

# Trajectories of childhood adversity and mortality in early adulthood: a population-based cohort study



Naja H Rod, Jessica Bengtsson, Esben Budtz-Jørgensen, Clara Clipet-Jensen, David Taylor-Robinson, Anne-Marie Nybo Andersen, Nadya Dich, Andreas Rieckmann

## Summary

**Background** Childhood is a sensitive period with rapid brain development and physiological growth, and adverse events in childhood might interfere with these processes and have long-lasting effects on health. In this study, we aimed to describe trajectories of adverse childhood experiences and relate these to overall and cause-specific mortality in early adult life.

**Methods** For this population-based cohort study, we used unselected annually updated data from Danish nationwide registers covering more than 1 million children born between 1980 and 1998. We distinguished between three different dimensions of childhood adversities: poverty and material deprivation, loss or threat of loss within the family, and aspects of family dynamics such as maternal separation. We used a group-based multi-trajectory clustering model to define the different trajectories of children aged between 0 and 16 years. We assessed the associations between these trajectories and mortality rates between 16 and 34 years of age using a Cox proportional hazards model and an Aalen hazards difference model.

**Findings** Between Jan 1, 1980 and Dec 31, 2015, 2 223 927 children were included in the Danish Life Course cohort. We excluded 1 064 864 children born after 1998, 50 274 children who emigrated before their 16th birthday, and 11 161 children who died before their 16th birthday, resulting in a final sample of 1 097 628 children. We identified five distinct trajectories of childhood adversities. Compared with children with a low adversity trajectory, those who had early-life material deprivation (hazard ratio 1·38, 95% CI 1·27–1·51), persistent deprivation (1·77, 1·62–1·93), or loss or threat of loss (1·80, 1·61–2·00) had a moderately higher risk of premature mortality. A small proportion of children (36 081 [3%]) had multiple adversities within all dimensions and throughout the entire childhood. This group had a 4·54 times higher all-cause mortality risk (95% CI 4·07–5·06) than that of children with a low adversity trajectory, corresponding to 10·30 (95% CI 9·03–11·60) additional deaths per 10 000 person-years. Accidents, suicides, and cancer were the most common causes of death in this high adversity population.

**Interpretation** Almost half of Danish children in our study experienced some degree of adversity, and this was associated with a moderately higher risk of mortality in adulthood. Among these, a small group of children had multiple adversities across social, health, and family-related dimensions. This group had a markedly higher mortality risk in early adulthood than that of other children, which requires public health attention.

**Funding** None.

**Copyright** © 2020 Elsevier Ltd. All rights reserved.

## Introduction

Childhood is a sensitive period in life, with rapid bodily, neurological, and cognitive development; adversity in early childhood might lead to lifelong impairments in health.<sup>1</sup> Childhood adversities cover a broad range of factors, from economic hardship to an unfavourable family environment. Even in countries with a high level of social security, almost one in ten children have more than three childhood adversities, such as bereavement, poverty, parental divorce, or parental alcohol abuse, between early infancy and late adolescence.<sup>2</sup>

Several studies have documented health effects of childhood adversity, including increased risk of premature death.<sup>3,4</sup> However, the focus on so-called risk syndemics emphasises the importance of understanding the complex interaction of biosocial risks over the

lifecourse.<sup>5</sup> Therefore, to understand the health consequences of childhood adversities, we need larger studies that can capture the clustering of multiple stressors in vulnerable groups of children over time. This is particularly important because the biological stress response system and coping mechanisms seem more likely to break down when confronted with multiple stressors over longer periods of time.<sup>6</sup>

In one of the few prospective studies to assess premature mortality related to multiple severe childhood adversities, Kelly-Irving and colleagues showed that the accumulation of adverse childhood experiences was associated with a higher mortality risk.<sup>7</sup> However, attrition could be a problem in this and other longitudinal studies, because individuals with continued participation over many years might be different from those who leave the cohort. This

*Lancet* 2020; 396: 489–97

See [Comment](#) page 449

Section of Epidemiology (Prof N H Rod PhD, J Bengtsson MS, C Clipet-Jensen MS, Prof D Taylor-Robinson PhD, Prof A-M N Andersen PhD, N Dich PhD, A Rieckmann PhD) and Section of Biostatistics (E Budtz-Jørgensen PhD), Department of Public Health, University of Copenhagen, Copenhagen, Denmark; and Institute of Population Health Sciences, University of Liverpool, Liverpool, UK (Prof D Taylor-Robinson)

Correspondence to: Prof Naja Hulvej Rod, Section of Epidemiology, Department of Public Health, University of Copenhagen, 1014 Copenhagen, Denmark [nahuro@sund.ku.dk](mailto:nahuro@sund.ku.dk)

### Research in context

#### Evidence before this study

We did a comprehensive literature review in PubMed with no language restrictions from inception to Sept 5, 2019, using the search terms “(“adverse childhood events” or “poverty” or “bereavement” or “adversity” or “stressors” or [life change events]) and ([mortality] or “premature mortality” or “death” or “suicide”)). We identified articles addressing childhood adversity and its effect on mortality in adult life. The health and mortality effects of childhood adversities might have been severely underestimated because these previous studies have mainly focused on the effects of single stressors or have been limited by design (recall bias or selective participation). Additionally, we established an interdisciplinary expert panel consisting of experts in child health, child psychology, medicine, statistics, and epidemiology to provide a strong theoretical and methodological foundation for our study.

