Adverse childhood experiences and premature mortality through mid-adulthood: A five-decade prospective study

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Summary

Background Adverse childhood experiences (ACEs) can have lasting effects on adult health and survival. In this study, we aimed to examine how the cumulative number and clustering patterns of ACEs were related to premature mortality.

Methods Participants (*N*=46 129; 45% White, 48% Black; 49·5% females) were offspring (born in 1959–1966) of participants enrolled in the Collaborative Perinatal Project (CPP). We conducted latent class analysis to examine the clustering patterns of ACEs assessed between children's birth and age seven. We also calculated the cumulative ACE scores of 13 individual ACEs. Cox regression models were used to examine the associations of ACE clusters and scores with risk of premature mortality from adolescence to mid-adulthood.

Findings At the start of the follow-up for mortality in 1979, participants were 12-20 years old (Mean=15·99 years), and within the 38-year follow-up through 2016, 3 344 deaths were observed among the 46 129 CPP offspring. Five latent classes of ACEs were identified. Compared to children with Low Adversity (48% of the sample), children in *Family Instability* (9%, HR=1·28, 95%CI 1·07-1·53), *Poverty & Crowded Housing* (21%, HR=1·41, 95%CI 1·24-1·62), and *Poverty & Parental Separation* (19%, HR=1·50, 95%CI 1·33-1·68) classes had higher hazards of premature mortality. In addition, children with 2 (HR=1·27, 95%CI 1·14-1·41), 3 (HR=1·29, 95%CI 1·15-1·45), and 4+ (HR=1·45, 95%CI 1·30-1·61) ACEs had higher hazards of mortality than those with no ACE. The clusters of Poverty & Crowded Housing (HR=1·28, 95%CI 1·10-1·49) and Poverty & Parental Separation (HR=1·23, 95%CI 1·02-1·48) remained associated with higher risk of premature mortality, beyond the cumulative risk of higher number of ACEs (HR=1·05, 95%CI 1·01-1·08).

Interpretation About half of the CPP cohort experienced early life adversities that clustered into four distinct patterns, which were associated with different risk of premature mortality. It is important to deepen our understanding of how specific clusters of childhood adversities affect health and premature mortality to better inform approaches to prevention and interventions.

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Keywords: Adverse childhood experiences; Premature mortality; Early adversity; Risk clustering; Cumulative risk

Introduction

Early life adversity can have an enduring impact on human development and health. The more adversities children are exposed to — e.g., physical, emotional, and sexual abuse, caregiver's mental illness, parental substance abuse, parental incarceration, domestic violence

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Research in context

Evidence before this study

We reviewed studies in PubMed from its inception to February 15, 2022, using the search terms "("adverse childhood experiences" or "childhood adversity" or "early life adversity") and ("mortality" or "premature mortality" or "death" or "premature death")". We identified studies that examined the association between adverse childhood experiences (ACEs) and the risk of mortality. Most of these studies measured childhood adversity retrospectively reported by adults, examined the number of adversities experienced, or considered exposure to a single type of adversity.

Added value of this study

We used data from a U.S.-based birth cohort study that prospectively assessed adversities in early childhood, including parent harshness and neglect, household challenges, and economic disadvantage. In addition to examining the cumulative risk of mortality associated with increasing exposure to childhood adversities, we also investigated exposure to empirically derived clusters of adversities and subsequent mortality risk through middle adulthood. We identified five patterns of adverse childhood experiences that were associated with 1.16-1.50 times higher risk of premature mortality: Low Adversity (48%), Parental Harshness & Neglect (4%), Family Instability (9%), Poverty & Crowded Housing (21%), and Poverty & Parental Separation (19%). Children exposed to the two distinct combinations of adversities linked with poverty had 1.23-1.28 times higher risk for premature mortality than children with low adversity, even beyond the cumulative effects of ACEs shown by previous studies.

Implications of all the available evidence

Prior studies evaluating the cumulative risk of health problems in adulthood among children exposed to adversity have enhanced public awareness of the enduring burden of early life adversity and led to studies evaluating the usefulness of screening practices for childhood adversities. Studies such as ours that examine the unique consequences of specific patterns of exposure to childhood adversities have the potential to further improve our understanding of the physiologic and developmental mechanisms linking adverse childhood experiences to adult health and premature mortality. The results of our study may also support evaluating personalized interventions (e.g., parenting support, addressing economic difficulties) to help children exposed to different clusters of adversities. Most importantly, the totality of evidence demands expanded efforts to prevent and reduce children's exposure to toxic stressors particularly poverty, poor housing conditions, and parental separation. Once adversities occur, findings such as ours highlight the importance of integrating anti-poverty programs with family-based interventions in mitigating the long-term consequences of early adversity.

