RESEARCH PAPER

Adverse Childhood Experiences and frailty in later life: a prospective population-based cohort study

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Abstract

Background: The deficit accumulation method considers the ageing process underlying frailty as a random accumulation of health deficits.
Objective: Although Adverse Childhood Experiences (ACE) have consistently been associated with the onset of mental disorders and somatic diseases during adolescence and midlife, it remains unknown whether ACE still exert detrimental health effects in late life. Therefore, we examined cross-sectionally and prospectively the association between ACE and frailty among community-dwelling older people.
Design: Based on the health-deficit accumulation method, a Frailty Index was calculated with values ≥ 0.25 considered as frail. ACE were measured by a validated questionnaire. The cross-sectional association was examined by logistic regression among 2,176 community dwelling participants aged 58–89 years. The prospective association was examined by Cox-regression among 1,427 non-frail participants during a 17-year follow-up. Interactions with age and sex were tested and analyses were adjusted for potential confounders.
Setting: The present study was embedded in the Longitudinal Aging Study Amsterdam.
Results: ACE and frailty were positively associated at baseline (OR = 1.88; 95% CI = 1.46–2.42; $P = 0.05$). Among non-frail participants at baseline ($n = 1,427$), ACE interacted with age on the prediction of frailty. Stratified analyses showed that a history of ACE only resulted in a higher hazard rate for the incidence of frailty among those aged ≥ 70 years (HR = 1.28; $P = 0.044$).
Conclusion: Even in the oldest-old, ACE still lead to an accelerated rate of the accumulation of health deficits and therefore contribute to the onset of frailty.

Keywords: Adverse Childhood Experiences, Frailty Index, ageing, deficit accumulation, aged, older people

Key Points

- Adverse Childhood Experiences (ACE) are associated with an increased prevalence of frailty, measured by the Frailty Index.
- ACE are associated with an accelerated rate of accumulation of non-specific age-related health deficits in late life.
- This is the first study that shows prospectively the impact of ACE on the onset of frailty in the oldest old (70+).
- The window of opportunity to treat the consequences of ACE seems to extend into the latest stages of life.

Background

Adverse Childhood Experiences (ACE) are proven to have a detrimental health impact over the life course for the people that have experienced them [1, 2]. People with ACE have higher rates of mental disorders, including depression, anxiety and substance use disorders, as well as somatic diseases such as diabetes, heart disease and respiratory disease [3, 4]. The association of ACE with these different health impairments, implies that ACE compromise different physiological systems [4]. If those compromises remain unresolved over the lifespan, it could explain why ACE may also be associated with frailty in later life [5, 6].

Frailty affects about one out of ten community dwelling adults over 65 years of age and is considered an 'emerging global health burden' as it promotes illness, disability, hospitalisation and mortality [7, 8]. Elucidating the risk factors that can cause frailty is therefore crucial in order to halt this worldwide growing disease burden of frailty. How to operationalise this biomedical concept of frailty in clinical practice and research is still controversial. Over the past two decades, however, two dominant operationalisations of biomedical frailty have emerged in the literature. First, the Frailty Phenotype (FP), which marks an underlying physiologic state of multisystem and energy dysregulation [9]. Second, the Frailty Index (FI) incorporating the deficit accumulation method, stating that the proportion of ageing-related deficits acquired reflects biological age on top of chronological age [10]. To our knowledge, two studies have examined the association between ACE and frailty. The first study demonstrated a significant association with the FP, the second study with the FI [5, 6]. The latter study implies that ACE is not only associated with an earlier onset of clinical conditions, but also with non-specific health deficits that accumulate over time [11, 12]. As ACE, by definition, occur before the onset of diseases later in life, it remains unknown at what ages the difference in frailty status has emerged and more importantly, it remains unknown whether the effect of ACE continues among the oldest old.

The first aim of our study is to test the hypothesis that a history of ACE is cross-sectionally associated with frailty based on the deficit accumulation method among community-dwelling older people. Secondly, we will test our hypothesis that the incidence of frailty, operationalised according to the FI, differs between older persons with and without a history of ACE hypothesising that ACE exert ongoing effects in later life.

