

1 **Association of childhood adversity with frailty and the mediating role of**
2 **unhealthy lifestyle: Findings from the UK biobank**

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35 **Abstract**

36 **Background:**

37 Childhood adversity and lifestyle have been associated with frailty in later life, but not
38 much is known about factors that may explain these associations. An unhealthy lifestyle
39 may play an important role in the pathway from childhood adversity to frailty. Therefore,
40 this study aims to investigate the association of childhood adversity with frailty, and the
41 mediating role of unhealthy lifestyle in the association.

42 **Methods:**

43 This lifespan analysis included 152914 adults aged 40-69 years old from the UK
44 Biobank. We measured childhood adversity with five items: physical neglect, emotional
45 neglect, sexual abuse, physical abuse, and emotional abuse through online mental
46 health survey. Frailty was measured by the frailty index; an unhealthy lifestyle score
47 (range: 0-5) was calculated based on unhealthy body mass index, smoking, drinking,
48 physical inactivity, and unhealthy diet at the baseline survey. Multiple logistic
49 regression and mediation analysis were performed.

50 **Results:**

51 A total of 10078 participants (6.6%) were defined as having frailty. Participants with
52 any childhood adversity had higher odds of frailty. For example, in the fully adjusted
53 model, with a one-point increase in cumulative score of childhood adversity, the odds
54 of frailty increased by 41% (Odds Ratio: 1.41; 95% Confidence Interval: 1.39, 1.44).
55 Unhealthy lifestyle partially mediated the associations of childhood adversity with
56 frailty (mediation proportion: 4.4%-7.0%). The mediation proportions were largest for
57 physical (8.2%) and sexual (8.1%) abuse.

58 **Conclusions:**

59 Among this large sample, childhood adversity was positively associated with frailty,

60 and unhealthy lifestyle partially mediated the association. This newly identified
61 pathway highlights the potential of lifestyle intervention strategies among those who
62 experienced childhood adversity (in particular, physical and sexual abuse) to promote
63 healthy aging.

64 **Keywords:**

65 Aging; Childhood adversity; Lifestyle; Frailty; Mediation analysis

66 **Introduction**

67 With population aging increasing worldwide, the promotion of healthy aging has gained
68 more attention in recent years. A crucial component of healthy aging is the prevention
69 of geriatric syndromes, such as frailty. The importance of the frailty concept,
70 characterized by the decline of physiological systems and the ability to regulate
71 stressors, is increasingly being acknowledged [1]. Additionally, frailty accounts for
72 many adverse health outcomes such as disability, falls, hospitalization, and mortality,
73 which brings a huge burden to society, caregivers, and families [2, 3].

74 Life course theory indicates that early exposure to environmental, psychosocial,
75 and physical factors can influence the aging process [4, 5], frailty [6-14], and late-life
76 health [15] (e.g. cardiovascular disease [16], mortality [17]). To date, five
77 epidemiological studies have found a positive association between childhood adversity
78 and frailty [18-22] while one study indicated a null association [23]. The conflicting
79 findings might be partially due to the limited sample size. More importantly, not much
80 is known about factors that may explain the childhood adversity-frailty association (if
81 it was established) [22]. Campbell et al. [24] found that people who had adverse
82 childhood experiences were more likely to be binge drinkers, heavy drinkers, smokers,
83 or obese. Recent evidence also highlights that unfavorable lifestyle including lack of
84 physical activity, poor nutrition, and sleep deprivation may synergistically influence
85 health in later life [25]. Thus, we hypothesize that childhood adversity may influence
86 frailty through unhealthy lifestyle, which, however, previous studies have not explored.

87 Therefore, this study aimed to examine the relationship between childhood
88 adversity and frailty as well as the mediating role of unhealthy lifestyle in this
89 association using data from approximately 150000 UK adults.

90

91 **Methods**

92 **Study participants**

93 This lifespan analysis used data from the UK Biobank (UKB), a large population-
94 based cohort study with approximately half a million participants aged 40-69 years at
95 recruitment in 2006-2010 [26]. UKB was approved by the North West-Haydock
96 Research Ethics Committee and all participants electronically wrote informed consent
97 at recruitment. A total of 156749 adults who were healthier, better educated, and had
98 higher socioeconomic status than the overall biobank sample participated in both the
99 baseline survey and the subsequent 2016 online mental health survey [27]. We excluded
100 participants with missing data on childhood adversity (N=3728) and frailty (N=107),
101 leaving 152914 participants in the analytic sample (**Figure S1**).

102 **Childhood adversity**

103 Data on childhood adversity was sourced from the 2016 online mental health
104 survey. Childhood adversity was characterized as physical neglect, emotional neglect,
105 sexual abuse, physical abuse, and emotional abuse using the Childhood Trauma
106 Screener [28] across five questions. Items were divided based on the options (“very
107 often true”, “often true”, “sometimes true”, “rarely true”, “never true”), which were
108 scored 0 or 1 according to the cut-off points shown in **Table S1** after inversely scoring
109 two positive items (i.e., emotional neglect, physical neglect) [29]. The cumulative score
110 of all five items ranged from 0 to 5, with a higher score indicating more childhood
111 adversity. The items included are:

- 112 (1) Someone to take to doctor when needed as a child (physical neglect);
- 113 (2) Felt loved as a child (emotional neglect);
- 114 (3) Sexually molested as a child (sexual abuse);
- 115 (4) Physically abused by family as a child (physical abuse);

116 (5) Felt hated by family member as a child (emotional abuse).

117 **Frailty measures**

118 Frailty was assessed at the baseline survey, using frailty index following the
119 methods of Rockwood et al. [30] based on a series of indicators of ill-health in
120 physiological and mental domains including diagnosed diseases, symptoms, and
121 disabilities. The frailty index is well-validated for predicting mortality [2] and
122 calculated through 49 self-reported items covering sensory, cranial, mental well-being,
123 infirmity, cardiometabolic, musculoskeletal, immunological, cancer, pain, and
124 gastrointestinal [31]. A frailty score, a continuous value ranging from 0 to 1, was
125 obtained by dividing the number of deficits by the total number of deficits. For instance,
126 a participant who has 10 items that scored 1 as opposed to 0 would have frailty scored
127 10/49 (i.e., 0.204). According to the literature [32], participants with a score over 0.21
128 were categorized as frailty, and those with a score less than 0.21 were categorized as
129 non-frailty.

