (n=1,066,153), we estimated both crude and adjusted incidence rate ratios (IRR) and 95% CI of type 1 diabetes in childhood (0–10 years), puberty (11–15 years), and young adulthood (≥16 years) using the low adversity trajectory group as reference. All analyses were performed separately for males and females and packages Epi[100] and popEpi[101] were used to conduct the analyses in the statistical software R.

3.5.4 Additional descriptive analyses

In Study II, descriptive analysis of the background characteristics of the study population according to exposure to accumulation of childhood adversities was performed separately for males and females. This analysis revealed that there were no sex differences in exposure to accumulation of adversities. Except for this descriptive analysis in Study II, no assessment of sex differences in the exposure to adversities was performed in the studies included in this thesis. Therefore, two additional descriptive analyses were performed. The first analysis investigated whether the prevalence of the 12 specific adversities in DANLIFE differed between males and females using the study population of Study II. The second analysis investigated whether the proportions belonging to each of the five trajectory groups of adversity in Study III were different among males and females. Cross-tabulations with sex and the 12 specific adversities, and sex and the five trajectory groups, were performed, and no statistical tests were applied.

4 Results

In this section, I provide an overview of the main results of the three studies in the thesis. For further details of the results, please refer to the individual papers. The results of the additional descriptive analyses of sex differences in the exposure to childhood adversities are presented at the end of this section.

4.1 DANLIFE cohort profile: Study I

Parental separation (29%), followed by parental long-term unemployment (25%) and parental somatic illness (12%), were the most frequently experienced adversities before 18 years of age in DANLIFE. Parental drug abuse (2%), sibling psychiatric illness (1%), and sibling death (1%) were the least common adversities. However, in the large population sample of DANLIFE, even these small proportions correspond to several thousand individuals (e.g., 10,543 individuals were exposed to sibling death before their 18th birthday). Figure 7 presents the proportions exposed to each specific childhood adversity in DANLIFE.

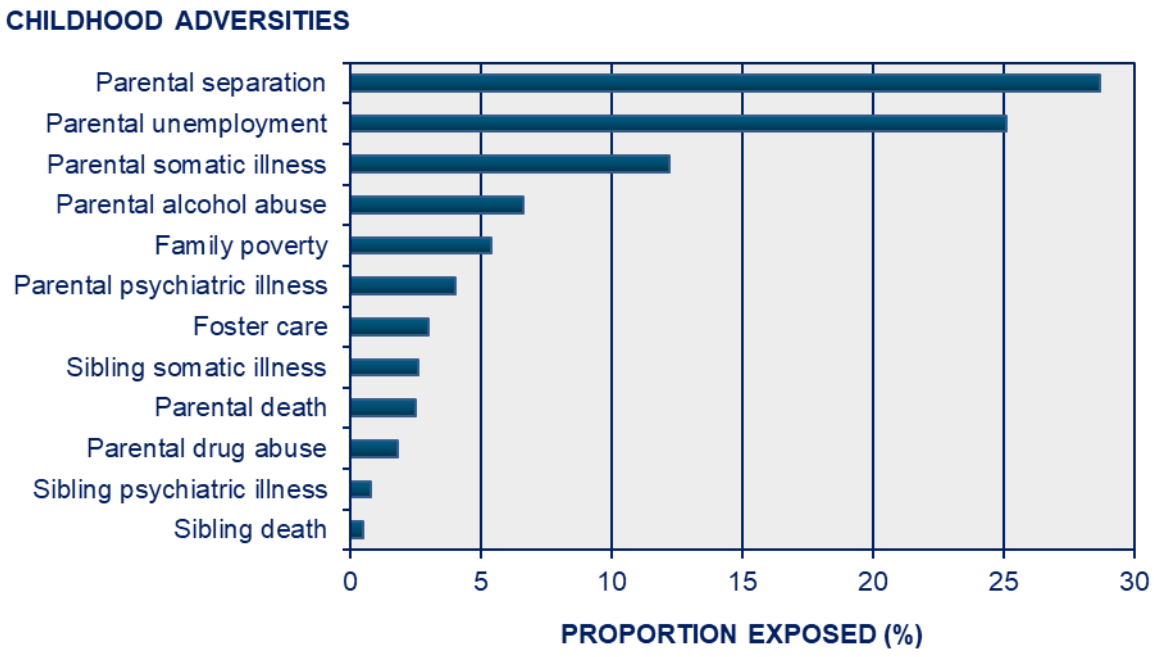

Figure 7 Proportions exposed to the specific childhood adversities in DANLIFE before the age of 18 years

Almost half (47%) of the study population did not experience any adversities, and one in 10 persons experienced three or more of the 12 specific adversities at least once before the age of 18 years. There was a strong social gradient in accumulation of childhood adversities where 20% of the persons born to mothers with a low level of education (≤9 years of education) had been exposed to three or more adversities compared with only 4% of the persons born to mothers with a high level of education (>12 years of education) (Figure 8). The mean number of adversities experienced was 1.5 among persons with low maternal education and 0.5 among persons with high maternal education.

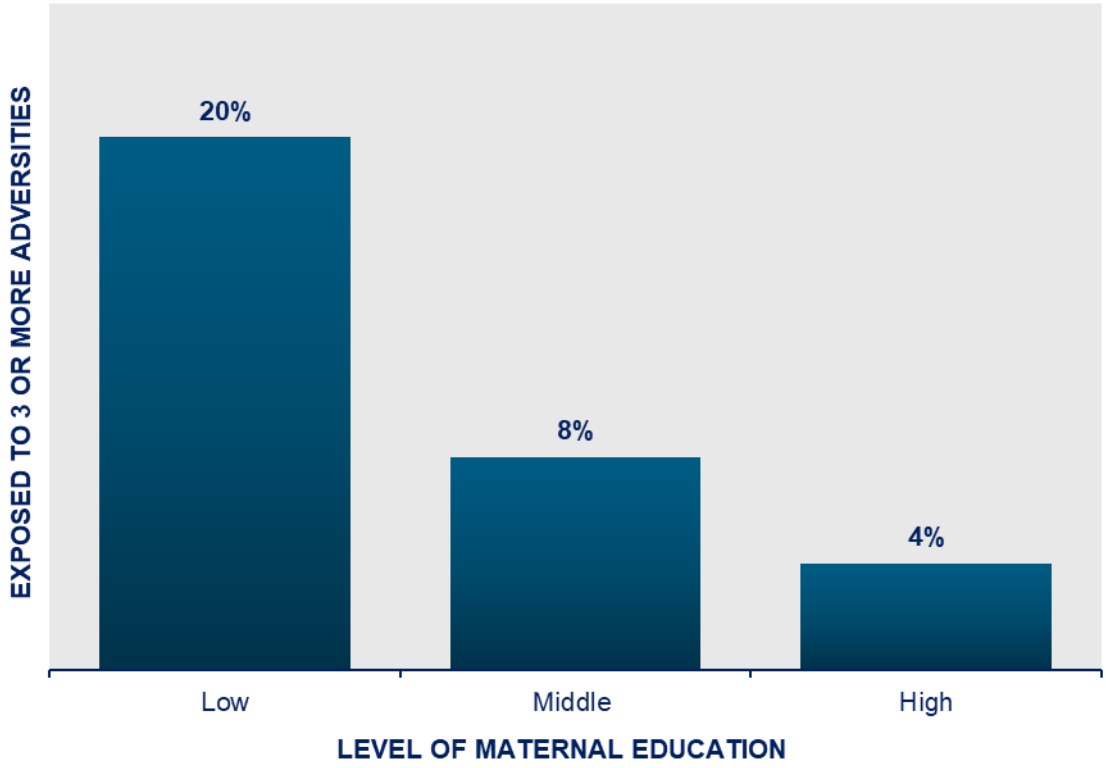

Figure 8 Accumulation of childhood adversities (three or more) among persons with low (≤9 years), middle (10–12 years), and high (>12 years) level of maternal education at the time of birth

4.2 Accumulation of childhood adversities and type 1 diabetes: Study II

Persons who experienced many adversities before their 18th birthday were more likely to have parents with a low level of education at the time of birth, to be born with low birth weight, to have younger mothers, and to have a parent with type 1 diabetes compared with those who experienced few adversities across childhood and adolescence. There was no difference in the number of adversities experienced between males and females.

Figure 9 shows the age-specific incidence rates of type 1 diabetes for males and females in the DANLIFE study population in Study II, disregarding exposure to adversities. The incidence rates in Figure 9 follow the well-known age-specific incidence pattern of type 1 diabetes[14] where the incidences for males and females follow each other until puberty with a peak at about 11 years of age for females and 14 years of age for males. Hereafter, the incidence is consistently higher among males compared with females. This familiar pattern confirms that the information on date of type 1 diabetes onset retrieved from the registers (see Section 3.4.2) is reliable.

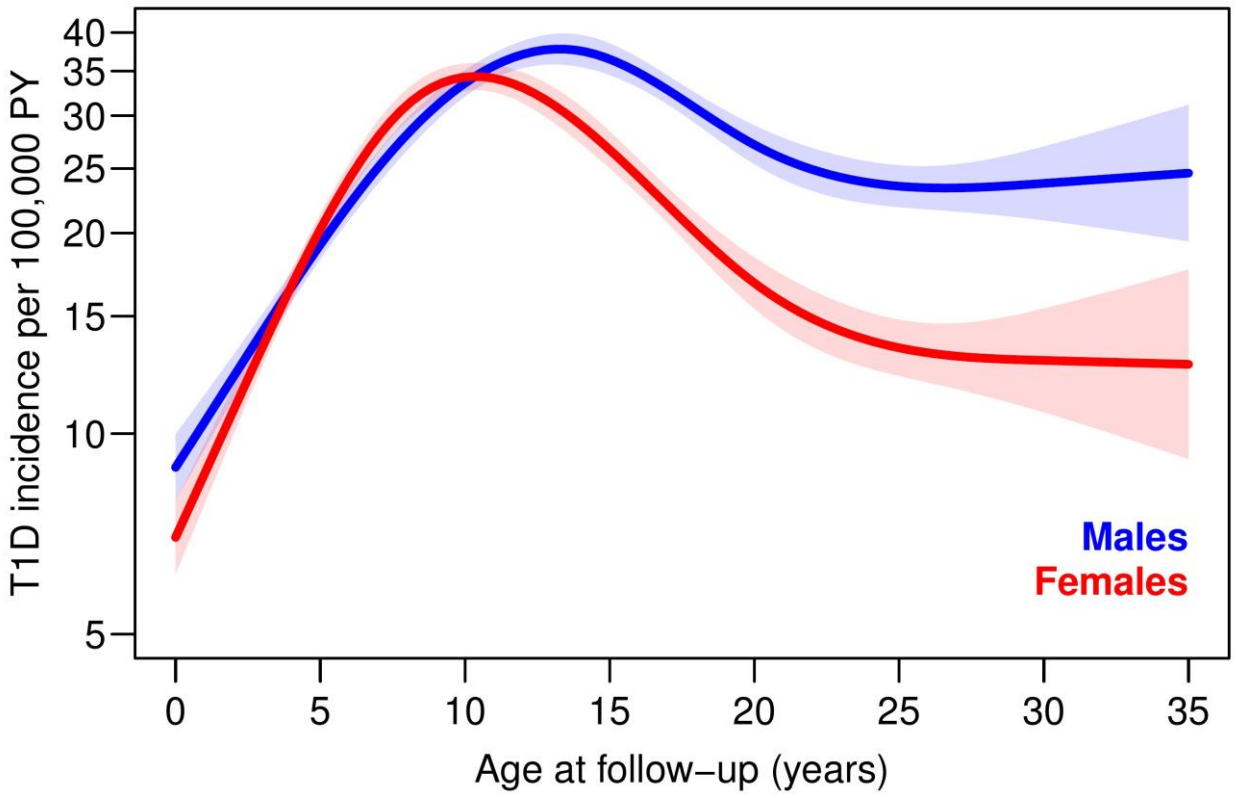

Figure 9 Age-specific incidence rates of type 1 diabetes (T1D) and 95% confidence intervals for males and females in the DANLIFE cohort per 100,000 person-years (PY)