#### Added value of this study

We used unselected annually updated nationwide register data covering more than 1 million Danish children to assess the complex and time-varying nature of childhood adversities by using the full range of information available on duration and timing of childhood adversities. Trajectories of childhood adversity across social, health, and family-related dimensions were identified from these high-resolution data. About half of

the children in our study had none or few isolated events, and the mortality rate in early adulthood was lowest in this group. A small subset of children (3%) had high and accelerating numbers of adversities across their entire childhood. These children had a 4-times higher mortality risk in early adult life than those in the low adversity group, which accounted for a substantial number of extra deaths. The elevated mortality was most pronounced for suicides and accidents, but a higher risk of somatic mortality, including cancer, was also observed.

#### Implications of all the available evidence

From a policy perspective, it is striking that such clear associations between childhood adversities and premature mortality are found even in the context of the Danish social security system, which promotes economic stability for families. Presumably, childhood adversities have even stronger mortality effects in societies with less social security. Our findings indicate the crucial importance of broader structural public health initiatives aimed at addressing the underlying social drivers of childhood adversities, including prevention of childhood poverty and social inequalities in health. Additionally, addressing the cumulative risks associated with multiple childhood adversities across social and family-related dimensions might help to identify vulnerable children who would benefit from targeted support.

potential selection bias might affect the assessment of the health effects of childhood adversities.<sup>8</sup> Concern has also been raised about the unhelpful conflation of conceptually different risks when considering childhood adversity, for example socioeconomic conditions and factors such as childhood abuse.<sup>9</sup>

To advance the existing literature, the aim of our study was twofold. First, we aimed to describe distinct trajectories of childhood adversity using a unique unselected cohort constructed from nationwide registers covering more than 1 million Danish children. Second, we aimed to relate these trajectories to overall and cause-specific mortality in early adult life. We acknowledged the complexity and time-varying nature of childhood adversities by incorporating the full range of information on duration and timing of childhood adversities based on annually updated data. Additionally, we aimed to distinguish between three different dimensions of adverse childhood experiences: material deprivation, loss or threat of loss within the family, and family dynamics.

### Methods

#### The Danish Life Course (DANLIFE) cohort

We used data from DANLIFE, a Danish register-based life course cohort study based on continuously updated information from nationwide registers.<sup>2</sup> Access to Danish registers is granted by Statistics Denmark and the Danish

Health Data Authorities in an anonymous and secure form. The DANLIFE cohort is registered with the Danish Data Protection Agency (number 514-0262/18-3000) and all data linkage is done according to Danish law. Every Danish citizen is given a unique personal identification number at birth, which allows exact individual-level linkage between registries in Denmark.<sup>10</sup> All children born in Denmark in 1980 or later have been included in the DANLIFE cohort, which comprises 2 223 927 children born between Jan 1, 1980 and Dec 31, 2015. To ensure that we followed up individuals with data covering their entire childhood (0 to 16 years of age), we excluded children born after 1998, those who died before their 16th birthday, and those who emigrated before their 16th birthday. The DANLIFE cohort is an open cohort, which means that we have continuously included new children born in Denmark from 1980 and onwards into the DANLIFE cohort. Therefore, although we were able to follow up the oldest children (ie, those born in 1980) for 18 years, those children born later could only be followed up for a shorter time span.<sup>2</sup>

#### Childhood adversities

The linkage between child, parents, and siblings in the registers enables the measurement of a range of childhood adversities; for this study, we have included 12 childhood adversities (table 1). A panel of experts in stress, child health, and child psychology decided on

the three predefined dimensions of childhood adversity after a thorough investigation of the literature. These dimensions included material deprivation (ie, family poverty and parental long-term unemployment), loss or threat of loss within the family (ie, parental severe somatic illness, sibling severe somatic illness, and death of a parent or a sibling), and family dynamics (ie, maternal separation, being placed in foster care, parental psychiatric illness, sibling psychiatric illness, and parental alcohol or drug abuse). Direct information on child abuse or neglect or domestic violence was unfortunately not available in the registers.

### Premature mortality

The study participants were followed up from their 16th birthday until emigration, death, or end of follow-up on Dec 31, 2014; therefore, they were followed up between ages 16–34 years. Individuals emigrating during follow-up were censored at the date of emigration. Cause-specific mortality was identified in the Danish Register of Causes of Death. Cancers, accidents, and suicides were the three most common causes of death in this age group. Cause-specific mortality was thus divided into cancers (International Classification of Diseases 10th edition [ICD-10] codes C00 to C97), accidents (ICD-10 codes V01 to X59), suicides (ICD-10 codes X60 to X84) and others (remaining ICD-10 codes for causes of death).

### Covariates

Covariates included sex, birthweight (g), household's highest education at the time of birth (defined as low [<10 years], middle [10–12 years], and high [>12 years]), origin of parents (predominantly European descent [Europe, North America, Australia, and New Zealand] or non-European descent, if at least one parent has another nationality), and parental age at time of birth (<20 years, 20–30 years, and >30 years).

### Statistical analysis

We used a group-based multi-trajectory model to determine trajectory groups of adversities based on the three prespecified dimensions of material deprivation, loss or threat of loss, and family dynamics. This approach allowed us to incorporate the full range of information from the high-resolution longitudinal data. We used the package TRA for Stata (version 14.2) to fit between one and eight trajectory clusters using zero-inflated Poisson regressions with a cubic trajectory function, yielding a probability for each individual of being in each trajectory group<sup>11</sup> (appendix 1, pp 1–3). We visually judged that five trajectory groups divided the individuals optimally, because most individuals had a very high probability of belonging to a specific group, while still allowing for a reasonable number of trajectory groups (a comparison of trajectories with 1 to 8 groups is shown in appendix 2, pp 1–8).