130 **Assessment of unhealthy lifestyle**

131 An unhealthy lifestyle score was constructed according to five lifestyle factors (i.e.,
132 smoking status, alcohol consumption, diet, body mass index (BMI), and physical
133 activity) sourced from structured questionnaires and 24 hours dietary recalls at the
134 baseline survey.

135 Based on the recommendations of the World Health Organization, smoking more
136 than 100 cigarettes in life was considered as unhealthy [33]. The daily consumption of
137 one alcoholic drink or more for females and two drinks or more for males was
138 considered as unhealthy [33]. For diet, having not achieved the intake goals for more
139 than half of the following components: vegetables, fruits, whole grains, (shell)fish,
140 vegetable oils, dairy products, unprocessed meats, sugar-sweetened beverages, and

141 refined grains was considered as unhealthy [34]. A BMI out of the range of 18.5-24.9
142 kg/m² was considered as unhealthy [35]. For physical activity, a) less than 150 minutes
143 or 5 days per week of moderate physical activity; or b) less than 75 minutes or once per
144 week of vigorous activity were considered as unhealthy levels of physical activity [36].

145 For each lifestyle factor, the unhealthy level was scored 1 and otherwise, was
146 scored 0. The unhealthy lifestyle score ranged from 0 to 5 and a higher score indicated
147 a higher level of unhealthy lifestyle.

148 **Covariates**

149 The following covariates collected at baseline survey were included: chronological
150 age, sex, ethnicity, educational level, occupation, Townsend deprivation index (TDI),
151 and maternal smoking around birth. Ethnicity was classified as white, mixed, south
152 Asian, black, Chinese, and others [37]. Educational level was defined as high (college
153 or university degree), intermediate (A/AS levels or O levels/GCSEs or equivalent), and
154 low (none of the aforementioned) [33]. The occupation was classified as working,
155 retired, and others (unemployed, unpaid/voluntary work, full/part-time student, looking
156 after home and/or family, unable to work because of sickness or disability, or did not
157 answer) [38]. TDI consisted of data on housing, social class based on the postal code,
158 and employment, with a higher TDI indicating a lower level of socioeconomic status
159 [38].

160 **Statistical Analyses**

161 The basic characteristics of the study participants were classed by frailty with
162 mean±standard deviation (SD) for continuous variables and counts (percentage) for
163 categorical variables. The basic characteristics across groups were compared by t-test
164 for continuous variables and χ^2 test for categorical variables, respectively. We imputed
165 the missing values of smoking status (N=1632), alcohol consumption (N=16299), diet

166 (N=1), physical activity (N=798), and covariates (N=20597) with the Multiple
167 Imputation by Chained Equations [39], using five copies of imputation.

168 First, multiple logistic regression models were performed to estimate the
169 associations between childhood adversity and frailty (**Figure 1**). We documented odds
170 ratios (ORs) and corresponding 95% confidence intervals (CIs) from three models.
171 Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for ethnicity,
172 occupation, educational level, TDI, and maternal smoking around birth. Model 3 was
173 additionally adjusted for unhealthy lifestyle score.

174 Second, to examine whether unhealthy lifestyle mediates the associations of
175 childhood adversity with frailty, we performed a mediation analysis. First, we used
176 linear regression models to evaluate the associations of childhood adversity with
177 unhealthy lifestyle score in two models. We controlled for age and sex in Model 1 and
178 further controlled for more covariates including ethnicity, occupation, educational level,
179 TDI, and maternal smoking around birth in Model 2. Second, we used multiple logistic
180 regression models to evaluate the associations between unhealthy lifestyle and frailty
181 in two similar models. Finally, we performed a mediation analysis using R package
182 “mediation” with 1000 simulations and documented the mediation proportions and
183 corresponding 95% CIs in an age- and sex-adjusted model. The method for calculating
184 the mediation proportions mediation was: average causal mediation effects/ (average
185 causal mediation effects +average direct effects) [40].

186 To test the robustness of the findings, we conducted several sensitivity analyses.
187 First, we repeated the primary analyses using another frailty measure — the frailty
188 phenotype. Details on frailty phenotype are described in **supplemental methods**.
189 Second, we re-estimated the associations of childhood adversity with frailty that was
190 inputted as a continuous variable. Third, we used 0.25 as an alternative cutoff to define

191 frailty and repeated the main analyses [3]. Fourth, we repeated the main analyses after
192 excluding participants with missing data on lifestyles and covariates.

193 We used SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.1.1 (2021-08-
194 10) to conduct all analyses. P values less than 0.05 were considered statistically
195 significant (two-tailed).

196

197 **Results**

198 **Characteristics of participants**

199 The characteristics of the participants are presented in **Table 1**. The age of
200 participants was 56.4 (SD=7.7) years, and 6.6% (N=10078) of participants were defined
201 as having frailty.

202 **Mediation analysis of unhealthy lifestyle on associations between childhood** 203 **adversity and frailty**

204 First, **Table 2** presents the associations of childhood adversity with unhealthy
205 lifestyle. Both individual items of childhood adversity (except for physical neglect) and
206 cumulative childhood adversity were associated with higher unhealthy lifestyle score
207 in the fully adjusted model (Model 2).

208 Second, **Figure S2** shows the associations of unhealthy lifestyle with frailty. In
209 Model 1, with a one-point increase in unhealthy lifestyle score, the odds increased by
210 46% (OR: 1.46, 95% CI: 1.43, 1.48). In Model 2, the results remain unchanged after
211 adjustment for other covariates.