Figure 10 presents the main finding of Study II. The figure shows the adjusted HRs of developing type 1 diabetes after exposure to accumulation of childhood adversities assessed both linearly and categorically using exposure to no adversities as the reference. Accumulation of childhood adversities was not associated with type 1 diabetes development among males. For females, there was a slight tendency toward a higher risk of developing type 1 diabetes with increasing number of adversities experienced (adjusted HR per adversity increase: 1.07; 95% CI: 1.02-1.11). No evidence against the appropriateness of the linearity specification of the model was identified. Among the very few females exposed to seven or more adversities (0.2%), the risk of developing type 1 diabetes was doubled compared with unexposed females (adjusted HR: 2.06; 95% CI: 1.10-3.86).

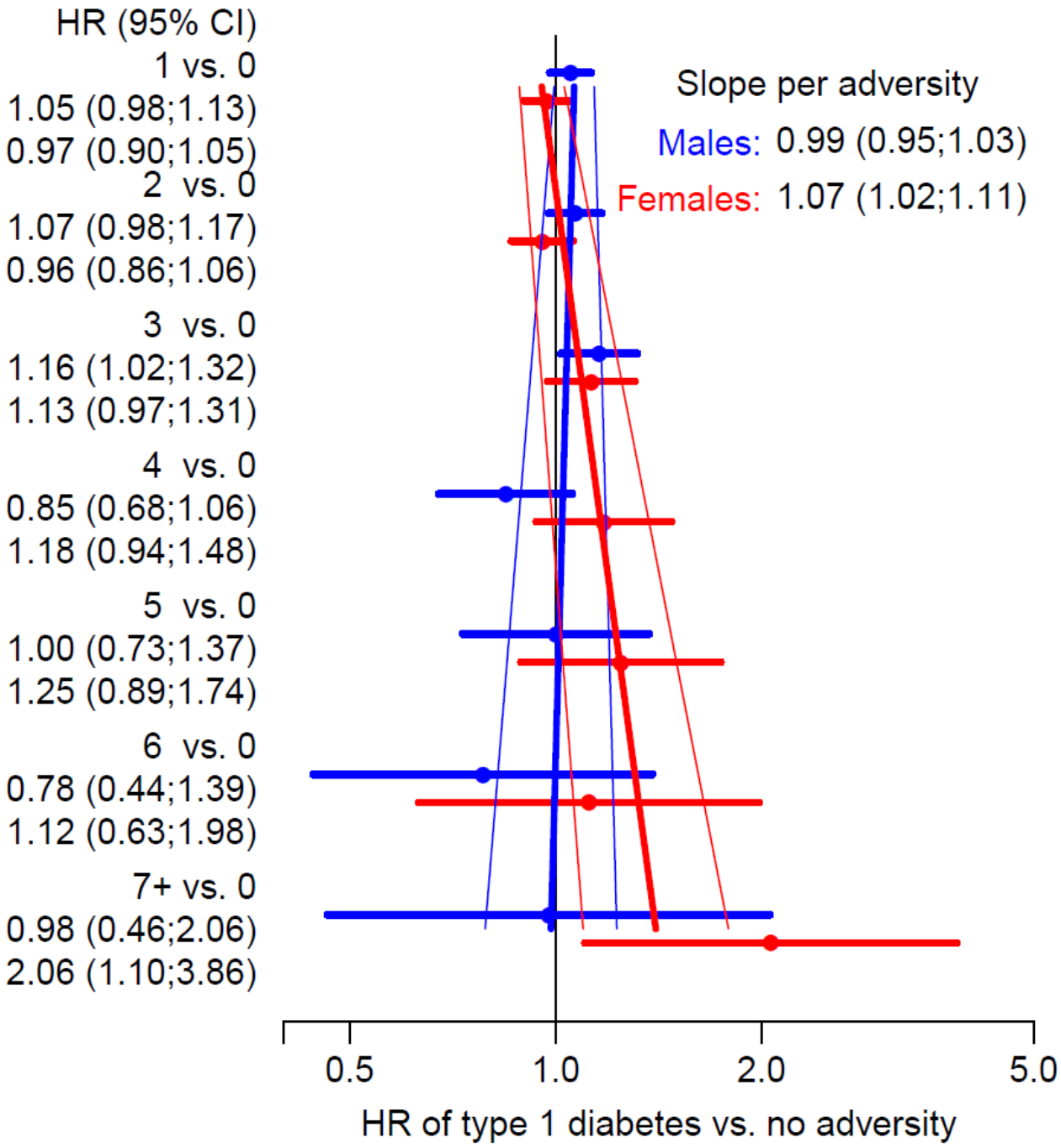

Figure 10 Adjusted hazard ratios (HR) and 95% confidence intervals (CI) of type 1 diabetes in each state of adversity exposure compared with no adversities and the adjusted linear trend and 95% CI (thin lines) from experiencing one adversity onward for males and females, respectively. The results are adjusted for age, date of birth, parental type 1 diabetes, sibling type 1 diabetes, parental education at the time of birth, birth order, birth weight, maternal age at birth, and parental area of origin.

In a sensitivity analysis, we estimated the effect of each of the 12 specific adversities on type 1 diabetes adjusted for potential confounders and the other adversities. None of the specific adversities had an effect of importance on type 1 diabetes independent of the other adversities.

4.3 Trajectories of childhood adversity and type 1 diabetes: Study III

In the study population of Study III, the proportions of persons with low parental education, low birth weight, and teenage mothers were markedly higher in the persistent material deprivation and the high adversity trajectory groups compared with the low adversity group. Figure 11 presents the proportions of the study population with low parental education in each of the five trajectory groups of adversity.

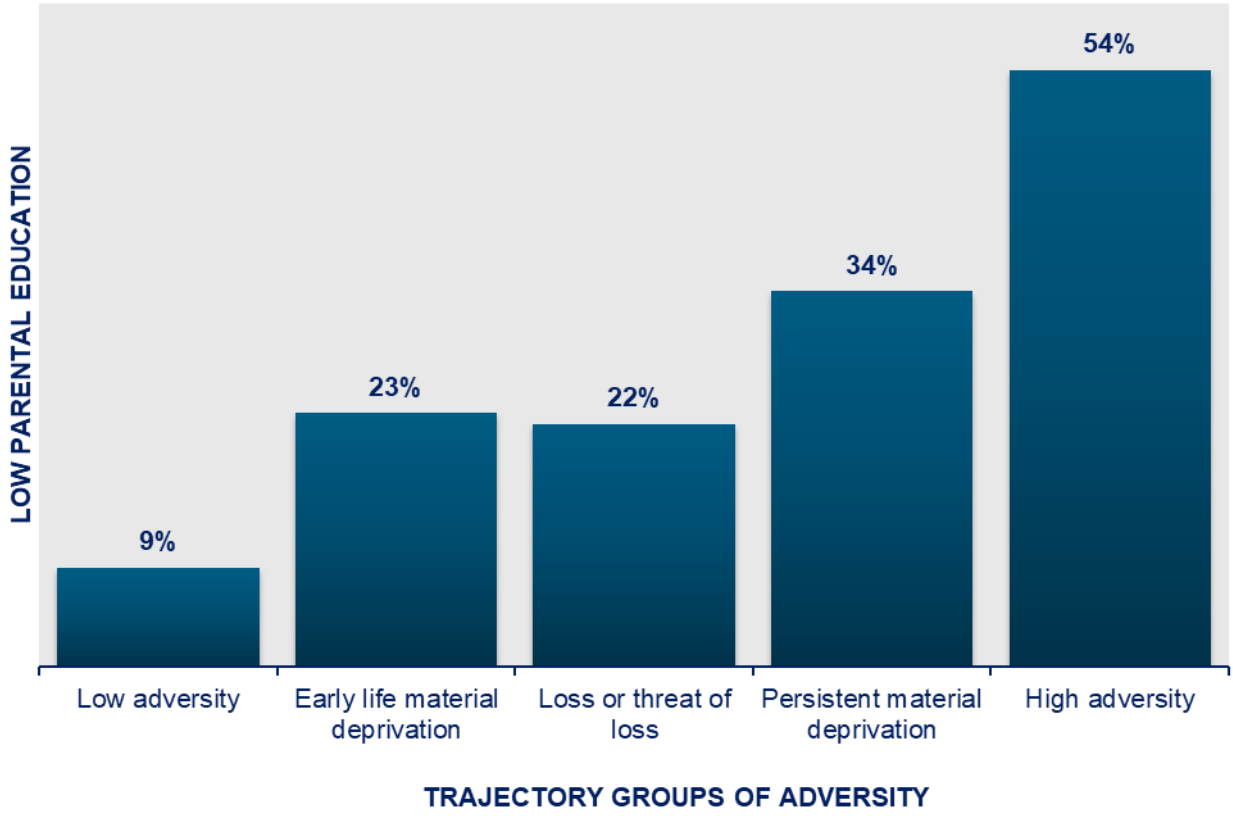

Figure 11 Proportions of the study population born to parents with low level of education (≤9 years) at the time of birth in each of the five trajectory groups of adversity in Study III

The age-specific incidence rates of type 1 diabetes for males and females in the low adversity trajectory group (left panel of Figure 12), including more than half of the study population, were similar to the incidence rates of type 1 diabetes found for the entire study population in Study II (see Figure 9). The rate ratios of type 1 diabetes incidence revealed no clear differences in the early life material deprivation, persistent material deprivation, and the loss or threat of loss groups compared with the low adversity group including 97% of the study population. However, in the high adversity group, males had a higher incidence rate of type 1 diabetes before 11 years of age (adjusted IRR: 1.78; 95% CI: 1.31-2.42) and females had a higher incidence rate of type 1 diabetes after 16 years of age (adjusted IRR: 2.19; 95% CI: 1.57-3.07) compared with males and females in the low adversity group. Figure 12 presents the age-specific incidence rates of type 1 diabetes for males and females in the low and high adversity groups and the rate ratio between them. Plots for all trajectory groups can be seen in Figure 1 of Study III.

