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Early life stress in relation with risk of overweight, depression, and their comorbidity across adulthood: findings from a British birth cohort

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Original Article

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Abstract

Background. Multimorbidity, known as the co-occurrence of at least two chronic conditions, has become of increasing concern in the current context of ageing populations, though it affects all ages. Early life risk factors of multimorbidity include adverse childhood experiences (ACEs), particularly associated with psychological conditions and weight problems. Few studies have considered related mechanisms and focus on old age participants. We are interested in estimating, from young adulthood, the risk of overweight-depression comorbidity related to ACEs while adjusting for early life confounders and intermediate variables.

Methods. We used data from the 1958 National Child Development Study, a prospective birth cohort study ($N = 18\,558$). A four-category outcome (no condition, overweight only, depression only and, overweight-depression comorbidity) was constructed at 23, 33, and 42 years. Multinomial logistic regression models adjusting for intermediate variables co-occurring with this outcome were created. ACEs and sex interaction on comorbidity risk was tested.

Results. In our study sample ($N = 7762$), we found that ACEs were associated with overweight-depression comorbidity risk throughout adulthood (RRR [95% CI] at 23y = 3.80 [2.10–6.88]) though less overtime. Comorbidity risk was larger than risk of separate conditions. Intermediate variables explained part of the association. After full-adjustment, an association remained (RRR [95% CI] at 23y = 2.00 [1.08–3.72]). Comorbidity risk related to ACEs differed by sex at 42.

Conclusion. Our study provides evidence on the link and potential mechanisms between ACEs and the co-occurrence of mental and physical diseases throughout the life-course. We suggest addressing ACEs in intervention strategies and public policies to go beyond single disease prevention.

Introduction

Multimorbidity, corresponding to 'the co-occurrence of at least two chronic conditions in the same individual'(Skou et al., 2022), affects, on average, about one-third of adults worldwide (Nguyen et al., 2019). Multimorbidity contributes to premature death, poorer functioning/quality of life, and increased health-care utilization (Menotti et al., 2001; van Oostrom et al., 2014; Vogeli et al., 2007). Deepening our understanding of types of multimorbidity and their implication on individuals' lives is important to improve patient-centered treatment recommendations, reduce the burden on health and health systems, and propose relevant preventive strategies (Bayliss et al., 2014; Salisbury, 2012).

The long-term consequences of events occurring during childhood in relation to multiple diseases development is of growing interest, especially early life psychosocial stress that can be studied by the concept of adverse childhood experiences (ACEs). ACEs capture cumulative effects of stressful intrafamilial experiences during childhood by using indicators measuring whether individuals were subjected to violence, abuse, neglect, or growing up in a household with substance use problems or mental health problems and combining them into a proxy measure (Felitti et al., 1998). ACEs have been previously associated with premature mortality (Bellis et al., 2015) as well as various individual chronic conditions, e.g. depression, stroke, or cancer (Bellis et al., 2015; Felitti et al., 1998; Hughes et al., 2017; Kelly-Irving, Mabile, Grosclaude, Lang, & Delpierre, 2013).

It has been hypothesized that ACEs may play an indirect role in morbidity through their influence on unhealthy behaviors (Hughes et al., 2017) and low SEP (Metzler, Merrick, Klevens, Ports, & Ford, 2017), but may also have a direct role through stress manifested by physiological disruptions.

Several recent studies have highlighted a strong relationship between ACEs and multimorbidity. Sinnott et al. (Sinnott, Mc Hugh, Fitzgerald, Bradley, & Kearney, 2015) found in an Irish cohort study that a history of ACEs was independently associated with multimorbidity across twenty chronic diseases. Subsequent research by Tomasdottir et al. (2015), Henchoz et al. (2019), Lin, Wang, Lu, Chen, & Guo (2021), and Yang, Hu, Silventoinen, & Martikainen (2020) further supported this association across thirteen, twenty-one and fourteen diseases. More recently, Chandrasekar et al. (2023) reinforced the association between ACEs and an increasing burden of multimorbidity using a national birth cohort (The 1946 MRC National Survey of Health and Development) involving eighteen health disorders from mid-adulthood into early old age. These studies considered many physical and psychological diseases and were carried out on populations aged 35 and over. Among all adult medical conditions which can be associated to ACEs, some manifest early signs during childhood (unmet developmental needs); these specific conditions are of special importance to target early prevention efforts of multimorbidity across the life course. Yet, to our knowledge, no studies have shed light on the link between ACEs and early-appearing morbidities from early adulthood and across the life course.

Common conditions in multimorbidity such as, excess body weight (Thomas-Eapen, 2021) and depression (Hunter et al., 2021; Zhen et al., 2022), often trace their origins back to childhood. These conditions have been associated with low SEP, unhealthy childhood and a higher prevalence among those exposed to ACEs. Researchers have also described a biological connection between depression and overweight, potentially linked to the disrupted physiological responses triggered by ACEs (Sonino & Fava, 2001; Wester et al., 2014). Previous studies have individually examined the risk of being overweight or depressed in relation to ACEs separately (Bellis et al., 2019; Thomas, Hyppönen, & Power, 2008). However, considering their co-occurrence and bidirectional relationship (Milaneschi, Simmons, van Rossum, & Penninx, 2019), exploring the simultaneous presence of depression and overweight is crucial in understanding how ACEs relate to the future risk of multimorbidity among both men and women.

A recent study found that men and women have distinct patterns of childhood adversities, with women experiencing more complex and varied patterns of childhood adversity (Haahr-Pedersen et al., 2020). Additionally, a previous study on adults in the United States suggests that a higher proportion of women (14%) could suffer from comorbid overweight-depression than men (7%) (Heo, Pietrobelli, Fontaine, Sirey, & Faith 2006). Despite these findings, the influence of sex in the association between ACEs and long-term overweight-depression comorbidity risk has not been thoroughly assessed.

Using data from the 1958 National Child Development Study (NCDS58), we propose to examine the relationship between stress-inducing psychosocial exposures, as measured through ACEs, and risk of overweight-depression comorbidity and each separate condition at multiple time points, from young adulthood, and to assess the potential pathways that link them. In this cohort, we firstly assessed whether ACEs were associated with a higher risk of overweight-depression comorbidity at 23, 33, and 42 years considering a set of baseline confounders and, if these associations were stronger than those observed for participants with only one condition. Secondly, we tested if adult SEP and health behaviors could explain any part of the association between ACEs and risk of overweight-depression comorbidity and each separate condition at all ages. Lastly, we explored whether the effect of ACEs on comorbidity's risk differed between men and women.

Methods

Study design and participants

We analyzed data from the NCDS58, an on-going prospective population cohort study, which included all live births during one week in Great Britain ($n = 18\,558$). Data collected at birth included participants' pre-natal, birth and parental characteristics (Power & Elliott, 2006). Subsequent data collections were carried out on cohort members to collect information on aspects of health, education, social and economic development from age 7 to 62. Written informed consent was obtained from parents for underage cohort members and, as adults, ethical approval was provided following guidelines of the National Research Ethics Advisory Panel.

Follow-up of the initial 18 558 birth cohort members was considered as being good (Clark, Caldwell, Power, & Stansfeld, 2010). Participants with missing data for the outcome and exposure were excluded leaving a total of 7764 participants for this study.

Adverse childhood experiences (ACEs)

ACEs were defined as 'a set of traumatic and stressful psychosocial conditions in the familial environment that tend to co-occur, persist over time and are outside of the child's control'(Gondek, Patalay, & Lacey, 2021; Kelly-Irving et al., 2013). Data were collected, through survey questions, at ages 7, 11, and 16 on six different dimensions of ACEs: (i) Child in care; (ii) Physical neglect; (iii) Contact with probation; (iv) Parental separation; (v) Family mental illness; (vi) Alcohol abuse. Health visitors, parents, and teachers helped in the administration and completion of the survey.