212 Finally, **Figure 2** and **Figure S3** present the prevalence of frailty and frailty score
213 by individual items and the cumulative score of childhood adversity. Compared with
214 participants who did not experience any adversity, those who experienced adversity had
215 a higher prevalence of frailty (P<0.001). **Table 3** shows significant associations of

216 childhood adversity with frailty and the mediation proportion of childhood adversity in
217 frailty attributed to unhealthy lifestyle. We found that childhood adversity was
218 positively associated with frailty. For example, compared with participants who did not
219 experience any adversity, those who experienced sexual abuse had increased odds (OR:
220 2.03; 95%CI: 1.91, 2.15) of frailty after adjustment for age and sex (Model 1). After
221 further adjustment for ethnicity, educational level, occupation, TDI, and maternal
222 smoking around birth, the strength of these associations decreased slightly but remained
223 statistically significant (Model 2). After further adjusting for unhealthy lifestyle score,
224 the associations remained robust (Model 3). For cumulative childhood adversity, a
225 dose-response association was observed. With a one-point increase in cumulative score
226 of childhood adversity, the odds of frailty increased by 41% (OR: 1.41; 95% CI: 1.39,
227 1.44) (Model 3). The mediation proportion of unhealthy lifestyle in associations
228 between childhood adversity and frailty ranged from 4.4%-7.0%. Regarding individual
229 items of childhood adversity, physical (mediation proportion: 8.2%) and sexual abuse
230 (mediation proportion: 8.1%) were more likely to influence frailty through unhealthy
231 lifestyle than other items.

232

233 **Sensitivity analyses**

234 First, with another frailty measure (i.e., frailty phenotype), similar associations
235 were observed with higher mediation proportion (ranging from 8.7%-17.2%) than that
236 of frailty index (**Table S2-S4**). Second, **Table S5** shows the positive associations
237 between cumulative childhood adversity and frailty score ($\beta=0.010$, $P<0.001$) in the
238 fully adjusted model. Third, when using an alternative cutoff of 0.25 for frailty, the
239 significant associations of childhood adversity with frailty and the mediating role of
240 unhealthy lifestyle on the associations were maintained (**Table S6**). Fourth, after

241 excluding participants with missing data on lifestyles, these associations remained
242 robust (**Table S7**).

243

244 **Discussion**

245 Our analyses of a large sample of 152914 participants of UKB aged 40-69 years,
246 resulted in two main findings. First, we confirmed significant associations of childhood
247 adversity with frailty, highlighting the importance of reducing traumatic experiences in
248 early life. Second, for the first time we found that unhealthy lifestyle partially mediated
249 the association between childhood adversity (in particular physical and sexual abuse)
250 and frailty. The finding reveals a novel pathway and the potential of lifestyle
251 interventions to prevent or reduce the severity of frailty among adults who have already
252 experienced some childhood adversities.

253 The findings of the positive associations between childhood adversity and frailty
254 are consistent with most previous studies [18-22]. However, one study among 182 older
255 patients with affective disorder did not find any association of childhood adversity with
256 frailty [23]. Our findings strengthen the associations in a large sample size of general
257 population and have important public implications for interventions on childhood
258 adversity in early life to diminish health inequality in late life. Frailty represents a
259 decline of the function of multiple systems [22]. Our findings may suggest a potential
260 of programs targeting childhood adversity in the prevention of frailty and physiological
261 dysfunction.

262 To the best of our knowledge, this was the first study to demonstrate that unhealthy
263 lifestyle partially mediated the associations of childhood adversity with frailty.
264 Childhood adversity is linked to inadequate ability to regulate emotions and cope with
265 stress from early-life to adulthood. As a way of managing feelings of anger and

266 powerless, people who experienced childhood adversity are more likely to adopt
267 unhealthy behaviors (e.g., smoking, drinking, unhealthy diet) [41, 42]. Frailty is widely
268 recognized to be linked with poor diet, sedentary lifestyles, physical inactivity, and
269 obesity [3]. Also, several studies have demonstrated that adherence to healthy lifestyle
270 is linked to a lower risk of frailty [43-45]. These observations support our findings that
271 childhood adversity may lead to frailty through unhealthy lifestyle. The mediating role
272 of unhealthy lifestyle highlights the importance of modifiable lifestyle interventions to
273 mitigate accelerated functional aging process (proportions mediation: 4.4%-8.2%)
274 among adults who have already experienced childhood adversity. Meanwhile, the
275 partial mediation suggests that modifiable lifestyle interventions are insufficient, and
276 more strategies should be explored.

277 Given the relatively large sample, we were able to further distinguish the mediation
278 proportions of unhealthy lifestyle in the associations between individual items of
279 childhood adversity and frailty. Relative to other items, physical and sexual abuse were
280 pronouncedly associated with frailty through unhealthy lifestyle. Similar to our
281 observation of the greater associations of physical and sexual abuse with unhealthy
282 lifestyle, previous study found that physical and sexual abuse were associated with a
283 higher risk of smoking [46]. This provides clues that pathways from childhood
284 adversity to health outcomes may differ by individual item of childhood adversity. A
285 longitudinal study has indicated that the association of physical abuse with glucose
286 metabolism may be largely explained by adulthood obesity while the association of less
287 severe adversities (e.g., emotional neglect) was mostly explained by childhood
288 socioeconomic factors [47]. Moreover, given the relatively small mediation proportion
289 in our study, other mediators of biological and psychological mechanisms including
290 adult socioeconomic status [48], attachment and mood symptoms [49] may exist. Thus,

291 comprehensively understanding the character of diverse childhood adversities and the
292 underlying mechanism of how they affect late-life health is necessary, and then we
293 could tailor the programs targeting childhood adversity.

294 The present study has some strengths including the large sample size of middle-
295 aged and older adults. Furthermore, a series of sensitivity analyses were performed to
296 confirm the validity of the findings. This study also has limitations. First, the mediator
297 (unhealthy lifestyle score) was assessed at the same time as the outcome (frailty) in the
298 study. Longitudinal studies are needed to examine the causal relationship. Second,
299 frailty was measured at baseline while the mental health survey was administered 6 to
300 10 years later, which may introduce some healthy selection. Third, recall bias was
301 inevitable given the retrospective information of childhood adversity. However,
302 retrospective childhood adversity records are reported to have moderate associations
303 between childhood adversity and adverse outcomes observed in perspective-records
304 studies [50]. Fourth, due to a lack of detailed data on childhood adversity, our study is
305 unable to assess the association of the duration and the severity of childhood adversity
306 with frailty. Further studies were demanded to reinforce the findings of the study. Fifth,
307 most participants in UKB are White and have relatively high socioeconomic status [51],
308 which may lead to selection bias and potential confounders.