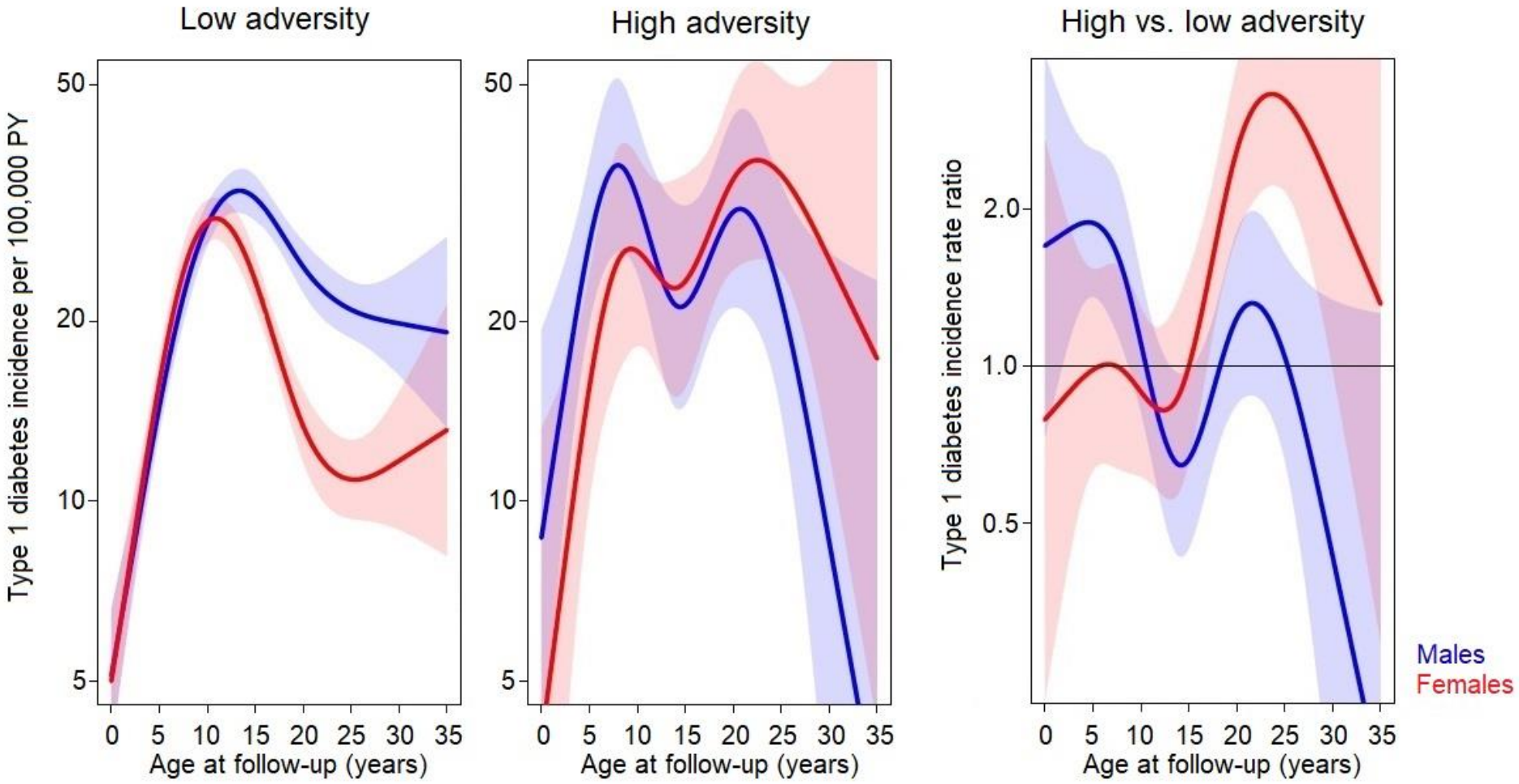

Figure 12 Age-specific incidence of type 1 diabetes per 100,000 person-years (PY) in the low and high adversity trajectory groups and the rate ratio of type 1 diabetes incidence between the two groups

4.4 Additional descriptive analyses

The additional descriptive analyses conducted specifically for this thesis to investigate whether the proportions exposed to the 12 specific childhood adversities in DANLIFE differed between males and females and whether the proportions in each of the five trajectory groups of adversity were similar among males and females, revealed no differences whatsoever. Since the proportions differed only by decimals between males and females, the results are not presented here.

5 Discussion

In this PhD thesis, the effects of cumulative patterns of childhood adversities on type 1 diabetes risk was examined among young males and females in Denmark. To do this, a prospective register-based cohort including all children born in Denmark since 1980 was set up to document the prevalence of exposure to specific and accumulated childhood adversities across age, sex, and social strata. Then the association between accumulation of childhood adversities and type 1 diabetes was quantified separately for males and females. Finally, the importance of timing of adversity exposure for type 1 diabetes development with onset in different age groups was investigated for males and females separately.

In the following section, I give a summary of the main findings of this thesis and discuss the findings in relation to previous evidence and potential mechanisms involved. This is followed by a reflection on methodological strengths and limitations.

5.1 Summary of main findings

The main findings of this thesis were as follows:

- Parental separation, parental long-term unemployment, and parental somatic illness were the most frequently experienced childhood adversities among all children born in Denmark since 1980 and the prevalence of both specific and accumulated adversities was similar among males and females.

- One in 10 children had experienced three or more childhood adversities between early infancy and late adolescence, and there was a strong social gradient in exposure to accumulation of childhood adversities.

- Generally, neither accumulation of 12 selected social and family-related childhood adversities nor trajectories of annually measured exposure to these adversities within dimensions of family dynamics, loss or threat of loss, and material deprivation were associated with type 1 diabetes.

- Only very high levels of accumulated exposure to the 12 different childhood adversities, and a very high and increasing annual rate of these adversities across all three dimensions, were associated with a higher risk of developing type 1 diabetes.

- Assessment of the importance of timing of adversity exposure and age at onset of type 1 diabetes revealed that a very high and increasing annual rate of childhood adversities was associated only with a higher incidence of type 1 diabetes in childhood (<11 years) among males and in young adulthood (≥16 years) among females.

5.2 Comparisons with previous studies

5.2.1 Prevalence, accumulation, and social gradient in exposure to childhood adversities

There is no consensus on what constitutes childhood adversity, and numerous studies have measured the proportion exposed to specific and accumulated childhood adversities using various definitions, methods, and study populations.

The most cited among these studies is the ACE (Adverse Childhood Experience) study,[20] which is often referred to as the first and thereby original study of the health effects of childhood adversities. In the ACE study, adversities were measured retrospectively in adulthood using items reflecting abuse, neglect, and household dysfunction among 60% of the 13,500 invited members of the Kaiser Permanente Health Plan in San Diego. Sharing household with a problem drinker or someone who used street drugs were the only specific adversities that overlapped with the adversities included in DANLIFE. The prevalence of these adversities was considerably higher in the ACE study, where 24% had lived with a problem drinker, and 5% had lived with someone who used street drugs.

In DANLIFE, parental alcohol and drug abuse were among the least prevalent exposures of childhood adversities where only 7% and 2% of the study population had been exposed, respectively. When using registers to measure parental alcohol abuse, only those who show up in the health care system will be detected. Therefore, it is expected that the prevalence of parental alcohol and drug abuse is substantially underestimated in DANLIFE, which, combined with potential cultural differences, may explain the prevalence discrepancy with the ACE study. The magnitude and implications of this information bias are discussed in Section 5.4.2.

In the DANLIFE cohort profile, there was a clear social gradient in exposure to accumulation of childhood adversities measured as maternal educational attainment at the time of birth. In addition to parental education, the proportions of other factors that also have been related to low socioeconomic status, such as low birth weight[102] and having many siblings,[103] increased, and the mean maternal age at the time of birth[104] decreased, with increasing number of adversities experienced in Study II. The same pattern was identified among persons in the persistent material deprivation and high adversity trajectory groups in Study III, where low parental education, low birth weight, and teenage mothers were more common compared with the low adversity trajectory group. In contrast, there was no clear gradient in the proportions exposed to four or more adversities in the ACE study, according to the study participants' own educational attainment.[20] However, a recent study updating the prevalence estimates of the childhood adversities in the ACE study, using a large, diverse, and more representative sample of US adults across 23 states, found a clear social gradient in the mean number of childhood adversities experienced both when measured as own educational attainment and as household income.[39]

Another common data source used in studies of the health consequences of childhood adversities is the 1958 British birth cohort (the National Child Development Study) applying a similar definition of childhood adversities as the ACE study with more than 50 years of follow-up.[105] The cohort consists of more than 17,000 individuals born in a single week in 1958.[105] About 50% of the cohort participated in the latest follow-up in 2008.[106] Studies using the cohort to investigate the effects of childhood adversities on various health outcomes report that 70–75% had not been exposed to any adversities, 20% had been exposed to one adversity, and 5–10% had been exposed to two or more adversities between 0 and 16 years of age.[106–110] Thus, the prevalence of childhood adversities in the 1958 British birth cohort was considerably lower compared with DANLIFE, where we found that 53% had been exposed to one or more childhood adversities, but also in comparison with cross-sectional studies using retrospective recall of childhood adversities in adulthood with definitions of childhood adversities similar to those of the ACE study.[8] This may reflect that disadvantaged children are commonly underrepresented in birth cohorts and disproportionately lost to follow-up.[111] To my knowledge, it has not been reported whether there was a social gradient in exposure to accumulation of childhood adversities in the 1958 British birth cohort.

A Swedish study investigating the effects of childhood adversities on alcohol-related illness included all children born in Sweden between 1973 and 1982 using register data.[112] The definitions of some of the selected adversities overlapped with the definitions used in DANLIFE. The

proportions exposed to these adversities before 18 years of age compared with DANLIFE were: 5% vs. 4% for parental psychiatric illness, 4% vs. 3% for foster care, 29% vs. 29% for parental separation, and 4% vs. 3% for parental death. There was also a strong social gradient (based on the parents' occupation) in exposure to accumulation of childhood adversities in the Swedish study.[112] These similarities are not surprising since Sweden as a country is highly comparable with Denmark with a similar system for social security and registration of information.