– the more their risk increases for a number of leading causes of death in adulthood (e.g., drug overdose, heart disease, cancer).[1–3] Exposure to a high number of adverse childhood experiences (ACEs), above four in most studies, is strongly linked with many negative psychosocial outcomes including suicide attempt, mental illness, sexual risk taking, and interpersonal violence.[4,5] The concept of an adverse childhood experience has broadened over the years, recognizing the unfortunately common occurrences in childhood that can disrupt the course of development and well-being: foster care, parental or sibling death, changes in parents' marital status, and childhood illness,[6–9] and the broader social determinants of health such as poverty, receipt of welfare, poor housing conditions, and discrimination.[8,10]

Few studies have examined the impact of ACEs on shortened life expectancy. Retrospective studies of adults generally have not found a strong association between ACEs and mortality risk.[7,11,12] Two birth cohort studies examined ACEs prospectively and risk of premature mortality. In the 1958 British birth cohort,[13] children with higher ACE scores (i.e., 2+) had nearly a twofold higher risk of premature mortality through middle adulthood than children without ACEs. In a Danish cohort of 1.5 million children born in 1981-2010,[14] children exposed to 1, 2, or ≥3 ACEs had 1·45, 1·72, and 2·28 higher mortality risks through age 18.

Because the adversities counted in ACE scores differ across studies, it is unclear which combinations of ACEs are associated with the highest health risks. ACEs tend to cluster together, and though studies of ACE scores are important for examining the cumulative toll of adversities on health, they obscure the health impacts of exposure to specific types or combinations of ACEs.[15,16] A U.S. study of 6 320 adults identified six clusters of ACEs using information on retrospectively reported childhood socioeconomic status (SES), family instability, and abuse.[17] Children exposed to low SES and frequent abuse had about 1·5 times higher odds of mortality within 20 years of follow-up than children in a low-risk cluster of ACEs characterized by high SES and absence of abuse. A Danish study of 1 million children born 1980–1998 identified five clusters of ACEs that took place from birth to age 16.[18] Children within clusters characterized by early-life material deprivation, persistent material deprivation, loss or threat of loss within the family, and high adversity had marked excess mortality risk through age 34.

Some combinations of ACEs may be especially problematic. For example, children exposed to both poverty and parental mental illness had a particularly high risk for poor health.[19,20] The combination of family conflict, psychological abuse, and emotional neglect has been associated with higher systemic inflammation, illustrating one of the many likely physiologic systems involved in causing the excess health burden of children exposed to adversity.[21] Ultimately, the toll of ACEs on children's

development and long-term health may be due to the burden of exposure to numerous adversities exceeding children's capacity for stress response and also to the deleterious consequences of specific clusters of adversities.[15] Our study therefore examines both 'cumulative risk' and 'risk clustering' effects of ACEs on premature mortality, an outcome given limited attention in prior work.

Methods

Sample

Participants were offspring of pregnant women enrolled in the Collaborative Perinatal Project (CPP) in the United States between 1959 and 1966. Written informed consent was obtained from CPP enrolees. The CPP was a large-scale U.S. pregnancy cohort[22] conducted at 12 academic centres that followed a racially and socioeconomically diverse sample of mothers and their offspring from pregnancy through the first seven years of children's life. Each academic centre followed its own recruitment strategy to enrol a sample that mirrored the demographics of the local community; while the CPP was not designed to be representative of any site or of the US population, the demographic characteristics of participants were very similar to those of the US overall[23] and remained one of the largest U.S. pregnancy cohorts to date. There were 52 989 CPP children known to be alive at age seven. We were able to successfully locate the identifying information of 49 853 CPP offspring for the National Death Index linkage which was overseen by the Institutional Review Board of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The current study included 46 129 of these offspring who had at least one measure of ACEs between birth and age seven.

Measures

Adverse childhood experiences (ACEs). Thirteen childhood adversities were assessed between birth and age seven years (Table 1). Parent harshness and neglect were coded based on psychologist ratings of mothers' maladaptive behaviour towards the child during the 8-month visit. Adversities in the domain of household dysfunction included parent or sibling mental illness, two or more changes in marital status, parent or sibling death, foster care, and parental divorce/separation. Adversities in the domain of social determinants of health included frequent residential changes, poverty, crowded housing conditions, welfare use, and being economically 'worse off' from birth to age seven. Information about adversities in the domains of household dysfunction and social determinants of health was obtained from maternal interviews administered at the age seven visit. Finally, an indicator of children's severe chronic conditions (e.g., asthma, emphysema, congenital heart defects, unusually recurrent or chronic infections) at age seven was extracted from the children's medical records. Correlations among the thirteen individual ACEs are presented in Supplementary Table S1.

All-cause mortality. Vital status of CPP offspring from 1979 to 2016 was determined via a probabilistic linkage of the cohort to the United States National Death Index (NDI), which captures all death certificates recorded in state registers. The linkage was based on comparing identifying information of cohort members (first and last name, date of birth, sex, state of birth, and race/ethnicity) to that on death certificates in the NDI and assigning each potential match between a cohort member and a death certificate. NDI's probabilistic score quantifies the quality of a possible match and is computed through an algorithm that assigns higher weights to elements of the match that are more unique in the population. If a cohort member matched to multiple death certificates, we retained the match with the highest probabilistic score. The cohort member was considered deceased if the probabilistic score was higher than the NDI's validated cut-off. Given the relatively young age of the cohort, records that were not matched were unlikely to be linkage failures, but rather individuals who were still living.

Covariates included maternal age at birth (<20 years, 20-30 years, and >30 years), race (Black, White, Other), child age in 1979, sex (male, female), and parent education (less than high school degree versus high school degree or higher) and occupation status (manual occupation or unemployed versus non-manual occupation) measured during pregnancy. A directed acyclic graph is presented in Supplementary Figure S1 to indicate why we adjusted for these covariates when estimating the effect of ACEs on premature all-cause mortality.

