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Adverse childhood experiences and adult health: the need for stronger study designs to evaluate impact

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Introduction

Early life is regarded as a crucial period of neurobiological, emotional, social, and physical development in all animal species, and may have long-term implications for health across the life course. The first studies examining the pre-adult origins of later chronic disease were probably published more than 50 years ago and based on rodent models.[1] By briefly administering a sub-optimal diet to newborn mice, Dubois and others[1] demonstrated a marked impact on subsequent growth and resistance to infection. In the 1970s, Forsdahl,[2] using infant mortality rates as a proxy for living conditions at birth, arguably provided the first evidence in humans for an association with heart disease in later life. In the last two decades, findings from longitudinal studies with extended mortality and morbidity surveillance have implicated a host of pre-adult characteristics as potential risk factors for several chronic disease outcomes, including peri- and post-natal growth,[3] coordination,[4] intelligence,[5,6] mental health,[7] overweight,[8,9] physical stature,[10] raised blood pressure,[11,12] cigarette smoking,[13] physical strength,[14] diet,[15], amongst many others.[16]

An array of prospective studies has also demonstrated associations of childhood socioeconomic disadvantage – indexed by paternal social class or education, the presence of household amenities, domestic overcrowding – with somatic health outcomes in adulthood, chiefly premature mortality and cardiovascular disease.[17,18] Parallel work has been undertaken by psychologists and psychiatrists exploring the consequences of childhood maltreatment for later psychopathologies – perhaps the most well examined health endpoint in this context.[19 20] Collectively, these early life circumstances have been more widely defined to comprise the separate themes of material deprivation (e.g., economic hardship, long-term unemployment); stressful family dynamics (e.g., physical and emotional abuse, psychiatric illness, or substance abuse by a family member); loss or threat of loss (e.g., death or serious illness of a parent or a sibling, parental separation, public care) – amongst many other characteristics – and a continuum of severity can be constructed (**Box**).[21,22] Broadly referred to as adverse childhood experiences (widely known as 'ACE'), survey data

suggest that as many as 6 in 10 adults in the general population report at least one childhood adversity,[23] though this prevalence is based on recall in adult populations which may lead to a distortion in its estimation (see later). Adverse childhood experiences, rather like poor health behaviours,[24] tend to cluster, and this has led to a growing body of work examining the impact of accumulated early adversity rather than a single characteristic.[21]

Given the considerable current research interest in adverse childhood experiences – according to Pubmed, in 2019, there were more than 1000 publications on the topic, representing a doubling over the prior two-year period (**Figure**) – in the present overview, we describe the potential mechanisms that may underlie the link between this early life characteristic and adult health; the current evidence for such an association; the validity of adversity data; and public health implications with future directions for the field.

Potential mechanisms of effect

Adverse childhood experiences may have an influence on subsequent health outcomes via biological, psychological, and social processes, and their effects may be direct or indirect. Of the direct mechanisms, a widely-held view is that people who experience a high and varied load of adversities in early life may become more susceptible to disease occurrence, and potentially have a worse illness prognosis, via differences in physiological development. These mechanisms of biological embodiment will be outcome-specific: those relevant to stroke, a disease, may have little in common with those for suicide, a behaviour, for instance. Over the life course, however, adverse childhood experiences are likely to be linked with an inter-related, extant, and serial set of behavioural, psychological, and physical disorders and diseases – as described in synergistic theory[25] – such that networks of disease and adverse behaviours cascade in people experiencing major socioeconomic adversity in adulthood.[26]

Although not a universal observation,[27-29] early adversity appears to lead to chronically elevated levels of cortisol[30] – the most common human glucocorticoid and a biomarker of psychosocial stress – and indicators of systemic inflammation[31,32] which themselves have been linked to major causes of adult disease, such as cardiovascular disease[33] and mental health.[34,35] Related, there is some support for epigenetic modification of certain characteristics, most notably NRC31 – the receptor to which cortisol and other glucocorticoids bind – in participants exposed to pre-adult disadvantage.[36] NRC31 codes for the glucocorticoid receptor and altered glucocorticoid levels have, in turn, been linked to adult mental health problems.[37,38] Complementary evidence suggests that, relative to their unaffected counterparts, maltreated children have a lower volume of prefrontal cortex and experience greater activation of the hypothalamic pituitary adrenal (HPA) axis which is central to the human stress response.[39]

Traumatic experiences in childhood have been repeatedly shown to have lasting impacts on psychopathology, such as major depression, substance abuse, and post-traumatic stress disorder,[40] and these mental health problems may link adverse childhood experiences to physical illnesses – as well as representing a key public health concern in their own right, psychiatric disorders have been implicated in the occurrence of chronic somatic disease (communicable[41,42] and non-communicable[43]), and injury (unintentional[44] and intentional[45]), in addition to hampering help-seeking behaviour, diagnosis, and treatment.[46] Further indirect mediating effects include the impact of pre-adult adversity on later socioeconomic status[47] and health behaviours, such as smoking, heavy alcohol intake, low exercise levels, and poor diet,[48] all of which have well established links with chronic disease in later life.[49]