309 **Conclusions**

310 In this large sample of more than 150000 UK adults, childhood adversity was positively
311 associated with frailty, and unhealthy lifestyle partially mediated the association,
312 especially for the associations of physical and sexual abuse with frailty. Our findings
313 highlight the potential of programs targeting on childhood adversity and lifestyle
314 intervention strategies to promote healthy aging. A comprehensive understanding of the
315 character of diverse childhood adversities and the underlying mechanism of how they

316 affect late-life health is needed.

317 **Availability of data and materials**

318 The datasets analysed during the current study are available in the UK Biobank
319 repository, <http://www.ukbiobank.ac.uk>.

320 **Abbreviations**

321 **UKB:** UK Biobank

322 **BMI:** Body mass index

323 **TDI:** Townsend deprivation index

324 **SD:** Standard deviation

325 **OR:** Odds ratio

326 **CI:** Confidence interval

327

328 **Reference:**

- 329 1. Beard JR, Officer A, de Carvalho IA, Sadana R, Pot AM, Michel JP, Lloyd-Sherlock P,
330 Epping-Jordan JE, Peeters GME, Mahanani WR *et al*: **The World report on ageing and**
331 **health: a policy framework for healthy ageing.** *Lancet* 2016, **387**(10033):2145-2154.
- 332 2. Kojima G, Iliffe S, Walters K: **Frailty index as a predictor of mortality: a systematic**
333 **review and meta-analysis.** *Age Ageing* 2018, **47**(2):193-200.
- 334 3. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP: **Frailty: implications for**
335 **clinical practice and public health.** *Lancet* 2019, **394**(10206):1365-1375.
- 336 4. Liu Z, Chen X, Gill TM, Ma C, Crimmins EM, Levine ME: **Associations of genetics,**
337 **behaviors, and life course circumstances with a novel aging and healthspan**
338 **measure: Evidence from the Health and Retirement Study.** *PLoS Med* 2019,
339 **16**(6):e1002827.
- 340 5. Schrempft S, Belsky DW, Draganski B, Kliegel M, Vollenweider P, Marques-Vidal P,
341 Preisig M, Stringhini S: **Associations between life course socioeconomic conditions**
342 **and the Pace of Aging.** *J Gerontol A Biol Sci Med Sci* 2021.
- 343 6. Gale CR, Booth T, Starr JM, Deary IJ: **Intelligence and socioeconomic position in**
344 **childhood in relation to frailty and cumulative allostatic load in later life: the**
345 **Lothian Birth Cohort 1936.** *J Epidemiol Community Health* 2016, **70**(6):576-582.
- 346 7. Alvarado BE, Zunzunegui MV, Beland F, Bamvita JM: **Life course social and health**
347 **conditions linked to frailty in Latin American older men and women.** *J Gerontol A*

- 348 *Biol Sci Med Sci* 2008, **63**(12):1399-1406.
- 349 8. Stolz E, Mayerl H, Waxenegger A, Rasky E, Freidl W: **Impact of socioeconomic position**
350 **on frailty trajectories in 10 European countries: evidence from the Survey of Health,**
351 **Ageing and Retirement in Europe (2004-2013).** *J Epidemiol Community Health* 2017,
352 **71**(1):73-80.
- 353 9. Soler-Vila H, García-Esquinas E, León-Muñoz LM, López-García E, Banegas JR,
354 Rodríguez-Artalejo F: **Contribution of health behaviours and clinical factors to**
355 **socioeconomic differences in frailty among older adults.** *J Epidemiol Community*
356 *Health* 2016, **70**(4):354-360.
- 357 10. Herr M, Robine JM, Aegerter P, Arvieu JJ, Ankri J: **Contribution of socioeconomic**
358 **position over life to frailty differences in old age: comparison of life-course models**
359 **in a French sample of 2350 old people.** *Ann Epidemiol* 2015, **25**(9):674-680 e671.
- 360 11. Haapanen MJ, Perala MM, Salonen MK, Kajantie E, Simonen M, Pohjolainen P, Pesonen
361 AK, Raikkonen K, Eriksson JG, von Bonsdorff MB: **Early life stress and frailty in old age:**
362 **the Helsinki birth cohort study.** *BMC Geriatr* 2018, **18**(1):179.
- 363 12. Van der Linden BWA, Cheval B, Sieber S, Orsholits D, Guessous I, Stringhini S, Gabriel R,
364 Aartsen M, Blane D, Courvoisier D *et al*: **Life Course Socioeconomic Conditions and**
365 **Frailty at Older Ages.** *J Gerontol B Psychol Sci Soc Sci* 2020, **75**(6):1348-1357.
- 366 13. Rogers NT, Blodgett JM, Searle SD, Cooper R, Davis DHJ, Pinto Pereira SM: **Early-Life**
367 **Socioeconomic Position and the Accumulation of Health-Related Deficits by**
368 **Midlife in the 1958 British Birth Cohort Study.** *Am J Epidemiol* 2021, **190**(8):1550-
369 1560.
- 370 14. Ye C, Aihemaitijiang S, Wang R, Halimulati M, Zhang Z: **Associations between Early-**
371 **Life Food Deprivation and Risk of Frailty of Middle-Age and Elderly People:**
372 **Evidence from the China Health and Retirement Longitudinal Study.** *Nutrients* 2021,
373 **13**(9).
- 374 15. Jones NL, Gilman SE, Cheng TL, Drury SS, Hill CV, Geronimus AT: **Life Course**
375 **Approaches to the Causes of Health Disparities.** *Am J Public Health* 2019,
376 **109**(S1):S48-s55.
- 377 16. Suglia SF, Koenen KC, Boynton-Jarrett R, Chan PS, Clark CJ, Danese A, Faith MS,
378 Goldstein BI, Hayman LL, Isasi CR *et al*: **Childhood and Adolescent Adversity and**
379 **Cardiometabolic Outcomes: A Scientific Statement From the American Heart**
380 **Association.** *Circulation* 2018, **137**(5):E15-E28.
- 381 17. Kelly-Irving M, Lepage B, Dedieu D, Bartley M, Blane D, Grosclaude P, Lang T, Delpierre
382 C: **Adverse childhood experiences and premature all-cause mortality.** *Eur J*
383 *Epidemiol* 2013, **28**(9):721-734.
- 384 18. Van Der Linden BWA, Sieber S, Cheval B, Orsholits D, Guessous I, Gabriel R, Von Arx M,
385 Kelly-Irving M, Aartsen M, Blane D *et al*: **Life-Course Circumstances and Frailty in Old**
386 **Age Within Different European Welfare Regimes: A Longitudinal Study With**
387 **SHARE.** *J Gerontol B Psychol Sci Soc Sci* 2020, **75**(6):1326-1335.
- 388 19. Li Y, Xue QL, Odden MC, Chen X, Wu C: **Linking early life risk factors to frailty in old**
389 **age: evidence from the China Health and Retirement Longitudinal Study.** *Age*
390 *Ageing* 2020, **49**(2):208-217.
- 391 20. Mian O, Anderson LN, Belsky DW, Gonzalez A, Ma J, Sloboda DM, Bowdish DME,