Methods

Sampling and design

We used data from the Longitudinal Aging Study of Amsterdam (LASA). LASA was founded to study the physical, emotional and cognitive functioning of older adults in the Netherlands and it is still ongoing [13]. The first wave of measurements started in 1992–93 with 3,107 participants aged between 55 and 85 years. Follow-up measurement waves were scheduled for approximately every 3 years. Data were mainly collected through face-to-face interviews. Participants had a main interview and an additional medical interview in which data were collected on smoking, alcohol, body mass index (BMI) and other health variables. In 1995–96, only participants aged 65 years or older had a medical interview. LASA has been approved by the Medical Ethical Committee of the VU University Medical Center and all participants have given informed consent [14].

For our current study, data from the second LASA measurement cycle (wave C) were used (1995–96), as the FI was most accurately measured from Wave C onwards [15]. Subsequently, we included five consecutive measurement waves for follow-up, totalling a study period of 17 years (baseline-T1 = 1995–96; T2 = 1998–99; T3 = 2001–02; T4 = 2005–06; T5 = 2008–09; T6 = 2011–12). From 2,545 participants at baseline, a total of 369 participants were excluded as they did not participate in the main interview and thus no frailty data were obtained (*n* = 243), had too many missing data to construct an FI (*n* = 84) or had missing data on ACE (*n* = 42). This resulted in a final study sample of 2,176 participants (1,148 women) with an age ranging from 58 to 89 years.

Primary outcome (FI)

The construction and validation of the LASA-FI has been previously described [15]. In our sample, the FI ranged from 0.0 to 0.7. Frailty is defined as an FI ≥0.25 [16].

Independent variable (ACE)

The ACE variable has been operationalised in a previous study within LASA [17]. Study participants were asked, using an open-ended question, whether they had experienced any significant life events before the age of 18 years that had a lasting impact on the rest of their lives. The reported ACE were categorised as follows: war experiences, death of a parent, death of an important other, excessive alcohol use of close relative, sexual abuse, severe problems at home, poverty or unemployment of parents, physical illness of respondent and 'other problems'. A dichotomous variable was created categorising participants in having or not having experienced significant ACE. There were no specific question items regarding physical or emotional abuse neither were there specific items on neglect.

Covariates

We selected demographics, lifestyle and social characteristics as covariates based on reported associations with both ACE and frailty. As demographics, we selected age, sex and total number of years spent in education. For lifestyle variables, we included alcohol consumption (self-reported number of alcohol units per week), current smoking (yes/no) and BMI. For social characteristics, we selected partner status (yes/no), subjective loneliness, and social network size. Subjective loneliness was measured with the 11-item self-report De Jong Gierveld loneliness scale [18]. The sum score (range 0–11) was treated as a continuous variable (range 0 and 11) with

Table I. Baseline characteristics of the whole study sample ($n = 2,176$)

Characteristics		No history of ACE ($n = 1,547$)	History of ACE-positive ($n = 629$)	Statistics
Demographics:				
• Age (years)	Mean (SD)	73.0 (8.4)	70.5 (8.4)	$P < 0.001$
• Female sex	n (%)	813 (52.6)	335 (53.3)	$P = 0.765$
• Education (years)[a]	Mean (SD)	8.8 (3.2)	9.6 (3.7)	$P < 0.001$
Lifestyle characteristics				
• Smoking	n (%)	198 (18.7)	76 (20.2)	$P = 0.080$
• Alcohol[a]	Mean (SD)	7.3 (10.8)	8.6 (13.2)	$P = 0.005$
• Body mass index (kg/m^2)	Mean (SD)	26.9 (4.2)	27.1 (4.3)	$P = 0.278$
Social characteristics:				
• Loneliness[a]	Mean (SD)	2.1 (2.5)	2.5 (2.9)	$P = 0.003$
• Network size	Mean (SD)	14.4 (8.3)	14.9 (9.4)	$P = 0.199$
• Partner, yes	n (%)	963 (62.2)	421 (66.9)	$P = 0.040$

increasing scores indicating increasing loneliness. The social network size was operationalised as a continuous variable following the domain-contact method [19]. Each participant reported the number of the people with whom they are in touch with regularly and who are important to them, ranging between 0 and 80 contacts.

We did not include variables as covariates when they were already included in the LASA-FI, such as the presence of mental/somatic diseases and measures of cognitive functioning and physical activity.

