

1 **Mechanisms of life-course socioeconomic inequalities in adult systemic**
2 **inflammation: findings from two cohort studies**

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36 None.

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47 **ABSTRACT**

48 Disadvantaged socioeconomic conditions in childhood heighten systemic inflammatory levels in
49 adulthood; however, life-course mechanisms underlying this association are largely unknown. In the
50 present observational study, we investigated the roles of adulthood socioeconomic and lifestyle
51 factors in mediating this association.

52 Participants were from two prospective Swiss population-based cohorts (N=5,152, mean age 60
53 years). We estimated the total effect of paternal occupational position on adult heightened systemic
54 inflammatory levels (C-reactive protein>3mg/L), and the indirect effects via adulthood socioeconomic
55 positions (SEPs: education and occupational position), financial hardship, and lifestyle factors (body
56 mass index, smoking status, physical inactivity, and alcohol consumption). We estimated odds ratio
57 (OR) and proportion mediated using counterfactual-based mediation models.

58 Individuals whose father had a low occupational position had an OR of 1.51 [95% confidence interval
59 (CI): 1.25, 1.84] for heightened inflammation compared to their more advantaged counterparts. This
60 was jointly mediated (33 [95% CI: 14, 69]%) by adulthood SEPs, whereby the pathway through
61 education followed by occupational position mediated 30 [95% CI: 11, 64]%, while the pathway via
62 occupational position only mediated 3 [95% CI: -4, 13]%. Individuals with the lowest life-course SEPs
63 had an OR of 2.27 [95% CI: 1.71, 2.98] for heightened inflammation compared to having the highest
64 life-course SEPs. This was jointly mediated (63 [95% CI: 44, 97]%) by financial hardship and lifestyle
65 factors.

66 Our study supports a cumulative effect of life-course SEPs on adult heightened systemic inflammation
67 along the pathway paternal occupational position -> education -> adult occupational position.
68 Financial hardship and lifestyle factors in adulthood mediate half of that effect.

69

70 **KEYWORDS:** childhood/adulthood socioeconomic positions, heightened inflammation,
71 counterfactual mediation, lifestyle factors, financial hardship.

72 INTRODUCTION

73 Disadvantaged socioeconomic conditions in childhood, such as parental socioeconomic position
74 (SEP), are linked to increased systemic inflammatory levels in adult life (Berger et al., 2019; Liu et al.,
75 2017; Pollitt et al., 2007; Tabassum et al., 2008). Various processes such as infection, adipose tissue,
76 or chronic activation of the stress response systems may lead to heightened inflammation, that has
77 consequences for health and survival (Li et al., 2017). For example, stressful experiences in childhood
78 such as abuse or cumulative socioeconomic disadvantage throughout can result in an over-solicited
79 stress response system, which in turn contributes to heightened inflammation and eventually
80 increases the risk of poor health in adulthood (Kivimäki and Steptoe, 2018). In this mechanistic
81 perspective, heightened inflammation represents a potential pathophysiological mechanism underlying
82 the development of several socially patterned diseases, including cardiovascular, metabolic and
83 psychotic disorders (Danesh et al., 2004; Dehghan et al., 2007; Ligthart et al., 2018).

84 The effect of childhood SEP on inflammatory processes, and subsequent poor health, may develop
85 through various life-course mechanisms that are not fully understood (Liu et al., 2017). An
86 interdisciplinary approach where models from life course epidemiology and social science are
87 combined in a unified theoretical framework has offered a way to study those complex mechanisms
88 (Ben-Shlomo and Kuh, 2002; Cohen et al., 2010; Kuh et al., 2003; Lynch and Smith, 2005). Based on
89 previous investigations of the life-course socioeconomic origin of adult inflammation, three life-
90 course scenarios have been described: the early life critical period model, whereby exposures
91 experienced in the critical window of childhood (such as parental low SEP) may directly affect adult
92 inflammatory levels by permanently modifying some biological parameters (Berens et al., 2017); the
93 accumulation or chain of risk additive model, whereby the effect of exposures to low SEP cumulates
94 across the life-course affecting inflammatory levels in a gradient-like manner (Camelo et al., 2014;
95 Gimeno et al., 2007; Ploubidis et al., 2014; Tabassum et al., 2008); and the social mobility model,
96 whereby the direction of SEP mobility across childhood and adulthood impacts adult inflammatory
97 responses (Castagné et al., 2016; Na-Ek et al., 2017). Furthermore, several multiple risk factors likely
98 mediate socioeconomic inequalities in adult heightened inflammation. Material factors such as housing

99 tenure (Clair and Hughes, 2019), financial hardship via material deprivation (Groffen et al., 2007),
100 psychosocial stress (individual, family-related or job-related) (Eddy et al., 2016; Sturgeon et al., 2016),
101 lifestyle factors (Berger et al., 2019; Davillas et al., 2017), psychological distress (Cohen et al., 2010)
102 and environmental exposures (Thompson et al., 2015), are some of the modifiable risk factors.