An ACEs score (scale[0;6]) was constructed by adding scores of 1 (ACE event) or 0 (no event) by ACE dimensions. A conservative approach of missing data was used: missing values in the score were defined as having missing values in all ACEs dimensions of all three questionnaires; otherwise, missing data points were regarded as zeros. Some dimensions of ACEs were not available in all surveys however, only one data point was necessary to create the ACE score. A score of 6 referred to 6 different types of adversities experienced between 7 and 16 years. The score was categorized into three groups: 0, 1 and, 2 or more adversities.

Overweight

Overweight was defined from BMI values at 23, 33, and 42 years; they were dichotomized as (i) 'overweight': above sex-specific median values of BMI and (ii) 'non-overweight': below sex-specific median values of BMI. Weight and height measures were self-reported (at 23 & 42 years) or measured during the interview (at 33 years). BMI was calculated as weight (kg) divided by the square of height (m2).

Depression

Depression symptoms were assessed using the Malaise Inventory (MI) questionnaire, an established scale to measure signs of

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psychological distress (Rodgers, Pickles, Power, Collishaw, & Maughan, 1999; Rutter, Tizard, & Whitmore, 1971) at ages 23, 33, and 42. The NCDS used the long version containing 24 questions. A score of 8 or more was defined as a high level of depression.

Overweight-depression comorbidity and each separate condition

The outcome of interest was created at 23, 33, and 42 years as four-category variable (no condition, overweight only, depression only and overweight-depression comorbidity). This variable configuration was essential to estimate the odds of being comorbid related to ACEs relative to the odds of not having either condition and comparing odd magnitudes with the risk of having either condition separately.

Covariates

Key potential confounders of ACEs, overweight and depression were selected based on previous research (Gondek et al., 2021). They were divided according to the life-stages that they corresponded to: early life and childhood factors, and adulthood factors. A detailed description is provided in online Supplementary Table S1.

At birth, social and biological confounders were collected from a questionnaire completed by the participant's mother: mother's age at birth, maternal smoking during pregnancy, mother's education level, parents' social class. Sex and birthweight were also registered. Information on mother's breastfeeding behavior was collected at age 7. A binary (presence/absence) childhood pathologies variable was constructed from records of congenita, chronic physiological dysfunctions, disabilities and special schooling at 7, 11, and 16 years.

Adulthood confounders included health behavior variables and SEP indicators for all outcome periods (23, 33, and 42 years). Smoking, alcohol consumption, physical activity patterns and diet (at 33 and 42 years only) were the health behaviors selected. Education (23 years), wealth (33 years), social class and marital status (33 and 42 years), housing tenure (42 years) were the selected SEP indicators.

Another group of confounders were available only at age 42: risky health behaviors such as continued alcohol problems and prior use of drugs.

Statistical analyses

Means and frequencies by ACEs and by the four-category outcome variable were reported for all continuous and categorical covariates, respectively. The χ^2 test or Fisher's exact test for categorical variables and *t* test or Wilcoxon rank test for continuous variables were performed to estimate bivariate associations.

Multinomial logistic regression models were used to examine the relationship between ACEs and the four-category outcome with relative risk ratio (RRR) coefficients and 95% confidence intervals (CI). After testing the crude association, we first fitted a model adjusted only for sex (model 1). We subsequently adjusted model 1 for each early-life factor to look at their individual influence on the association and built a model adjusted on all early-life factors (model 2). Similarly, we adjusted model 2 for each adult covariate and by blocks of variables (i.e. health behaviors and adulthood SEP). Finally, we constructed a fully adjusted model including all variables simultaneously (model 3). These models were ran at each time point.

A moderating effect of sex on the relationship between ACEs and the four-category outcome was investigated at all ages (23, 33, and 42 years) given that overweight and depression are recorded as sex-patterned in the literature. Significance of ACEs and sex interaction term was tested. Likelihood ratio tests testing the goodness of fit between fully adjusted models including and not including an interaction term were performed. To further understand interaction effects at the outcome period where the likelihood ratio test favored a statistically difference in goodness of fit (at 42 years), a 6-category variable combining the sex and ACEs variables was constructed and fully-adjusted model was ran: men with 0 ACEs, men with 1 ACE, men with $\geqslant$ 2 ACEs, women with 0 ACEs, women with 1 ACE, women with $\geqslant$ 2 ACEs. Men with 0 ACEs were the reference level.

Additional analyses

At age 42, we added two models where model 2 and model 3 (as detailed above) were further adjusted for variables related to adult risky health behaviors.

To justify the use of overweight and depression as comorbidity candidates related to ACEs in the NCDS58 cohort, we checked the association between ACEs and the binary overweight and depression variables through logistic regression models. Additionally, these analyses assessed the overweight and depression independent risks while maximizing the sample size of these categories of interest (*v.* 'overweight only' and 'depression only' categories of the four-category outcome). This helped elucidate on the fact that the differences in risk magnitude observed across categories (independent condition *v.* co-occurring conditions) of the four-category outcome were not solely due to created group size variations. Models were adjusted for early-life factors.

Missing data

To control for possible bias due to missing data in the study population, covariates with missing data were imputed via multiple imputation using the MICE R package (van Buuren & Groothuis-Oudshoorn, 2011). All variables considered in this study including those used for additional analyses were used for carrying out the imputations and are listed in online Supplementary Table S1. Fifteen imputations were conducted taking the missing-at-random assumption. To obtain summary regression estimates from the fifteen multiply imputed datasets, Rubin's combination rules were used (Rubin, 1976).

Sensitivity analyses

To test the robustness of our results, we wanted to run analyses in a subsample of complete cases ($N = 3901$). However, the small number of participants with comorbid overweight-depression did not provide enough statistical power ($N = 33$(0.8%), 75 (1.9%) and 181(4.6%) individuals who were comorbid at 23, 33, and 42 years) and instead, complete cases analysis was only conducted on the association between ACEs and binary variables (i.e. overweight and depression).

Also, main analyses were repeated when replacing the binary overweight variable with a binary obese indicator (more severe condition defined as the upper sex-specific quartile of BMI).

As well, consistent influence of health behaviors and adulthood SEP intermediate variables at prior waves of the studied outcome (ex: outcome 33 and 42 years) was tested on the link between ACEs and overweight-depression comorbidity and each

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separate condition. The influence of varying dimensions of health behaviors and socioeconomic factors was assessed since these variables differed across time points.

All statistical analyses were performed using R version 3.1.2 within the R Studio environment.

Results

The sample selection flowchart is provided in Fig. 1. Our study sample consisted of a total of 7762 individuals (41,8% of the initial total population).

The distribution of individuals by study variable did not differ by more than 10% between the included and excluded participants except for education at 23, wealth at 33 and use of illegal drugs. Excluded individuals had a lower education level at 23, lower wealth at 33 and fewer records of illegal drug use (online Supplementary Table S2). Description of all variables considered for the study sample is provided in Table 1.

Women represented 52.0% of the study population. In the sample, 24.2% experienced at least one adversity. The proportion of overweight and depressed people increased respectively over time, consequently, the proportion of individuals with a comorbid overweight-depression went from 1.3% at 23 years to 6.5% at 42 years. Characteristics of the study population according to ACEs and to overweight-depression comorbidity and each separate condition, respectively, are shown in Table 1 and online Supplementary Table S3.

Participants who suffer from comorbid overweight-depression were more likely to be women, to come from disadvantaged parental socioeconomic backgrounds, to have experienced childhood pathologies, to have had skilled manual professions at 42 years, to have low wealth, to be abstainers and to be physically inactive.

Association between ACEs and overweight-depression comorbidity each separate condition

Results from multinomial logistic regression on ACEs exposure and the risk of overweight-depression comorbidity and each separate condition are given in Table 2.