- 392 Verschoor CP: **Associations of Adverse Childhood Experiences with Frailty in Older**
393 **Adults: A Cross-Sectional Analysis of Data from the Canadian Longitudinal Study**
394 **on Aging.** *Gerontology* 2021;1-10.
- 395 21. Wang Q: **Association of Adverse Childhood Experiences With Frailty Index Level and**
396 **Trajectory in China.** *JAMA Netw Open* 2022, **5**(8):e2225315.
- 397 22. Dos Santos Gomes C, Pirkle CM, Zunzunegui MV, Taurino Guedes D, Fernandes De
398 Souza Barbosa J, Hwang P, Oliveira Guerra R: **Frailty and life course violence: The**
399 **international mobility in aging study.** *Arch Gerontol Geriatr* 2018, **76**:26-33.
- 400 23. Schmahl OC, Jeuring HW, Aprahamian I, Naarding P, Marijnissen RM, Hendriks GJ,
401 Fluiters M, Rhebergen D, Lugtenburg A, Lammers MW *et al.* **Impact of childhood**
402 **trauma on multidimensional frailty in older patients with a unipolar depressive-,**
403 **anxiety- or somatic symptom disorder.** *Arch Gerontol Geriatr* 2021, **96**:104452.
- 404 24. Campbell JA, Walker RJ, Egede LE: **Associations Between Adverse Childhood**
405 **Experiences, High-Risk Behaviors, and Morbidity in Adulthood.** *Am J Prev Med* 2016,
406 **50**(3):344-352.
- 407 25. Vineis P, Kelly-Irving M, Rappaport S, Stringhini S: **The biological embedding of social**
408 **differences in ageing trajectories.** *J Epidemiol Community Health* 2016, **70**(2):111-113.
- 409 26. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J,
410 Landray M *et al.* **UK biobank: an open access resource for identifying the causes of a**
411 **wide range of complex diseases of middle and old age.** *PLoS Med* 2015,
412 **12**(3):e1001779.
- 413 27. Davis KAS, Coleman JRI, Adams M, Allen N, Breen G, Cullen B, Dickens C, Fox E, Graham
414 N, Holliday J *et al.* **Mental health in UK Biobank - development, implementation and**
415 **results from an online questionnaire completed by 157 366 participants: a**
416 **reanalysis.** *BJPsych Open* 2020, **6**(2):e18.
- 417 28. Grabe HJ, Schulz A, Schmidt CO, Appel K, Driessen M, Wingenfeld K, Barnow S, Spitzer
418 C, John U, Berger K *et al.* **[A brief instrument for the assessment of childhood abuse**
419 **and neglect: the childhood trauma screener (CTS)].** *Psychiatr Prax* 2012, **39**(3):109-
420 115.
- 421 29. Soares ALG, Hammerton G, Howe LD, Rich-Edwards J, Halligan S, Fraser A: **Sex**
422 **differences in the association between childhood maltreatment and cardiovascular**
423 **disease in the UK Biobank.** *Heart* 2020, **106**(17):1310-1316.
- 424 30. Mitnitski AB, Mogilner AJ, Rockwood K: **Accumulation of deficits as a proxy measure**
425 **of aging.** *TheScientificWorldJournal* 2001, **1**:323-336.
- 426 31. Williams DM, Jylhava J, Pedersen NL, Hagg S: **A Frailty Index for UK Biobank**
427 **Participants.** *J Gerontol A Biol Sci Med Sci* 2019, **74**(4):582-587.
- 428 32. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K: **A standard procedure for**
429 **creating a frailty index.** *BMC Geriatr* 2008, **8**:24.
- 430 33. Zhang YB, Chen C, Pan XF, Guo J, Li Y, Franco OH, Liu G, Pan A: **Associations of healthy**
431 **lifestyle and socioeconomic status with mortality and incident cardiovascular**
432 **disease: two prospective cohort studies.** *Bmj* 2021, **373**:n604.
- 433 34. Said MA, Verweij N, van der Harst P: **Associations of Combined Genetic and Lifestyle**
434 **Risks With Incident Cardiovascular Disease and Diabetes in the UK Biobank Study.**
435 *JAMA Cardiol* 2018, **3**(8):693-702.

