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Hughes, Karen ; Bellis, Mark; Hardcastle, Katherine; Sethi, Dinesh; Butchart, Alexander; Mikton, Christopher ; Jones, Lisa ; Dunne, Michael

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The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis

Karen Hughes, Mark A Bellis, Katherine A Hardcastle, Dinesh Sethi, Alexander Butchart, Christopher Mikton, Lisa Jones, Michael P Dunne

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College of Health and Behavioural Sciences, Bangor University, Bangor, UK (Prof K Hughes PhD, Prof M A Bellis DSc); **Directorate of Policy, Research and International Development, Public Health Wales, Clwydian House, Wrexham, UK** (Prof K Hughes, Prof M A Bellis, K Hardcastle MSc); **World Health Organization Regional Office for Europe, Division of NonCommunicable Diseases and Promoting Health through the Life-Course, Copenhagen, Denmark** (D Sethi MD); **World Health Organization, Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention, Geneva, Switzerland** (A Butchart PhD); **Faculty of Health and Applied Sciences, University of the West of England, Bristol, UK** (C Mikton PhD); **Public Health Institute, Liverpool John Moores University, Liverpool, UK** (L Jones BSc); **and School of Public Health and Social Work, Queensland University of Technology, Queensland, Australia** (Prof M P Dunne PhD)

Correspondence to: Prof Mark A Bellis, Directorate of Policy, Research and International Development, Public Health Wales, Wrexham, LL13 7YP, UK **m.a.bellis@bangor.ac.uk**

Summary

Background A growing body of research identifies the harmful effects that adverse childhood experiences (ACEs; occurring during childhood or adolescence; eg, child maltreatment or exposure to domestic violence) have on health throughout life. Studies have quantified such effects for individual ACEs. However, ACEs frequently co-occur and no synthesis of findings from studies measuring the effect of multiple ACE types has been done.

Methods In this systematic review and meta-analysis, we searched five electronic databases for cross-sectional, case-control, or cohort studies published up to May 6, 2016, reporting risks of health outcomes, consisting of substance use, sexual health, mental health, weight and physical exercise, violence, and physical health status and conditions, associated with multiple ACEs. We selected articles that presented risk estimates for individuals with at least four ACEs compared with those with none for outcomes with sufficient data for meta-analysis (at least four populations). Included studies also focused on adults aged at least 18 years with a sample size of at least 100. We excluded studies based on high-risk or clinical populations. We extracted data from published reports. We calculated pooled odds ratios (ORs) using a random-effects model.

Findings Of 11 621 references identified by the search, 37 included studies provided risk estimates for 23 outcomes, with a total of 253 719 participants. Individuals with at least four ACEs were at increased risk of all health outcomes compared with individuals with no ACEs. Associations were weak or modest for physical inactivity, overweight or obesity, and diabetes (ORs of less than two); moderate for smoking, heavy alcohol use, poor self-rated health, cancer, heart disease, and respiratory disease (ORs of two to three), strong for sexual risk taking, mental ill health, and problematic alcohol use (ORs of more than three to six), and strongest for problematic drug use and interpersonal and self-directed violence (ORs of more than seven). We identified considerable heterogeneity (I^2 of >75%) between estimates for almost half of the outcomes.

Interpretation To have multiple ACEs is a major risk factor for many health conditions. The outcomes most strongly associated with multiple ACEs represent ACE risks for the next generation (eg, violence, mental illness, and substance use). To sustain improvements in public health requires a shift in focus to include prevention of ACEs, resilience building, and ACE-informed service provision. The Sustainable Development Goals provide a global platform to reduce ACEs and their life-course effect on health.

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Introduction

Studies are increasingly identifying the importance of early life experiences to people's health throughout the life course. Individuals who have adverse childhood experiences (ACEs; during childhood or adolescence) tend to have more physical and mental health problems as adults than do those who do not have ACEs and ultimately greater premature mortality.[1,2] ACEs include harms that affect children directly (eg, abuse and neglect) and indirectly through their living environments (eg, parental conflict, substance abuse, or mental illness). Physiological and biomolecular studies are increasingly establishing how childhood exposure to chronic stress leads to changes in development of nervous, endocrine, and immune systems, resulting in impaired cognitive, social, and emotional functioning and increased allostatic load (ie, chronic physiological damage).[3,4] Thus, individuals who have ACEs can be more susceptible to disease development through both differences in physiological development and adoption and persistence of health-damaging behaviours.

Although studies linking childhood experiences to health go back decades,[5] examination of multiple ACEs enables a better assessment of the breadth of childhood adversity and its relation with adult health than does examination of single ACEs. The first major ACE study[1,6] examined relations between the number of ACEs reported by more than 17 000 individuals in the USA and their health as adults. It found that the more ACE types that individuals reported, the greater their risks of health-harming behaviours (eg, smoking or sexual risk taking) and both infectious and non-communicable

Research in context

Evidence before this study

Previous reviews have synthesised evidence for the long-term health effects of individual adverse childhood experience (ACE) types. However, ACEs often cluster in children's lives and a growing body of research is identifying cumulative relations between multiple ACEs and poor health. Initial evidence of this relation was published in the 1990s. Since then, an increasing number of studies have used similar methods to identify how multiple ACEs affect health-harming behaviours and development of health conditions, including non-communicable diseases.