Statistical analyses

Descriptive statistics were used to compare our study sample with the excluded participants at baseline, as well as to compare participants with and without ACE. To study the association between ACE and frailty cross-sectionally, multiple logistic and linear regression analyses were performed with the FI as the dependent variable (≥ 0.25 classifying as frail and <0.25 classifying as not frail in the logistic regression and with the actual FI value ranging from 0 to 1) and ACE as the independent variable.

To study the incidence of frailty, Cox-regression analyses were performed among non-frail (FI < 0.25) participants at baseline (T1, 1995–96). An event was defined as an FI score ≥ 0.25 at any time during the follow-up. Participants were censored when either they dropped-out of the study or when they reached the end of the study without becoming frail. The variable 'time in the study' was constructed to indicate the number of years a participant was part of the study before the participant had an event or became censored.

As previous literature found that frailty increases with age and that female sex is associated with both a higher prevalence of both ACE and frailty [7, 9] we tested the interaction of ACE with either age or sex. In the case of significant results, subsequent analyses were stratified at the median age of 70 years to ensure approximately equal group sizes.

For better understanding of the associations, separate adjusted models will be presented to explore the impact of each group of covariates, i.e. only adjusting for demographics, adjusting for demographics and lifestyle characteristics, for demographics and social characteristics, and for all covariates combined.

Because of missing values on smoking, alcohol and BMI due to the medical interview being implemented only for the participants older than 65 at T1, multiple imputation was performed using 30 imputations and 50 iterations. This resulted in 795 participants with imputed data for these variables. The primary analyses are conducted on the imputed dataset, whereas sensitivity analyses were conducted on the participants with complete data.

All analyses have been conducted in SPSS version 23. P-values < 0.05 were considered statistically significant.

Results

Population characteristics

Table 1 shows the baseline characteristics of our study sample ($n = 2,176$) stratified by the presence of ACE. The participants with ACE ($n = 629$) were younger ($P < 0.001$), had attained more years of education ($P < 0.001$), felt more lonely ($P = 0.003$), were more often without a partner ($P = 0.040$) and drank more alcohol ($P = 0.005$) than the participants without ACE. There were no sex differences between these groups.

Compared to our study sample, excluded participants ($n = 369$) were significantly older ($P < 0.001$), had fewer years of attained education ($P < 0.001$), used less alcohol ($P = 0.004$), had a smaller network size ($P = 0.013$), felt more lonely ($P < 0.001$), were more often without a partner ($P < 0.001$) and were more frail ($P < 0.001$).

ACE and frailty prevalence

The prevalence of frailty was significantly higher among persons with ACE (27.5%) compared with persons without ACE (21.8%) ($P = 0.005$). Table 2 shows that ACE were significantly associated with the presence of frailty in the

Table 2. Association between a history of ACE and frailty by logistic regression analysis (n = 2,176)

Logistic regression model	Original dataset			Imputed dataset (pooled)		
	OR	[95% CI]	*P*-value	OR	[95% CI]	*P*-value
Unadjusted	1.36	[1.10–1.68]	0.005	1.36	[1.10–1.68]	0.005
Adjusted for:						
● Demographics[a]	2.00	[1.57–2.55]	<0.001	2.01	[1.58–2.56]	<0.001
● Demographics + lifestyle[b]	1.83	[1.36–2.45]	<0.001	2.00	[1.57–2.56]	<0.001
● Demographics + social[c]	1.85	[1.44–2.38]	<0.001	1.89	[1.47–2.42]	<0.001
● All covariates	1.74	[1.29–2.36]	0.001	1.88	[1.46–2.42]	<0.001

[a]Age, female sex, years of education; [b]Smoking, alcohol, BMI; [c]Loneliness, partner status, network size

Table 3. Baseline characteristics of the longitudinal sample (n = 1,427)