Statistical analysis

To test the risk clustering effects of ACEs, we conducted a latent class analysis (LCA) of the 13 ACEs in M*plus* version 8 where missing data were handled using full information maximum likelihood. Model fit of LCA models was evaluated using the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample-adjusted BIC, the Vuong-Lo-Mendell-Rubin adjusted likelihood ratio test (VLMR LRT), and bootstrapped likelihood ratio test (BLRT).[24] Once the optimal number of classes was determined, we used entropy and average posterior probabilities to assess classification quality. We then related class membership to the risk of premature mortality through joint modelling of LCA and Cox regression analysis.[25] Survival time was calculated by subtracting offspring's age on January

Individual ACE (Prevalence)	Reference Period for the Measurement of Each ACE	Definition of Each ACE
Parent harshness (10%)	At 8 months	Negative or harsh to the child, never expressed affection, or used physical actions to discipline the child
	At 8 months	Consistently made critical and derogatory remarks about the child
Parent neglect (9%)	At 8 months	Seemed unaware of and unresponsive to any needs of the child
	At 8 months	Child's clothing appeared soiled or grooming suggested neglect
Family mental illness (12%)	From birth to age 7	Neuropsychiatric and convulsive disorders of parents and siblings
Divorce/separation (22%)	At 7 years	Parents divorced or separated
Marital changes (14%)	From birth to age 7	Two or more changes in marital status
Parent/sibling death (8%)	At ages 1 and 7	Parental death
	From birth to age 7	Sibling death
Foster care (2%)	At ages 1 and 7	Placed in foster care
Residential changes (12%)	From birth to age 7	Family frequent move (>= 5)
Crowded housing (22%)	At 7 years	Household highly crowded (person/room > 1.5)
Welfare receipt (26%)	At 7 years	Receipt of welfare
Poverty (34%)	At 7 years	Poverty
Income decline (12%)	From birth to age 7	Income decreased compared to when child was born
Severe chronic conditions of children (19%)	At 7 years	Any definite severe chronic conditions, such as seizure, coma, asthma, and unusually recurrent or chronic infections

***Table 1*: Adverse childhood experiences (ACEs) measured within the first seven years of life.**

1, 1979, from their age on the day they died (for decedents) or on December 31, 2016 (for censored participants). To examine cumulative risk effects, ACE scores were created by summing the 13 individual ACEs and analysed as a continuous variable and as a categorical variable (0, 1, 2, 3, and 4+ ACEs) in Cox regression models.

We first fitted unadjusted and adjusted individual survival models for latent class membership and cumulative number of ACEs. To explore the joint effects of ACE classes and scores on mortality, we then fitted mutually adjusted survival models in two ways: 1) a model that contained ACE classes along with ACE scores to examine their independent effects; and 2) a model testing the cumulative risk effect of ACEs separately within each latent class, which evaluates the extent to which a cumulative risk effect of ACEs persists independent of exposure to specific clusters of adversities.

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. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The study sample was 45% White (n = 20 896), 48% Black (n = 22 142), and 7% Other (n = 3 091); 51% of offspring were males (n = 23 295) and 49% were females (n = 22 834). About half of the parents had lower than high school education (n = 20 850; 45%) and manual occupation or unemployed (n = 29 338; 64%). Less than a quarter of participants' mothers were younger than 20 years old (n = 10 840; 24%), 57% were 20-30 years old (n = 26 432), and 19% were older than 30 years old (n = 8 857). Offspring were 12-20 years old (Mean = 15·99 years, SD = 1·90) at the start of the follow-up period in 1979. By December 31, 2016, after a median follow up time of 38 years, we observed 3 344 deaths (7% of the study sample); the mortality rate of the sample was 136·9 per 100 000 person-years. Offspring were 13-58 years old (Mean = 53·01 years, SD = 4·80) when they were last observed (the day they died or December 31, 2016). The associations of individual ACEs with premature mortality are presented in Supplementary Table S2.

Latent class analysis of adverse childhood experiences

We evaluated eight LCA solutions for model fit to determine the optimal number of classes (Supplementary Table S3). The AIC, BIC, and SABIC values showed relatively large decreases from 1-class to 5-class models, whereas the changes from 5-class to 8-class models were very small. The VLMR LRT and BLRT were significant for all the models tested and would support models with more classes but the decreases in BIC after the 5-class solution did not justify greater model complexity. Therefore, the 5-class LCA model was retained for further analysis, with a medium entropy (·65) and