	Definition	Registers
<b>Material deprivation</b>		
Family poverty	One count per year of life when the family income is lower than 50% of the median national family income	The Income Statistics Register
Long-term unemployment	One count per year of life for each parent being unemployed for at least 12 months	The Integrated Database for Labour Market Affiliation
<b>Loss or threat of loss</b>		
Death of a parent	One count in the year a parent dies	The Danish Civil Registration System
Death of a sibling	One count for each death of a sibling	The Danish Civil Registration System
Parental somatic illness	One count per year of life for each parent diagnosed with one of the illnesses related to mortality included in the Charlson comorbidity index	The Danish National Patient Register
Sibling somatic illness	One count per year of life for each sibling diagnosed with one of the seven most common somatic illnesses related to mortality in children aged 0–18 years in Denmark: malignant neoplasm, congenital anomalies of the heart and circulatory system, congenital anomalies of the nervous system, cerebral palsy, epilepsy, cardiomyopathy, and congenital disorders of lipid metabolism	The Danish National Patient Register
<b>Family dynamics</b>		
Foster care	One count per year of life overlapping with a calendar year in which the child was registered as placed in out-of-home care	The Register of Support for Children and Adolescents
Parental psychiatric illness	One count per year of life for each parent with a hospital admission with a diagnosis related to psychiatric illness (excluding main diagnoses related to alcohol and drug abuse)	The Danish Psychiatric Central Research Register
Sibling psychiatric illness	One count per year of life for each sibling with a hospital admission with a diagnosis related to psychiatric illness	The Danish Psychiatric Central Research Register
Parental alcohol abuse	One count per year of life for each parent diagnosed with an illness related to alcohol abuse or receiving a prescription of a drug used in treatment of alcohol addiction	The Danish Psychiatric Central Research Register, the Danish National Patient Register, and the Danish National Prescription Registry
Parental drug abuse	One count per year of life for each parent diagnosed with an illness related to drug abuse or receiving a prescription of drugs used in treatment of drug addiction	The Danish Psychiatric Central Research Register, the Danish National Patient Register, and the Danish National Prescription Registry
Maternal separation	One count per year of life overlapping with a calendar year in which the mother was separated from a partner	The Danish Civil Registration System
Each adversity is defined under the dimension in which it is included.		
<b>Table 1: Dimensions and definitions of adverse childhood experiences</b>		

We first estimated the overall cumulative mortality for each trajectory group. We also estimated age-adjusted hazard ratios (HR) and 95% CIs for all-cause mortality in a Cox proportional hazards model with the trajectory groups as exposure variable. Age was used as the underlying time scale. The assumption of proportional hazards was met. We estimated hazard differences using Aalen's additive hazards model, in which the hazard is modelled as a linear function of the explanatory variables. This approach provided an estimate of the absolute burden of excess mortality in one trajectory group compared with that of another. The assumption of time-invariant

See [Online](#) for appendix 1

See [Online](#) for appendix 2

associations was met. We also showed the cumulative mortality decomposed into the most common causes of death for each trajectory group using a multistate survival analysis accounting for competing risks. All analyses were stratified by sex in a supplementary analysis.

Although our aim was to describe multi-dimensional patterns of childhood adversities and how they relate to mortality patterns, an obvious next question was whether these associations are driven by other early-life risk factors. Family adversity could affect the health of children already in utero, and birthweight was thus perceived as

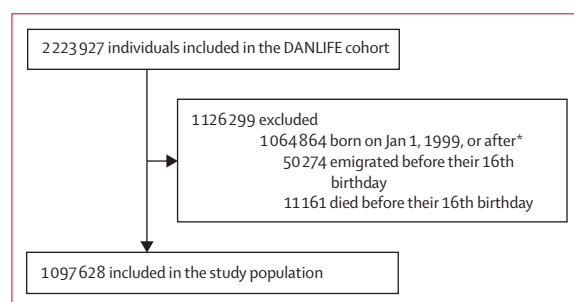
a potential mediator and not included in the main analyses. Additionally, parental education, parental origin, and teenage pregnancies are highly correlated with material deprivation, making it difficult to disentangle causes from effects. To assess the effect of these factors, we also ran a supplementary analysis adjusting for these variables.