Survey studies from the US have reported sex differences in the prevalence of specific adversity exposures where, for example, males were more likely to report violence and traumatic accidents and females were more likely to experience sexual abuse and physical assault by a romantic partner.[113,114] However, there are no registers with information on sexual abuse and maltreatment in Denmark (discussed in Section 5.4.2). Instead, all specific adversities included in DANLIFE were related to family members and material deprivation of the family, and there was, as expected, no difference in the proportions exposed to these specific or accumulated childhood adversities between males and females.

In conclusion, while exposure to some of the adversities is expected to be underestimated in DANLIFE due to information bias, adversities may be underestimated in birth cohorts using self-reported information due to selection both into and out of the study. These potential biases, and differences in the definitions of childhood adversities, make comparisons between studies and countries difficult. Differing definitions also explain why some studies find sex differences in the exposure to specific childhood adversities while the specific adversities included in DANLIFE affected males and females equally often. However, there is consistent evidence for a social gradient in exposure to accumulation of childhood adversities across study populations and study designs.

5.2.2 Accumulation of childhood adversities and type 1 diabetes risk

Several case-control studies have compared the frequency of adverse experiences between type 1 diabetes cases and controls for males and females combined, and they generally found a positive association.[14,58,62,63,69,75,77] Thus, the results of these studies contradict the results of Study II and Study III where accumulation of childhood adversities, measured as a cumulative score and as trajectories of childhood adversities, respectively, was not associated with type 1 diabetes risk in the vast majority of the study population.

Recall bias is a concern in case-control studies because persons with type 1 diabetes may remember adverse exposures in childhood differently compared with controls. It is likely that severe adversities such as abuse and neglect are not easily forgotten, but such adversities were rarely included in the exposure measure in the studies on childhood adversities and type 1 diabetes identified in Section 2.4. Instead, the majority of these studies used checklists of up to 45 stressful events often inspired by the checklist developed by Coddington in 1972, including events (positive and negative) that require readjustment among children in different age groups.[64,115] Examples of such events were death and severe illness or injury of a family member, but also changing schools, break-ups, change in financial status, and loss of job by a parent. Recall of such adversities are known to be attenuated over longer periods of time[116] and may differ between type 1 diabetes cases and controls, especially because persons with type 1 diabetes may be concerned that stressful events have contributed to the development of the disease. Such recall bias would overestimate the association between accumulation of childhood adversities and type 1 diabetes and may explain the contradictory results between previous case-control studies and the results of Study II and Study III in this thesis.

Nygren et al. investigated the effect of exposure to at least one serious life event across childhood (0–14 years) on type 1 diabetes using a Swedish birth cohort of more than 10,000 participants. They found a three times higher risk of developing type 1 diabetes after exposure to at least one serious life event in a Cox regression model where 41 persons developed type 1 diabetes during follow-up.[16] This result is in contrast with the results of Study II and Study III, where exposure to few adversities across childhood and adolescence was not associated with a higher risk of developing type 1 diabetes. One reason for the contradicting results could be that very few persons developed type 1 diabetes in the study by Nygren et al. When cases are few, the estimates may change substantially if just a couple of cases move from one exposure category to the other.[117] A potential contributing explanation for the contradicting results is the substantial loss to follow-up in the study by Nygren et al. (51%), which may be related to exposure to serious life events and type 1 diabetes to some extent, even though the authors do not consider this a likely explanation for their results.[16]

No prospective study has had the statistical power to assess the effect of accumulation of childhood adversities on type 1 diabetes. However, Dube et al. used the same study population as the ACE study[20] (introduced in Section 5.2.1) to assess the effects of accumulation of childhood adversities (0–3+) on a composite outcome of 21 selected autoimmune diseases in adulthood including type 1

diabetes.[52] They followed persons prospectively from the date of their participation in the ACE study until hospitalisation with an autoimmune disease or the end of follow-up 10 years later. The mean age of the study population was 56 years. A test for linear trend showed that the likelihood of a first hospitalisation with an autoimmune disease was 20% higher for women and 10% higher for men for every increase in the adversity score. This result is somewhat similar to the results of Study II, where the risk of type 1 diabetes increased slightly per adversity (7%) among females (but not among males). However, timing of exposure to childhood adversities and age at onset of type 1 diabetes were neither considered in the study by Dube et al. nor in Study II, and these studies may, therefore, not provide the full picture of the association. However, these aspects were taken into account in Study III, which, therefore, constitutes a more advanced attempt to estimate the effect of accumulation of childhood adversities on type 1 diabetes risk.

5.2.3 Timing of adversity exposure and age at onset of type 1 diabetes

Several of the case-control studies identified in Section 2.4 measured exposure to stressful life events in different periods, most often in the year(s) before type 1 diabetes onset,[18,58,60,62,63,65,66,69,74–76] and all but one[18] found a positive association, albeit sometimes only in specific age groups.[63,65,66] Other case-control studies measured exposure to stressful life events at any time before type 1 diabetes onset[56,57,59,61,67,68,77,80] but provide a mixed picture since exposure was often associated with type 1 diabetes development only if it occurred in specific periods, which varied considerably between studies.[63,65–68,77] Therefore, it is difficult to lean on any of these studies in the comparison with the results of Study III.

The study that is most comparable with Study III is Study II in which we assessed the effect of accumulation of the 12 childhood adversities included in DANLIFE on type 1 diabetes. In Study II, we saw that females exposed to many of the adversities had a higher risk of developing type 1 diabetes compared with unexposed females. Study III added to this result by showing that the association is present only after 16 years of age. There was no association between accumulation of childhood adversities and type 1 diabetes among males in Study II. However, Study III revealed that males in the high adversity trajectory group had a higher incidence of type 1 diabetes before 11 years of age compared with males in the low adversity trajectory group. In addition to the assessment of timing of adversity exposure and age at onset of type 1 diabetes, Study III added an extra layer of complexity by letting the adversities occur annually and the effects of the adversities vary between dimensions and across time. The results of Study III are, therefore, assumed to be

closer to the true effect of childhood adversities on type 1 diabetes compared with previous studies, including Study II.

However, the temporality between exposure to adversities and onset of type 1 diabetes before 16 years of age was not clear in Study III (as it was in Study II), and the results for this age-group may be an artefact of reverse causality. There are some indications that the strains of having a child with type 1 diabetes may lead to adversities such as divorce[118] and psychiatric illness,[119,120] and this risk may be higher in socially disadvantaged families due to lack of resources to cope with such strains. However, if this were true, the same association would be present among females, which was not the case.

5.3 Sex differences in the effect of excessive exposure to childhood adversities on type 1 diabetes

As described in Section 2.3.1, some evidence indicates that females experience higher levels of stress in their relationships with family and friends compared with males and that these differences become more salient in adolescence.[15] Females have also been shown to respond with increased and prolonged cortisol output when exposed to biological and physiological stress in adolescence.[50,51] This may provide some explanation for the higher incidence of type 1 diabetes from 16 years onward observed among females but not among males in the high adversity trajectory group in Study III and among females exposed to accumulation of seven or more childhood adversities in Study II.

Why we saw a higher incidence of type 1 diabetes with onset before 11 years of age among males in the high adversity trajectory group in Study III is difficult to explain. The hypothesis that exposure to childhood adversities in infancy may result in dysregulation of the stress response system would be relevant if we had observed the same result among females, which we did not. I have not been able to identify any evidence explaining why there could be sex differences in the reaction to stressful adversities with possible importance for type 1 diabetes development this early in life. However, it is important to note that very few males and females in the high adversity trajectory group developed type 1 diabetes in the different age groups, and the results are, therefore, correspondingly uncertain since each person who developed type 1 diabetes may have a dramatic influence on the estimates.[117]

5.4 Methodological considerations

5.4.1 Strengths

The advantages of Study II and Study III in this thesis compared with previous studies on childhood adversities and type 1 diabetes are all relatable to the strengths of the DANLIFE cohort (Study I). The most important strengths of DANLIFE are the unselected study population and the large sample size. Selection is often the primary concern in prospective studies of the effects of childhood adversities on health outcomes because exposure to adversity is associated with barriers of participation and higher rates of non-response.[111] All children born in Denmark since 1980 were included in DANLIFE, and only those who emigrated or died were lost to follow-up, which is unique to register-based cohorts.

The DANLIFE study population is still young, and the prevalence of many health outcomes is, therefore, low. However, even low prevalence rates translate to substantial absolute numbers of cases in the large sample size of DANLIFE. For example, the prevalence of type 1 diabetes was 0.4% in DANLIFE, corresponding to more than 8000 type 1 diabetes cases, which is a considerably higher absolute number than in any previous study on childhood adversities and type 1 diabetes. Thus, DANLIFE provides an unprecedented data source for investigation of the effects of childhood adversities on rare clinical health outcomes among young individuals, including type 1 diabetes.

Another important strength of Study II and Study III provided by the DANLIFE cohort is the objective nature of the information on childhood adversities obtained from the Danish registers since it is not subject to biases related to self-reports such as recall and social desirability bias. The yearly updated information is another great advantage of using register data providing higher time-resolution of information on exposures and covariates than most birth cohorts and a great advantage compared with retrospective recall of timing of childhood adversities in adulthood, which is known to be unreliable.[121]

Finally, DANLIFE provided the opportunity to apply more refined measures of exposure to childhood adversities and advanced statistical methods for estimating their effects on type 1 diabetes compared with previous studies. Constructing a cumulative adversity score is the most frequently used approach in the literature on accumulation of childhood adversities and health outcomes where each adversity exposure is dichotomised and summed into a score.[8,22] This

approach was advanced in Study II by using many states of exposure to adversities and a prospective design taking the risk-time spent in each state of adversity exposure into account.

Study III took advantage of the annually registered information on all 12 childhood adversities in DANLIFE by applying the five trajectory groups of adversity identified by Rod et al.[19] as the exposure measure. The effects of the adversities were allowed to vary between dimensions and across time and incorporated the five most common patterns of exposure to adversities that the total Danish population born in 1980–1998 actually experienced. This approach allowed us to model some of the complex structures of childhood adversities that may affect type 1 diabetes risk to an extent that is unseen in previous studies.

Thus, the nationwide register information in DANLIFE enabled investigation of the effects of accumulation of annually and objectively measured childhood adversities on age at onset of type 1 diabetes in males and females separately, addressing many of the methodological limitations of previous studies in this field of research.

5.4.2 Limitations

Confounding, selection bias, and information bias may threaten the internal validity of any observational study, and the studies included in this thesis are no exception. The magnitude and implications of these threats are discussed in the following sections.