Among those who experienced only 1 ACE, an association was not observed with overweight only yet was observed with depression only (RRR_{23y} [95% CI] = 1.79 [1.41–2.27], RRR_{33y} [95% CI] = 1.79 [1.35–2.37], RRR_{42y} [95% CI] = 1.54 [1.20–1.96], model 1).

At each time point, participants who experienced 2^{+}ACEs were more likely to be overweight only (RRR_{23y} [95% CI] = 1.39 [1.07–1.81], RRR_{33y} [95% CI] = 1.33 [1.07–1.64], RRR_{42y} [95% CI] = 1.27 [1.02–1.58], model 1) compared to those who experienced 0 ACEs. These associations were partly explained by early-life factors, especially parent's social class (RRR_{23y} [95% CI] = 1.22 [0.93–1.59], RRR_{33y} [95% CI] = 1.23 [0.99–1.53], RRR_{42y} [95% CI] = 1.13 [0.91–1.42]) and further explained by adulthood intermediate variables and no longer significant in the fully adjusted model (RRR_{23y} [95% CI] = 1.01 [0.77–1.32], RRR_{33y} [95% CI] = 1.08 [0.86–1.35], RRR_{42y} [95% CI] = 1.04 [0.82–1.31], model 3).

At each time point, participants who experienced 2^{+}ACEs were more likely to be depressed only (RRR_{23y} [95% CI] = 2.71 [1.90–3.86], RRR_{33y} [95% CI] = 2.85 [1.87–4.34], RRR_{42y} [95% CI] = 1.74 [1.14–2.65], model 1) compared to those who experienced 0ACEs. Associations with depression only at all time points were partially explained by baseline characteristics, especially parents' social class, and intermediate variables however, a relationship remained in the fully adjusted model at 23 and 33 years (RRR_{23y} [95% CI] = 1.59 [1.10–2.31], RRR_{33y} [95% CI] = 1.70 [1.09–2.66], model 3).

At each time point, a strong graded association between ACEs and risk of comorbid overweight-depression was observed: those who experienced 1ACE had a higher risk of being comorbid

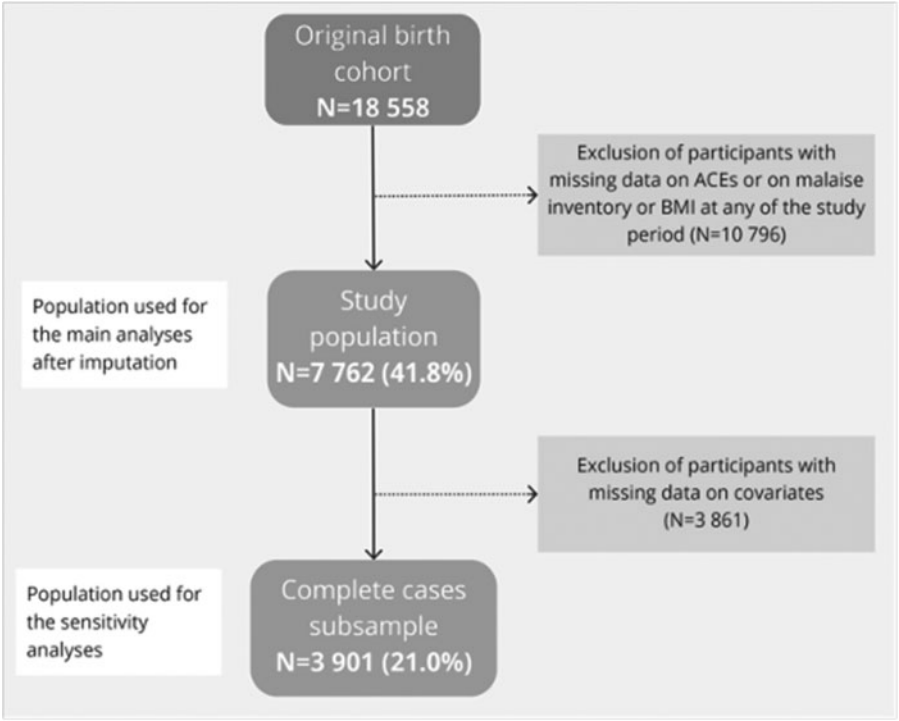

Figure 1. Study sample selection flowchart.

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Table 1. Characteristics of the study population from the NCDS cohort by ACEs

Variables	Missing	Description	By ACEs			
			0	1	2 or more	*p*
ACEs	0	*n* = 7762				
0, *n* (%)		5881 (75.77)				
1, *n* (%)		1456 (18.76)		–		
2 or more, *n* (%)		425 (5.48)				
Overweight-depression comorbidity and each separate condition						
At 23	0	*n* = 7762	*n* = 5881	*n* = 1456	*n* = 425	<0001
No conditions, *n* (%)		6081 (78.34)	4685 (79.66)	1104 (75.82)	292 (68.71)	
Overweight, *n* (%)		1175 (15.14)	876 (14.9)	221 (15.18)	78 (18.35)	
Depressed, *n* (%)		405 (5.22)	258 (4.39)	106 (7.28)	41 (9.65)	
Comorbid overweight-depression, *n* (%)		101 (1.3)	62 (1.05)	25 (1.72)	14 (3.29)	
At 33	0	*n* = 7762	*n* = 5881	*n* = 1456	*n* = 425	<0001
No conditions, *n* (%)		4226 (54.44)	3280 (55.77)	757 (51.99)	189 (44.47)	
Overweight, *n* (%)		3030 (39.04)	2281 (38.79)	568 (39.01)	181 (42.59)	
Depressed, *n* (%)		290 (3.74)	186 (3.16)	75 (5.15)	29 (6.82)	
Comorbid overweight-depression, *n* (%)		216 (2.78)	134 (2.28)	56 (3.85)	26 (6.12)	
At 42	0	*n* = 7762	*n* = 5881	*n* = 1456	*n* = 425	<0001
No conditions, *n* (%)		3337 (42.99)	2578 (43.84)	610 (41.9)	149 (35.06)	
Overweight, *n* (%)		3504 (45.14)	2678 (45.54)	623 (42.79)	203 (47.76)	
Depressed, *n* (%)		414 (5.33)	284 (4.83)	102 (7.01)	28 (6.59)	
Comorbid overweight-depression, *n* (%)		507 (6.53)	341 (5.8)	121 (8.31)	45 (10.59)	
Early-life factors						
Sex	0	*n* = 7762	*n* = 5881	*n* = 1456	*n* = 425	0120
Men, *n* (%)		3723 (47.96)	2786 (47.37)	717 (49.24)	220 (51.76)	
Women, *n* (%)		4039 (52.04)	3095 (52.63)	739 (50.76)	205 (48.24)	
Parent's social class	391 (5.04%)	*n* = 7371	*n* = 5578	*n* = 1384	*n* = 409	<0001
Professional/Managerial, *n* (%)		1420 (19.26)	1207 (21.64)	192 (13.87)	21 (5.13)	
Skilled non-manual, *n* (%)		782 (10.61)	626 (11.22)	122 (8.82)	34 (8.31)	
Skilled manual, *n* (%)		3667 (49.75)	2740 (49.12)	723 (52.24)	204 (49.88)	
Semi-unskilled, *n* (%)		1502 (20.38)	1005 (18.02)	347 (25.07)	150 (36.67)	
Mother's education (years)	366 (4.72%)	*n* = 7396	*n* = 5585	*n* = 1401	*n* = 410	<0001
Left school> or equal 15, *n* (%)		1975 (26.7)	1588 (28.43)	319 (22.77)	68 (16.59)	
Left school < 15, *n* (%)		5421 (73.3)	3997 (71.57)	1082 (77.23)	342 (83.41)	
Mother's age at birth (years)	331 (4.26%)	*n* = 7431	*n* = 5610	*n* = 1407	*n* = 414	<0001
<24, *n* (%)		1926 (25.92)	1385 (24.69)	405 (28.78)	136 (32.85)	
[24:27], *n* (%)		2107 (28.35)	1638 (29.2)	360 (25.59)	109 (26.33)	
[28:31], *n* (%)		1600 (21.53)	1256 (22.39)	269 (19.12)	75 (18.12)	
>31, *n* (%)		1798 (24.2)	1331 (23.73)	373 (26.51)	94 (22.71)	
Breastfeeding	861 (11.09%)	*n* = 6901	*n* = 5234	*n* = 1297	*n* = 370	<0001
> 1 month, *n* (%)		3141 (45.52)	2481 (47.4)	523 (40.32)	137 (37.03)	
< 1 month, *n* (%)		1711 (24.79)	1290 (24.65)	319 (24.6)	102 (27.57)	
none, *n* (%)		2049 (29.69)	1463 (27.95)	455 (35.08)	131 (35.41)	