Current evidence for an association of early adversity with adult health

The existing literature features an array of health outcomes in adulthood that have been correlated with adverse childhood experiences,[21,50-55] the different operationalisations of which can make

synthesis of findings challenging. For inclusion in a recent systematic review, investigators required studies to report on risk estimates for multiple (four or more) early adversities, and for there to be a minimum of 3 published papers featuring the same health endpoint/risk factor; this resulted in 22 outcomes across 37 studies.[21] The outcomes with the strongest relationship with adversity were behaviours (odds ratios 5.2 to 37.5) – violence victimisation or perpetration, drug use, suicide – rather than those characterised by disease processes that occur over years and possible decades such as liver or digestive disease, respiratory disease (odds ratio ~3), vascular disease[56] and malignancies[57] (odds ratio <=2.3). This is suggestive of a temporal order for the health impact of adversity.

Inevitably, the evidence base for a role of early adversity in the aetiology of adult disease needs to be viewed against the quality of available studies. Strikingly, in the described review,[21] within the constraints of the inclusion criteria, there were no studies with prospectively gathered data on adverse childhood experiences that met inclusion requirements. Rather, included studies fell into two broad categories: cross-sectional, whereby exposure and outcome were assessed simultaneously in adults, usually via self-report; or quasi-prospective, whereby study members again provide distant recall of pre-adult events and only the endpoint was in fact prospectively captured.

Genuine prospective studies – those with an assessment of adverse experiences that was made in childhood followed by prospective ascertainment of health outcome in adulthood are rare and largely limited to a few birth cohort studies either conducted in the field[27,29] or generated from the linkage of routinely gathered data.[22,58] Field-based studies with the required extended follow-up period have typically been carried out in the era preceding the current research interest in childhood adversities, thus, construction of the exposure variable in often *post hoc* and often found wanting relative to contemporary, theory-driven definitions of this exposure. Meanwhile, electronic record studies, while typically offering high statistical power, miss undiagnosed morbidity, perhaps capture

only those cases of adversity that come to the attention of social services, and often lack a breadth of data, most obviously on confounding factors.

Validity of early adversity data and other methodological considerations

The genuine prospective studies apart, a core issue in the synthesis of evidence on the health sequalae of adversity is the validity of the distantly recalled exposure data. There are obvious reasons to expect several biases to exert an impact on the quality of the data elicited many years following adverse events, including simply forgetting – potentially as a protective mechanism – infantile amnesia, and the influence of intervening life events such that it is unlikely that an individual with contemporary experience of somatic illness and, particularly, mental health problems will provide the same unbiased account of early life misery as a person free of such conditions. Perhaps unsurprisingly then, agreement between retrospective and prospective assessments of childhood maltreatment is poor, with a recent aggregation of kappa statistics across 16 studies which had both prospective and retrospective measurement being as low as 0.2,[59] an observation that accords with earlier narrative reviews.[60] Expressed differently, this indicates that prospective and retrospective measurement of early disadvantage tend to capture almost mutually exclusive groups of people. What makes this finding more striking is that, in 15 of the 20 studies identified, 'distant' recall was made earlier in the adult life course (<30 years of age), and in several, participants were in adolescence.[59] Even mid-life recollection of early life socioeconomic status based on occupational social class – essentially an enquiry about the type of job held by the study member's father – showed only moderate levels of agreement with reports from the earlier era.[61]

The implications of these unfavourable psychometric characteristics for the examination of associations adult health outcomes may be acute. For studies exploring mental health outcomes, effects seem to be stronger when based on the retrospectively-captured adversity data.[62] For

somatic outcomes, in analyses of data from a birth cohort study, overcrowding at age 11 based on prospectively gathered parental reports when the study member was aged 11 years was unrelated to standard queries about asthma or wheezy bronchitis at age 50, whereas retrospectively gathered data on this marker of pre-adult adversity appeared to confer *protection* against the same respiratory outcome.[63] In a rare study with objective health outcomes, retrospectively captured data on early life poverty showed no relation with death or vascular disease events, whereas prospectively gathered records on hygiene and living conditions revealed the expected gradients.[64] Despite these concerns of distant recall of early adversity, however, a cross-sectional study regarded by some observers as the progenitor study in the field of early adversity and adult health was in fact based on the simultaneous assessment of exposures and outcomes made via self-report in middle- and older-aged people. Published two decades ago,[65] it has, according to Scopus, been cited a striking 6,500 times and has recently been reprinted.[66]

A concern that may impact on all field-based studies is health-related selection into and out of the study population, such that children exposed to the greatest degree of adversity are perhaps least likely to participate. This issue is perhaps less problematic when cohort studies are based on electronic linkage to health, social and welfare registries although, as described, it is likely that only treated illnesses[67] and the most severe cases of adversity are captured.