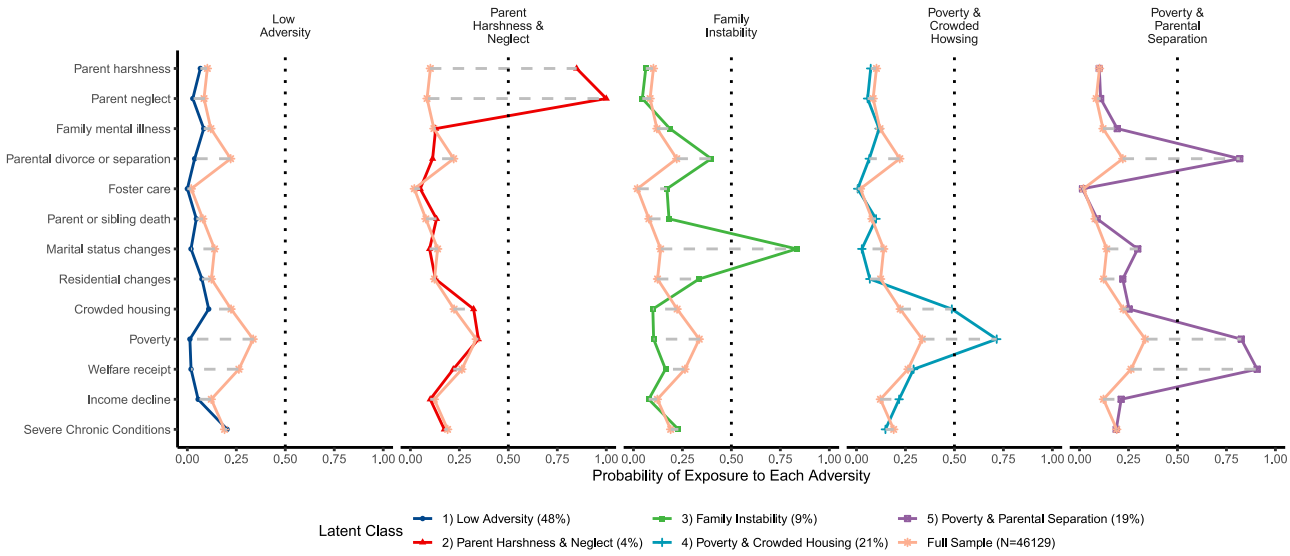

Figure 1. Five latent classes of early childhood adversities identified in the CPP cohort.

Note: Children in Class 1 had low risk of experiencing any adversity. Children in Class 2 were highly likely to experience physical or emotional harshness and physical neglect. Children in Class 3 had relatively high probabilities of experiencing family instability (e.g., marital changes, residential changes, parent/sibling death, foster care, or divorce/separation). Children in Class 4 were mainly exposed to poverty and crowded housing. Children in Class 5 had particularly high probabilities of experiencing poverty, welfare use, and parental divorce/separation and some risk of marital and residential changes as well.

adequate average posterior probabilities (77 to ·86). Each class had a distinctive pattern of exposure to ACEs as illustrated in Figure 1, which shows the likelihood of experiencing each ACE among participants given their class membership.

We labelled the classes based on the predominant ACEs that differentiate each class from the others. Class 1 (n = 21 941, 48% of children) was characterized by low probabilities for all ACEs and labelled as "*Low Adversity*." Class 2 (n = 1 738, 4%) was characterised by high probabilities of physical or emotional harshness (·85) and physical neglect (1·00) and labelled as "*Parental Harshness & Neglect*." Class 3 (n = 4 165, 9%) was characterised by high probabilities of two or more marital changes (·83), and higher than average probabilities of residential changes (·43), parental divorce or separation (·40), parent or sibling death (·18), and foster care (·17), and was labelled "*Family Instability*." Class 4 (n = 9 648, 21% of the sample) was characterised by relatively high probabilities for poverty (·72) and crowded housing conditions (·49) and labelled as "*Poverty & Crowded Housing*." Class 5 (n = 8 638, 19%) was characterised by high probabilities of welfare use (·91), poverty (·83), parental divorce/separation (·82), and higher than average risk of marital changes (·30), residential changes (·22), and income decline (·21), and labelled as "*Poverty & Parental Separation*."

Table 2 shows the sociodemographic characteristics of participants and the number of ACEs in the full study sample and within each of the five latent classes of ACEs. Over two thirds of the children in the *Poverty & Crowed Housing* (n = 6 638; 69%) and the *Poverty & Parental Separation* (n = 5 727; 66%) classes were Black. The proportion of males and females was similar across classes. Children in the *Poverty & Crowed Housing*, *Poverty & Parental Separation*, and *Parental Harshness & Neglect* classes were more likely to have parents with lower education (56%–65%) and lower occupation (67%–84%). Teenage mothers were relatively more common in the *Family Instability*, *Poverty & Parental Separation*, and *Parental Harshness & Neglect* classes (29%–38%). The average number of ACEs was 1·64 overall, 4·13 among children in the *Poverty & Parental Separation* class, 3·20 among children in the *Parental Harshness & Neglect* class, between 2 and 3 among children in the *Family Instability* and *Poverty & Crowed Housing* classes, and less than 1 among children in the *Low Adversity* class (depicted in Supplementary Figure S2).