(*Continued*)

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Table 1. (*Continued.*)

			By ACEs			
Variables	Missing	Description	0	1	2 or more	*p*
Mother smoked during pregnancy	415 (5.35%)	*n* = 7347	*n* = 5551	*n* = 1390	*n* = 406	<0001
No, *n* (%)		5022 (68.35)	3912 (70.47)	898 (64.6)	212 (52.22)	
Yes, *n* (%)		2325 (31.65)	1639 (29.53)	492 (35.4)	194 (47.78)	
Birthweight (kilograms)	549 (7.07%)	*n* = 7213	*n* = 5442	*n* = 1368	*n* = 403	
Mean (s.d.)		3.3 (0.5)	3.4 (0.5)	3.3 (0.5)	3.3 (0.5)	0010
Childhood pathologies	20 (0.26%)	*n* = 7742	*n* = 5862	*n* = 1455	*n* = 425	<0001
No, *n* (%)		5821 (75.19)	4510 (76.94)	1035 (71.13)	276 (64.94)	
Yes, *n* (%)		1921 (24.81)	1352 (23.06)	420 (28.87)	149 (35.06)	
Covariates at 23 years						
Education level	5 (0.06%)	*n* = 7757	*n* = 5876	*n* = 1456	*n* = 425	<0001
Passed a levels, *n* (%)		1824 (23.51)	1574 (26.79)	220 (15.11)	30 (7.06)	
Passed o levels, *n* (%)		3295 (42.48)	2569 (43.72)	586 (40.25)	140 (32.94)	
No qualifications, *n* (%)		2638 (34.01)	1733 (29.49)	650 (44.64)	255 (60)	
Smoking status	0	*n* = 7762	*n* = 5881	*n* = 1456	*n* = 425	<0001
Never smoker, *n* (%)		2426 (31.25)	1965 (33.41)	361 (24.79)	100 (23.53)	
Former smoker, *n* (%)		2350 (30.28)	1848 (31.42)	410 (28.16)	92 (21.65)	
Current smoker, *n* (%)		2986 (38.47)	2068 (35.16)	685 (47.05)	233 (54.82)	
Alcohol consumption	4 (0.05%)	*n* = 7758	*n* = 5878	*n* = 1456	*n* = 424	0002
Moderate, *n* (%)		3954 (50.97)	3039 (51.7)	725 (49.79)	190 (44.81)	
Abstainer, *n* (%)		1869 (24.09)	1380 (23.48)	354 (24.31)	135 (31.84)	
Heavy drinker, *n* (%)		1935 (24.94)	1459 (24.82)	377 (25.89)	99 (23.35)	
Physical activity	6 (0.08%)	*n* = 7756	*n* = 5877	*n* = 1454	*n* = 425	0001
Physically active, *n* (%)		2485 (32.04)	1945 (33.1)	425 (29.23)	115 (27.06)	
Moderately active, *n* (%)		1323 (17.06)	1019 (17.34)	236 (16.23)	68 (16)	
Inactive, *n* (%)		3948 (50.9)	2913 (49.57)	793 (54.54)	242 (56.94)	
Covariates at 33 years						
Social class	488 (6.29%)	*n* = 7274	*n* = 5536	*n* = 1354	*n* = 384	<0001
Professional-managerial, *n* (%)		2692 (37.01)	2204 (39.81)	406 (29.99)	82 (21.35)	
Skilled nonmanual, *n* (%)		1823 (25.06)	1436 (25.94)	309 (22.82)	78 (20.31)	
Skilled manual, *n* (%)		1436 (19.74)	1013 (18.3)	319 (23.56)	104 (27.08)	
Semi-unskilled, *n* (%)		1323 (18.19)	883 (15.95)	320 (23.63)	120 (31.25)	
Wealth	139 (1.79%)	*n* = 7623	*n* = 5774	*n* = 1439	*n* = 410	<0001
Owner (Medium / high price, *n* (%)		2958 (38.8)	2402 (41.6)	464 (32.24)	92 (22.44)	
Owner (Low / medium-low price, *n* (%)		2899 (38.03)	2174 (37.65)	581 (40.38)	144 (35.12)	
Non-owner, *n* (%)		1766 (23.17)	1198 (20.75)	394 (27.38)	174 (42.44)	
Marital status	60 (0.77%)	*n* = 7702	*n* = 5836	*n* = 1446	*n* = 420	<0001
Couple, *n* (%)		6288 (81.64)	4785 (81.99)	1178 (81.47)	325 (77.38)	
Single, *n* (%)		896 (11.63)	695 (11.91)	154 (10.65)	47 (11.19)	
Divorced or widowed, *n* (%)		518 (6.73)	356 (6.1)	114 (7.88)	48 (11.43)	
Smoking status	45 (0.58%)	*n* = 7717	*n* = 5846	*n* = 1448	*n* = 423	<0001
Never smoker, *n* (%)		3893 (50.45)	3132 (53.58)	610 (42.13)	151 (35.7)	

(*Continued*)

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Table 1. (*Continued.*)