Added value of this study

To our knowledge, no previous attempt has been made to synthesise evidence for the risks of poor health associated with multiple ACEs across various health-related behaviours and conditions. We found that individuals with at least four ACEs were at increased risk of all outcomes examined. Associations were weak or modest for physical inactivity, overweight or obesity, and diabetes (ORs of less than two), moderate for smoking, heavy alcohol use, poor self-rated health, cancer, heart disease, and respiratory disease (ORs of two to three), strong for sexual risk taking, mental ill health, and problematic alcohol use (ORs of more than three to six), and strongest for problematic drug use and interpersonal and self-directed violence (ORs of more than seven)

Implications of all the available evidence

This systematic review and meta-analysis highlights the pervasive harms that ACEs place on health throughout the life-course and the importance of addressing the various stressors that can occur in children's lives, rather than limiting attention to any one type. Although further work is required to establish causality, the strong relations between multiple ACEs and poor health suggest that a reduction in ACEs and building of resilience to enable those affected to avoid their harmful effects could have a major effect on health. International resolutions, including the Sustainable Development Goals, provide crucial opportunities to address ACEs and our findings offer key information to advocate and inform development of more sustainable life-course approaches to health and health care than at present.

diseases (NCDs). Supported by international work to standardise measurement of ACEs and their effects on health, these findings have since been replicated in studies from low-income and middle-income[7,8] and high-income[2,9] countries. However, although previous reviews[10,11] have collated literature on the health effects of any ACE exposure or specific ACE types, no systematic attempt has been made to synthesise findings from studies of the effect of multiple ACEs across multiple outcomes. Consequently, no global estimates have been made of the strength of associations between multiple ACEs and adoption of health-harming behaviours, occurrence of conditions such as obesity and chronic health conditions, or risk of further exposure to violence in adult years.

In this study, we present findings from a systematic review and meta-analysis of studies measuring associations between multiple ACEs and health outcomes. The primary outcomes of interest were pooled measures of relations between multiple ACEs and health outcomes. Following precedent in the literature,[1,6] we restricted analyses to exposure to at least four types of adversity during childhood, with individuals reporting no ACEs as the comparator.

Methods

Search strategy and selection criteria

The search strategy of this systematic review and meta-analysis is summarised in the panel. Searches focused on six categories of health outcomes: substance use, sexual health, mental health, weight and physical exercise, violence, and physical health status and conditions. We excluded studies based on high-risk (eg, the homeless or those in prison) or clinical populations because of often few individuals with low ACE exposure in such populations. Included studies met the following criteria: cross-sectional, case control, or cohort study, using a cumulative measure of at least four ACEs spanning both direct (eg, maltreatment) and indirect (eg, household dysfunction) types, focused predominantly on adults aged at least 18 years, a sample size of at least 100, and reported odds ratios (ORs), comparable statistics (hazard ratios or prevalence ratios), or data to enable their calculation for a health outcome. We also excluded outcomes with fewer than four studies reporting results suitable for meta-analysis. The initial literature search was done by two reviewers (KH and KAH), who then also retrieved and independently screened full-text articles. Conflicts over inclusion were resolved through discussion with MAB. Data were extracted by one reviewer (KH) and checked by two others (KAH and MAB).

Data analysis

Included articles were independently assessed for quality by two reviewers (KH and KAH) using criteria based on the standard principles of quality assessment.[12] Studies received a point for each quality criterion that they met, for a maximum score of 7. For each article, we extracted data for study type, setting, participants, ACEs, and outcomes. We extracted ORs or equivalent measures for participants with at least four ACEs versus those with none. When such data were not published, we included studies when adequate information was available to allow their calculation, including sample sizes within

each ACE category and adequate ACE categories for recalculation of pertinent ORs, linear relationships between ACE counts and ORs, or changes in prevalence with ACE count. One article[13] combined data from eight studies; for this article, original data were available to us because we were authors of the article, allowing ORs to be calculated for each sample. However, our study was not an independent-participant-data meta-analysis. When multiple studies reported data for the same outcome and sample, we included one study on the basis of largest sample size or data presentation (closest fit to study requirements).

We calculated pooled ORs with 95% CIs for the risk of health outcomes among individuals with at least four ACEs (*vs* no ACEs) using a random-effects model in StatsDirect version 2.8.0. When ORs were presented at a subgroup level within samples, we pooled ORs before analysis. We used the I^2 statistic to estimate the effect of heterogeneity among pooled studies. We explored risk of publication bias using the Begg-Mazumdar and Egger tests and visual inspection of funnel plots when sufficient studies were included in the meta-analysis (at least ten samples; appendix). We generated forest plots showing ORs and 95% CIs for each study and the overall random-effects pooled estimate. We did sensitivity analyses by excluding outlying studies (so that study 95% CIs did not overlap those of pooled measures). We further explored potential sources of heterogeneity by visual inspection of data and forest plots and, when possible (for outcomes with at least ten samples and high heterogeneity between estimates), by meta-regression. We did univariate analyses using Stata version 14 to test the individual association of the following covariates (when relevant) with pooled estimates: sample size, country income level (low-income or middle-income *vs* high-income), ACEs measured (fewer than ten *vs* ten or more), sample age range (old [age ≥35 years] *vs* other), outcome timeframe (recent *vs* lifetime), quality score (<5 *vs* ≥5), OR data (adjusted *vs* unadjusted), and data collection point (past decade [2006 onwards] *vs* older [pre-2006]).