Characteristics		No history of ACE (n = 1,015)	History of ACE (n = 412)	Statistics
ssDemographics:				
● Age (years)	Mean (SD)	70.6 (7·8)	68.1 (7.2)	*P* < 0.001
● Female sex	*n* (%)	518 (51.0)	211 (51.2)	*P* = 0.951
● Education (years)	Mean (SD)	9.2 (3.2)	9.8 (3.6)	*P* < 0.001
Lifestyle characteristics				
● Smoking	*n* (%)	116 (17.5)	43 (19.5)	*P* = 0.517
● Alcohol	Mean (SD)	7.6 (10.1)	9.7 (14.1)	*P* = 0.010
● Body mass index (kg/m^2)	Mean (SD)	26.7 (3.8)	26.9 (3.8)	*P* = 0.212
Social characteristics:				
● Loneliness	Mean (SD)	1.7 (2.1)	2.1 (2.7)	*P* < 0.001
● Network size	Mean (SD)	15.3 (8.5)	15.8 (10.0)	*P* < 0.001
● Partner, yes	*n* (%)	706 (69.6)	306 (74.3)	*P* = 0.076

unadjusted as well as the adjusted, logistic regression models. No interaction between ACE and either age or sex was found. The sensitivity analyses based on participants with non-missing covariates revealed similar results (see Table 2, original dataset).

In univariable linear regression, there was no significant association between ACE and FI score (B = 0.010; CI −0.001 to 0.02; P = 0.069) and no significant interaction between ACE and age or ACE and sex. In multivariable analyses, ACE were significantly associated with FI score, after adjustment for demographics (B = 0.027; CI 0.022–0.032; P < 0.001), as well as demographics with lifestyle characteristics (B = 0.027; CI: 0.017–0.036; P = 0.015), or demographics with social characteristics (B = 0.022; CI 0.013–0.032; P < 0.001). In the fully adjusted model, ACE remained significantly associated with the FI score (B = 0.022; CI 0.012–0.031; P < 0.001). Here, the sensitivity analyses based on participants with non-missing covariates also revealed similar results.

ACE and incidence of frailty

Of the 1,598 non-frail participants at baseline, 231 dropped out before their next follow-up, leaving 1,427 participants for the longitudinal analyses. Table 3 shows the results of the characteristics of these 1,427 non-frail participants.

A total of 692/1427 (48.5%) participants became frail during a median follow-up of 6 years (range 3–15 years), which did not differ between those with (195/412; 47.3%) and without (497/1015; 49.0%) a history of ACE (Chi^2 = 0.3, df = 1, P = 0.575).

The Cox-regression analysis, however, yielded a significant interaction between ACE and age (HR = 1.024; CI 1.02–1.028; P < 0.001), but not between ACE and sex (P = 0.320) for the total sample of 1,427 participants. Therefore, age-stratified analyses were conducted.

A total of 280/779 (35.9%) younger (<70 years) participants had a history of ACE. In this subgroup, 312 participants became frail and 250 were censored during the follow-up. Cox-regression revealed no association between ACE and the incidence of frailty (unadjusted model: HR = 0.90; 95% CI 0.71–1.14; P = 0.376; fully adjusted model: HR = 0.87; 95% CI 0.69–1.11; P = 0.271).

A total of 132/648 (20.4%) older (≥70 years) participants had a history of ACE. In this subgroup, 380 participants became frail and 241 censored during follow-up. Cox-regression analyses revealed statistically significant associations between ACE and incidence of frailty, as shown in the Kaplan–Meier curve in Figure 1 (unadjusted model: HR = 1.28; 95% CI 1.01–1.63; P = 0.044). These results remained significant in all subsequent adjusted models, i.e. adjusted for demographics (HR = 1.31; 95% CI 1.03–1.67; P = 0.026), for demographics with lifestyle
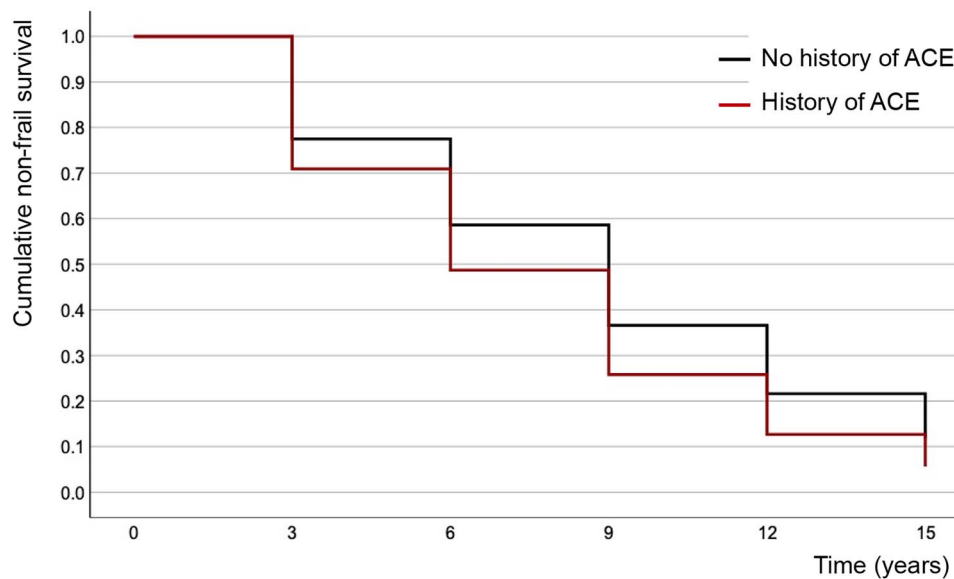
Figure 1. Kaplan–Meier curve for the cumulative non-frail survival time