Confounding

Study I is a cohort profile; only descriptive analyses were conducted, and adjustment for confounders was, therefore, not undertaken. In both Study II and Study III, we were able to adjust for several important confounders, including family history of type 1 diabetes. Identification of potential confounders for the association between childhood adversities and type 1 diabetes was based on previous evidence and guided by the method of directed acyclic graphs, and we were able to control for all factors identified as potential confounders using this method. The quality of the information of the identified potential confounders provided by the registers is considered high. Therefore, I do not expect that residual confounding has biased the results to any important extent.

Selection bias

Selection bias arises in cohort studies if the association between exposure and outcome is different between those who participate in the study and those who decline to do so or are lost to follow-up.[122] It is known that participation and loss to follow-up are highly correlated with material, social, and educational factors and that deprived individuals are underrepresented in cohort studies.[123,124] It is also known that experiences of childhood adversities tend to cluster among children growing up in socially deprived families and these children can, therefore, be expected to be underrepresented in traditional birth cohorts.[111]

Selection bias is not considered an important issue in DANLIFE because the cohort was based on the entire population born in Denmark since 1980, and participation and follow-up were based on automated register information. A small proportion of the study population died during follow-up, but undiagnosed type 1 diabetes is an unlikely cause of death in Denmark. Emigration during follow-up is not expected to be related to type 1 diabetes either. The small loss to follow-up due to death and emigration is, therefore, not likely to have caused any selection bias in the results of Study II and in the results derived after 16 years of age in Study III.

However, in Study III, we restricted the study population to those alive and resident in Denmark until their 16th birthday. While emigrations are not likely to be related to type 1 diabetes, mortality has been shown to be higher among persons with type 1 diabetes compared with the general population in Denmark.[125] Since exposure to childhood adversities is also related to mortality in this age group,[126] this study design may have introduced an underestimation[122] of the effect of childhood adversities on type 1 diabetes before 16 years of age in Study III. However, the mortality rate in this age group is very low, and the magnitude of this selection bias is, therefore, expected to be small.

Information bias

A discussion of information bias requires an assessment of the discrepancy between the underlying construct and the operational measures.[127] Information bias in the measure of childhood adversities is undoubtedly the largest threat to the internal validity of this thesis. It relates primarily to the definition of childhood adversities in DANLIFE and the availability and crudeness of the information in the Danish registers. The magnitude and implications of information bias in this thesis are discussed below.

This thesis builds on the beta cell stress hypothesis suggesting that any factor that increases insulin resistance should be considered a risk factor for type 1 diabetes, including psychosocial stress acting via increased levels of cortisol[6] (see Section 2.3 for further details). The 12 childhood adversities in DANLIFE were selected because they, based on previous evidence, constitute important sources of stress in children and are, therefore, relevant exposure measures. However, the prevalence of some of the adversities in DANLIFE will inevitably be underestimated since many cases are never reported. For example, we used medical records and prescriptions for medications used in the treatment of alcohol dependence to identify parental alcohol abuse and found that 7% of the DANLIFE study population had been exposed. In 2012, the Danish Health Authority estimated that at least 12% of all Danes between 0 and 18 years grow up in families affected by alcohol abuse, which was also considered a conservative estimate since affected persons are less likely to participate in investigations.[128]

The definitions of some of the adversities in DANLIFE may also have contributed to an underestimation of their prevalence. For example, there may be other somatic illnesses that will cause psychosocial stress in children of affected parents and siblings that were not considered in DANLIFE. Also, adversities related to important individuals in the lives of the study population other than biological parents and full siblings were not included. Adversities that are not social or family-related may also induce psychosocial stress in children (e.g., school performance and relations with peers) but were not considered in DANLIFE. These unmeasured aspects of adversities may lead to an underestimation of the true association between childhood adversities and type 1 diabetes. However, by combining repeated information on 12 central adversities known to be important sources of stress in children, I believe a general pattern of stressful adversity exposure was captured even though not all types of adversities were included and the measures of some of the specific adversities were not perfect.

Also, exposure to maltreatment, abuse, and neglect may be extremely stressful for a child and has been shown to be strongly associated with morbidity[20] and mortality[129] later in life. Unfortunately, there are no registers with information on child maltreatment, abuse, or neglect available in Denmark, and these adversities could, therefore, not be included in DANLIFE. There are ICD-codes for child abuse and neglect, but using these hospitalisations is known to highly underestimate the true prevalence in Denmark.[130] However, the very severe cases of maltreatment have likely been captured by information on foster care. Also, since exposure to childhood adversities tends to cluster among socially deprived persons, it is likely that those who were exposed to severe but

unmeasured adversities such as maltreatment, abuse, and neglect are to be found among those highly exposed to adversities in Study II and Study III.

Moreover, when applying an adversity score as the measure of adversity exposure in Study II, we made the naïve assumption that each of the 12 adversities in DANLIFE were equally stressful, which is unrealistic and may further delude the true association between childhood adversities and type 1 diabetes. Similar bias may have affected the results of Study III even though the effect of adversities were allowed to differ between the three dimensions of adversity and over time. Thus, even though the approaches to estimate the effects of multiple childhood adversities on type 1 diabetes were more advanced in both Study II and Study III compared with any previous study, the effect estimates are likely biased to some degree due to the operational measures of cumulative adversity exposure.

Finally, persons with type 2 diabetes with onset in early adult life may have been misclassified as having type 1 diabetes based on their young age.[131] This potential bias would lead to an overestimation of the effect since both the prevalence of childhood adversities and type 2 diabetes is known to be higher among socially disadvantaged individuals. Because the information on diabetes type is based on repeated clinical assessments, the effect of this misclassification is expected to be modest.

In conclusion, the effect of childhood adversities on type 1 diabetes may have been distorted due to underestimated and unmeasured exposure to childhood adversities in DANLIFE. Since this information bias is unrelated to type 1 diabetes, it is non-differential and, therefore, likely to have attenuated the effect. However, because DANLIFE includes several important and repeated indicators of childhood adversities, I believe a general pattern of stressful adversity exposure was captured and that the overall lack of association between childhood adversities and type 1 diabetes found in the vast majority of the study population in both Study II and Study III is valid.

5.4.3 External validity

Using information from the Danish registers does not require informed consent, and the entire Danish population born since 1980 could, therefore, be included and followed over time in DANLIFE. The only deviation from the general Danish population in DANLIFE is that individuals who were not born in Denmark were excluded from the study population due to missing

information before immigration. Thus, the results generated from the DANLIFE data in this thesis may not readily be generalisable to first-generation immigrants if the effect of childhood adversities on type 1 diabetes is different among them compared with persons born in Denmark. There may be some cultural differences in the perception of adversity exposure and genetic differences in type 1 diabetes development, but it seems unlikely that the effect would be substantially different among immigrants living in Denmark. The results of the studies in this thesis are, therefore, deemed highly representative of the general Danish population and young populations in countries similar to Denmark with an extensive social security system.

The Danish welfare system provides universal childcare and promotes economic stability for families. The effects of childhood adversities on type 1 diabetes (and other health outcomes) may be larger in countries with less social security and should be kept in mind when generalising the results of this thesis to other contexts.

6 Conclusions

The overall objective of this thesis was to document the level of childhood adversities across age, sex, and social strata in Denmark and, based on this knowledge, thoroughly assess the effects of cumulative patterns of adversity exposure across childhood and adolescence on type 1 diabetes risk in males and females.

The first aim of the thesis was to assemble a large, register-based cohort of all children born in Denmark since 1980 and to define and construct measures of repeated exposure to childhood adversities that would provide an adequate data source for the investigation of the association between exposure to childhood adversities and type 1 diabetes. The cohort was named DANLIFE, and the registers that were used, the data management that took place, and the decisions that were made along the way to define 12 social and family-related childhood adversities were documented in a cohort profile (Study I). DANLIFE proved a highly valuable data source in the assessment of the effects of cumulative exposure to childhood adversities on type 1 diabetes risk that allowed us to address many methodological limitations that have affected previous studies such as recall bias, selection bias, and lack of statistical power. DANLIFE has also proven a valuable data source for the assessment of the effects of childhood adversities on premature mortality,[19] and more studies on other health outcomes are in the pipeline.

In relation to the second aim, I hypothesised that the prevalence of childhood adversities among young males and females in Denmark would be as high as in other high-income countries. However, the large heterogeneity in definitions, methods, and populations between studies made it difficult to compare across countries. Since more than half of the DANLIFE study population had been exposed to at least one childhood adversity and one in 10 had been exposed to three or more adversities, I conclude that the prevalence of childhood adversities can be considered high and that there is a social gradient in exposure to childhood adversities even in a welfare state like Denmark with high social security. As expected, males and females are equally exposed to childhood adversities.

The third aim was to quantify the association between accumulation of childhood adversities and type 1 diabetes among males and females. In contrast to my hypothesis, and in contrast to previous studies, exposure to accumulation of childhood adversities was not associated with type 1 diabetes

risk in the vast majority of the DANLIFE study population. I expect that this large part of the study population is representative to many of those who are concerned that stressful adverse life events or circumstances have contributed to the development of the disease. These results, therefore, provide type 1 diabetes clinicians with a reassuring answer when they encounter this concern.

Subsequently, the fourth aim assessed the timing of exposure to childhood adversities and age at onset of type 1 diabetes. Only the small group (3%) of males and females who experienced high and increasing annual rates of adversity exposure across childhood and adolescence had a higher risk of developing type 1 diabetes, but only among males who were diagnosed before 11 years of age and among females diagnosed after 16 years of age. Thus, the mechanisms behind these associations seem to differ between males and females. Despite efforts to identify plausible explanations, the underlying mechanisms influencing age at onset of type 1 diabetes remain unknown.

These conclusions should be considered in the context of the limitations of this thesis. Most importantly, the prevalence of some of the specific adversities are assumed to be underestimated due to the definition of childhood adversities in DANLIFE and the availability and crudeness of the information in the Danish registers. This is not, however, expected to have had a major impact on the conclusions of this thesis; I argue that if there were an association of importance between exposure to childhood adversities and type 1 diabetes, it would have been detected by the general patterns of adversity exposure that I believe was captured by the high-resolution information in DANLIFE.

The results reflecting a higher type 1 diabetes risk among the very few males and females exposed to extremely high levels of adversity were based on very few type 1 diabetes cases and are, therefore, highly uncertain and should be explored further.

7 Future research

The main finding of this thesis was that exposure to childhood adversities was generally not associated with type 1 diabetes risk. However, being exposed to a high and increasing annual rate of childhood adversities across childhood and adolescence appeared to influence type 1 diabetes development with onset at different ages among males and females. This result is highly uncertain, however, since few of the males and females who were highly exposed to childhood adversities also developed type 1 diabetes and it needs to be investigated further.