Variables	Missing	Description	By ACEs			
			0	1	2 or more	*p*
Former smoker, *n* (%)		1453 (18.83)	1132 (19.36)	250 (17.27)	71 (16.78)	
Current smoker, *n* (%)		2371 (30.72)	1582 (27.06)	588 (40.61)	201 (47.52)	
Alcohol consumption	314 (4.05%)	*n* = 7448	*n* = 5643	*n* = 1402	*n* = 403	0001
Moderate, *n* (%)		4993 (67.04)	3828 (67.84)	925 (65.98)	240 (59.55)	
Abstainer, *n* (%)		1842 (24.73)	1376 (24.38)	337 (24.04)	129 (32.01)	
Heavy drinker, *n* (%)		613 (8.23)	439 (7.78)	140 (9.99)	34 (8.44)	
Physical activity	1622 (20.9%)	*n* = 6140	*n* = 4692	*n* = 1126	*n* = 322	0212
Physically active, *n* (%)		5424 (88.34)	4167 (88.81)	978 (86.86)	279 (86.65)	
Moderately active, *n* (%)		494 (8.05)	368 (7.84)	99 (8.79)	27 (8.39)	
Inactive, *n* (%)		222 (3.62)	157 (3.35)	49 (4.35)	16 (4.97)	
Fruits and vegs diet	0	*n* = 7762	*n* = 5881	*n* = 1456	*n* = 425	<0001
Frequent, *n* (%)		2843 (36.63)	2238 (38.05)	477 (32.76)	128 (30.12)	
Occasionally, *n* (%)		2684 (34.58)	2040 (34.69)	498 (34.2)	146 (34.35)	
Hardly never, *n* (%)		2235 (28.79)	1603 (27.26)	481 (33.04)	151 (35.53)	
Junk food diet	1 (0.01%)	*n* = 7761	*n* = 5880	*n* = 1456	*n* = 425	0016
Hardly never, *n* (%)		1977 (25.47)	1454 (24.73)	393 (26.99)	130 (30.59)	
Occasionally, *n* (%)		1867 (24.06)	1452 (24.69)	330 (22.66)	85 (20)	
Frequent, *n* (%)		3917 (50.47)	2974 (50.58)	733 (50.34)	210 (49.41)	
Covariates at 42 years						
Social class	1045 (13.5%)	*n* = 6717	*n* = 5169	*n* = 1216	*n* = 332	<0001
Professional-managerial, *n* (%)		2938 (43.74)	2390 (46.24)	451 (37.09)	97 (29.22)	
Skilled nonmanual, *n* (%)		1482 (22.06)	1174 (22.71)	251 (20.64)	57 (17.17)	
Skilled manual, *n* (%)		1290 (19.21)	914 (17.68)	274 (22.53)	102 (30.72)	
Semi-unskilled, *n* (%)		1007 (14.99)	691 (13.37)	240 (19.74)	76 (22.89)	
Household tenure	20 (0.26%)	*n* = 7742	*n* = 5866	*n* = 1452	*n* = 424	<0001
Own, *n* (%)		6508 (84.06)	5057 (86.21)	1161 (79.96)	290 (68.4)	
Rent, *n* (%)		1015 (13.11)	648 (11.05)	249 (17.15)	118 (27.83)	
Others, *n* (%)		219 (2.83)	161 (2.74)	42 (2.89)	16 (3.77)	
Marital status	0	*n* = 7762	*n* = 5881	*n* = 1456	*n* = 425	<0001
Married, *n* (%)		5656 (72.87)	4334 (73.69)	1045 (71.77)	277 (65.18)	
Single, *n* (%)		881 (11.35)	662 (11.26)	168 (11.54)	51 (12)	
Divorced or widowed, *n* (%)		1225 (15.78)	885 (15.05)	243 (16.69)	97 (22.82)	
Smoking status	1 (0.01%)	*n* = 7761	*n* = 5880	*n* = 1456	*n* = 425	<0001
Never smoker, *n* (%)		3603 (46.42)	2902 (49.35)	564 (38.74)	137 (32.24)	
Former smoker, *n* (%)		1984 (25.56)	1522 (25.88)	360 (24.73)	102 (24)	
Current smoker, *n* (%)		2174 (28.01)	1456 (24.76)	532 (36.54)	186 (43.76)	
Alcohol consumption	0	*n* = 7762	*n* = 5881	*n* = 1456	*n* = 425	<0001
Moderate, *n* (%)		4026 (51.87)	3139 (53.38)	698 (47.94)	189 (44.47)	
Abstainer, *n* (%)		1742 (22.44)	1245 (21.17)	361 (24.79)	136 (32)	
Heavy drinker, *n* (%)		1994 (25.69)	1497 (25.45)	397 (27.27)	100 (23.53)	

(*Continued*)

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Table 1. (*Continued.*)

			By ACEs			
Variables	Missing	Description	0	1	2 or more	*p*
Physical activity	1 (0.01%)	*n* = 7761	*n* = 5880	*n* = 1456	*n* = 425	<0001
Physically active, *n* (%)		5136 (66.18)	3973 (67.57)	913 (62.71)	250 (58.82)	
Moderately active, *n* (%)		683 (8.8)	518 (8.81)	128 (8.79)	37 (8.71)	
Inactive, *n* (%)		1942 (25.02)	1389 (23.62)	415 (28.5)	138 (32.47)	
Fruits and vegs diet	0	*n* = 7762	*n* = 5881	*n* = 1456	*n* = 425	<0001
Frequent, *n* (%)		3576 (46.07)	2825 (48.04)	585 (40.18)	166 (39.06)	
Occasionally, *n* (%)		2202 (28.37)	1683 (28.62)	407 (27.95)	112 (26.35)	
Almost never, *n* (%)		1984 (25.56)	1373 (23.35)	464 (31.87)	147 (34.59)	
Junk food diet	0	*n* = 7762	*n* = 5881	*n* = 1456	*n* = 425	0065
Hardly never, *n* (%)		2836 (36.54)	2116 (35.98)	544 (37.36)	176 (41.41)	
Occasionally, *n* (%)		1841 (23.72)	1431 (24.33)	317 (21.77)	93 (21.88)	
Frequent, *n* (%)		3085 (39.74)	2334 (39.69)	595 (40.87)	156 (36.71)	
Problem with alcohol (ever)	0	*n* = 7762	*n* = 5881	*n* = 1456	*n* = 425	<0001
No, *n* (%)		7676 (98.89)	5830 (99.13)	1435 (98.56)	411 (96.71)	
Yes, *n* (%)		86 (1.11)	51 (0.87)	21 (1.44)	14 (3.29)	
Ever tried illegal drugs	0	*n* = 7762	*n* = 5881	*n* = 1456	*n* = 425	<0001
Never, *n* (%)		5220 (67.25)	4049 (68.85)	917 (62.98)	254 (59.76)	
Yes, one, *n* (%)		1557 (20.06)	1139 (19.37)	319 (21.91)	99 (23.29)	
Yes, two or more, *n* (%)		985 (12.69)	693 (11.78)	220 (15.11)	72 (16.94)	

than those exposed to 0ACEs (RRR_{23y} [95% CI] = 1.75 [1.09–2.80], RRR_{33y} [95% CI] = 1.83 [1.33–2.53], RRR_{42y} [95% CI] = 1.49 [1.19–1.87], model 1) and, among those who experienced 2^{+}ACEs, the relative risk was even stronger (RRR_{23y} [95% CI] = 3.80 [2.10–6.88], RRR_{33y} [95% CI] = 3.45 [2.21–5.39], RRR_{42y} [95% CI] = 2.26 [1.59–3.22], model 1). The relationships between ACEs and comorbid overweight-depression were larger in effect size compared to associations with overweight or depression only, particularly with exposure to 2^{+}ACEs.

The risk of comorbid overweight-depression was reduced after adjustment for baseline variables and early life SEP (RRR_{23y} [95% CI] = 2.62 [1.42–4.83], RRR_{33y} [95% CI] = 2.44 [1.54–3.85], RRR_{42y} [95% CI] = 1.65 [1.15–2.37]), model 2, 2^{+}ACEs). Associations were further explained by adult social characteristics or health behaviors though a relative risk was maintained after controlling for all intermediate variables (RRR_{23y} [95% CI] = 2.00 [1.08–3.72], RRR_{33y} [95% CI] = 1.68 [1.05–2.70], RRR_{42y} [95% CI] = 1.27 [0.87–1.86], model 3, 2^{+}ACEs).

Association between a combined variable of ACEs and sex on overweight-depression comorbidity and each separate condition

Sex and ACEs interaction term was not significant in our models at all ages however, as presented in online Supplementary Table S4, likelihood ratio tests on imputed data showed a statistically different fit of goodness between models with and without interaction for the four-category outcome at 42y (p value < 0.10).

Figure 2 shows that, at 42y, the risk of comorbid overweight-depression increased for men who experienced ACEs ($OR_{men2+ACEs}$ [95% CI] = 1.58 [0.93–2.69]) and decreased for women with or without record of ACEs ($OR_{women1ACE}$ [95% CI] = 0.82 [0.57–1.18]), compared to men who experienced no adversities. Here, there was no clear evidence that the relative risk for women with 2 + ACEs goes in the opposite direction to their women counterparts since confidence intervals overlap ($OR_{women2+ACEs}$ [95% CI] = 0.80 [0.46–1.38]). Results seemed also to differ for overweight and depression modalities, where risk of depression increased for men experiencing ACEs and women with 0 or one adversity but not for women with two or more adversities compared to men who experienced no adversities. Regarding overweight, no clear trend appeared for men experiencing ACEs although women with and without ACEs had a decreased risk compared to men who experienced no adversities.