characteristics (HR = 1.30; 95%-CI = 1.02–1.66, P = 0.033), for demographics with social characteristics (HR = 1.30; 95% CI 1.02–1.65; P = 0.035) and in the fully adjusted model (HR = 1.28; 95% CI 1.01–1.64; P = 0.044).

The sensitivity analyses on participants with non-missing covariates revealed similar results. Only among participants ≥70 years, ACE were significantly associated with the incidence of frailty (fully adjusted model: HR = 1.35; 95% CI 1.05–1.73; P = 0.019).

Discussion

Main results

This study replicated previous findings on the association between a history of ACE and frailty, while also showing that a history of ACE is associated with an accelerated rate of accumulation of health deficits in the oldest old (figure 1). This novel finding suggests that interventions targeting ACE or its physiological sequelae can contribute to successful ageing even in the oldest old. In an ageing world population, this is of paramount importance.

Impact of a history of ACE in later life

Our study contributes to the accumulating evidence that having a history of ACE has a detrimental effect on a person's physical health status throughout the lifespan. Biological as well as psychosocial mechanisms have been postulated to explain these effects.

From the biological perspective, ACE may result in a dysregulation of a person's stress response. A history of ACE has been associated with increased cortisol levels due to an overdrive of the hypothalamus-pituitary-adrenal axis, increased levels of low-grade inflammation as well as a dysregulation of the autonomic nervous system [20]. These physiological pathways have also been implicated in the development of frailty [12]. Nonetheless, studies examining the possible mediating effect of these biological mechanisms in the association between ACE and frailty are lacking.

From a psychosocial perspective, the well-known association of ACE with an early onset of a plethora of mental health disorders [4, 21] may be the start of a causal chain, resulting in an unhealthy lifestyle and socioeconomic disadvantages in adult life. In a previous study, socioeconomic factors in adulthood indeed explained a significant level of variance in the association between ACE and frailty according to the Fried criteria in later life [22]. Socioeconomic disadvantages, however, did not fully explain the association. This can be explained by the fact that ACE have several negative consequences and frailty is a multifactorial condition.

The FI represents nothing more than a stochastic accumulation of health deficits [10]. Therefore, the process of deficit accumulation can also be regarded as an underlying mechanism in itself. Nonetheless, the onset of each specific health deficit associated with ACE might be explained by a different pathophysiological mechanism. In other words, a single mediatory pathway for the association between ACE and frailty, being either biological or psychosocial, is rather unlikely.

Interestingly, a history of ACE was only prospectively associated with the onset of frailty among the oldest old, i.e. people aged 70 years and over. Several explanations can be put forward for the lack of any prospective effect among people aged between 58 and 70 years.

First, frailty was originally conceptualised to understand why phenotypically healthy older people could disproportionally react on mild stressors due to homeostenosis. Younger people are assumed to be resilient enough to withstand and reset changes in their homeostasis, so their frailty status may be less susceptible to change. Most studies

indeed show a logarithmic increase of the prevalence of frailty after the age of 65 [8].