- 436 35. Li Y, Schoufour J, Wang DD, Dhana K, Pan A, Liu X, Song M, Liu G, Shin HJ, Sun Q *et al*.
437 **Healthy lifestyle and life expectancy free of cancer, cardiovascular disease, and type**
438 **2 diabetes: prospective cohort study.** *Bmj* 2020, **368**:l6669.
- 439 36. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hypponen E, Kuzma E, Llewellyn DJ:
440 **Association of Lifestyle and Genetic Risk With Incidence of Dementia.** *JAMA* 2019,
441 **322**(5):430-437.
- 442 37. Cao Z, Zheng X, Yang H, Li S, Xu F, Yang X, Wang Y: **Association of obesity status and**
443 **metabolic syndrome with site-specific cancers: a population-based cohort study.** *Br*
444 *J Cancer* 2020, **123**(8):1336-1344.
- 445 38. Chudasama YV, Khunti K, Gillies CL, Dhalwani NN, Davies MJ, Yates T, Zaccardi F:
446 **Healthy lifestyle and life expectancy in people with multimorbidity in the UK**
447 **Biobank: A longitudinal cohort study.** *PLoS Med* 2020, **17**(9):e1003332.
- 448 39. van Buuren S, Groothuis-Oudshoorn K: **mice: Multivariate Imputation by Chained**
449 **Equations in R.** *J Stat Softw* 2011, **45**(3):1 - 67.
- 450 40. Dustin Tingley TY, Kentaro Hirose, Luke Keele, Kosuke Imai: **mediation: R Package for**
451 **Causal Mediation Analysis.** *J Stat Softw* 2014.
- 452 41. Duffy KA, McLaughlin KA, Green PA: **Early life adversity and health-risk behaviors:**
453 **proposed psychological and neural mechanisms.** *Ann N Y Acad Sci* 2018,
454 **1428**(1):151-169.
- 455 42. Amianto F, Spalatro AV, Rainis M, Andriulli C, Lavagnino L, Abbate-Daga G, Fassino S:
456 **Childhood emotional abuse and neglect in obese patients with and without binge**
457 **eating disorder: Personality and psychopathology correlates in adulthood.**
458 *Psychiatry Res* 2018, **269**:692-699.
- 459 43. Fan J, Yu C, Pang Y, Guo Y, Pei P, Sun Z, Yang L, Chen Y, Du H, Sun D *et al*: **Adherence**
460 **to Healthy Lifestyle and Attenuation of Biological Aging in Middle-Aged and Older**
461 **Chinese Adults.** *J Gerontol A Biol Sci Med Sci* 2021, **76**(12):2232-2241.
- 462 44. Kehler DS, Theou O: **The impact of physical activity and sedentary behaviors on**
463 **frailty levels.** *Mech Ageing Dev* 2019, **180**:29-41.
- 464 45. Abe T, Nofuji Y, Seino S, Murayama H, Yoshida Y, Tanigaki T, Yokoyama Y, Narita M,
465 Nishi M, Kitamura A *et al*: **Healthy lifestyle behaviors and transitions in frailty status**
466 **among independent community-dwelling older adults: The Yabu cohort study.**
467 *Maturitas* 2020, **136**:54-59.
- 468 46. Chang X, Jiang X, Mkandawire T, Shen M: **Associations between adverse childhood**
469 **experiences and health outcomes in adults aged 18-59 years.** *PLoS One* 2019,
470 **14**(2):e0211850.
- 471 47. Thomas C, Hypponen E, Power C: **Obesity and type 2 diabetes risk in midadult life:**
472 **the role of childhood adversity.** *Pediatrics* 2008, **121**(5):e1240-1249.
- 473 48. Yazawa A, Shiba K, Inoue Y, Okuzono SS, Inoue K, Kondo N, Kondo K, Kawachi I: **Early**
474 **childhood adversity and late-life depressive symptoms: unpacking mediation and**
475 **interaction by adult socioeconomic status.** *Soc Psychiatry Psychiatr Epidemiol* 2022,
476 **57**(6):1147-1156.
- 477 49. Sideli L, Murray RM, Schimmenti A, Corso M, La Barbera D, Trotta A, Fisher HL:
478 **Childhood adversity and psychosis: a systematic review of bio-psycho-social**
479 **mediators and moderators.** *Psychol Med* 2020, **50**(11):1761-1782.

- 480 50. Reuben A, Moffitt TE, Caspi A, Belsky DW, Harrington H, Schroeder F, Hogan S,
481 Ramrakha S, Poulton R, Danese A: **Let us not forget: comparing retrospective and**
482 **prospective assessments of adverse childhood experiences in the prediction of**
483 **adult health.** *J Child Psychol Psychiatry* 2016, **57**(10):1103-1112.
484 51. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R, Allen NE:
485 **Comparison of Sociodemographic and Health-Related Characteristics of UK**
486 **Biobank Participants With Those of the General Population.** *Am J Epidemiol* 2017,
487 **186**(9):1026-1034.

488

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504 **Authors' contributions**

505 ZL contributed to the conception and design of the work; ZL acquired the data; GY

506 and XC performed the analysis. All authors contributed to the interpretation of data.

507 GY wrote the first draft of the manuscript. All authors substantively revised the

508 manuscript, read and approved the final manuscript.

509 **Ethics approval and consent to participate:**

510 The UK Biobank study was approved by the North West Multi-Centre Research

511 Ethics Committee (11/NW/0382) and written informed consent was provided by each

512 participant before the study. UK Biobank also has approval from the North West

513 Multi-Centre Research Ethics Committee as a Research Tissue Bank (RTB) approval

514 in 2011 and is renewed every 5 years. According to RTB approval, researchers are

515 allowed to use data from UK Biobank without an additional ethical clearance.

516 **Consent for publication**

517 Not applicable.

518 **Competing interests**

519 The authors declare that they have no competing interests.

Table 1. Basic characteristics of study participants.

Variables	Total (N=152914)	Without frailty (N=142836)	With frailty (N=10078)	P value
Age, years	56.4±7.7	56.3±7.7	57.7±7.4	<0.001
Sex				<0.001
Female	86142 (56.3)	80003 (56.0)	6139 (60.9)	
Male	66772 (43.7)	62833 (44.0)	3939 (39.1)	
Ethnicity				0.004
White	148599 (97.2)	138,823 (97.2)	9776 (97.0)	
Multiple	798 (0.5)	745 (0.5)	53 (0.5)	
South Asian	1262 (0.8)	1169 (0.8)	93 (0.9)	
Black	1071 (0.7)	1003 (0.7)	68 (0.7)	
Chinese	348 (0.2)	337 (0.2)	11 (0.1)	
Other ^a	836 (0.5)	759 (0.5)	77 (0.8)	
Educational level ^b				<0.001
High	70866 (46.3)	67488 (47.2)	3378 (33.5)	
Intermediate	50281 (32.9)	46688 (32.7)	3593 (35.7)	
Low	31767 (20.8)	28660 (20.1)	3107 (30.8)	
Occupation				<0.001
Working	97657 (63.9)	92871 (65.0)	4786 (47.5)	
Retired	45121 (29.5)	41542 (29.1)	3579 (35.5)	
Other	10136 (6.6)	8423 (5.9)	1713 (17.0)	
TDI	-1.7±2.8	-1.8±2.8	-1.0±3.2	<0.001
BMI, kg/m ²	26.8±4.6	26.6±4.4	29.7±6.0	<0.001
<18.5	857 (0.6)	806 (0.6)	51 (0.5)	
18.5-24.9	56952 (37.2)	54882 (38.4)	2070 (20.5)	
≥24.9	95105 (62.2)	87148 (61.0)	7957 (79.0)	
Smoking, yes	64140 (41.9)	58885 (41.2)	5255 (52.1)	<0.001
Drinking, yes	60764 (39.7)	56145 (39.3)	4619 (45.8)	<0.001
Physical inactivity, yes	39463 (25.8)	35669 (25.0)	3794 (37.6)	<0.001
Unhealthy diet, yes	94074 (61.5)	87675 (61.4)	6399 (63.5)	<0.001
Maternal smoking around birth, yes	44282 (29.0)	40481 (28.3)	3801 (37.7)	<0.001

Notes: BMI, body mass index; TDI, Townsend deprivation index.