Additional analyses

Further additional adjustment for risky behaviors at 42 years only slightly lowered the association between ACEs and comorbid overweight-depression risk (RRR_{2+ACEs} [95% CI] = 1.51 [1.04–2.17], model 2 + risky behaviors, Fig. 3).

Association between ACEs and overweight or depression outcomes examined individually at each period are given and described in online Supplementary Table S5a and S5b respectively together with the results of the ACEs and sex combined variables on overweight or depression outcomes examined individually (online Supplementary Fig. S1). Same tendencies were observed than those in the main analyses.

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Table 2. Multiple regression analyses for ACEs in association with overweight-depression comorbidity and each separate condition at 23, 33, and 42 years after accounting for all baseline confounders, early life SEP and intermediate variables (fully adjusted models) measured at the same time as the studied outcome from imputed data on the NCDS58 ($N = 7762$)

	Overweight only ($N = 7762$)					
	at 23y		at 33y		at 42y	
Model	1 ACE	2 or more ACEs	1 ACE	2 or more ACEs	1 ACE	2 or more ACEs
Model 1 (Sex)	1.06 (0.90–1.24)	1.39 (1.07–1.81)	1.06 (0.94–1.20)	1.33 (1.07–1.64)	0.96 (0.85–1.09)	1.27 (1.02–1.58)
Model 2 (Sex + all early-life factors)	0.95 (0.81–1.12)	1.13 (0.87–1.48)	1.00 (0.88–1.13)	1.16 (0.94–1.45)	0.89 (0.78–1.01)	1.07 (0.86–1.35)
Model 2						
+ Education	0.89 (0.75–1.05)	1.01 (0.77–1.33)	–	–	–	–
+ Social class	–	–	0.98 (0.86–1.11)	1.12 (0.90–1.40)	0.89 (0.78–1.01)	1.06 (0.84–1.33)
+ Wealth	–	–	0.98 (0.87–1.11)	1.12 (0.90–1.39)	–	–
+ Marital status	–	–	1.00 (0.88–1.13)	1.18 (0.95–1.46)	0.89 (0.79–1.02)	1.09 (0.87–1.37)
+ Household tenure	–	–	–	–	0.89 (0.78–1.01)	1.04 (0.83–1.31)
+ Social characteristics	0.89 (0.75–1.05)	1.01 (0.77–1.33)	0.97 (0.85–1.10)	1.10 (0.88–1.37)	0.88 (0.77–1.00)	1.05 (0.83–1.31)
+ Smoking	0.94 (0.80–1.11)	1.11 (0.85–1.45)	1.00 (0.88–1.13)	1.16 (0.93–1.45)	0.91 (0.80–1.03)	1.11 (0.88–1.39)
+ Alcohol	0.95 (0.81–1.12)	1.12 (0.86–1.47)	0.99 (0.88–1.13)	1.14 (0.91–1.41)	0.88 (0.78–1.01)	1.05 (0.83–1.31)
+ Physical activity	0.95 (0.80–1.12)	1.12 (0.86–1.47)	1.00 (0.88–1.13)	1.16 (0.93–1.44)	0.88 (0.78–1.00)	1.06 (0.84–1.33)
+ Fruit and vegetables	–	–	1.00 (0.88–1.13)	1.17 (0.94–1.45)	0.89 (0.79–1.02)	1.08 (0.86–1.35)
+ Junk food	–	–	0.99 (0.88–1.13)	1.15 (0.93–1.44)	0.89 (0.78–1.01)	1.07 (0.85–1.34)
+ Health behaviors	0.94 (0.79–1.1)	1.09 (0.84–1.43)	0.99 (0.88–1.13)	1.13 (0.90–1.40)	0.89 (0.78–1.02)	1.06 (0.84–1.34)
Model 3 (Fully adjusted)	0.89 (0.75–1.05)	1.01 (0.77–1.32)	0.97 (0.85–1.10)	1.08 (0.86–1.35)	0.88 (0.78–1.01)	1.04 (0.82–1.31)
	Depressed only ($N = 7762$)					
	at 23y		at 33y		at 42y	
Model	1 ACE	2 or more ACEs	1 ACE	2 or more ACEs	1 ACE	2 or more ACEs
Model 1 (Sex)	1.79 (1.41–2.27)	2.71 (1.90–3.86)	1.79 (1.35–2.37)	2.85 (1.87–4.34)	1.54 (1.20–1.96)	1.74 (1.14–2.65)
Model 2 (Sex + all early-life factors)	1.60 (1.26–2.04)	2.13 (1.48–3.07)	1.61 (1.21–2.13)	2.25 (1.46–3.46)	1.36 (1.06–1.75)	1.39 (0.91–2.14)
Model 2						
+ Education	1.44 (1.13–1.84)	1.76 (1.22–2.55)	–	–	–	–
+ Social class	–	–	1.53 (1.15–2.04)	2.03 (1.31–3.13)	1.35 (1.05–1.73)	1.36 (0.88–2.1)
+ Wealth	–	–	1.55 (1.17–2.07)	2.03 (1.31–3.13)	–	–
+ Marital status	–	–	1.61 (1.21–2.14)	2.18 (1.41–3.36)	1.36 (1.06–1.74)	1.35 (0.87–2.08)
+ Household tenure	–	–	–	–	1.31 (1.02–1.68)	1.22 (0.79–1.89)

(*Continued*)

Table 2. (*Continued.*)