Role of the funding source

Members of the funder contributed to study design, data collection, data analysis, data interpretation, and 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

From a total of 11621 references identified through the literature search, full-text copies of 2334 (20%) articles were retrieved and screened; 194 (8%) of these articles were considered for inclusion, with 37 (19%) articles[1,2,6–9,13–43] selected to contribute to the review, with a total of 253719 participants (figure, table 1). 21 used population samples from the USA,[1,6,14–32] seven used samples from the UK,[2,9,33–37] two used samples from Finland,[38,39] and one study each used samples from Canada,[40] China,[41] New Zealand,[42] the Philippines,[8] Saudi Arabia,[7] and Sri Lanka.[43] One article[13] included data from eight studies done in Albania, Latvia, Lithuania, Macedonia, Montenegro, Romania, Russia, and Turkey; we treated these samples separately in analyses. Most studies were done in high-income countries, with nine samples from middle-income countries and none from low-income countries. 26 articles used data from cross-sectional studies and 11 used data from cohort studies; however, all studies used retrospective, self-reported ACEs. 21 studies used general population (predominantly household) samples, with other samples from primary care, education, community, military, and workplace settings. Sample sizes ranged from 210 to 53998 individuals, with most studies covering broad age ranges and both sexes, although young, old, and single-sex samples were included. 144725 (57%) of 252467 participants across all studies reported at least one ACE and 31795 (13%) of 244979 reported at least four.

The mean number of ACEs measured was nine, with most studies using a similar core set (table 2), and all using a similar timeframe for exposure (from up to age 16 years to up to age 18 years). Prevalence of zero ACEs ranged from 12% to 67% and prevalence of at least four ACEs ranged from 1% to 38% (table 1). Included outcomes and associated definitions are shown in table 3,

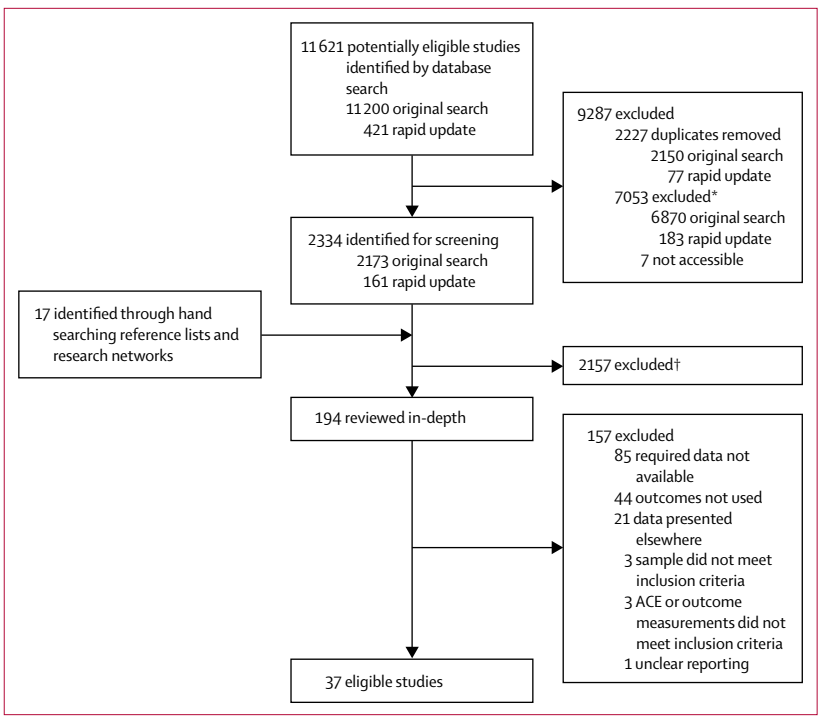

Figure: **Study selection**
ACE=adverse childhood experience. *Review or case report, sample inappropriate, or no relevant ACE or outcome measurement. †No available data, sample did not meet inclusion criteria, or ACE or outcome measurements did not meet inclusion criteria.

See Online for appendix

	Study characteristics									Quality assessment*							
	Country	Study type	Population	Sample size (n)	Age range (years)	Sex	ACEs measured (n)	0 ACE prevalence (%)†	≥4 ACE prevalence (%)†	Sample representativeness‡	Bias§	ACE¶	Response‖	Refusers**	Subjects††	Control‡‡	Total quality score
Almuneef et al (2014)[7]	Saudi Arabia	CS	General	931	≥18	M and F	12	18%	32%	0	0	1	0	0	1	1	3
Anda et al (2002)[14]	USA	C	HMO	7399	≥19	M	8	37%	9%	1	1	1	1	1	1	1	7
Anda et al (2006)[1]	USA	C	HMO	17 337	≥19	M and F	8	36%	13%	1	1	1	1	0	1	1	6
Bellis et al (2014)[33]	UK	CS	General	1500	18–70	M and F	11	53%	12%	1	1	1	1	0	1	1	6
Bellis et al (2014)[9]	UK	CS	General	3885	18–69	M and F	9	54%	8%	1	1	1	1	0	1	1	6
Bellis et al (2014)[13]	Various	CS	Students	10 696	18–25	M and F	10	47%§§	7%¶¶	0	0	1	1	0	1	1	4
Bellis et al (2015)[2]	UK	CS	General	3885	18–69	M and F	9	54%	8%	1	1	1	1	0	1	1	6
Bellis et al (2015)[34]	UK	CS	General	2028	18–69	M and F	9	54%	14%	0	1	1	0	0	1	1	4
Cabrera et al (2007)[15]	USA	CS	Military	6921	≥18	M	6	47%	7%	0	0	1	0	0	1	1	3
Campbell et al (2016)[16]	USA	CS	General	48 526	≥18	M and F	11	45%	14%	1	1	1	0	0	1	1	5
Chartier et al (2010)[40]	Canada	CS	General	9953	≥15	M and F	6	28%	7%	1	1	1	0	0	1	1	5
Cunningham et al (2014)[17]	USA	CS	General	45 561	≥18	M and F	8	37%	14%	1	1	1	1	0	1	1	6
Dube et al (2003)[18]	USA	C	HMO	17 337	≥19	M and F	8	36%	13%	1	1	1	1	1	1	1	7
Felitti et al (1998)[6]	USA	C	HMO	9508	≥19	M and F	7	48%	6%	1	1	1	1	1	1	1	7
Fonseka et al (2015)[43]	Sri Lanka	CS	General	1252	18–49	M	8	NR	31%	0	1	1	1	0	1	1	5
Ford et al (2011)[19]	USA	CS	General	25 809	≥18	M and F	8	41%	15%	1	1	1	1	0	1	1	6
Ford et al (2016)[35]	UK	CS	General	5454	18–69	M and F	9	57%	9%	1	1	1	1	0	1	1	6
Gilbert et al (2015)[20]	USA	CS	General	53 998	≥18	M and F	9	41%	15%‖‖	1	1	1	0	0	1	1	5
Goodwin et al (2004)[42]	New Zealand	C	General	1053	21 (mean)	M and F	10	26%	21%‖‖	1	1	1	1	0	0	1	5
Harkonmäki et al (2007)[38]	Finland	CS	General	8817	40–54	M and F	6	37%	8%‖‖	1	1	0	0	0	1	1	4
Hillis et al (2004)[21]	USA	C	HMO	9159	≥18	F	8	34%	15%	1	1	1	1	0	1	1	6
Hughes et al (2016)[36]	UK	CS	General	3885	18–69	M and F	9	54%	8%	1	1	1	1	0	1	1	6
Koss et al (2003)[22]	USA	CS	Tribal communities	1660	20–81	M and F	9	14%	NR	1	1	1	1	0	1	1	6