Survival analysis of adverse childhood experiences and premature mortality

The cumulative incidence of mortality (i.e., one minus the Kaplan-Meier curve) was highest for participants in the *Poverty & Crowded Housing* and *Poverty & Parental Separation* classes, followed by *Family Instability*, *Parental Harshness & Neglect*, and *Low Adversity* classes (Figure 2). The mortality rate (i.e., number of deaths per 100 000 individuals per year) was 183 among

		Study Sample (*N*=46 129)	Class 1: Low Adversity (*n*=21 941)	Class 2: Parental Harshness & Neglect (*n*=1 738)	Class 3: Family Instability (*n*=4 165)	Class 4: Poverty & Crowded Housing (*n*=9 648)	Class 5: Poverty & Parental Separation (*n*=8 638)
Race	White	20 896 (45%)	12 221 (56%)	893 (51%)	2 799 (67%)	2 480 (26%)	2 488 (29%)
	Black	22 142 (48%)	7 679 (35%)	815 (47%)	1 274 (31%)	6 638 (69%)	5 727 (66%)
	Other	3 091 (7%)	2 041 (9%)	30 (2%)	92 (2%)	531 (6%)	423 (5%)
Sex	Male	23 295 (51%)	10 729 (49%)	850 (49%)	2 170 (52%)	4 930 (51%)	4 293 (50%)
	Female	22 834 (49%)	11 212 (51%)	888 (51%)	1 995 (48%)	4 718 (49%)	4 345 (50%)
Parent education	<high school	20 850 (45%)	6 297 (29%)	966 (56%)	1 808 (43%)	6 290 (65%)	5 511 (64%)
	>=high school	25 279 (55%)	15 644 (71%)	772 (44%)	2 357 (57%)	3358 (35%)	3 127 (36%)
Parent occupation	Manual occupation or unemployed	29 338 (64%)	10 444 (48%)	1 166 (67%)	2 599 (62%)	8 085 (84%)	7 066 (82%)
	Non-manual occupation	16 791 (36%)	11 497 (52%)	572 (33%)	1 566 (38%)	1 563 (16%)	1 572 (18%)
Mother age	< 20 years	10 840 (24%)	4 432 (20%)	497 (29%)	1 574 (38%)	1 775 (18%)	2 557 (30%)
	20-30 years	26 432 (57%)	13 494 (62%)	933 (54%)	2 195 (53%)	5 181 (54%)	4 613 (53%)
	> 30 years	8 857 (19%)	4 015 (18%)	308 (18%)	396 (10%)	2 692 (28%)	1 468 (17%)
ACE scores	Mean (SD)	1·64 (1·69)	0·56 (0·75)	3·20 (1·36)	2·38 (1·14)	2·55 (1·05)	4·13 (1·45)
	0 ACE	15 545 (34%)	12 638 (58%)	0	0	0	0
	1 ACE	10 517 (23%)	6 758 (31%)	56 (3%)	1 008 (24%)	1 418 (15%)	337 (4%)
	2 ACE	7 565 (16%)	2 106 (10%)	624 (36%)	1491 (36%)	3 695 (38%)	605 (7%)
	3 ACE	5 397 (12%)	417 (2%)	443 (26%)	966 (23%)	2 837 (29%)	1 952 (23%)
	4+ ACE	7 104 (15%)	44 (0·2%)	615 (35%)	700 (17%)	1 688 (18%)	5 744 (67%)

***Table 2*: Characteristics of the overall sample and each adverse childhood experiences (ACEs) class.**
Note: Column percentages are presented to describe distributions of background variables (e.g., what proportions of the full sample and each ACE class are male and female).

children in the *Poverty & Crowded Housing* class, 177 in the *Poverty & Parental Separation* class, 135 in the *Family Instability* class, 139 in the *Parental Harshness & Neglect* class, and 114 in the *Low Adversity* class.

In the Cox regression model with ACEs alone, children in the *Poverty & Crowded Housing* (hazard ratio (HR) = 1·93, 95% CI 1·69-2·19) and *Poverty & Parental Separation* (HR = 1·86, 95% CI 1·66-2·08) classes had nearly twofold higher hazards of mortality than those in the *Low Adversity* class. Children in the *Family Instability* (HR = 1·32, 95% CI 1·10-1·58) and *Parental Harshness & Neglect* (HR = 1·47, 95% CI 1·16-1·87) classes also had higher hazards of premature mortality than those in the *Low Adversity* class. After controlling for sociodemographic covariates (Table 3, first column), the magnitude of the HRs linking ACEs with mortality was somewhat smaller, with HR's ranging from 1·28 to 1·50 for the three clusters of ACEs that were associated with higher risk of mortality.

Children with higher ACE scores had elevated risks for premature mortality: the unadjusted HR for mortality was 1·12 for each unit increase in ACE score (95% CI 1·10-1·14), and the adjusted HR was 1·08 (95% CI 1·05-1·10) (Table 3, second column). Children with 1, 2, 3, and ≥4 ACEs had a 1.14 (95% CI 1·04-1·26), 1.44 (95% CI 1·30-1·59), 1.54 (95% CI 1·37-1·72), and 1.74 (95% CI 1·57-1·92) times higher hazard of mortality through middle adulthood than children exposed to none. After adjusting for sociodemographic variables (Table 3, third column), having 2 or more ACEs remained associated with higher mortality risk, though with smaller magnitudes (HRs = 1·27-1·45).

Joint influences of cumulative risk and risk clustering of ACEs on mortality

Table 3 also presents the independent associations of ACE classes and scores with mortality from mutually adjusted models. Children in the *Poverty & Crowded Housing* (HR = 1·28, 95% CI 1·10-1·49) and *Poverty & Parental Separation* (HR = 1·23, 95% CI 1·02-1·48) classes had higher risks of premature mortality than children in the *Low Adversity* class, independent from the cumulative risk effects of ACE scores (HR = 1·05, 95% CI 1·01-1·08) (Table 3, fourth column). Moreover, the cumulative effect appeared to be limited to children in the *Low Adversity* (HR = 1·13, 95% CI 1·03-1·23), *Parental Harshness & Neglect* (HR = 1·16, 95% CI 0·99-1·35), and *Poverty & Crowded Housing* (HR = 1·10, 95%CI 1·01-1·19) classes.