	Depressed only (*N* = 7762)					
	at 23y		at 33y		at 42y	
Model	1 ACE	2 or more ACEs	1 ACE	2 or more ACEs	1 ACE	2 or more ACEs
+ Social characteristics	1.44 (1.13–1.84)	1.76 (1.22–2.55)	1.52 (1.14–2.02)	1.88 (1.21–2.93)	1.30 (1.01–1.67)	1.21 (0.78–1.88)
+ Smoking	1.45 (1.14–1.85)	1.83 (1.27–2.65)	1.42 (1.06–1.89)	1.92 (1.24–2.97)	1.25 (0.97–1.60)	1.23 (0.79–1.89)
+ Alcohol	1.60 (1.26–2.04)	2.11 (1.46–3.03)	1.59 (1.20–2.12)	2.23 (1.45–3.43)	1.34 (1.04–1.71)	1.33 (0.86–2.05)
+ Physical activity	1.57 (1.23–1.99)	2.09 (1.45–3.01)	1.61 (1.21–2.14)	2.25 (1.46–3.47)	1.33 (1.04–1.71)	1.34 (0.87–2.07)
+ Fruit and vegetables	–	–	1.57 (1.18–2.09)	2.17 (1.41–3.35)	1.29 (1.01–1.66)	1.32 (0.85–2.03)
+ Junk food	–	–	1.60 (1.20–2.12)	2.22 (1.44–3.42)	1.36 (1.06–1.74)	1.39 (0.91–2.15)
+ Health behaviors	1.43 (1.12–1.82)	1.79 (1.24–2.58)	1.40 (1.04–1.87)	1.87 (1.21–2.90)	1.19 (0.93–1.54)	1.14 (0.74–1.77)
Model 3 (Fully adjusted)	1.34 (1.05–1.71)	1.59 (1.10–2.31)	1.36 (1.01–1.82)	1.70 (1.09–2.66)	1.19 (0.92–1.53)	1.08 (0.69–1.69)
	Overweight and depression comorbidity (*N* = 7762)					
	at 23y		at 33y		at 42y	
Model	1 ACE	2 or more ACEs	1 ACE	2 or more ACEs	1 ACE	2 or more ACEs
Model 1 (Sex)	1.75 (1.09–2.80)	3.80 (2.10–6.88)	1.83 (1.33–2.53)	3.45 (2.21–5.39)	1.49 (1.19–1.87)	2.26 (1.59–3.22)
Model 2 (Sex + all early-life factors)	1.45 (0.90–2.33)	2.62 (1.42–4.83)	1.55 (1.12–2.15)	2.44 (1.54–3.85)	1.30 (1.03–1.64)	1.65 (1.15–2.37)
Model 2						
+ Education	1.26 (0.78–2.04)	2.08 (1.12–3.84)	–	–	–	–
+ Social class	–	–	1.44 (1.03–2.01)	2.13 (1.34–3.39)	1.26 (1.00–1.59)	1.56 (1.08–2.25)
+ Wealth	–	–	1.45 (1.05–2.02)	2.06 (1.30–3.27)	–	–
+ Marital status	–	–	1.54 (1.11–2.14)	2.41 (1.52–3.81)	1.30 (1.03–1.63)	1.62 (1.13–2.33)
+ Household tenure	–	–	–	–	1.23 (0.98–1.55)	1.41 (0.97–2.03)
+ Social characteristics	1.26 (0.78–2.04)	2.08 (1.12–3.84)	1.37 (0.98–1.91)	1.88 (1.18–3.00)	1.21 (0.96–1.52)	1.36 (0.93–1.97)
+ Smoking	1.39 (0.86–2.25)	2.47 (1.34–4.57)	1.44 (1.03–2.00)	2.21 (1.39–3.51)	1.26 (1.00–1.58)	1.57 (1.09–2.26)
+ Alcohol	1.45 (0.90–2.33)	2.52 (1.37–4.65)	1.55 (1.12–2.15)	2.33 (1.47–3.69)	1.27 (1.01–1.60)	1.55 (1.08–2.24)
+ Physical activity	1.40 (0.87–2.26)	2.52 (1.37–4.66)	1.54 (1.11–2.13)	2.42 (1.53–3.84)	1.27 (1.01–1.60)	1.57 (1.09–2.26)
+ Fruit and vegetables	–	–	1.52 (1.10–2.11)	2.37 (1.50–3.76)	1.25 (1.00–1.58)	1.59 (1.11–2.29)
+ Junk food	–	–	1.53 (1.10–2.12)	2.35 (1.48–3.72)	1.30 (1.03–1.63)	1.65 (1.15–2.37)
+ Health behaviors	1.36 (0.84–2.20)	2.33 (1.25–4.31)	1.40 (1.00–1.95)	2.01 (1.26–3.19)	1.19 (0.94–1.51)	1.43 (0.99–2.07)
Model 3 (Fully adjusted)	1.25 (0.77–2.02)	2.00 (1.08–3.72)	1.29 (0.92–1.81)	1.68 (1.05–2.70)	1.16 (0.92–1.47)	1.27 (0.87–1.86)

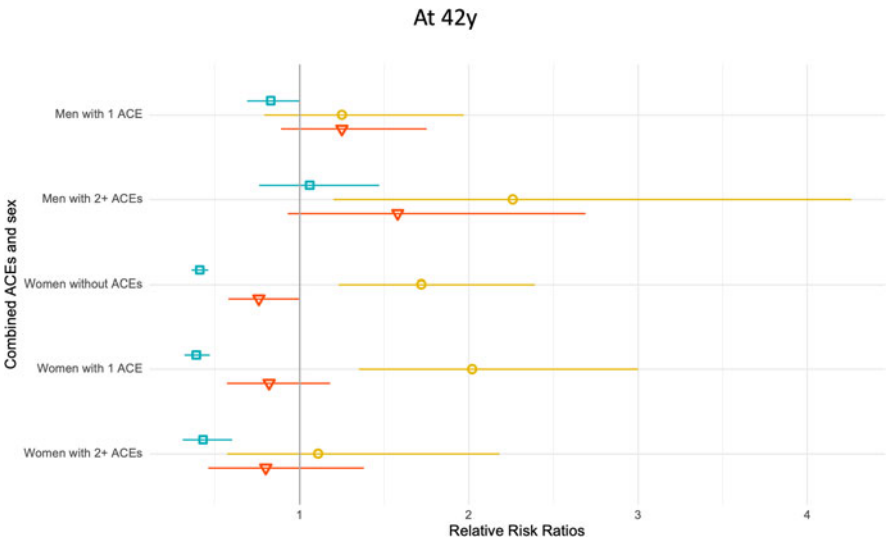

Figure 2. Multiple regression analyses for a combined variable of ACEs and sex in association with overweight-depression comorbidity and each separate condition (Modality overweight only = square; depression only = circle; both overweight and depression = triangle) at 42 years after accounting for all baseline confounders and early life SEP and intermediate variables (fully adjusted models) measured at the same time as the studied outcome from imputed data on the NCDS58 ($N = 7762$).

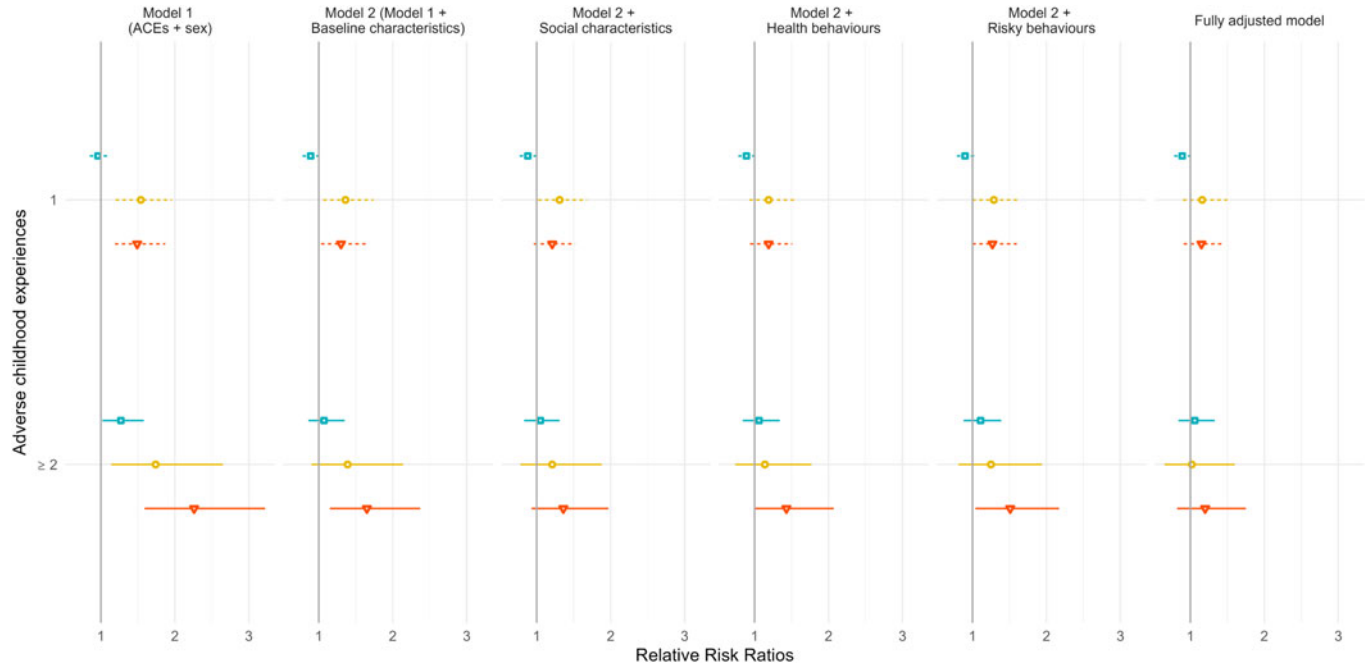

Figure 3. Multiple regression analyses for ACEs and comorbidity at 42 years old after accounting for an additional block of risky behaviors measured at the same time as the studied outcome from imputed data on the NCDS58 ($N = 7762$).