(Table 1 continues on next page)

	Study characteristics									Quality assessment*							
	Country	Study type	Population	Sample size (n)	Age range (years)	Sex	ACEs measured (n)	0 ACE prevalence (%)†	≥4 ACE prevalence (%)†	Sample representativeness‡	Bias§	ACE¶	Response‖	Refusers**	Subjects††	Control‡‡	Total quality score
(Continued from previous page)																	
LaNoue et al (2012)[23]	USA	CS	Primary care	210	48 (mean)	M and F	8	12%	38%	0	0	0	0	0	1	1	2
Leung et al (2016)[37]	UK	C	Civil servants	7870	45–69	M and F	6	67%	1%‖‖	1	0	0	0	0	1	1	3
Mersky et al (2013)[24]	USA	C	Urban minority	1142	22–24	M and F	8	21%	15%‖‖	0	0	1	0	0	1	1	3
Miller et al (2011)[25]	USA	CS	General	5130	≥21	M and F	12	47%	8%	1	1	1	1	0	1	1	6
Mouton et al (2016)[26]	USA	C	Primary care	22 227	40–79	M and F	10	42%	18%	0	0	1	0	0	1	1	3
Pirkola et al (2005)[39]	Finland	CS	General	4706	30–64	M and F	11	42%	9%	1	1	0	0	0	0	1	3
Ports et al (2016)[27]	USA	C	HMO	7272	≥19	M and F	10	33%	16%	1	1	1	0	0	1	1	5
Ramiro et al (2010)[8]	Philippines	CS	General	1068	≥35	M and F	11	27%	9%	1	1	1	0	0	1	1	5
Randell et al (2015)[28]	USA	CS	Head Start parents	215	NR	NR	9	24%	32%	0	0	1	1	0	0	1	3
Raposo et al (2014)[29]	USA	CS	General	7080	≥65	M and F	6	57%	NR	1	0	1	1	0	0	1	4
Su et al (2015)[30]	USA	C	Public schools	394	20–38	M and F	10	31%	19%	0	0	1	0	0	1	1	3
Wade Jr et al (2016)[31]	USA	CS	General	1784	≥18	M and F	9***	33%	20%	0	0	1	1	0	1	1	4
Xiao et al (2008)[41]	China	CS	Medical students	2073	22 (F); 23 (M; means)	M and F	10	32%	10%	1	1	1	1	0	1	1	6
Ye et al (2014)[32]	USA	CS	General	5928	≥18	M and F	8	42%	14%	1	1	1	1	0	1	1	6

ACE=adverse childhood experience. CS=cross-sectional. M=male. F=female. C=cohort. HMO=Health Maintenance Organization. NR=not reported. *Quality assessment scoring: 1=study met the criteria; 0=study did not meet the criteria, or not reported. †Decimals have been rounded. ‡Study used a random-sample or whole-population approach. §Study sample not considered to have additional bias. ¶Validated or well described ACE measurement tool. ‖Response rate of 50% or higher—methods of calculating response rates varied between studies, thus rating is based on available data. **Information provided about individuals that chose not to participate in the study. ††Demographic description of sample provided. ‡‡Appropriate control group used. §§For individual country samples: Albania 30%, Latvia 28%, Lithuania 47%, Macedonia 60%, Montenegro 57%, Romania 46%, Russia 50%, and Turkey 57%. The weighted average across all studies (excluding duplicate samples and missing data) is 43%. ¶¶For individual country samples: Albania 7%, Latvia 14%, Lithuania 7%, Macedonia 2%, Montenegro 5%, Romania 8%, Russia 5%, and Turkey 5%. The weighted average across all studies (excluding duplicate samples and missing data) is 13%. ‖‖Estimates based on data reported across other ACE count values. ***Study measured an additional five ACEs, but relevant analyses limited to nine conventional ACEs.

Table 1: **Characteristics of included articles**

	Studies (n)
Childhood physical abuse	34
Household substance abuse	34
Childhood sexual abuse	33
Household mental illness	31
Exposure to domestic violence	31
Emotional, psychological, or verbal abuse	30
Parental separation or divorce	28
Household criminality	27
Neglect	14
Family financial problems	4
Family conflict or discord	4
Bullying	3
Death of parent or close relative or friend	3
Separation from family (eg, out-of-home care)	3
Serious childhood illness or injury	3
Other (measured in fewer than three studies)*	9

Questions used to establish ACEs varied between studies. *Childhood hunger, child protection record, family instability, frequent fear of family member, household dysfunction, absence of male parental figure, low parental education, low standard of living, low socioeconomic status, non-intact family, parental unemployment, poor parent-child relationship, severe illness in family, single-parent family, victim or witness of violent crime, and witness of community violence.