^aOther includes any races or ethnicities not otherwise specified.

^bHigh educational level: college or university degree; Intermediate educational level: A/AS levels or equivalent, O levels/GCSEs or equivalent; Low educational level: none of the aforementioned.

1 **Table 2. Associations of childhood adversity with unhealthy lifestyle score.**

Childhood adversity	Model 1		Model 2	
	β (95% CI)	P value	β (95% CI)	P value
Physical neglect	0.066 (0.050, 0.082)	<0.001	0.012 (-0.004, 0.028)	0.147
Emotional neglect	0.153 (0.139, 0.167)	<0.001	0.115 (0.101, 0.129)	<0.001
Sexual abuse	0.200 (0.179, 0.221)	<0.001	0.171 (0.151, 0.192)	<0.001
Physical abuse	0.204 (0.189, 0.219)	<0.001	0.170 (0.155, 0.185)	<0.001
Emotional abuse	0.188 (0.172, 0.204)	<0.001	0.155 (0.139, 0.171)	<0.001
Cumulative childhood adversity score (0-5)	0.086 (0.081, 0.091)	<0.001	0.067 (0.062, 0.073)	<0.001
0	Ref.	—	Ref.	—
1	0.083 (0.069, 0.097)	<0.001	0.063 (0.049, 0.077)	<0.001
2	0.172 (0.153, 0.191)	<0.001	0.133 (0.114, 0.152)	<0.001
3	0.255 (0.230, 0.281)	<0.001	0.201 (0.175, 0.226)	<0.001
4	0.331 (0.296, 0.367)	<0.001	0.255 (0.220, 0.291)	<0.001
5	0.468 (0.405, 0.531)	<0.001	0.355 (0.292, 0.418)	<0.001

2 Notes: CI, confidence interval.

3 Model 1: adjusted for age and sex.

4 Model 2: further adjusted for ethnicity, educational level, occupation, TDI, and maternal smoking around birth based on Model 1.

5 **Table 3. Associations of childhood adversity with frailty and mediation proportion of childhood adversity in frailty attributed to**
6 **unhealthy lifestyle.**

Childhood adversity	Model 1	Model 2	Model 3	Mediation proportion (%) (95% CI) ^a	P value
	OR (95% CI)	OR (95% CI)	OR (95% CI)		
Physical neglect	1.90 (1.81, 1.99)	1.64 (1.56, 1.72)	1.65 (1.57, 1.73)	3.1 (2.4, 4.0)	<0.001
Emotional neglect	2.34 (2.25, 2.44)	2.12 (2.03, 2.22)	2.07 (1.98, 2.16)	5.4 (4.8, 6.0)	<0.001
Sexual abuse	2.03 (1.91, 2.15)	1.84 (1.73, 1.95)	1.79 (1.69, 1.90)	8.1 (7.0, 9.0)	<0.001
Physical abuse	2.14 (2.05, 2.24)	1.96 (1.87, 2.05)	1.89 (1.80, 1.98)	8.2 (7.4, 9.0)	<0.001
Emotional abuse	2.76 (2.63, 2.88)	2.48 (2.37, 2.61)	2.41 (2.30, 2.53)	5.1 (4.6, 6.0)	<0.001
Cumulative childhood adversity score (0-5)	1.51 (1.49, 1.53)	1.44 (1.41, 1.46)	1.41 (1.39, 1.44)	—	—
0	Ref.	Ref.	Ref.	—	—
1	1.60 (1.52, 1.69)	1.53 (1.45, 1.62)	1.52 (1.44, 1.60)	7.0 (5.7, 9.0)	<0.001
2	2.39 (2.25, 2.54)	2.18 (2.05, 2.33)	2.13 (2.00, 2.27)	6.6 (5.8, 7.0)	<0.001
3	3.48 (3.25, 3.74)	3.03 (2.82, 3.26)	2.92 (2.72, 3.15)	5.8 (5.1, 7.0)	<0.001
4	4.96 (4.55, 5.39)	4.02 (3.68, 4.40)	3.88 (3.55, 4.24)	5.0 (4.4, 6.0)	<0.001
5	8.04 (7.07, 9.14)	5.85 (5.10, 6.71)	5.49 (4.80, 6.29)	4.4 (3.8, 5.0)	<0.001

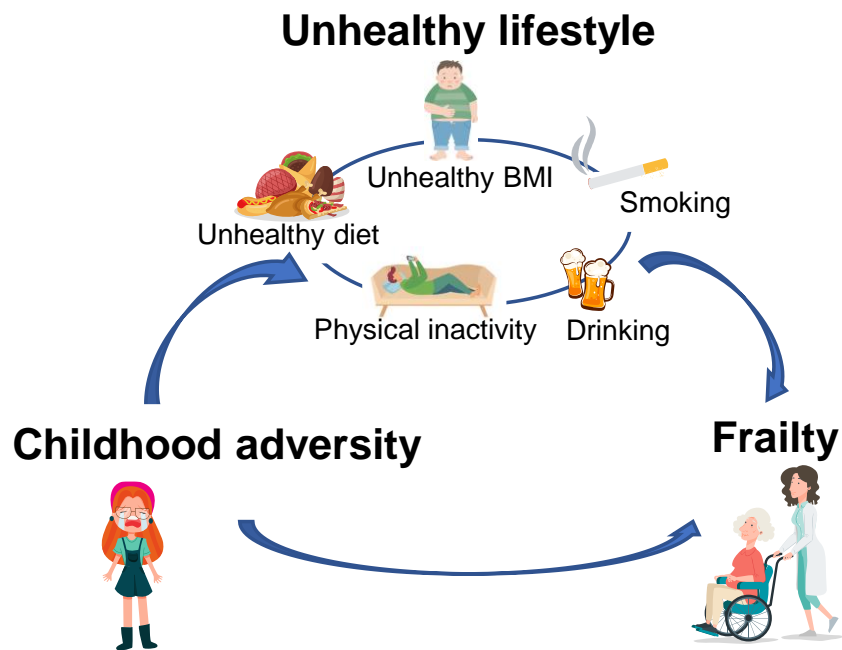
7 Notes: OR, odds ratio; CI, confidence interval.