103 To our knowledge, no studies have investigated the mediating roles of those risk factors within a life-
104 course framework and using counterfactual-based mediation methods. Accounting for the full
105 mechanistic pathways of potential life-course socioeconomic aetiology of heightened inflammation, in
106 combination with modifiable later-in-life risk factors such as financial hardship and lifestyle factors, is
107 key to understanding and therefore mitigating socioeconomic inequalities in this outcome. In this
108 study, we advance the existing literature by: 1) elucidating path-specific mechanisms where
109 disadvantaged SEP affects inflammatory levels in adulthood across three life periods (childhood, early
110 and full adulthood); 2) assessing the joint contribution of unhealthy lifestyle behaviour and financial
111 hardship in adulthood in mediating life-course socioeconomic inequalities in heightened inflammation;
112 and 3) applying counterfactual-based mediation models, which provide unbiased estimates when
113 mediators and/or outcome are not measured on the continuous scale as in our study and in most
114 previous studies (VanderWeele et al., 2014).

115 To explore multiple causal mechanisms linking early life SEP to adult heightened inflammation, we
116 used longitudinal data from two Swiss population studies (5,152 participants) and applied path-specific
117 mediation based on a counterfactual framework. We evaluated socioeconomic inequalities in adult
118 C-reactive protein (CRP). CRP is a clinical biomarker that may indicate exposure to chronic stress,
119 and previous studies have identified an increase in CRP with lower parental SEP (Liu et al., 2107). We
120 also determined the mediating role of financial hardship and lifestyle factors in adulthood since they
121 are modifiable risk factors, the target of global policies (Stringhini et al., 2017) or welfare programs
122 (Courtin et al., 2018), and consistently associated with later-in-life poor health outcomes (Carstairs
123 and Morris, 1990; Stringhini et al., 2017; Stringhini et al., 2018). By disentangling these complex life-
124 course models and mechanisms of systemic heightened inflammation in adulthood, this work could

125 extend into potential social investment and policy recommendations to inform interventions to
126 improve population health.

127

128 **MATERIALS AND METHODS**

129 **Study Populations**

130 Individual-participant data from two prospective Swiss cohorts were used: SKIPOGH (Alwan et al.,
131 2014) and CoLaus/PsyCoLaus (Firmann et al., 2008). The SKIPOGH study began in December 2009
132 and ended in April 2013, and included 1,128 participants aged between 18 and 90 years recruited in
133 Western Switzerland. A follow-up survey on 1,033 individuals started in October 2012 and was
134 completed in December 2016. The CoLaus/PsyCoLaus study began between 2003 and 2006 and
135 included 6,733 participants living in Lausanne, aged between 35 and 75 years; the first follow-up
136 survey was conducted 5.5 years afterwards and included 5,064 participants. The second follow-up
137 assessment was conducted between 2014 and 2017 and included 4,881 participants. Both studies
138 were approved by ethical committees (see Supplementary Material).

139 **Causal models and measures**

140 The proposed causal structures underlying our study are shown in the directed acyclic graphs
141 (DAGs) displayed in Figure 1. We based our causal modeling to evaluate path-specific mechanisms of
142 socioeconomic inequalities in adulthood heightened inflammation (outcome). The first two causal
143 models (Figure 1A,B) focus on inequalities driven by socioeconomic position experienced in
144 childhood (exposure). The total effect of exposure is broken down into a non transmitted (direct
145 effect) and transmitted (indirect effect) portion by examined intermediate mechanisms. In DAG₁
146 (Figure 1A) the indirect effect represents the joint mediated effect by adulthood SEPs (individual's
147 highest educational attainment and occupational position), financial hardship and lifestyle factors (BMI,
148 alcohol intake, smoking status, physical inactivity) en-bloc, and we do not posit any assumption on
149 the causal order of the mediators. A null indirect effect in DAG₁ would support an early critical
150 period model (Howe et al., 2016). In DAG₂ (Figure 1B), the indirect effect represents the joint
151 mediated effects by both adulthood SEPs and we assumed i) education causes occupational position, a
152 known temporal order, and ii) downstream risk factors of financial hardship and lifestyle factors are
153 caused by those individual's SEPs (not displayed in DAG₂). By comparing the joint mediated effects in

154 DAG₁ vs DAG₂ we can understand whether financial hardship and lifestyle behaviour in adulthood
155 provide additional mediation compared to socioeconomic positions only. Furthermore, DAG₂
156 enabled us to investigate the paths (via education or via occupational position only) whereby SEP in
157 childhood may propagate to affect inflammatory levels in adulthood.