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

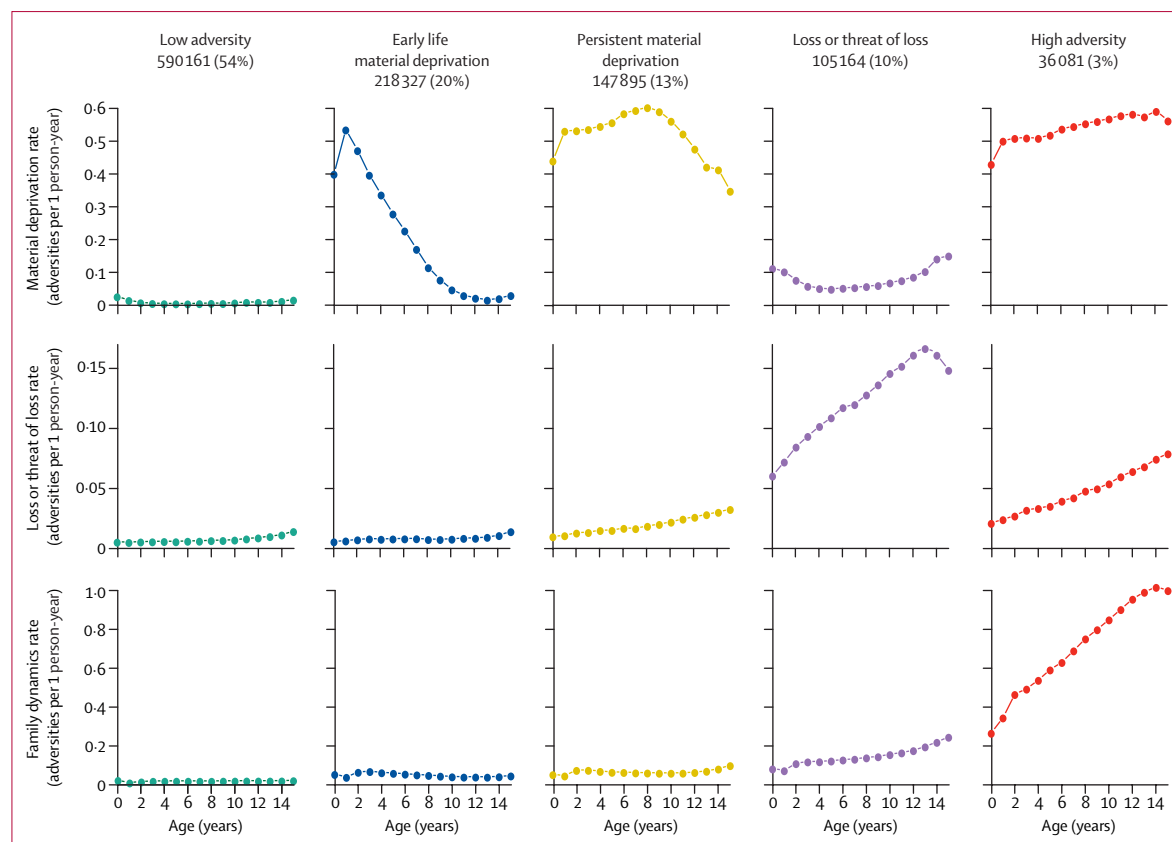
### Results

Between Jan 1, 1980 and Dec 31, 2015, 2 223 927 children were included in the DANLIFE cohort. We excluded 1 064 864 children born after 1998, 50 274 children who emigrated before their 16th birthday, and 11 161 children who died before their 16th birthday (figure 1). Almost half of these deaths (5051 [45%]) were neonatal deaths (within the first 28 days of life), and 7860 (70%) of the deaths occurred in children younger than 1 year. These exclusions resulted in a final sample of 1 097 628 children.



**Figure 1: Study flow chart**

\*We could not follow-up these children to their 16th birthday and assign them to a trajectory group.



**Figure 2: Estimated trajectory groups of childhood adversities among Danish children**

1 097 628 Danish children were divided into the five estimated trajectory groups of childhood adversities.

We identified five distinct trajectory groups on the basis of combinations of subtrajectories within the three predefined dimensions (figure 2). The trajectory group of low adversity comprised 590 161 (54%) of the children. This group was characterised by a very low rate of adversities in all dimensions, meaning that some children in the trajectory might have experienced a few isolated adversities, but the annual rate was very low. The trajectory group of early-life material deprivation comprised 218 327 (20%) of the children. This group was characterised by a high annual rate of material deprivation during the first 4–5 years of life, after which the rate of material deprivation became very low. The annual rates of adversities in the other two dimensions were very low. The trajectory group of persistent material deprivation comprised 147 895 (13%) of the children. This group was characterised by a high annual rate of material deprivation during the entire childhood, but had a low rate of adversities in the other two dimensions. The trajectory group of loss or threat of loss comprised 105 164 (10%) of the children. This group was characterised by a moderate to high and increasing annual rate of loss or threat of loss during the course of childhood, while the rates of adversities in the two other dimensions remained low. The trajectory group of high adversity comprised 36 081 (3%) of the children. This group was characterised by a high and increasing annual rate of adversities in all three dimensions. The annual rate of adversities was especially high and increasing in the family dynamics dimension, especially during adolescence, when children on average had almost one adversity every year.

In our cohort, the proportion of individuals with low birthweight was lowest in the low adversity group and highest in the high adversity group (table 2). We also observed a clear education gradient, with 8.8% of children in the low adversity group being born into a household with low education compared with 54.1% of children in the high adversity group. Children with persistent material deprivation were more often born to parents of non-European origin compared with those of all other groups. Teenage mothers are uncommon in Denmark and only 1.0% of children in the low adversity group were born to teenage mothers, whereas this proportion was markedly higher among those in the persistent material deprivation group (7.3%) and in the high adversity group (10.7%). The proportion of teenage fathers is lower than that of teenage mothers but follows a similar pattern.