Secondly, our findings may point to cohort effects with respect to reporting ACE as well as with social circumstances at the time the oldest old were in their younger years. The oldest old might have been more reluctant to confide in the researchers about their ACE [6, 23, 24]. This might have skewed the ACE inventoried from that age group towards only the most adverse, the ones with the most undeniable consequences. At the same time, the younger age group might have been less reluctant to openly talk about possible ACE, due to the societal movement of freely talking about these topics [23]. This may have resulted in either over-reporting of ACE in the younger age groups or dilution of an effect by inclusion of less severe ACE.

Finally, our results might partly be explained by a healthy survivor effect. Younger participants having the most detrimental effects of ACE may have dropped out due to these serious health consequences of ACE, eventually even because of death. It is known that frailty is not synonymous with disability and multimorbidity [9], which both may act as competing risk factors. Non-frail participants aged ≥70 years were apparently the most resilient of their age group, but also the most susceptible for the occurrence of future health deficits based on their age, making them the most suitable group to evaluate the impact of a history of ACE on frailty.

Methodological considerations

An important strength of our study is the opportunity to study the association between ACE and frailty over a 17 year follow-up period with repeated follow-up measurements every three years [25, 26]. Nonetheless, some methodological points need to be addressed. First, data on ACE were collected retrospectively, which may have resulted in recall bias. This could have resulted in either underreporting, e.g. due to memory loss or unwillingness to report negative experiences of the past, as well as over-reporting due to a current negative mood state. On the other hand, studies on the reliability of retrospective questionnaires have shown that recall bias is quite limited [27, 28]. Secondly, although our results suggest a non-specific effect of ACE, it cannot be excluded that the results were still driven by specific adverse events. For example, 162 people reported war experiences, whereas only 13 reported sexual abuse. There were also no questions regarding emotional neglect or abuse both important aspects of ACE that might have led to over/under appreciation of the effect of ACE. Finally, the FI in LASA has been based on 'only' 32 items. This fits with the minimum of 30 health deficits of a reliable FI, but we were not able to disregard specific health deficits, like cognitive or mood deficits, which would have enabled us to additionally adjust for these covariates and/or examine these parameters as potentially mediating variables.

Conclusion

Acknowledging that becoming frail seems to be a gradual process already starting in midlife [6], it is important to apply a life course approach for the prevention of frailty instead of addressing frailty solely in later life. Interestingly, our findings imply that interventions targeting ACE may ameliorate the devastating consequences of ACE in mid- and later life by possibly delaying or preventing frailty.

For instance, this recent lab study showed that interventions such as aerobic exercise might be useful as a secondary prevention of the negative effects of ACE, by upregulating BDNF expression, as BDNF expression seems blunted in individuals with ACE [29, 30]. Furthermore, future studies should focus on uncovering the mediating pathways from ACE to frailty, as this will guide the development of other treatment strategies. ACE has been linked to higher levels of inflammatory biomarkers as well as higher cortisol, possibly allowing anti-inflammatory and cortisol regulating treating regimes (pharmacotherapy, diet, exercise) to play a more active role in the management and prevention of frailty.

References

1. Felitti VJ, Anda RF, Nordenberg D *et al.* Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults the Adverse Childhood Experiences (ACE) study. Am J Prev Med 1998; 14: 245–58.
2. Bellis MA, Hughes K, Ford K, Ramos Rodriguez G, Sethi D, Passmore J. Life course health consequences and associated annual costs of Adverse Childhood Experiences across Europe and North America: a systematic review and meta-analysis. Public Health 2019; 4: e521–e526.
3. Bellis MA, Hughes K, Leckenby N, Hardcastle KA, Perkins C, Lowey H. Measuring mortality and the burden of adult disease associated with Adverse Childhood Experiences in England: a national survey. J Public Health Med 2015; 37: 445–54.
4. Hughes K, Bellis MA, Hardcastle KA *et al.* The effect of multiple Adverse Childhood Experiences on health: a systematic review and meta-analysis. Public Health 2017; 2: e356–66.
5. van der Linden BWA, Sieber S, Cheval B *et al.* Life-course circumstances and frailty in old age within different European welfare regimes: a longitudinal study with SHARE. J Gerontol 2020; 75: 1326–35.
6. Mian O, Anderson LN, Belsky DW *et al.* Associations of Adverse Childhood Experiences with frailty in older adults: a cross-sectional analysis of data from the Canadian Longitudinal Study on Aging. Gerontology 2022; 68: 1091–100.
7. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet 2019; 394: 1365–75.

8. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc 2012; 60: 1487–92.

9. Fried LP, Tangen CM, Walston J *et al.* Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146–57.

10. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. Sci World J 2001; 1: 323–36.

11. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol 2007; 62: 722–7.

12. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet (London, England) 2013; 381: 752–62.

13. Huisman M, Poppelaars J, van der Horst M *et al.* Cohort profile: the Longitudinal Aging Study Amsterdam. Int J Epidemiol 2011; 40: 868–76.

14. Hoogendijk EO, Deeg DJH, Poppelaars J *et al.* The Longitudinal Aging Study Amsterdam: cohort update 2016 and major findings. Eur J Epidemiol 2016; 31: 927–45.

15. Hoogendijk EO, Theou O, Rockwood K, Onwuteaka-Philipsen BD, Deeg DJH, Huisman M. Development and validation of a Frailty Index in the Longitudinal Aging Study Amsterdam. Aging Clin Exp Res 2017; 29: 927–33.

16. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Med Sci 2007; 62: 738–43.

17. Korten NCM, Penninx BWJH, Pot AM, Deeg DJH, Comijs HC. Adverse childhood and recent negative life events: contrasting associations with cognitive decline in older persons. J Geriatr Psychiatry Neurol 2014; 27: 128–38.

18. de Jong-Gierveld J, Kamphuls F. The development of a Rasch-Type Loneliness Scale. Appl Psychol Measur 1985; 9: 289–99.

19. Broese Van Groenou M, Hoogendijk EO, Van Tilburg TG. Continued and new personal relationships in later life: differential effects of health. J Aging Health 2013; 25: 274–95.

20. Danese A, McEwen BS. Adverse Childhood Experiences, allostasis, allostatic load, and age-related disease. Physiol Behav 2012; 106: 29–39.

21. Petruccelli K, Davis J, Berman T. Adverse Childhood Experiences and associated health outcomes: a systematic review and meta-analysis. Child Abuse Negl 2019; 97: 104127. https://doi.org/10.1016/J.CHIABU.2019.104127.

22. van der Linden BWA, Cheval B, Sieber S *et al.* Life course socioeconomic conditions and frailty at older ages. J Gerontol B Psychol Sci Soc Sci 2020; 75: 1348–57.

23. Degli Esposti M, Humphreys DK, Jenkins BM *et al.* Long-term trends in child maltreatment in England and Wales, 1858–2016: an observational, time-series analysis. Public Health 2019; 4: e148–58.

24. Solís CB, Kelly-Irving M, Fantin R *et al.* Adverse Childhood Experiences and physiological wear-and-tear in midlife: findings from the 1958 British birth cohort. Proc Natl Acad Sci USA 2015; 112: E738–46.

25. Herr M, Robine JM, Aegerter P, Arvieu JJ, Ankri J. Contribution of socioeconomic position over life to frailty differences in old age: comparison of life-course models in a French sample of 2350 old people. Ann Epidemiol 2015; 25: 674–680.e1.

26. Herzog JI, Schmahl C. Adverse Childhood Experiences and the consequences on neurobiological, psychosocial, and somatic conditions across the lifespan. Front Psych 2018; 9: 420. https://doi.org/10.3389/fpsyt.2018.00420.

27. Brewin CR, Andrews B, Gotlib IH. Psychopathology and early experience: a reappraisal of retrospective reports. Psychol Bull 1993; 113: 82–98.

28. Hardt J, Rutter M. Validity of adult retrospective reports of Adverse Childhood Experiences: review of the evidence. J Child Psychol Psychiatry 2004; 45: 260–73.

29. Campbell TS, Donoghue KM, Ghosh U, Nelson CM, Roth TL. Early life stress affects Bdnf regulation: a role for exercise interventions. Int J Mol Sci 2022; 23: 11729. https://doi.org/10.3390/IJMS231911729.

30. Dimitriadis M, van den Brink RHS, Comijs HC, Oude Voshaar RC. Prognostic effect of serum BDNF levels in late-life depression: moderated by childhood trauma and SSRI usage? Psychoneuroendocrinology 2019; 103: 276–83.