Discussion

Cumulative risk and risk clustering processes were both implicated in the association between ACEs and higher

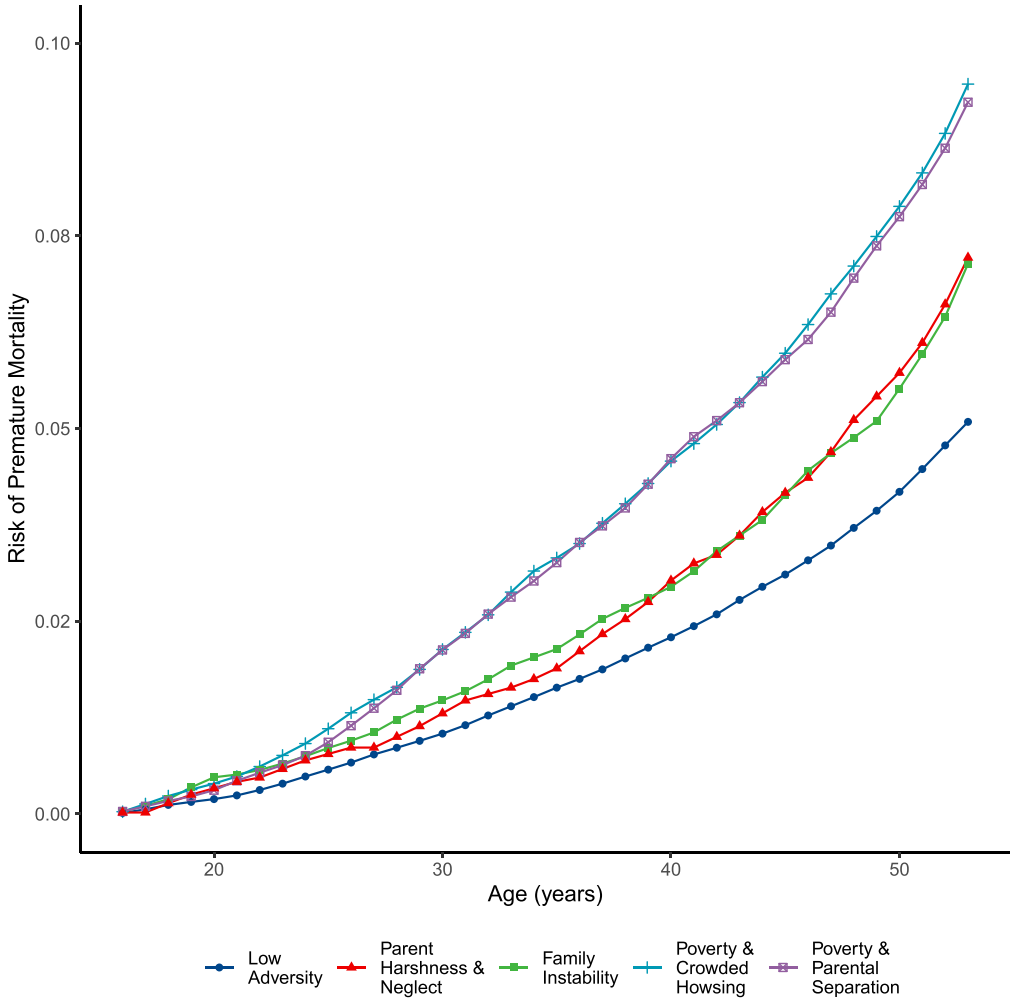

Figure 2. Risk of premature mortality for individuals in each latent class of ACEs.

Note: All the other ACE classes had higher mortality risk than the low adversity class. The mortality rate (i.e., number of deaths per 100 000 individuals per year) was 183 for the *Poverty & Crowded Housing* class, 177 for the *Poverty & Parental Separation* class, 135 for the *Family Instability* class, 139 for the *Parental Harshness & Neglect* class, and 114 for the *Low Adversity* class.

mortality risk. Most prior studies examining this association focused on the number of ACEs to which children were exposed. Consistent with some of these studies,[12–14] we found that higher ACE scores led to an increasing risk of premature mortality, with each additional adversity associated with about a 10% higher risk of premature mortality, and exposure to ≥4 ACEs associated with a 45% higher risk of premature mortality. When analysed jointly with clusters of adversities, there was a cumulative risk effect of ACEs on mortality among children in the *Parental Harshness & Neglect, Poverty & Crowded Housing,* and *Low Adversity* clusters. An important implication of this finding is that even in a "low adversity" group, identified through empirically based approaches focusing on clusters of ACEs, there could be an elevated risk of long-term harm but such risk may be overlooked with "low adversity" cluster often treated as the reference group in analysis. In our study, children in the *Low Adversity* class had a much lower probability of exposure to any adversities measured than the prevalence of these adversities in the full study sample, except for severe chronic conditions. Although severe chronic conditions did not strongly cluster with other adversities, as an individual type of adversity, it was significantly associated with risk of premature mortality[7] (see Supplementary Table S2). Thus, childhood illnesses might have contributed to the cumulative risk for premature mortality observed in our "low adversity" cluster.