We recorded 3827 deaths during a mean follow-up time of 8.6 years (SD 5.3), ranging from 1 day to 18 years. 69 412 individuals emigrated during follow-up. As expected, the crude mortality rate was low at this young age, with only 2.9 deaths per 10 000 person-years in the low adversity group (figure 3). Compared with that of the low adversity group, the mortality rate was higher in all other groups. The most pronounced

difference was a 4.54 times higher risk of premature mortality (95% CI 4.07–5.06) in the high adversity group compared with that in the low adversity group, corresponding to 10.30 (95% CI 9.03–11.60) additional deaths per 10 000 person-years. The relative effects were similar between men and women, but the absolute effects were larger in men because of an overall higher mortality rate in young men than in young women (appendix 2, pp 9–10). For example, being in the high adversity group was associated with 13.70 (95% CI 11.70–15.70) additional deaths in men and 6.11 (4.66–7.56) additional deaths per 10 000 person-years in women compared with being in the low adversity group. In a subpopulation with full information (1043 495 individuals), we adjusted for sex, birthweight, household education, parental origin, and parental age at birth (appendix 2, p 11). This adjustment resulted in a slight attenuation of the risk estimates when comparing high adversity versus low adversity groups (unadjusted HR 4.74, 95% CI 4.22–5.32 vs adjusted HR 3.82,

	Low adversity (n=590 161)	Early-life material deprivation (n=218 327)	Persistent material deprivation (n=147 895)	Loss or threat of loss (n=105 164)	High adversity (n=36 081)
<b>Sex</b>					
Boys	302 800 (51.3%)	111 655 (51.1%)	75 654 (51.2%)	53 511 (50.9%)	19 560 (54.2%)
Girls	287 361 (48.7%)	106 672 (48.9%)	72 241 (48.8%)	51 653 (49.1%)	16 521 (45.8%)
<b>Birthweight, g</b>					
<2500	24 340 (4.1%)	10 933 (5.0%)	8290 (5.6%)	6725 (6.4%)	3619 (10.0%)
2500–4500	543 076 (92.0%)	200 603 (91.9%)	135 337 (91.5%)	94 818 (90.2%)	31 552 (87.4%)
>4500	15 661 (2.7%)	4763 (2.2%)	2744 (1.9%)	2410 (2.3%)	470 (1.3%)
Missing	7084 (1.2%)	2028 (0.9%)	1524 (1.0%)	1211 (1.2%)	440 (1.2%)
<b>Highest household education</b>					
Low	51 666 (8.8%)	49 768 (22.8%)	49 489 (33.5%)	22 524 (21.4%)	19 534 (54.1%)
Medium	288 448 (48.9%)	120 351 (55.1%)	71 179 (48.1%)	52 615 (50.0%)	12 654 (35.1%)
High	247 506 (41.9%)	47 377 (21.7%)	26 100 (17.6%)	29 570 (28.1%)	3497 (9.7%)
Missing	2541 (0.4%)	831 (0.4%)	1127 (0.8%)	455 (0.4%)	396 (1.1%)
<b>Parental origin</b>					
Other origins	7440 (1.3%)	9233 (4.2%)	13 265 (9.0%)	3864 (3.7%)	1106 (3.1%)
Predominantly European*	581 705 (98.6%)	209 054 (95.8%)	134 580 (91.0%)	101 275 (96.3%)	34 963 (96.9%)
Missing	1016 (0.2%)	40 (<0.1%)	50 (<0.1%)	25 (<0.1%)	12 (<0.1%)
<b>Maternal age, years</b>					
<20	5832 (1.0%)	8184 (3.7%)	10 774 (7.3%)	3671 (3.5%)	3847 (10.7%)
20–30	394 592 (66.9%)	162 869 (74.6%)	105 764 (71.5%)	68 285 (64.9%)	24 655 (68.3%)
>30	189 214 (32.1%)	47 261 (21.6%)	31 338 (21.2%)	33 195 (31.6%)	7573 (21.0%)
Missing	523 (0.1%)	13 (<0.1%)	19 (<0.1%)	13 (<0.1%)	6 (<0.1%)
<b>Paternal age, years</b>					
<20	1281 (0.2%)	1649 (0.8%)	2378 (1.6%)	784 (0.7%)	838 (2.3%)
20–30	280 555 (47.5%)	123 566 (56.6%)	81 123 (54.9%)	48 243 (45.9%)	18 239 (50.6%)
>30	292 420 (49.5%)	82 975 (38.0%)	57 344 (38.8%)	52 357 (49.8%)	13 009 (36.1%)
Missing	15 905 (2.7%)	10 137 (4.6%)	7050 (4.8%)	3780 (3.6%)	3995 (11.1%)

Data are n (%). \*Includes Europe, North America, Australia, and New Zealand.

**Table 2: Background characteristics of the cohort at time of birth by the five estimated trajectory groups**

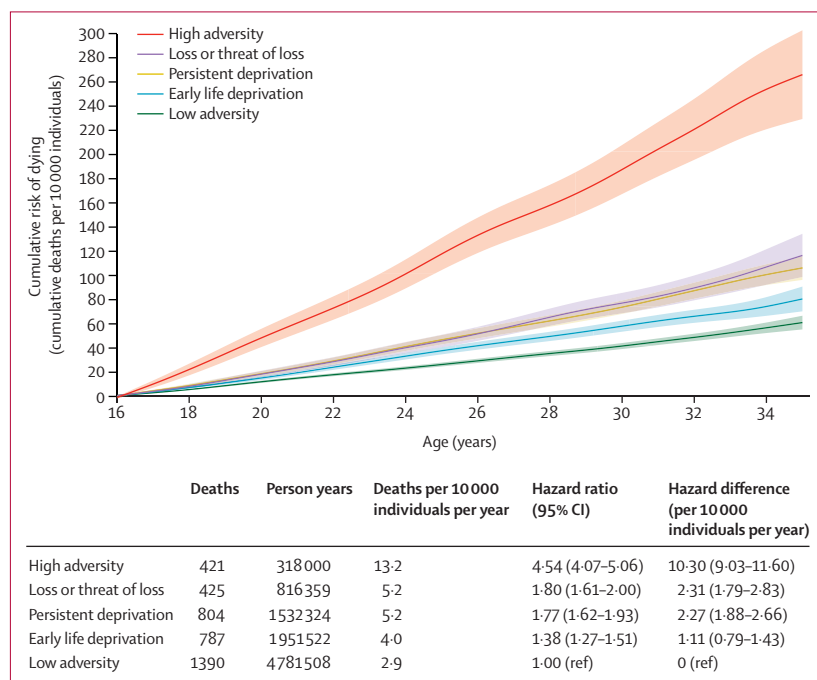


3.38–4.32). The risk estimates were similar in the other groups before and after adjustment.