Table 2: **Adverse childhood experience categories measured by included studies**

along with the number of studies, samples, and countries for each outcome.

Pooled ORs for individuals with four or more ACEs (*vs* individuals with no ACEs) for each outcome are presented in table 4. Corresponding forest plots are provided in the appendix. Funnel plots showing risk of publication bias for outcomes with at least ten samples are also given in the appendix. Smoking, alcohol use, and drug use ORs ranged from 2·20 (95% CI 1·74–2·78) for heavy alcohol use to 10·22 (7·62–13·71) for problematic drug use, all with high heterogeneity between estimates (except for problematic drug use, which had low heterogeneity). Although statistical tests were non-significant, visual assessment of the funnel plot indicated that smaller studies tended to report greater risk of smoking than did larger studies (appendix). Despite variation in outcome measurement for heavy alcohol use (table 3), this variation had no visible effect on study estimates. We did not note any evidence of reporting biases for illicit drug use (appendix).

Pooled ORs for sexual health outcomes ranged from 3·64 (95% CI 3·02–4·40) for multiple sexual partners to 5·92 (3·21–10·92) for sexually transmitted infections (table 4). Heterogeneity between estimates was low for multiple sexual partners and high for other outcomes. For teenage pregnancy, four studies[9,33–35] had measured unintended teenage pregnancy and these studies reported higher estimates than did those measuring any teenage pregnancy[8,14,21] (appendix). For early sexual initiation, visual assessment of the funnel plot suggested that small studies showing significant effects were missing (appendix).

Physical inactivity had the weakest relationship with multiple ACEs (table 4). We noted moderate heterogeneity between estimates, but no evidence of reporting biases (appendix). For overweight or obesity, the pooled OR was slightly higher, with high heterogeneity between estimates. Higher ORs were reported by studies using higher body-mass indices (appendix). We noted an about four-times higher risk in individuals with at least four ACEs across the three indicators of mental distress or disorders (table 4). Heterogeneity between estimates was low for low life satisfaction and high for anxiety and depression. For anxiety, estimates were lower for studies measuring more recent anxiety than for those measuring longer-term anxiety (appendix). We did not identify this difference among estimates for depression, with no evidence of asymmetry in the funnel plot (appendix).

Pooled ORs were 7·51 (95% CI 5·60–10·08) for violence victimisation and 8·10 (5·87–11·18) for violence perpetration (table 4). Heterogeneity was moderate between estimates. Suicide attempt had the strongest relation with ACEs. However, five of the seven samples comprised students aged 18–25;[13] pooling of the remaining two samples[8,18] resulted in an OR of 12·53 (6·71–23·37; appendix). Across the five chronic diseases examined, the lowest pooled OR was for diabetes and the highest was for respiratory disease. Other diseases had between a two-times and three-times increase in odds with at least four ACEs (table 4). Heterogeneity was low between estimates pooled for all chronic diseases. A similar increase in risk was identified for poor self-reported health, with low heterogeneity.

We assessed studies against seven quality criteria (table 1). Summed quality scores ranged from 2 to 7, with three articles obtaining the maximum 7 points. 11 articles reported on studies that had not used random or whole-population approaches. All included studies are likely to be affected by bias given relations between ACEs and harms that remove people from population surveys (eg, homelessness, institutionalisation, and premature death). Thus, studies scored positively if they did not appear to include further bias in their recruitment strategies, with 11 articles not meeting this criterion. All articles used an appropriate control group and all but four used validated or clearly defined ACE measurement tools. 15 had response rates of less than 50% and although only four did not adequately describe study participants, 34 provided no information about non-participating individuals.

Sensitivity analyses (excluding outlying studies) reduced pooled ORs for physical inactivity, diabetes, heavy alcohol use, smoking, and illicit drug use and increased those for early sexual initiation, depression,