Few studies have examined the clustering of ACEs in relation to mortality.[17,18] We identified five distinct patterns of adverse childhood experiences in the offspring.

	ACE Class HR (95% CI)	Continuous ACE Score HR (95% CI)	Categorical ACE Score HR (95% CI)	ACE Class + Continuous ACE Score HR (95% CI)
ACE Class				
Class 1: Low Adversity	1	..	..	1
Class 2: Parental Harshness & Neglect	1·16 (0·91, 1·48)	..	..	1·00 (0·76, 1·30)
Class 3: Family Instability	1·28 (1·07, 1·53)	..	..	1·16 (0·95, 1·41)
Class 4: Poverty & Crowded Housing	1·41 (1·24, 1·62)	..	..	1·28 (1·10, 1·49)
Class 5: Poverty & Parental Separation	1·50 (1·33, 1·68)	..	..	1·23 (1·02, 1·48)
Continuous ACE score		1·08 (1·05, 1·10)		1·05 (1·01, 1·08)
Categorical ACE score				
0 ACE	..	..	1	..
1 ACE	..	..	1·09 (0·98, 1·20)	..
2 ACEs	..	..	1·27 (1·14, 1·41)	..
3 ACEs	..	..	1·29 (1·15, 1·45)	..
≥4 ACEs	..	..	1·45 (1·30, 1·61)	..
Offspring Age in 1979	1·10 (1·08, 1·12)	1·10 (1·08, 1·12)	1·10 (1·08, 1·12)	1·10 (1·08, 1·12)
Sex				
Female	1	1	1	1
Male	1·84 (1·71, 1·97)	1·83 (1·71, 1·97)	1·83 (1·71, 1·97)	1·84 (1·71, 1·97)
Race				
White	1	1	1	1
Black	1·40 (1·29, 1·52)	1·45 (1·33, 1·57)	1·45 (1·34, 1·58)	1·42 (1·30, 1·54)
Other	0·92 (0·78, 1·08)	0·99 (0·84, 1·16)	1·00 (0·85, 1·17)	0·96 (0·81, 1·12)
Parent education				
High school or higher	1	1	1	1
Lower than high school	1·19 (1·10, 1·29)	1·21 (1·12, 1·31)	1·20 (1·11, 1·30)	1·19 (1·10, 1·29)
Parent occupation				
Non-manual occupation	1	1	1	1
Manual occupation or unemployed	1·23 (1·12, 1·35)	1·24 (1·13, 1·37)	1·24 (1·13, 1·36)	1·23 (1·12, 1·35)
Maternal age				
20-30 years old	1	1	1	1
<20 years old	1·01 (0·93, 1·10)	1·00 (0·92, 1·09)	1·01 (0·93, 1·10)	1·01 (0·93, 1·10)
>30 years old	1·06 (0·97, 1·16)	1·06 (0·96, 1·16)	1·05 (0·96, 1·15)	1·05 (0·96, 1·16)

***Table 3*: Results of survival analyses of the associations of adverse childhood experience (ACE) with premature mortality.**
Note: N=45 178 for covariate-adjusted models. HR = hazard ratio. CI = confidence interval. ACE = adverse childhood experience.

About half of the sample was exposed to zero or one type of adversity, whereas the other half of the sample experienced two or more adversities that were clustered in four different combinations. The *Parental Harshness & Neglect* class was very small (4% of the sample) and children in this class did not have a higher long-term risk of mortality than children in the *Low Adversity* class. The *Family Instability* class represented 9% of the sample; children in this class had about 30% higher risk of mortality than children in the *Low Adversity* class. The *Poverty & Crowded Housing* and *Poverty & Parental Separation* classes were the most concerning, with each class representing about 20% of the sample. Children in these poverty-related classes had nearly 50% higher risks of premature mortality than children in the *Low Adversity* class, even after controlling for significant mortality risk due to the disproportionate distributions of racial minorities and children of parents with low education and occupation status in these clusters. Finally, after adjusting for the number of adversities, children in these classes remained associated with 20–30% higher risk of premature mortality, indicating that the combinations of childhood poverty with crowded housing or parental divorce/separation carried heightened risk for reducing children's long-term survival.

ACEs may lead to worse health because they elevate the body's allostatic load during developmentally sensitive periods: prolonged exposure to chronic stress could lead to dysregulated stress response systems (failure to shut-off or to adequately respond) through chronic adaptation to adversity.[26] The cost of this adaptation encompasses a wide range of cascading neurobiological effects of early adversity on children's brain development, epigenetic responses to ACEs, disrupted attachment systems, and impairment of children's social,

emotional, and cognitive competence,[27,28] all of which may lead to poor adult social relationships, mental illness, cardiovascular disease, cancer, substance use disorders, lower adult socioeconomic status, and ultimately risk for premature mortality.