Of the 3827 deaths observed, the most common cause was accidents (1433 [37%] deaths). The mortality

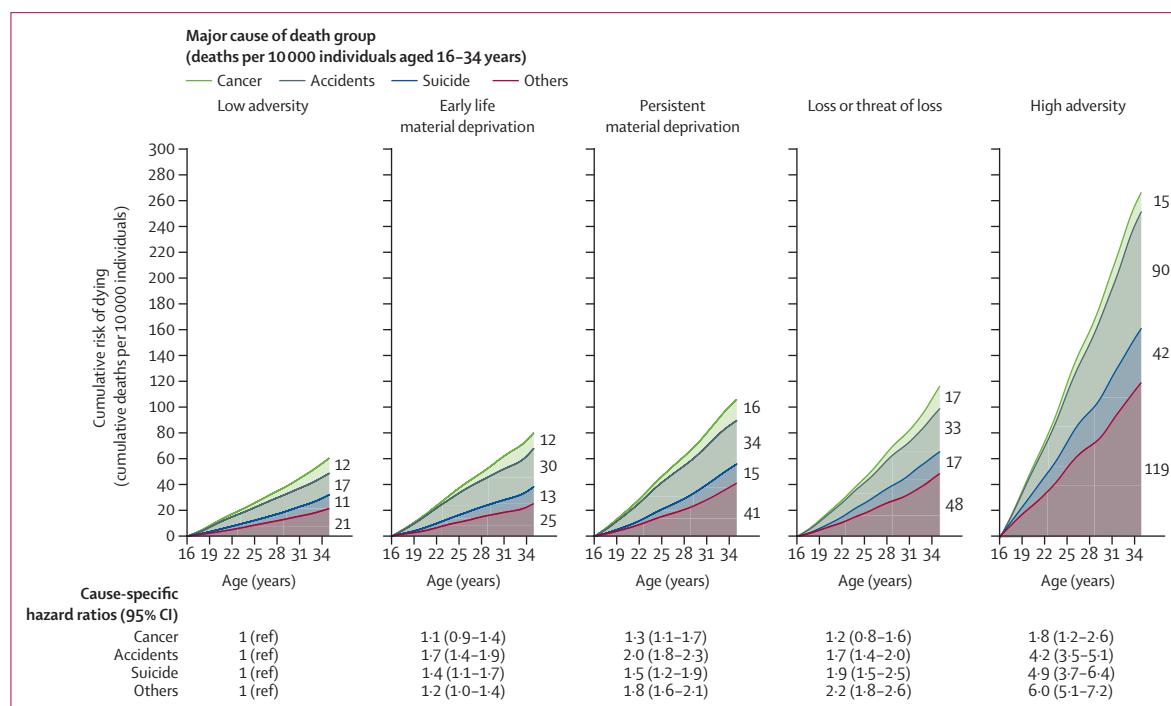
patterns for deaths due to accidents were similar to that of overall mortality, with a moderately higher mortality risk in the early-life material deprivation group, the persistent material deprivation group, and the loss or threat of loss group compared with that of the low adversity group (figure 4). As with overall mortality, we observed a markedly higher risk of death due to accidents in the high adversity group compared with that in the low adversity group, corresponding to 3.3 (95% CI 2.6–4.1) extra deaths due to accidents per 10000 person-years (figure 4).

586 (15%) deaths were due to suicide, with a very low risk among children in the low adversity group and a moderately higher risk among children in the early-life material deprivation, persistent deprivation, and loss or threat of loss groups. Again, we observed a markedly higher risk of suicide among individuals in the high adversity group compared with that in the low adversity group, corresponding to 1.8 (95% CI 1.3–2.3) extra deaths due to suicide per 10000 person-years (figure 4). 491 (13%) deaths were due to cancer. Although the differences between groups were smaller than those with other causes of death, we still observed a moderately higher risk of cancer mortality in the persistent material deprivation group and the high adversity group compared with that in the low adversity group (figure 4). The remaining 1317 (34%) deaths were due to a combination of other causes and, although the patterns were similar to those for overall mortality, cause-specific comparisons were difficult to make because of the small numbers of deaths per cause. The two most common causes of death among the



**Figure 3: Cumulative all-cause mortality among Danish children**

1 097 628 Danish children were divided into the five estimated trajectory groups of childhood adversities.



**Figure 4: Cumulative cause-specific mortality among Danish children**

1 097 628 Danish children were divided into the five estimated trajectory groups of childhood adversities.

remaining were diseases of the nervous system (191 deaths) and circulatory system (178 deaths; appendix 2, p 12).