The first step would be to investigate whether the results can be replicated in similar settings. The studies of this thesis could, for example, be conducted in the other Nordic countries which have equivalent welfare systems and similar traditions for registration of information.

If similar results were found, the concern that this is a chance finding could be dismissed and further investigation into the possible mechanisms underlying the sex differences in age at onset of type 1 diabetes among persons highly exposed to childhood adversities would be warranted. Also, further investigation into the constellations of adversity exposure among these highly exposed males and females, and assessment of the possibilities for conducting analyses where each of the specific adversities is weighted according to impact, would be justified.[132]

It is important to remember that these persons are highly disadvantaged. A more urgent concern among clinicians than the cause of type 1 diabetes is likely the implications of adversity exposure for the management of the disease. It is plausible that exposure to childhood adversities may contribute to poorly controlled glucose levels that, in turn, will affect the risk of developing diabetes-related complications. Future research into the consequences of childhood adversities for type 1 diabetes management could assist the decision to allocate more resources to support disadvantaged children and their families in the management of type 1 diabetes.

8 Public health perspectives

In this thesis, exposure to accumulation of childhood adversities was generally not associated with type 1 diabetes development. These results may provide clinicians with a reassuring answer when asked whether exposure to childhood adversities may have contributed to the development of type 1 diabetes. If this will prevent some persons with type 1 diabetes and their relatives from blaming themselves for the development of the disease, I believe this thesis has provided highly valuable results.

However, even though childhood adversities do not have a major effect on type 1 diabetes risk, exposure to childhood adversities is still an important public health issue. Even in a welfare state like Denmark, with a high quality of life and high level of social security, we found that one in 10 children had been exposed to three or more childhood adversities before the age of 18 years. We also identified a strong social gradient in exposure to accumulation of childhood adversities. Thus, exposure to childhood adversities may be more detrimental for medical conditions with a stronger socioeconomic gradient than type 1 diabetes. Mounting results already point toward a major impact of childhood adversities on physical and mental health issues that are known to be socioeconomically skewed.[10,21,22,40] Adults who have experienced childhood adversities are, for example, more prone to develop alcoholism,[133,134] depression,[135,136] and attempt suicide[137,138] as well as develop cardiovascular disease[7,139] and many other chronic diseases.[20] Childhood adversities may also have a negative influence on the management of medical conditions, adding further to the social inequality in health.[140]

Although there are examples of individuals overcoming the most disadvantageous early conditions, for most, childhood adversities have long-lasting effects that may even persist to the next generation.[10,40,140] Sound investments in interventions that reduce exposure to childhood adversities have been shown to strengthen the foundations of physical and mental health and generate substantial returns to all of society.[10,40] The prevalence of childhood adversities could be addressed in a structural manner, dealing with overall sources of psychosocial adversity in society,[140] and the effects of childhood adversities could be tackled with a more individual approach identifying and supporting the most vulnerable children and their families.[140] The impact of childhood adversities can be attenuated or even reversed if detected early enough.[140] Clinicians and professionals working with children are key in early detection and, therefore, need to be aware of the detrimental consequences of adversities for children's future health and take action.[40] From a societal point of

view, it is important to reduce the costs of excess healthcare need, loss of employment and productivity, as well as human suffering. To do this, we need to create a safe environment where children can develop into competent adults and become healthy stakeholders in a productive society.[10,140]

Even though much is already known about the multiple effects of childhood adversities for health across the life course, the complex interactive, modifying, and mediating mechanisms of childhood adversities are far from being fully elucidated.[37] Information on childhood adversities with high time-resolution in whole populations is an invaluable asset in this aspect, and I believe DANLIFE will be instrumental in the future unravelling of the health effects of childhood adversities that I look forward to contributing to.

9 References

1. Knip M. Descriptive epidemiology of type 1 diabetes—is it still in? *Diabetologia*. 2012 May 1;**55**(5):1227–1230.

2. Rewers M, Ludvigsson J. Environmental risk factors for type 1 diabetes. *The Lancet*. 2016 Jun 4;**387**(10035):2340–2348.

3. Dahlquist G. Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. *Diabetologia*. 2006 Jan;**49**(1):20–24.

4. Knip M, Veijola R, Virtanen SM, Hyöty H, Vaarala O, Åkerblom HK. Environmental Triggers and Determinants of Type 1 Diabetes. *Diabetes*. 2005 Jan 12;**54**(suppl 2):S125–S136.

5. Peng H, Hagopian W. Environmental factors in the development of Type 1 diabetes. *Rev Endocr Metab Disord*. 2007 Jan 10;**7**(3):149–162.

6. Ludvigsson J. Why diabetes incidence increases—A unifying theory. *Ann N Y Acad Sci*. 2006 Oct 1;**1079**(1):374–382.

7. Suglia Shakira F., Koenen Karestan C., Boynton-Jarrett Renée, et al. Childhood and Adolescent Adversity and Cardiometabolic Outcomes: A Scientific Statement From the American Heart Association. *Circulation*. 2018 Jan 30;**137**(5):e15–e28.

8. Hughes K, Bellis MA, Hardcastle KA, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health*. 2017 Aug 1;**2**(8):e356–e366.

9. Sepa A, Ludvigsson J. Psychological stress and the risk of diabetes-related autoimmunity: a review article. *Neuroimmunomodulation*. 2006;**13**(5–6):301–308.

10. Shonkoff JP, Garner AS, Siegel BS, et al. The Lifelong Effects of Early Childhood Adversity and Toxic Stress. *Pediatrics*. 2012 Jan 1;**129**(1):e232–e246.

11. Agorastos A, Pervanidou P, Chrousos GP, Kolaitis G. Early life stress and trauma: developmental neuroendocrine aspects of prolonged stress system dysregulation. *Hormones*. 2018 Dec 1;**17**(4):507–520.

12. Nicolaides NC, Kyratzi E, Lamprokostopoulou A, Chrousos GP, Charmandari E. Stress, the Stress System and the Role of Glucocorticoids. *Neuroimmunomodulation*. 2015;**22**(1–2):6–19.

13. Faresjö M. The Link between Psychological Stress and Autoimmune Response in Children. *Crit Rev Immunol*. 2015;**35**(2):117–134.

14. Soltesz G, Patterson C, Dahlquist G, EURODIAB Study Group. Worldwide childhood type 1 diabetes incidence – what can we learn from epidemiology? *Pediatr Diabetes*. 2007 Oct 1;**8**:6–14.

15. Rudolph KD. Gender differences in emotional responses to interpersonal stress during adolescence. *J Adolesc Health*. 2002 Apr 1;**30**(4, Supplement 1):3–13.

16. Nygren M, Carstensen J, Koch F, Ludvigsson J, Frostell A. Experience of a serious life event increases the risk for childhood type 1 diabetes: the ABIS population-based prospective cohort study. *Diabetologia*. 2015 Jun;**58**(6):1188–1197.

17. Nygren M. Family psychological stress early in life and development of type 1 diabetes: The ABIS prospective study. *Diabetes Res Clin Pract*. 2013;**100**(2):257–264.

18. Littorin B, Sundkvist G, Nyström L, et al. Family characteristics and life events before the onset of autoimmune type 1 diabetes in young adults a nationwide study. *Diabetes Care*. 2001 Jan 6;**24**(6):1033–1037.

19. Rod NH, Bengtsson J, Budtz-Jørgensen E, et al. Trajectories of childhood adversity and premature mortality in early adulthood: A population-based cohort study in Denmark. *Lancet (in press)*.

20. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. 1998 May;**14**(4):245–258.

21. Kessler RC, McLaughlin KA, Green JG, et al. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *Br J Psychiatry J Ment Sci*. 2010 Nov;**197**(5):378–385.

22. Evans GW, Li D, Whipple SS. Cumulative risk and child development. *Psychol Bull*. 2013 Nov;**139**(6):1342–1396.

23. Troxel WM, Matthews KA. What Are the Costs of Marital Conflict and Dissolution to Children's Physical Health? *Clin Child Fam Psychol Rev*. 2004 Mar;**7**(1):29–57.

24. Gottman JM, Katz LF. Effects of marital discord on young children's peer interaction and health. *Dev Psychol*. 1989;**25**(3):373–381.

25. Ganzel BL, Morris PA. Allostasis and the developing human brain: explicit consideration of implicit models. *Dev Psychopathol*. 2011 Nov;**23**(4):955–974.

26. Tarullo AR, Gunnar MR. Child maltreatment and the developing HPA axis. *Horm Behav*. 2006 Nov;**50**(4):632–639.

27. Luecken LJ, Lemery KS. Early caregiving and physiological stress responses. *Clin Psychol Rev*. 2004 May;**24**(2):171–191.

28. Andel HW van, Jansen L, Grietens H, Knorth EJ, Gaag RJ van der. Salivary cortisol: a possible biomarker in evaluating stress and effects of interventions in young foster children? *Eur Child Adolesc Psychiatry*. 2014 Jan;**23**(1):3–12.

29. Lewandowski LA. Needs of children during the critical illness of a parent or sibling. *Crit Care Nurs Clin North Am*. 1992 Dec;**4**(4):573–585.

30. Luecken LJ, Appelhans BM. Early parental loss and salivary cortisol in young adulthood: the moderating role of family environment. *Dev Psychopathol*. 2006;**18**(1):295–308.

31. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychol Bull*. 2011;**137**(6):959–997.

32. Cohen S, Janicki-Deverts D, Chen E, Matthews KA. Childhood socioeconomic status and adult health. *Ann N Y Acad Sci*. 2010 Feb;**1186**(1):37–55.

33. Evans GW, Kim P. Childhood Poverty, Chronic Stress, Self-Regulation, and Coping. *Child Dev Perspect*. 2013 Mar 1;**7**(1):43–48.

34. Evans GW, Kim P. Childhood poverty and health: cumulative risk exposure and stress dysregulation. *Psychol Sci*. 2007 Nov;**18**(11):953–957.

35. Rutter M. Stress, coping and development: some issues and some questions. *J Child Psychol Psychiatry*. 1981 Oct;**22**(4):323–356.

36. Rutter M. Protective factors in children's responses to stress and disadvantage. *Ann Acad Med Singapore*. 1979 Jul;**8**(3):324–338.

37. Agorastos A, Pervanidou P, Chrousos GP, Baker DG. Developmental Trajectories of Early Life Stress and Trauma: A Narrative Review on Neurobiological Aspects Beyond Stress System Dysregulation. *Front Psychiatry*. 2019;**10**:118.

38. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. *J Epidemiol Community Health*. 2003 Oct;**57**(10):778–783.