	Samples (n)	Articles (n)	Countries (n)	Combined study sample size*	References
Physical inactivity: fewer than three physical exercise sessions per week (4, C); physical inactivity (6, C; 2, NR)	12	7	9	32 760	6,7,9,13,32,33,35
Overweight or obesity: obesity (1, NR); BMI ≥25 (2, C), BMI ≥30 (3, C), BMI ≥35 (1, C); Weight ≥170 lbs (1, NR)	8	8	5	84 840	1,7,8,16,31,33,35,38
Diabetes: diabetes (6, L); type 2 diabetes (2, L)	8	8	4	123 659	2,6–8,16,20,31,35
Cardiovascular disease: coronary heart disease (3, L), coronary heart disease or heart attack (1, L); cardiovascular disease (2, L), ischaemic heart disease (2, L)	8	8	4	123 663	2,6–8,16,20,31,35
Heavy alcohol use: binge drinking (1, NR); regular binge drinking (3, C); high risk drinker (1, C); hazardous drinking (1, C); frequent intoxication (1, C); heavy drinking (1, L; 1, NR)	9	9	4	84 904	9,16,32–35,37,38,41
Poor self-rated health: poor health (1, C); fair or poor health (2, NR); fair or poor general health (1, C); worse than very good health (1, NR)	5	5	3	74 005	6,8,20,24,40
Cancer: any cancer (4, L)	4	4	3	17 989	2,6,7,35
Liver or digestive disease: liver disease (1, L); digestive or liver disease (3, L); hepatitis or jaundice (1, L); liver problems or hepatitis (1, L)	6	6	4	20 775	2,6–8,33,35
Smoking: smoking (12, C; 1, L; 1, O); cigarette smoking (3, C), smoking or e-cigarette use (1, C); daily smoking (3, C); frequent tobacco use (1, C)	22	15	12	152 830	1,8,9,13,16,19,24,26,30–35,38
Respiratory disease: respiratory disease (3, L); chronic respiratory disease (1, L); chronic obstructive pulmonary disease (2, L); chronic bronchitis or emphysema (1, L); tuberculosis (1, L)	8	8	4	72 050	2,6–8,17,32,33,35
Multiple sexual partners: three or more (1, NR), five or more (7, L), 30 or more (1, L)	9	3	9	26 903	1,8,13
Anxiety: anxiety (1, C; 1, L; 1, NR), frequent anxiety (1, C), anxiety disorder (2, 1 year; 1, 5 year)	7	7	4	38 092	1,8,24,29,32,39,42
Early sexual initiation: sexual intercourse before the age of 15 years (1), sexual intercourse before the age of 16 years (11), sexual intercourse before the age of 17 years (1)	13	7	10	38 259	1,8,9,13,33–35
Teenage pregnancy: having or causing teenage pregnancy younger than 19 years (2); having or causing unintended teenage pregnancy younger than 18 years (4)	6	7	3	29 715	8,9,14,21,33–35
Low life satisfaction: low life satisfaction (4, C); dissatisfied or very dissatisfied with life (1, C)	5	5	2	17 675	24,32,33,35,36
Depression: depression (4, L; 2, C), depressed affect (1, L), major depression (1, 5 years), moderate or severe depression (1, C), depressive symptoms (1, C), frequent depressive symptoms (1, C), depressive disorders (1, 1 year), mood disorder (1, 1 year)	13	13	5	104 672	1,7,8,15,16,23,24,29,31,32,38,39,42
Illicit drug use: drug use (1, L; 1, NR); illicit drug use (1, O;† 1, NR); street drug use (7, L); cannabis use (4, L), frequent cannabis use (1, C)	16	10	11	42 816	1,7,8,9,13,24,30,33–35
Problematic alcohol use: alcoholism (1, L); problem drinker or alcoholic (6, L); self-reported alcoholic (1, L); alcohol disorders (1, 1 year; 1, L)	10	5	9	33 992	1,13,22,39,41
Sexually transmitted infections: having had a sexually transmitted infection (6, L)	6	6	4	28 014	7,8,18,31,33,35
Violence victimisation: been hit (4, 1 year); physical dating violence younger than 21 years (1); sexual violence (1, adulthood)	6	6	2	25 119	9,25,27,33–35
Violence perpetration: intimate partner violence (2, L); hit someone (4, 1 year); physical dating violence younger than 21 years (1); child neglect (1, C)	8	8	3	27 935	1,9,25,28,33–35,43
Problematic drug use: injected drug use (1, L), heroin or crack cocaine use (4, L)	5	5	2	30 101	1,9,33–35
Suicide attempt: attempted suicide (7, L)	7	3	7	24 858	8,13,18

Data for outcomes are definition (number of samples, timeframe). C=current (including past month). NR=not reported. BMI=body-mass index. L=lifetime. O=other. *Including all study participants; analysis limited to cases with no ACEs and four or more ACEs. †Current at any measurement point over the 23 year study.

Table 3: **Outcome definitions, study numbers, and combined study sample sizes for each outcome**

problematic alcohol use, and suicide attempt (table 4). We identified no outliers for other outcomes. For physical inactivity, both outlying studies were student samples, with estimates tending to be higher among such samples than among general population samples. For problematic alcohol use, the outlying study used a past year measurement (*vs* lifetime elsewhere). We identified no clear explanatory factors for other outcomes.

We did meta-regression for smoking, problematic alcohol use, illicit drug use, early sexual initiation, and depression. We noted no significant relationships between ORs and any measured covariate for illicit drug use, problematic alcohol use, or depression (appendix). For smoking, studies focusing on old participants (≥35 years) reported lower odds of smoking than did those including general or young samples (β=–0·54; se[β]=0·26; p=0·05). For early sexual initiation, studies measuring fewer ACEs reported significantly higher odds (β=–0·58; se[β]=0·22; p=0·03).

Discussion

To our knowledge, this study is the first to synthesise evidence for the effect of multiple ACEs and measure the relative magnitude of associations with many of the lifestyle behaviours and health conditions that challenge public health globally. For all outcomes examined, pooled ORs indicated increased risk among individuals with at least four ACEs compared with those reporting none.