## Discussion

In an unselected sample of more than 1 million Danish children, we identified five distinct trajectories of childhood adversities. About half of the children had none or few isolated events, and the mortality rate in early adulthood was lowest in this group. However, a substantial proportion of children (about 45%) had childhood adversities in specific dimensions, such as material deprivation or loss in the family. These children had a moderately higher mortality risk in early adult life than that of children who had few or no adversities. A small proportion of children (3%) had a high and increasing rate of adversities in all three dimensions during their entire childhood. This group of disadvantaged children had a more than 4 times higher risk of premature mortality in early adult life than that of children who had few or no adversities. Accidents and suicides were the most common causes of death and the mortality patterns for these events followed that of overall mortality. Cancer was the third most common cause of death and, although less pronounced, a moderately higher risk of cancer mortality was found in children in the high adversity group compared with that in the low adversity group.

Our findings corroborate several smaller studies<sup>7,12–17</sup> We add to this literature by using high-resolution data to distinguish between different dimensions of childhood adversities and by studying premature deaths in young adulthood. We documented how the accumulation and interrelation between these dimensions are important to fully understand the mortality risk associated with childhood adversities. Our findings are pertinent to the ongoing discussion in life-course epidemiology about sensitive periods versus accumulation of risk.<sup>18</sup> Using annually repeated measures, which cover entire childhoods, we have shown that these two concepts are highly intertwined, and that they cannot be understood independently of each other. For example, if we had focused solely on material deprivation in early childhood, children in three of the five identified trajectory groups (ie, early-life material deprivation, persistent deprivation, and high adversity groups) would have been lumped into one group. This would have hidden the very different mortality risks we observed for children after each of these trajectories.

The concept of syndemics has been taken up in the medical literature as a conceptual framework for understanding intertwined and accumulated effects of social and biomedical factors, and how they shape distributions of diseases across populations.<sup>5</sup> Our results point to a potential childhood adversity syndemic in a small subset of children with high and accelerating adversities across various dimensions, ending in a negative biosocial feedback loop associated with a markedly

higher mortality risk in early adult life. Although we have studied the dynamic interplay between different types of adversities and their effects on mortality, the underlying interacting and mutually reinforcing social and health conditions generating this higher mortality need further investigation.

Our study population is nested within a social welfare system with universal child care and a social security system that promotes economic stability for families. It is striking that such clear associations between childhood adversities and premature mortality are found even within this social structure, and stronger effects might be found in societies with less social security. Investigation into how effects of underlying structures materialise, and whether the trajectories through childhood adversity dimensions are mutually causal, synergistically interacting, or serially causal for the effect on premature mortality needs to be further explored.<sup>19</sup>

An eco-biodevelopmental framework underscored how early experiences can leave a lasting signature on emerging brain architecture and long-term health.<sup>1</sup> This theoretical framework highlights the fundamental importance of the early years of life, when the brain is particularly sensitive to elevated levels of stress hormones, which can interfere with its developing architecture. Shonkoff and colleagues argue that toxic stress might produce physiological disruptions in the development of the body's response system and affect the developing brain, immune, cardiovascular, and metabolic systems, with associated long-lasting effects on health.<sup>1</sup> The child's intrafamilial environment is important for coping and learning, and children exposed to a cumulative toxic stress might also be more likely than other children to adopt unhealthy behaviours such as excessive alcohol drinking or drug abuse,<sup>20,21</sup> which might partly explain the higher risk of accidents observed in the high adversity group compared with that of the low adversity group.

Accidents and suicides accounted for the majority of deaths in our study, and extensive literature exists on the association between exposure to childhood adversities and suicide, which supports our findings.<sup>22,23</sup> By contrast, no large studies exist on childhood events and accidents, to the best of our knowledge. We also add to this literature by showing that childhood adversities accumulate over time and across social, health, and family-related dimensions, which indicates that multifaceted interventions are needed to address the problem.

Cancer was the third most common cause of death in our study. We found a moderately higher risk of cancer mortality in the persistent material deprivation and high adversity groups compared with that in the low adversity group. Some studies have addressed the effect of single major stressors, such as bereavement, on cancer mortality and they generally found no overall effect or a very small effect of childhood adversities on cancer mortality risk.<sup>24</sup> The effect of childhood adversities on the incidence and survival of various subtypes of cancer with different

underlying causes needs to be addressed in future studies.

Our study had several strengths and limitations. Relying on register-based information ensured a very large sample size and prevented problems with selective inclusion and exclusion from the cohort. However, only a selection of childhood adversities were available in the registers. For example, we did not have direct information on child physical or sexual abuse, which is also associated with higher mortality.<sup>25</sup> Likewise, we did not have direct information on domestic violence and child neglect. Although we lacked this kind of information, the very severe cases are likely to have been captured by information on foster care. Furthermore, we derived information on alcohol abuse from hospitalisations and medication use related to alcohol abuse, but it is well known that most cases of alcohol abuse are never registered. A similar situation occurred for several other indicators, where we only caught the tip of the iceberg. Maternal separation and parental psychiatric illness are used as indicators of family dynamics, whereas a home environment with a high conflict level, or even violence, would not necessarily have been captured by these measures. By using many and repeated indicators of childhood adversities, we hope to have captured some general patterns, but we might have underestimated the true effect of childhood adversities to some degree.

We excluded children who died before the age of 16 years. Most of these children died within the first year of life because of neonatal complications, congenital anomalies, or preterm birth, among other causes. The drivers of these deaths are mainly established before the child is born and constitute a related, but different, question that is not within the scope of this study. Although the child mortality rate is very low in Denmark, some children die between 1 and 16 years of age, and those deaths might be related to childhood adversities. For example, in a study published in 2019, Grey and colleagues reported that the experience of four or more childhood adversities versus none was associated with increased child mortality.<sup>26</sup> Therefore, we might have underestimated the effect of childhood adversities on mortality by excluding childhood mortality.