Public health implications and future research priorities

While cross-sectional studies suggest there may be emerging links between adverse childhood experiences and a wide range of health outcomes, not all of which have clear explanatory mechanisms, this evidence base is not yet of sufficient quality to make definitive conclusions regarding public health impact. Findings in social epidemiology should be subject to the same level of scrutiny and doubt deployed in other spheres of science. In cardiovascular medicine, for instance, following very encouraging signals from an abundance of well-designed prospective

cohort studies,[68-70] pharmacological control of blood pressure,[71] serum cholesterol,[72] and diabetes[73] in randomised controlled trials has been shown to *cause* reductions in cardiovascular event rates. Genuine prospective cohort studies, natural experiments, and trials – the latter also very rare in our search of the databases[74] – are now needed in the field of adverse childhood experiences to quantify health consequences, specify the most harmful exposures, and then confidently steer policy.

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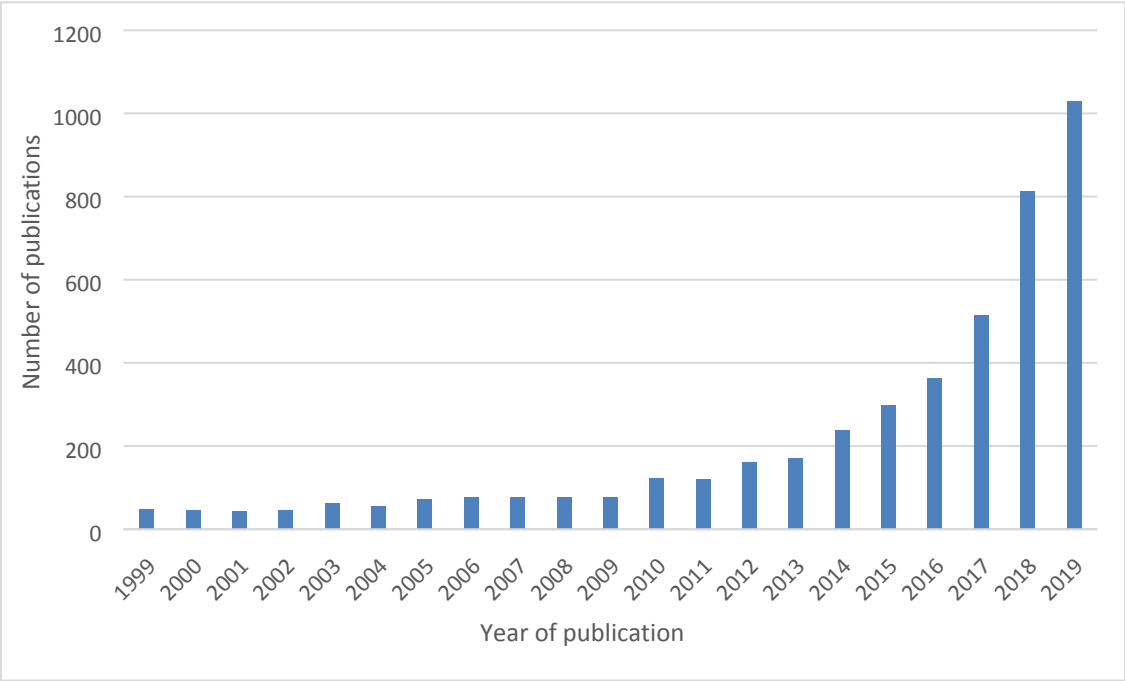
Box. Selected indicators of early adverse experience linked to adult health based on existing reviews[21,51,53]

Indirect	**Direct**
Family financial problems	Neighbourhood safety
Parental separation or divorce	Emotional, psychological, or verbal abuse
Family conflict or discord	Neglect
Death of parent or close relative or friend	Bullying
Parental incarceration/criminality	Separation from family (e.g., public care)
Witnessing violence or violence victimization	Serious childhood illness or injury
Household drug/substance abuse	Homelessness
Household mental illness	Dating violence
	Physical abuse
	Sexual abuse

Adversities are categorised according to their mode of action (indirect or direct), though other groupings have been advanced.[53] Adversities are arranged in ascending order of severity within each group, though this is moot: certain 'adversities' may actually be positive when the carer is abusive, such as parental separation, death, and incarceration, or when the child moves into public care. Adversities may have featured in studies of adult health outcomes either individually or comprising a summary score.

Figure. Number of publications by year in the area of adverse childhood experience



Based on a search of Pubmed using the following terms "adverse childhood experiences"[MeSH Terms] OR ("adverse"[All Fields] AND "childhood"[All Fields] AND "experiences"[All Fields]) OR "adverse childhood experiences"[All Fields] OR ("adverse"[All Fields] AND "childhood"[All Fields] AND "experience"[All Fields]) OR "adverse childhood experience"[All Fields]