39. Merrick MT, Ford DC, Ports KA, Guinn AS. Prevalence of Adverse Childhood Experiences From the 2011-2014 Behavioral Risk Factor Surveillance System in 23 States. *JAMA Pediatr*. 2018 Nov 1;**172**(11):1038–1044.

40. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, Molecular Biology, and the Childhood Roots of Health Disparities: Building a New Framework for Health Promotion and Disease Prevention. *JAMA*. 2009 Jun 3;**301**(21):2252–2259.

41. IDF Atlas 9th edition and other resources. [cited 2020 May 10]. Available from: https://www.diabetesatlas.org/en/resources/

42. Svensson J, Lyngaae-Jørgensen A, Carstensen B, Simonsen LB, Mortensen HB, Danish Childhood Diabetes Registry. Long-term trends in the incidence of type 1 diabetes in Denmark: the seasonal variation changes over time. *Pediatr Diabetes*. 2009 Jun 1;**10**(4):248–254.

43. Svensson J, Carstensen B, Mølbak A, et al. Increased risk of childhood type 1 diabetes in children born after 1985. *Diabetes Care*. 2002 Dec;**25**(12):2197–2201.

44. Svensson J, Cerqueira C, Kjærsgaard P, et al. Danish Registry of Childhood and Adolescent Diabetes. *Clin Epidemiol*. 2016;**8**:679–683.

45. Mead V. Trauma Triggers Type 1 Diabetes and Other Diseases (Buffers, ACEs, Delayed Onset after Trauma+). *Chronic Illn. Trauma Stud.* 2017 [cited 2020 May 14]. Available from: https://chronicillnesstraumastudies.com/serious-life-events-increase-type-1-diabetes-research-review/

46. McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. *Horm Behav*. 2003 Jan 1;**43**(1):2–15.

47. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med*. 1998 Jan 15;**338**(3):171–179.

48. Wilkin TJ. The convergence of type 1 and type 2 diabetes in childhood: the accelerator hypothesis. *Pediatr Diabetes*. 2012 Jun;**13**(4):334–339.

49. Nygren M. Stress in childhood and the risk of type 1 diabetes [PhD thesis]. Linköping University; 2015. Available from: http://liu.diva-portal.org/smash/get/diva2:851358/FULLTEXT01.pdf

50. Stroud LR, Papandonatos GD, Williamson DE, Dahl RE. Sex differences in cortisol response to corticotropin releasing hormone challenge over puberty: Pittsburgh Pediatric Neurobehavioral Studies. *Psychoneuroendocrinology*. 2011 Sep 1;**36**(8):1226–1238.

51. Gunnar MR, Wewerka S, Frenn K, Long JD, Griggs C. Developmental changes in hypothalamus–pituitary–adrenal activity over the transition to adolescence: Normative changes and associations with puberty. *Dev Psychopathol*. 2009;**21**(1):69–85.

52. Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, Croft JB. Cumulative childhood stress and autoimmune diseases in adults. *Psychosom Med*. 2009 Feb;**71**(2):243–250.

53. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol*. 2002 Jan 4;**31**(2):285–293.

54. Viner RM, Ross D, Hardy R, et al. Life course epidemiology: recognising the importance of adolescence. *J Epidemiol Community Health*. 2015 Feb 2;

55. Williams AJK, Bingley PJ. Worth the wait: type 1 diabetes prospective birth cohort studies enter adolescence. *Diabetologia*. 2012 Jul;**55**(7):1873–1876.

56. Stein SP, Charles E. Emotional factors in juvenile diabetes mellitus: a study of early life experience of adolescent diabetics. *Am J Psychiatry*. 1971 Dec;**128**(6):700–704.

57. Leaverton DR, White CA, McCormick CR, Smith P, Sheikholislam B. Parental loss antecedent to childhood diabetes mellitus. *J Am Acad Child Psychiatry*. 1980;**19**(4):678–689.

58. Robinson N, Fuller JH. Role of life events and difficulties in the onset of diabetes mellitus. *J Psychosom Res*. 1985;**29**(6):583–591.

59. Kisch ES. Stressful events and the onset of diabetes mellitus. *Isr J Med Sci*. 1985 Apr;**21**(4):356–358.

60. Robinson N, Lloyd CE, Fuller JH, Yateman NA. Psychosocial factors and the onset of type 1 diabetes. *Diabet Med J Br Diabet Assoc*. 1989 Feb;**6**(1):53–58.

61. Vialettes B, Ozanon JP, Kaplansky S, et al. Stress antecedents and immune status in recently diagnosed type I (insulindependent) diabetes mellitus. *Diabète Métabolisme*. 1989 Feb;**15**(1):45–50.

62. Siemiatycki J, Colle E, Campbell S, Dewar RAD, Belmonte MM. Case-Control Study of IDDM. *Diabetes Care*. 1989 Mar 1;**12**(3):209–216.

63. Hägglöf B, Blom L, Dahlquist G, Lönnberg G, Sahlin B. The Swedish childhood diabetes study: indications of severe psychological stress as a risk factor for Type 1 (insulin-dependent) diabetes mellitus in childhood. *Diabetologia*. 1991 Aug 1;**34**(8):579–583.

64. Coddington RD. The significance of life events as etiologic factors in the diseases of children—II a study of a normal population. *J Psychosom Res*. 1972 Jun;**16**(3):205–213.

65. Dahlquist G, Blom L, Lönnberg G. The Swedish Childhood Diabetes Study - a multivariate analysis of risk determinants for diabetes in different age groups. *Diabetologia*. 1991 Oct;**34**(10):757–762.

66. Soltész G, Jeges S, Dahlquist G. Non-genetic risk determinants for type 1 (insulin-dependent) diabetes mellitus in childhood. Hungarian Childhood Diabetes Epidemiology Study Group. *Acta Paediatr Oslo Nor 1992*. 1994 Jul;**83**(7):730–735.

67. Hägglöf B, Fransson P, Lernmark B, Thernlund G. Psychosocial aspects of type 1 diabetes mellitus in children 0-14 years of age. *Arctic Med Res*. 1994;**53 Suppl 1**:20–29.

68. Thernlund GM, Dahlquist G, Hansson K, et al. Psychological stress and the onset of IDDM in children. *Diabetes Care*. 1995 Oct;**18**(10):1323–1329.

69. Djarova T, Dube N. Influence of stressful life events on the onset of Type 1 diabetes in childhood. *Afr J Health Sci*. 1998 Dec;**5**(3–4):190–197.

70. Sarason IG, Johnson JH, Siegel JM. Assessing the impact of life changes: development of the Life Experiences Survey. *J Consult Clin Psychol*. 1978 Oct;**46**(5):932–946.

71. Sepa A, Frodi A, Ludvigsson J. Mothers' attachment insecurity and diabetes-related autoantibodies in their infants. *Ann N Y Acad Sci*. 2004 Dec;**1037**:110–113.

72. Sepa A, Frodi A, Ludvigsson J. Mothers' experiences of serious life events increase the risk of diabetes-related autoimmunity in their children. *Diabetes Care*. 2005 Oct;**28**(10):2394–2399.

73. Sepa A, Wahlberg J, Vaarala O, Frodi A, Ludvigsson J. Psychological Stress May Induce Diabetes-Related Autoimmunity in Infancy. *Diabetes Care*. 2005 Jan 2;**28**(2):290–295.

74. Vlajinac H, Sipetić S, Marinković J, Bjekić M, Kocev N, Sajić S. The Belgrade childhood diabetes study - comparison of children with type 1 diabetes with their siblings. *Paediatr Perinat Epidemiol*. 2006 May;**20**(3):238–243.

75. Sipetic S, Vlajinac H, Marinkovi J, et al. Stressful Life Events and Psychological Dysfunctions Before the Onset of Type 1 Diabetes Mellitus. *J Pediatr Endocrinol Metab*. 2007;**20**(4):527–534.

76. Djarova T, Dube S, Tivchev G, Chivengo A. Frequency of stressful life events as risk indicating factors for the onset of type 1 diabetes in African children. *South Afr J Sci*. 2007 Aug;**103**(7–8):286–288.

77. Karavanaki K, Tsoka E, Liacopoulou M, et al. Psychological stress as a factor potentially contributing to the pathogenesis of Type 1 diabetes mellitus. *J Endocrinol Invest*. 2008 May;**31**(5):406–415.

78. Zung A, Blumenfeld O, Shehadeh N, et al. Increase in the incidence of type 1 diabetes in Israeli children following the Second Lebanon War. *Pediatr Diabetes*. 2012 Jun;**13**(4):326–333.

79. Virk J, Ritz B, Li J, Obel C, Olsen J. Childhood bereavement and type 1 diabetes: a Danish national register study. *Paediatr Perinat Epidemiol*. 2016 Jan 1;**30**(1):86–92.

80. Antonela B, Ivana G, Ivan K, et al. Environmental Risk Factors for Type 1 Diabetes Mellitus Development. *Exp Clin Endocrinol Diabetes Off J Ger Soc Endocrinol Ger Diabetes Assoc*. 2017 Jul 27;

81. Lundgren M, Ellström K, Elding Larsson H, DiPiS study group. Influence of early-life parental severe life events on the risk of type 1 diabetes in children: the DiPiS study. *Acta Diabetol*. 2018 Aug;**55**(8):797–804.

82. Steck AK, Johnson K, Barriga KJ, et al. Age of Islet Autoantibody Appearance and Mean Levels of Insulin, but Not GAD or IA-2 Autoantibodies, Predict Age of Diagnosis of Type 1 Diabetes: Diabetes Autoimmunity Study in the Young. *Diabetes Care*. 2011 Jun 1;**34**(6):1397–1399.

83. Barker JM, Barriga KJ, Yu L, et al. Prediction of Autoantibody Positivity and Progression to Type 1 Diabetes: Diabetes Autoimmunity Study in the Young (DAISY). *J Clin Endocrinol Metab*. 2004 Aug 1;**89**(8):3896–3902.

84. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011 Jan 7;**39**(7 suppl):22–25.

85. Bliddal M, Broe A, Pottegård A, Olsen J, Langhoff-Roos J. The Danish Medical Birth Register. *Eur J Epidemiol*. 2018 Jan;**33**(1):27–36.

86. Christensen K, Schmidt MM, VÆth M, Olsen J. Absence of an Environmental Effect on the Recurrence of Facial-Cleft Defects. *N Engl J Med*. 1995 Jul 20;**333**(3):161–165.

87. Evans GW, Kim P. Childhood poverty and health: cumulative risk exposure and stress dysregulation. *Psychol Sci*. 2007 Nov;**18**(11):953–957.

88. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011 Jul 1;**39**(7_suppl):54–57.

89. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015 Nov 17;**7**:449–490.

90. Wallach Kildemoes H, Toft Sørensen H, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011 Jul 1;**39**(7_suppl):38–41.