In our study, we have identified five distinct trajectories of childhood adversity that are associated with mortality risk in early adult life. A small group of children had a high and accelerating rate of adversities across intertwined dimensions of deprivation, loss, and family dynamics during the entire childhood, leading to a very high mortality risk in early adulthood, particularly from suicide and accidents, but from somatic conditions as well, such as cancer. These findings also suggest a substantial burden of underlying morbidity that will probably translate into a substantial public health problem as the cohort ages. Our findings indicate the crucial importance of broader structural public health

initiatives, as well as help to identify vulnerable children who would benefit from targeted support.

#### Contributors

NHR, AR, DT-R, ND, and A-MNA conceived the idea and designed the study. JB did the data linkage and data cleaning for DANLIFE. AR, EB-J, and CC-J did the trajectory analyses. NHR, JB, EB-J, and AR had access to all the data. NHR wrote the first draft of the manuscript. All authors discussed the results and contributed to the final manuscript. All authors have seen and approved of the final text.

#### Declaration of interests

DT-R reports grants from the Medical Research Council during the conduct of the study and outside the submitted work. All other authors report no competing interests.

#### Acknowledgments

DT-R is funded by the Medical Research Council with a Clinician Scientist Fellowship (MR/P008577/1). We thank Dr Ulrik Becker for valuable advice on the use of Danish registers regarding alcohol and drug misuse.

#### References

- Shonkoff JP, Garner AS, Siegel BS, et al. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics* 2012; **129**: e232–46.
- Bengtsson J, Dich N, Rieckmann A, Rod NH. Cohort profile: the DANish LIFE course (DANLIFE) cohort. *BMJ Open* 2019; **9**: e027217.
- Palusci VJ. Adverse childhood experiences and lifelong health. *JAMA Pediatr* 2013; **167**: 95–96.
- 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; **2**: e356–66.
- Singer M, Bulled N, Ostrach B, Mendenhall E. Syndemics and the biosocial conception of health. *Lancet* 2017; **389**: 941–50.
- Evans GW, Li D, Whipple SS. Cumulative risk and child development. *Psychol Bull* 2013; **139**: 1342–96.
- Kelly-Irving M, Lepage B, Dedieu D, et al. Adverse childhood experiences and premature all-cause mortality. *Eur J Epidemiol* 2013; **28**: 721–34.
- Hawkes D, Plewis I. Modelling non-response in the National Child Development Study. *J R Stat Soc Ser A Stat Soc* 2006; **169**: 479–91.
- Taylor-Robinson DC, Straatmann VS, Whitehead M. Adverse childhood experiences or adverse childhood socioeconomic conditions? *Lancet Public Health* 2018; **3**: e262–63.
- Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014; **29**: 541–49.
- Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. *Stat Methods Med Res* 2018; **27**: 2015–23.
- Bellis MA, Hughes K, Leckenby N, Hardcastle KA, Perkins C, Lowey H. Measuring mortality and the burden of adult disease associated with adverse childhood experiences in England: a national survey. *J Public Health* 2015; **37**: 445–54.
- Gao M, Brännström L, Almquist YB. Exposure to out-of-home care in childhood and adult all-cause mortality: a cohort study. *Int J Epidemiol* 2017; **46**: 1010–17.
- Campbell CD, Lee JZ. Long-term mortality consequences of childhood family context in Liaoning, China, 1749–1909. *Soc Sci Med* 2009; **68**: 1641–48.
- Juon HS, Ensminger ME, Feehan M. Childhood adversity and later mortality in an urban African American cohort. *Am J Public Health* 2003; **93**: 2044–46.
- van Dijk IK, Janssens A, Smith KR. The long harm of childhood: childhood exposure to mortality and subsequent risk of adult mortality in Utah and the Netherlands. *Eur J Popul* 2018; **35**: 851–71.
- Yu Y, Liew Z, Cnattingius S, et al. Association of mortality with the death of a sibling in childhood. *JAMA Pediatr* 2017; **171**: 538–45.
- Hardy R, Tilling K. Commentary: the use and misuse of life course models. *Int J Epidemiol* 2016; **45**: 1003–05.
- Tsai AC. Syndemics: a theory in search of data or data in search of a theory? *Soc Sci Med* 2018; **206**: 117–22.
- Felitti VJ. Adverse childhood experiences and adult health. *Acad Pediatr* 2009; **9**: 131–32.



- 
- 21 Rothman EF, Edwards EM, Heeren T, Hingson RW. Adverse childhood experiences predict earlier age of drinking onset: results from a representative US sample of current or former drinkers. *Pediatrics* 2008; **122**: e298–304.
- 22 Björkenstam C, Kosidou K, Björkenstam E. Childhood adversity and risk of suicide: cohort study of 548721 adolescents and young adults in Sweden. *BMJ* 2017; **357**: 1334.
- 23 Andrade LH, Bruffaerts R, de Girolamo G, et al. Childhood adversities as risk factors for onset and persistence of suicidal behaviour. *Br J Psychiatry* 2010; **197**: 20–27.
- 24 Momen NC, Olsen J, Gissler M, Cnattingius S, Li J. Early life bereavement and childhood cancer: a nationwide follow-up study in two countries. *BMJ Open* 2013; **3**: e002864.
- 25 Chen E, Turiano NA, Mroczek DK, Miller GE. Association of reports of childhood abuse and all-cause mortality rates in women. *JAMA Psychiatry* 2016; **73**: 920–27.
- 26 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.