Sensitivity analyses

Complete cases analyses indicated that our findings were not affected by the imputation process (online Supplementary Table S6). Sensitivity analyses using obesity instead of overweight condition resulted in weaker associations (online Supplementary Tables S7, S8).

Results after adjustment for adulthood confounders from a prior period to the outcome studied did not explain further the association compared to equivalent confounder adjustment co-occurring with the outcome (online Supplementary Table S9).

Discussion

Our study suggests that adversities in childhood are associated with a higher risk of comorbid overweight-depression compared to either condition taken separately. These associations are observed in all three periods from young adulthood but weakened over time. Part of the association between ACEs and comorbid overweight-depression was explained by adjustment for baseline confounders and early life SEP as well as by age-specific adult SEP and health behaviors. An association remained after considering all of these factors. Additionally, our results suggest that

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men and women have a different ACEs-comorbid overweight-depression risk relationship at age 42, where the risk for men increases with cumulated exposure to ACEs but not for women.

In our analyses, among potential early-life confounders considered, those related to household SEP had the greater influence on the association, especially parents' social class. This suggests that part of the effect of ACEs on overweight, depression and comorbid overweight-depression is related to the socioeconomic environment in which the child lives. In 2021, Khanolkar & Patalay (2021) showed that socioeconomic disadvantage in childhood and adulthood are associated with greater risk of suffering from the co-occurrence of mental ill-health and overweight across the lifecourse in NCDS58. Disadvantaged childhood social class was associated with increased risk of comorbidity in adulthood even after accounting for adulthood socioeconomic circumstances, which is consistent with our findings.

In line with previous studies investigating the association between ACEs and multimorbidity in older age, part of the association was explained by adjustment for health behaviors and/or adulthood SEP (Henchoz et al., 2019; Lin et al., 2021; Sinnott et al., 2015; Tomasdottir et al., 2015; Yang et al., 2020). Overweight and depression are known to share common risk factors, which are associated to ACEs (Anda, Butchart, Felitti, & Brown, 2010; Hoare, Skouteris, Fuller-Tyszkiewicz, Millar, & Allender, 2014; Smith, Fu, & Kobayashi, 2020), like the adoption of hazardous lifestyle behaviors, such as smoking, unhealthy diet or problems with alcohol consumption (Felitti et al., 1998). ACEs could also affect adult SEP, which in turn can lead to unhealthy lifestyle practices in adulthood (Shonkoff, Garner, Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, & Section on Developmental and Behavioral Pediatrics, 2012). Persisting associations are observed after adjusting for all covariates simultaneously, except for the outcome at 42 years. Some explanation to the loss of association only found at age 42 could be that the non-adjusted risk estimation at start was lower in magnitude compared to the ones at 23 and 33 years. It is noteworthy that although the association was no longer statistically significant at 42 years, adjustment by intermediate variables individually did not have a major influence on risk reduction (e.g. the most reduced $OR_{2+ACEs\ at\ 42y}$ remained at 1.41 after controlling for household tenure, Table 2).

Overall, the persisting associations imply the existence of other mechanisms.

While many of the mechanisms underlying these associations remain unclear, it has been proposed that disruptions in stress response systems may be at play. Specifically, prolonged exposure to childhood adversities, especially early in development, may elicit sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis and its glucocorticoid hormone cortisol in basal and stressful contexts, which may wear and tear the future capacity of the HPA axis to support adaptive responses to stress, and compromise the activity of other physiological systems over time. This alteration of physiological mechanisms can be captured through a measure of allostatic load which has been previously found to be associated with ACEs (Barboza Solís et al., 2015). Recently, a study investigated the association between childhood experiences, allostatic load and multimorbidity (Tomasdottir et al., 2015). They found a general, graded association between self-reported childhood difficulties and multimorbidity, on the one hand, and individual disease burden and biological perturbations, on the other.

Another physiological system that could be of interest is inflammation (Breton, Fotso Soh, & Booij, 2022). An overactivation of the HPA axis is also associated with inflammation (Slopen, Kubzansky, McLaughlin, & Koenen, 2013) and changes in immunoinflammatory processes, which may influence an individual's susceptibility to mental disorders (Kramer et al., 2019) and obesity (Pervanidou & Chrousos, 2012). Changes in pro-inflammatory markers (e.g. C-reactive protein) observed in obese individuals could have a mediating role in the link between obesity and depressive symptoms (Chu, Cadar, Iob, & Frank, 2023; Daly, 2013). These biological mechanisms in the association between ACEs and multimorbidity need to be further explored. In the NCDS58, the biological survey was conducted when cohort members were 45 years, after the last measure of our outcomes, therefore we could not use these data to examine possible biological mechanisms.

Some studies hint to a multimorbidity risk related to childhood experience that is sex-patterned, such as we observed in our findings. In a study of the relation between self-reported childhood quality, biological perturbations and multimorbidity in adulthood, (Tomasdottir et al., 2015) reported that introducing age and sex in combination with allostatic load into the model to estimate the risk of multimorbidity, explained part of the relationship. Chandrasekar et al. showed a graded relationship between number of ACEs and multimorbidity in stratified sex samples. Risk estimates were larger for women compared to men (Chandrasekar et al., 2023). Nonetheless, given different samples in stratified analyses, comparisons cannot be made with respect to the relative influence of sex in the studied relationship, such as those explored in our study.

Strengths and limitations

This study contains design limitations, warranting caution when interpreting results. Although cohort retention at each follow-up in the NCDS58 is satisfactory, we cannot exclude selection bias due to attrition and loss to follow-up. This could also have been exacerbated by our initial selection of individuals with no missing data on ACEs, BMI and MI. Indeed, the proportion of individuals who experienced ACEs in our study population is lower compared to those excluded from the initial cohort because of missing data (24.2% *v.* 30.0%, online Supplementary Table S2) potentially leading to an underestimation of the effect of childhood adversities on comorbid overweight-depression. To allow for uncertainty about the missing data, multiple imputations were used for confounding variables taking the missing at random assumption and we additionally ran all analyses on complete cases i.e. individuals with no missing data for any of the selected characteristics. Another limitation originates in the cohort and period specificities. The most common family of stressors in children from Europe in 1958 could differ from those of relevance nowadays. Characterizing societal characteristics to understand current components of ACEs is important in attempting adapted replicability in other contexts.

Despite these limitations, the data used in this study contains many strengths. We used a longitudinal population-based birth cohort with prospectively measured data across the life span, which reduces the risk of recall bias. As well, exposure-outcome temporal sequencing of events allows to control for reverse causality. Additional analyses showed that results with independent components of the comorbidity's status display similar trends. Additionally, the wealth of detailed data from early life within

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the cohort allowed us to control for a number of potential confounding factors. Also, the design of our analysis allows for characterization of comorbid overweight-depression in young adult populations which contributes to early prevention knowledge.

Conclusion

This study provides evidence that the risk of comorbid overweight-depression associated to ACEs is larger than the associated risk of overweight or depression conditions separately. Further investigations are needed to understand the mechanisms at play in this relationship and to explore sex-specific differences to extend on the work presented in this study. These results emphasize the importance of challenging the single-disease framework of medical research and health care. Recommendations include reinforcing patient-centered care and continuity of care in multimorbidity, with considerations of psychosocial causes and consequences of disease. Additionally, efforts need to be made to target early life stressors and promote positive, supportive environments during childhood development. Policymakers should endorse supportive learning environments for children and guarantee equitable resource allocation.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003823

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