	OR	Heterogeneity (I^2)	References
Physical inactivity	1·25 (1·03–1·52)	65·2% (23·6–79·7)	6,7,9,13,32,33,35
Excluding outliers	1·12 (0·97–1·29)	35·7% (0–68·2)	6,7,9,13*,32,33,35
Overweight or obesity	1·39 (1·13–1·71)	75·1% (39·6–86·0)	1,7,8,16,31,33,35,38
Diabetes	1·52 (1·23–1·89)	48·3% (0–75·2)	2,6–8,16,20,31,35
Excluding outliers	1·38 (1·20–1·60)	0% (0–58·5)	6–8,16,20,31,35
Cardiovascular disease	2·07 (1·66–2·59)	23·7% (0–65·9)	2,6–8,16,20,31,35
Heavy alcohol use	2·20 (1·74–2·78)	75·0% (43·5–85·6)	9,16,32–35,37,38,41
Excluding outliers	2·00 (1·69–2·37)	46·4% (0–73·5)	9,16,32,33,35,37,38,41
Poor self-rated health	2·24 (1·97–2·54)	0% (0–64·1)	6,8,20,24,40
Cancer	2·31 (1·82–2·95)	0% (0–67·9)	2,6,7,35
Liver or digestive disease	2·76 (2·25–3·38)	0% (0–61·0)	2,6–8,33,35
Smoking	2·82 (2·38–3·34)	87·1% (82·1–90·2)	1,8,9,13,16,19,24,26,30–35,38
Excluding outliers	2·70 (2·34–3·11)	71·9% (51·4–81·4)	8,9,13†,16,19,24,26,30–33,35
Respiratory disease	3·05 (2·47–3·77)	0% (0–56·3)	2,6–8,17,32,33,35
Multiple sexual partners	3·64 (3·02–4·40)	16·5% (0–61·5)	1,8,13
Anxiety	3·70 (2·62–5·22)	82·2% (59·7–89·7)	1,8,24,29,32,39,42
Early sexual initiation	3·72 (2·88–4·80)	75·5% (54·0–84·5)	1,8,9,13,33–35
Excluding outliers	3·83 (3·05–4·82)	56·7% (0–76·3)	8,9,13†,33–35
Teenage pregnancy	4·20 (2·98–5·92)	77·1% (33·6–88·0)	8,9,14,21,33–35
Low life satisfaction	4·36 (3·72–5·10)	0% (0–64·1)	24,32,33,35,36
Depression	4·40 (3·54–5·46)	80·0% (64·8–86·9)	1,7,8,15,16,23,24,29,31,32,38,39,42
Excluding outliers	4·74 (3·88–5·80)	75·2% (51·7–84·6)	1,7,8,15,16,23,24,,31,32,38,39,42
Illicit drug use	5·62 (4·46–7·07)	76·4% (59·6–84·3)	1,7,8,9,13,24,30,33–35
Excluding outliers	5·17 (4·48–5·96)	24·1% (0–61·2)	1,7,8,9,13§,24,30,33,35
Problematic alcohol use	5·84 (3·99–8·56)	79·7% (60·0–87·5)	1,13,22,39,41
Excluding outliers	6·86 (5·36–8·78)	37·6% (0–70·0)	1,13,22,41
Sexually transmitted infections	5·92 (3·21–10·92)	78·4% (39·7–88·5)	7,8,18,31,33,35
Violence victimisation	7·51 (5·60–10·08)	59·0% (0–81·3)	9,25,27,33–35
Violence perpetration	8·10 (5·87–11·18)	68·2% (12·8–83·1)	1,9,25,28,33–35,43
Problematic drug use	10·22 (7·62–13·71)	12·0% (0–68·2)	1,9,33–35
Suicide attempt	30·14 (14·73–61·67)	77·4% (42·5–87·5)	8,13,18
Excluding outliers	37·48 (22·19–63·31)	23·9% (0–69·6)	13,18

Data in parentheses are 95% CIs. OR=odds ratio. *Excluding Latvian and Lithuanian samples. †Excluding Albanian sample. ‡Excluding Russian sample. §Excluding Russian, Latvian, and Lithuanian samples.

Table 4: **Pooled ORs from random-effects meta-analyses**

Associations were weak or modest for physical inactivity, overweight or obesity, and diabetes; moderate for smoking, heavy alcohol use, poor self-rated health, cancer, heart disease, and respiratory disease; strong for sexual risk taking, mental ill health, and problematic alcohol use; and strongest for problematic drug use and interpersonal and self-directed violence. We found considerable heterogeneity between estimates for almost half of the outcomes.

This study supports substantially increased health risks to adults who report multiple ACEs, but others identify how having such ACEs is common globally.[44] A billion children aged 2–17 years were estimated to have been victims of violence worldwide in 2014.[45] Across the east Asia and Pacific region, the health consequences of child maltreatment have been estimated to cost around 2% of gross domestic product.[46] Global estimates of the prevalence and costs of many other ACEs among children, such as witnessing of domestic violence, are not yet available. Despite accumulating knowledge about the lifelong effects of ACEs, their prevention and the development of resilience and support for those affected have been slow to move up political agendas. International attention is increasingly focusing on prevention of violence against children, often emphasising protection of girls.[47] Although girls are especially vulnerable to certain ACEs (eg, sexual abuse), both sexes are routinely victims of multiple ACEs and both feel their long-term effects.[48] In fact, the high prevalence of ACEs combined with their effect on life-course health suggests a substantial but largely hidden contribution to Global Burden of Disease estimates, which include childhood sexual abuse, yet not many other ACEs.[49] Thus, smoking and alcohol use are leading risk factors for burden of disease,[49] and in this study, individuals who had had at least four ACEs were more than twice as likely to be current smokers or heavy drinkers and almost six times as likely to drink problematically than were those who had had no ACEs. Consistent with such elevated risks, NCDs including respiratory disease, diabetes, cancers, and heart disease (the leading cause of death globally[50]), were also substantially more likely in those with at least four ACEs than in those with none.

Most studies included in this systematic review and meta-analysis were done in high-income countries, with nine samples from middle-income countries and none from low-income countries. The World Mental Health Surveys across 21 countries found little variation in ACE prevalence between country income groups, with 38–39% of participants reporting at least one ACE and the prevalence of at least four ACEs being 2–3%.[51] These levels are lower than those measured by studies in this systematic review and meta-analysis, with 57% of participants across all studies reporting at least one ACE and 13% reporting at least four. Little is known about how ACEs predict health outcomes in low-income, high-violence settings, where exposure to adversity is widespread across the life-course. However, evidence suggests that ACEs are associated with substance abuse, mental illness, and HIV risk in such settings.[52]