The allostatic load concept is important for understanding cumulative risk effects of ACEs because allostatic load explains the physiologic toll of repeated or persistent exposure to adversity. Alternatively, in light of evidence that ACEs have both cumulative risk and risk clustering effects, it may be useful to consider the dimensional model which proposes that ACEs reflecting *threat* of harm and *deprivation* of social and cognitive stimulation may invoke distinct mechanistic pathways to development and health.[29] Specifically, threat (e.g., physical and emotional abuse, domestic violence) is expected to have strong influences on fear learning and emotional development processes (e.g., heightened emotional reactivity, emotion regulation difficulties), whereas deprivation (e.g., neglect, parental separation, and material deprivation) is posited to have pronounced influences on reward learning and higher-order cognitive development (e.g., language and executive functions).[30] Environmental *unpredictability* (e.g., loss of a parent, residential changes, paternal transitions) is another important dimension being examined and considered to uniquely shape human life history traits such as risk-taking, partnering and relationship outcomes, and temporal discounting.[31]

Our results from analyses of clustering patterns of ACEs partly support the dimensional model. For instance, children experiencing 'deprivation' (the *Poverty & Crowded Housing* cluster) may die prematurely due to long-term behavioural, psychological, and physiological consequences of deficits in early cognitive development, whereas children experiencing 'unpredictability' (the *Family Instability* cluster) may have distorted perceptions of time and risk that impair later health and mortality. From the developing children's point of view, however, as our data reveal, exposure to multiple types of adversities is common; to the extent there exist distinct mechanistic pathways leading to worse health in adulthood, these may operate simultaneously. For example, the *Parental Harshness and Neglect* cluster of ACEs implicates both 'threat' (of physical or emotional harm) and 'deprivation' (i.e., neglect) whereas the *Poverty and Parental Separation* class implicates both 'deprivation' and 'unpredictability' (e.g., residential changes). Ultimately, the physiological stress dysregulation likely common to all ACEs compounded by additional psychological and physiological harms of particular clusters of adversities likely converge to produce the profound long-term effects on shorted life span that we observed in the CPP sample. In addition to efforts aimed at preventing exposure to early childhood adversity and resolving risk-benefit trade off of screening for ACEs,[32] clarifying these mechanisms will be critical for developing integrative, effective, and targeted early interventions to reduce the negative consequences of childhood adversities.[33] Importantly, our study focused on the association between ACEs and risk for mortality from all causes. Identifying and potentially targeting the intervening mechanisms may therefore have significant long-term benefits given that exposure to ACEs is associated with so many health problems in adulthood that are known to shorten life expectancy.[4]

Following are the study's limitations. First, the gap in the coverage of deaths between the age 7 visits and the end of 1978 may lead to an under-coverage of premature deaths among CPP offspring. Second, despite the advantages of the CPP (e.g., prospective measurement and long-term follow-up), it did not capture some of the most severe forms of ACEs such as sexual abuse and domestic violence. Accordingly, we were unable to examine how these ACEs cluster with other adversities and how they relate to premature mortality. Furthermore, we measured parental harshness and neglect at 8 months which may also occur between 8 months and age 7 and were not captured given our limited time window to observe these parental behaviours. The same limitation applies to other adversities measured only at age seven (e.g., poverty, welfare use). Third, the CPP as a whole was not designed to be a nationally representative sample of pregnancies, which is a limitation relative to whole population studies.[18] Unfortunately, there is no analogue in the U.S. to kinds of population registries available in the Scandinavian countries. Therefore, although generalizability of our findings to the whole U.S. population is not easily established, the CPP's in-depth assessments of the social contexts of children's development and the 5-decade follow-up of offspring provide an important window into the long-term effects of early childhood adversity for U.S. children. Finally, the clusters of ACEs that we could identify depends on the specific types of adversities measured in our study; thus, the co-occurring patterns we identified may not be the same as in other studies. With the scope of ACEs expanded over time, it indeed becomes a challenge to compare across studies given that different sets of ACEs may be captured in different studies. Comprehensive (in terms of both types and timing) and more standardized assessments of ACEs are needed to further advance knowledge about long-term harms of adversities and mitigation strategies.[34]

Hamby et al.[35] argued that the strong cumulative effect of ACEs was the most prominent finding of the ACEs literature, with extensive evidence for ≥4 ACEs associated with elevated risk of more than 40 health and developmental outcomes. The cumulative ACE score approach has promoted public awareness of the burden of early life adversity and facilitated changes in screening practices. Yet the count of ACEs obscures

potentially important information about the specific types and patterns of adversities that are most problematic.[15,20] In our study, children exposed to a combination of poverty and crowded housing conditions, or economic difficulties and parental divorce/separation, are most at risk for premature mortality. Accordingly, there is a strong basis for considering the patterns of ACEs to which children are exposed in order to identify children at greatest risk, to better understand life course mechanisms, and to improve prevention and interventions.

Contributors

JY and SEG conceptualized the study, assessed and verified the underlying data, and formulated the analysis plan. JY and RP prepared the analysis data. JY conducted the analyses and RS reviewed the statistical approach. JY conducted the literature search and wrote the first draft of the manuscript. All authors discussed the results and critically reviewed and edited the manuscript. All authors have seen and approved of the final text.

Data sharing statement

The CPP data are publicly available at https://www.archives.gov/research/electronic-records/nih.html. The NDI data are not publicly available. The dataset creation plan for this study and underlying analytic code are available from the corresponding author upon request.

Declaration of interests

All authors declare no competing interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100349.

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