91. Christensen S, Johansen MB, Christiansen CF, Jensen R, Lemeshow S. Comparison of Charlson comorbidity index with SAPS and APACHE scores for prediction of mortality following intensive care. *Clin Epidemiol*. 2011 Jun 17;**3**:203–211.

92. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011 Mar 15;**173**(6):676–682.

93. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health*. 2011 Jul 1;**39**(7_suppl):103–105.

94. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health*. 2011 Jan 7;**39**(7 suppl):95–98.

95. Jørgensen ME, Kolding J, Husted GR, Cerqueira CS, Rossing P. The Danish Adult Diabetes Registry. *ResearchGate*. 2016 Oct 1;**8**:429–434.

96. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiol Camb Mass*. 1999 Jan;**10**(1):37–48.

97. Jensen VM, Rasmussen AW. Danish Education Registers. *Scand J Public Health*. 2011 Jul;**39**(7 Suppl):91–94.

98. Publikation: Børn og deres familier 2018. [cited 2019 Apr 8]. Available from: https://www.dst.dk/da/Statistik/Publikationer/VisPub?cid=31407

99. Carstensen B, Plummer M. Using Lexis Objects for Multi-State Models in R. *J Stat Softw*. 2011;**38**(6):18.

100. Carstensen B, Plummer M, Laara E, Hills M. (2018). Epi: A Package for Statistical Analysis in Epidemiology. R package version 2.26. URL https://CRAN.R-project.org/package=Epi.

101. Miettinen J, Rantanen M. (2018). popEpi: Functions for Epidemiological Analysis using Population Data. R package version 0.4.5. ULR https://CRAN.R-project.org/package=popEpi.

102. Parker JD, Schoendorf KC, Kiely JL. Associations between measures of socioeconomic status and low birth weight, small for gestational age, and premature delivery in the United States. *Ann Epidemiol*. 1994 Jul 1;**4**(4):271–278.

103. Blumenshine P, Egerter S, Barclay CJ, Cubbin C, Braveman PA. Socioeconomic Disparities in Adverse Birth Outcomes: A Systematic Review. *Am J Prev Med*. 2010 Sep;**39**(3):263–272.

104. Nilsen ABV, Waldenström U, Hjelmstedt A, Hjelmsted A, Rasmussen S, Schytt E. Characteristics of women who are pregnant with their first baby at an advanced age. *Acta Obstet Gynecol Scand*. 2012 Mar;**91**(3):353-362x.

105. Power C, Elliott J. Cohort profile: 1958 British birth cohort (National Child Development Study). *Int J Epidemiol*. 2006 Feb 1;**35**(1):34–41.

106. Kelly-Irving M, Lepage B, Dedieu D, et al. Childhood adversity as a risk for cancer: findings from the 1958 British birth cohort study. *BMC Public Health*. 2013 Dec;**13**(1):1–13.

107. Solís CB, Kelly-Irving M, Fantin R, et al. Adverse childhood experiences and physiological wear-and-tear in midlife: Findings from the 1958 British birth cohort. *Proc Natl Acad Sci*. 2015 Feb 17;**112**(7):E738–E746.

108. Kelly-Irving M, Lepage B, Dedieu D, et al. Adverse childhood experiences and premature all-cause mortality. *Eur J Epidemiol*. 2013 Sep 1;**28**(9):721–734.

109. Delpierre C, Fantin R, Barboza-Solis C, Lepage B, Darnaudéry M, Kelly-Irving M. The early life nutritional environment and early life stress as potential pathways towards the metabolic syndrome in mid-life? A lifecourse analysis using the 1958 British Birth cohort. *BMC Public Health*. 2016 Aug 18;**16**(1):815.

110. Chen M, Lacey RE. Adverse childhood experiences and adult inflammation: Findings from the 1958 British birth cohort. *Brain Behav Immun*. 2018 Mar 1;**69**:582–590.

111. Doidge JC, Edwards B, Higgins DJ, Segal L. Adverse childhood experiences, non-response and loss to follow-up: Findings from a prospective birth cohort and recommendations for addressing missing data. *Longitud Life Course Stud*. 2017 Oct 26;**8**(4):382–400.

112. Gauffin K, Hjern A, Vinnerljung B, Björkenstam E. Childhood Household Dysfunction, Social Inequality and Alcohol Related Illness in Young Adulthood. A Swedish National Cohort Study. *PLOS ONE*. 2016 Mar 18;**11**(3):e0151755.

113. McLaughlin KA, Koenen KC, Bromet EJ, et al. Childhood adversities and post-traumatic stress disorder: evidence for stress sensitisation in the World Mental Health Surveys. *Br J Psychiatry*. 2017 Nov;**211**(5):280–288.

114. Child Maltreatment: Facts at a Glance. :1.

115. Coddington RD. The significance of life events as etiologic factors in the diseases of children: I—A survey of professional workers. *J Psychosom Res*. 1972 Feb 1;**16**(1):7–18.

116. Raphael KG, Cloitre M, Dohrenwend BP. Problems of recall and misclassification with checklist methods of measuring stressful life events. *Health Psychol 1991*. 1991;**10**(1):62–74.

117. Walsh M, Srinathan SK, McAuley DF, et al. The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index. *J Clin Epidemiol*. 2014 Jun;**67**(6):622–628.

118. DiFazio D. Divorce and children with chronic disorders: diabetes as an exemplar. *J Pediatr Nurs*. 2013 Jun;**28**(3):311–312.

119. Rechenberg K, Grey M, Sadler L. Stress and Posttraumatic Stress in Mothers of Children With Type 1 Diabetes. *J Fam Nurs*. 2017 May 1;**23**(2):201–225.

120. Whittemore R, Jaser S, Chao A, Jang M, Grey M. Psychological Experience of Parents of Children With Type 1 Diabetes. *Diabetes Educ*. 2012 Jul;**38**(4):562–579.

121. Hardt J, Rutter M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *J Child Psychol Psychiatry*. 2004 Feb;**45**(2):260–273.

122. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiol Camb Mass*. 2004 Sep;**15**(5):615–625.

123. Nohr EA, Liew Z. How to investigate and adjust for selection bias in cohort studies. *Acta Obstet Gynecol Scand*. 2018;**97**(4):407–416.

124. Jacobsen TN, Nohr EA, Frydenberg M. Selection by socioeconomic factors into the Danish National Birth Cohort. *Eur J Epidemiol*. 2010 May;**25**(5):349–355.

125. Sandahl K, Nielsen LB, Svensson J, et al. Increased mortality in a Danish cohort of young people with Type 1 diabetes mellitus followed for 24 years. *Diabet Med J Br Diabet Assoc*. 2016 Mar 30;

126. Grey HR, Ford K, Bellis MA, Lowey H, Wood S. Associations between childhood deaths and adverse childhood experiences: An audit of data from a child death overview panel. *Child Abuse Negl*. 2019;**90**:22–31.

127. Savitz DA. Interpreting Epidemiologic Evidence: Strategies for Study Design & Analysis. Oxford University Press; [cited 2020 May 31]. Available from: http://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780195108408.001.0001/acprof-9780195108408

128. Forebyggelsespakke - Mental sundhed. [cited 2020 Apr 13]. Available from: https://www.sst.dk/da/udgivelser/2018/forebyggelsespakke-mental-sundhed

129. Chen E, Turiano NA, Mroczek DK, Miller GE. Association of Reports of Childhood Abuse and All-Cause Mortality Rates in Women. *JAMA Psychiatry*. 2016 Sep 1;**73**(9):920–927.

130. Oldrup H, Nationale forskningscenter for velfærd (Denmark), editors. Vold mod børn og unge. København: SFI--Det nationale forskningscenter for velfærd; 2011.

131. Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. *Lancet Diabetes Endocrinol*. 2018 Feb 1;**6**(2):122–129.

132. Schilling EA, Aseltine RH, Gore S. The impact of cumulative childhood adversity on young adult mental health: Measures, models, and interpretations. *Soc Sci Med*. 2008 Mar 1;**66**(5):1140–1151.

133. Anda RF, Felitti VJ, Bremner JD, et al. The enduring effects of abuse and related adverse experiences in childhood. *Eur Arch Psychiatry Clin Neurosci*. 2006 Apr 1;**256**(3):174–186.

134. Levenson J, Grady M. Childhood Adversity, Substance Abuse, and Violence: Implications for Trauma-Informed Social Work Practice. *J Soc Work Pract Addict*. 2016 Apr 2;**16**(1–2):24–45.

135. Liu RT. Childhood Adversities and Depression in Adulthood: Current Findings and Future Directions. *Clin Psychol Publ Div Clin Psychol Am Psychol Assoc*. 2017 Jun;**24**(2):140–153.

136. Wiersma JE. Childhood Adversity and Depression. *J Clin Psychiatry*. 2015 Jul 22;**76**(7):906–907.

137. Björkenstam C, Kosidou K, Björkenstam E. Childhood adversity and risk of suicide: cohort study of 548 721 adolescents and young adults in Sweden. *BMJ*. 2017 Apr 19;j1334.

138. Afifi TO, Enns MW, Cox BJ, Asmundson GJG, Stein MB, Sareen J. Population Attributable Fractions of Psychiatric Disorders and Suicide Ideation and Attempts Associated With Adverse Childhood Experiences. *Am J Public Health*. 2008 May 1;**98**(5):946–952.

139. Su S, Jimenez MP, Roberts CTF, Loucks EB. The Role of Adverse Childhood Experiences in Cardiovascular Disease Risk: a Review with Emphasis on Plausible Mechanisms. *Curr Cardiol Rep*. 2015 Aug 20;**17**(10):88.

140. Brent DA, Silverstein M. Shedding Light on the Long Shadow of Childhood Adversity. *JAMA J Am Med Assoc*. 2013 May 1;**309**(17):1777–1778.

Studies I-III

Study I

Cohort profile: the DANish LIFE course (DANLIFE) cohort, a prospective register-based cohort of all children born in Denmark since 1980

Bengtsson J, Dich N, Rieckmann A, Rod NH

BMJ Open 2019 Sep 20;**9**(9):e027217.

Study II

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

Bengtsson J, Byberg S, Carstensen B, et al. Accumulation of childhood adversities and type 1 diabetes risk: a register-based cohort study of all children born in Denmark between 1980 and 2015. *Int J Epidemiol*. 2020 Oct 1;**49**(5):1604–1613.

Study III

Trajectories of childhood adversity and type 1 diabetes: a nationwide study of 1 million children

Bengtsson J, Rieckmann A, Carstensen B, Svensson J, Jørgensen ME, Rod NH. Trajectories of Childhood Adversity and Type 1 Diabetes: A Nationwide Study of One Million Children. *Diabetes Care*. 2021 Mar;**44**(3):740–747.