To date, efforts to prevent NCDs, for instance, have focused predominantly on tackling of proximal determinants (eg, behavioural modifications, advertising, or pricing).[53] Sustained prevention gains might require a shift in focus to include the early drivers of poor health. Policies that capture the environmental and societal causes of adversity in childhood offer new opportunities to address ACEs rather than just their consequences. Specifically, through the UN 2030 Agenda for Sustainable Development, countries have committed to action to

meet 17 global Sustainable Development Goals (SDGs) by 2030. Although several SDGs (eg, Goal 5 [gender equality] and Goal 16 [peace and justice]) address violence directly, many others support focus on broad ACEs and their risk factors (eg, Goal 3 [good health and wellbeing], Goal 4 [quality education], and Goal 10 [reduced inequalities]). Crucially, the SDGs also place major focus on early childhood development as a means of securing lifelong health and provide strong political endorsement and a multisectoral framework for this approach.[54]

Along with the outcomes covered in this analysis, studies are now identifying associations between multiple ACEs and broad harms to life prospects, including education, employment, and poverty.[55] Strengthening understanding of the combined effect of ACEs across multiagency priorities should catalyse multidisciplinary prevention focused on early intervention. Thus, work to address a single ACE in children exposed to many might have little effect,[51] with treatment and prevention of many health conditions requiring multiple underlying ACEs to be addressed. Collaborative, trauma-informed services can address the various adversities that affect individuals and families across the life course, providing integrated services to support individuals and reduce the likelihood that their own children in turn will be affected by ACEs. A body of evidence suggests that many different agencies can contribute to prevention of ACEs and reduction of their effects.[56,57] In health settings, for example, primary prevention can be supported through maternity and home visiting services that strengthen parenting skills[58] and screening of families for risk factors for ACEs as part of routine child health care, providing support and referral.[59] Screening of adult patients for a history of ACEs can help both patients and professionals understand the underlying causes of health problems and enable better-informed treatment options than without this approach.[60] ACE-informed practice can be developed across multiple settings, including schools, criminal justice agencies, and social care. Although eradication of ACEs remains aspirational, development of children's personal resilience to enable them to overcome adversity and avoid its harmful effects is crucial. Resilience programmes to develop problem solving and coping skills, for example, can be delivered universally in schools and tailored to meet the needs of vulnerable children in youth justice, social services, and community settings.[57,61]

This systematic review and meta-analysis has several limitations that could contribute to heterogeneity between study estimates. All included studies incorporated retrospective ACE reports, which could be affected by recall or reporting biases, although retrospective reports of major, easily defined ACEs are deemed to have acceptable psychometric properties.[62,63] The number and types of ACEs recorded by studies varied and although summing of ACEs is a recognised approach,[1,9,51,63] it does not account for potential variations in effects of different combinations of ACEs. Equally, although most studies measured ACEs at any point in childhood or adolescence (typically <18 years of age), the approach does not account for variation in age at or length of exposure. Furthermore, although many risk estimates controlled for confounding factors (mainly sociodemographics), such factors varied and some studies included no such adjustments. Genetic variation and environmental risks (eg, drinking during pregnancy or parental smoking), which are likely to influence relations between ACEs and health, were largely unmeasured. These limitations suggest a need for greater standardisation in ACE studies, and work to support this standardisation has already begun,[64] with many studies now using consistent measurement and analytical approaches. However, our criteria also meant that studies were excluded because of alternative data analysis methods (eg, analysis of the World Mental Health Surveys[51]). A strength of our systematic review and meta-analysis is that it highlights consistency between studies in the links between exposure to multiple ACEs and poor health, despite likely variation in type and extent of exposure. Further work to synthesise dose-response relations between ACEs and poor health and better understand the relative effects of specific ACE types and combinations are needed to better inform effective targeting of prevention.

We focused on studies in community settings, which are likely to exclude those with the most complex health problems (eg, homeless populations) and those who have already had ACE-related premature mortality. Interpretation of results is also challenged by variation in measurements within grouped outcomes and in the prevalence of included outcomes, with rarer outcomes (eg, suicide attempt) less well covered by population surveys than those such as smoking. Furthermore, in the case of prevalent outcomes like smoking, increased odds will represent substantial increases in absolute risk, whereas increased odds for rare outcomes represent small increases in absolute risk. Included outcomes probably also differ in validity, with difficulties in measurement of physical inactivity, for example, potentially contributing to its low association with multiple ACEs in this study. Finally, this study was only able to measure associations; biomedical evidence is increasing to support plausible causal relations between childhood trauma and poor health, with studies identifying neurological, hormonal, immunological, and epigenetic changes in those exposed to ACEs.[3,65,66] Future studies would benefit from designs that allow stronger causal inference and control for factors that attenuate or amplify observed relations.

This systematic review and meta-analysis identifies the pervasive effects that childhood adversity can have on health across the life course, with exposure to multiple ACEs affecting all 23 of the health outcomes examined, including some of the leading causes of the global

For the **Sustainable Development Goals** see http://www.un.org/sustainabledevelopment/sustainable-development-goals/

burden of disease. Outcomes showing the strongest relations with multiple ACEs (violence, mental illness, and problematic substance abuse) can represent ACEs for the next generation (exposure to parental domestic violence, mental illness, and substance use) and thus are indicative of the intergenerational effects that can lock families into cycles of adversity, deprivation, and ill health. Although research into ACEs is far from complete, a compelling case exists for increased international focus on prevention of ACEs, development of programmes to bolster resilience, and implementation of policies that support a sustainable life-course approach to health.

Contributors

KH and MAB developed the study and oversaw its implementation. KH and KAH did review activities, consisting of searches, study selection, data extraction, and quality assessment. KH did the meta-analyses and LJ did the meta-regression. KH and MAB wrote the manuscript with contributions from DS, AB, CM, LJ, and MPD. All authors reviewed the study findings and read and approved the final version before submission.

Declaration of interests

We declare no competing interests.

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