8 Model 1: adjusted for age and sex.

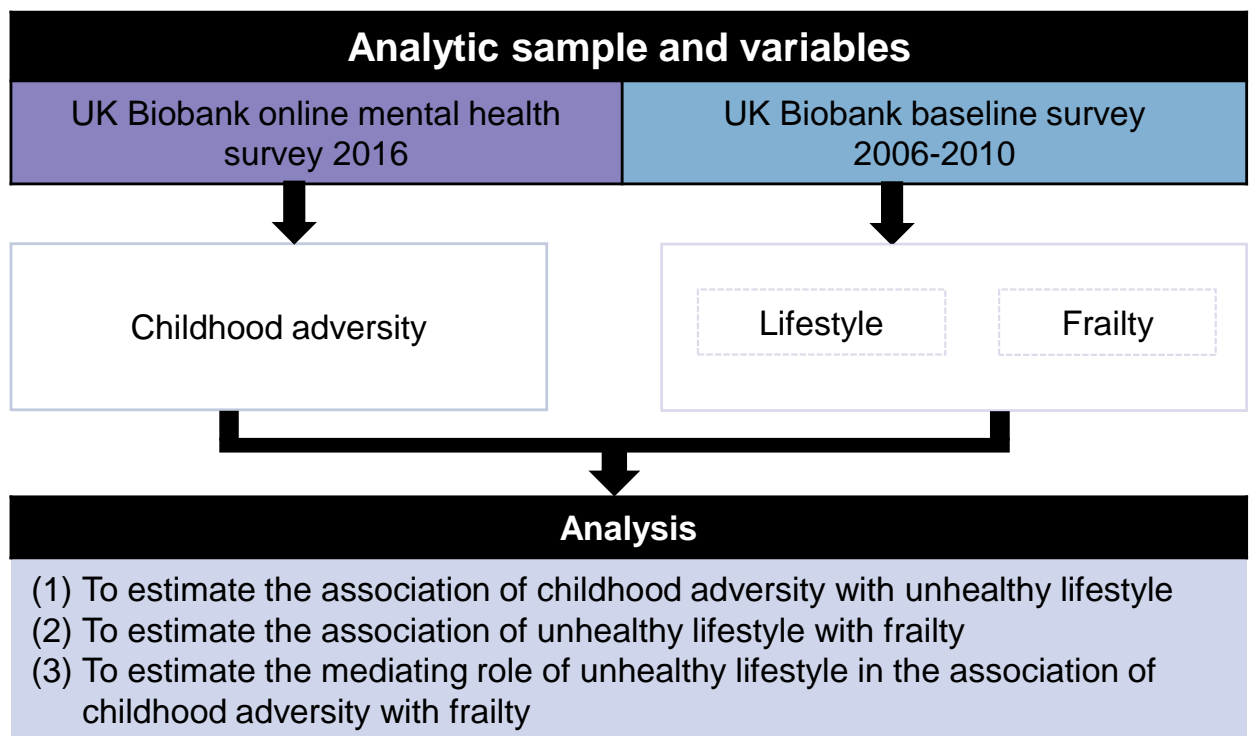
9 Model 2: further adjusted for ethnicity, educational level, occupation, TDI, and maternal smoking around birth based on Model 1.

10 Model 3: further adjusted for unhealthy lifestyle score based on Model 1.

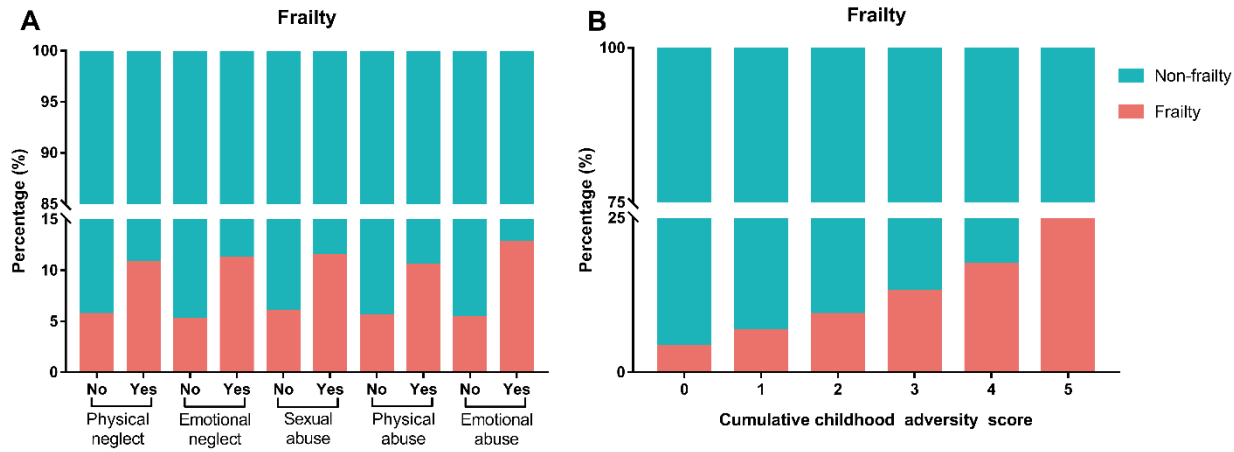
11 A



12 B



13 **Figure 1. Roadmap for evaluating associations between childhood adversity,**
14 **unhealthy lifestyle, and frailty.**



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Figure 2. Prevalence of frailty by individual items and the cumulative score of childhood adversity. A prevalence of frailty by individual items of childhood adversity (all $P < 0.001$); B prevalence of frailty by the cumulative score of childhood adversity ($P < 0.001$).