158 Where a substantive indirect effect in DAG₂ was assessed, we investigated life-course socioeconomic
159 positions models of inequalities in heightened inflammation by two exposures: life-course trajectories
160 of socioeconomic position and a score of disadvantaged SEPs accumulating in the course of life. The
161 social mobility model holds if only upward/downward trajectories have a substantive effect, while the
162 chain of risk additive model holds if a trajectory of stable (across childhood and adulthood)
163 disadvantaged SEPs has higher effect size than upward/downward trajectories. In themselves, these
164 have a substantive effect (Howe et al., 2016). In DAG₃ (Figure 1C) we disentangled the direct effect
165 of the score of accumulation of life-course SEPs on heightened inflammation, and the indirect effect
166 through financial hardship and lifestyle factors as en-bloc mediators. We did not further evaluate
167 path-specific effects via lifestyle factors or financial hardship as their causal structure cannot be
168 determined unequivocally.

169 Childhood socioeconomic position was measured through participants self-reported occupation of
170 their fathers when they were children. Answers were classed into four categories according to the
171 European SocioEconomic Classification (ESEC) scheme (Rose and Harrison, 2007), as done
172 elsewhere (Stringhini et al., 2017). We categorised occupational class into high, intermediate, low,
173 and non-working (see Supplementary Material). Paternal occupational position is a commonly used
174 indicator of socioeconomic position in early life (Galobardes et al., 2007) and is closely related to
175 parental occupational position in the Swiss context until the early 1970s (see Supplementary
176 Material).

177 Adulthood SEPs were measured by self-reported individual's highest level of attained education
178 (emerging adulthood) and last known occupational position (adulthood). We categorised education
179 into university, high school, vocational and compulsory or lower (see Supplementary Material).

180 Occupational position was reported at baseline in SKIPOGH and first follow-up in
181 CoLaus/PsyCoLaus and was classed into four levels as done for father's occupational position.

182 Life-course trajectories of socioeconomic position were also addressed as an exposure. Individuals
183 were classed into five trajectories: stable high (high father's and individual's occupational position),
184 downward (high father's and intermediate or low individual's occupational position, or intermediate
185 father's and low individual's occupational position), upward (low father's and intermediate or high
186 individual's occupational position, or intermediate father's and high individual's occupational position),
187 stable intermediate (intermediate father's and individual's occupational position) and stable low (low
188 father's and individual's occupational position). Participants not working or whose father was not
189 working were not included in examining trajectories. Finally, a score of disadvantaged SEPs
190 accumulating along the life-course was computed by adding up the three levels of paternal
191 occupational position, the four levels of education and the three levels of occupational position.
192 Score ranged from a value of one (high SEP at all life phases) to eight (low SEP at all life phases),
193 where increasing values of the score represented an accumulating exposure to disadvantaged SEP at
194 any of the three examined life phases (childhood, emerging adulthood and adulthood).

195 Lifestyle factors, financial hardship and co-morbidities (only in sensitivity analyses, see Supplementary
196 Material) in adulthood were considered as mediators. Lifestyle factors were collected at baseline in
197 SKIPOGH and first follow-up in CoLaus/PsyCoLaus. Self-reported smoking, alcohol consumption and
198 measured body mass index (BMI) were categorized according to WHO standards (see
199 Supplementary Material). Leisure physical activity was measured with different questions in each
200 cohort so we dichotomised it into sedentary and active using population specific thresholds (see
201 Supplementary Material). Self-reported financial difficulties in meeting basic needs as food, rent or
202 health insurance were categorized as not having / having financial hardship. They were reported at
203 first follow-up of SKIPOGH and second follow-up of CoLaus/PsyCoLaus.

204 Systemic inflammatory levels were assessed through the amount of circulating C-reactive protein
205 (CRP) in plasma. CRP is a sensitive marker of inflammatory levels and elevated amounts of CRP have
206 been associated with increased risk for several diseases (Ligthart et al., 2018). CRP was measured

207 through standard immunoturbidimetry in SKIPOGH, and through high-sensitivity
208 immunoturbidimetry in CoLaus/PsyCoLaus. We binarized CRP values by arbitrarily defining
209 heightened inflammatory levels as CRP>3mg/L (main analysis) or 4mg/L (sensitivity analysis).

210 Age, sex, cohort and self-identified ethnicity (white/other) were included as confounders in all
211 models.

212 **Mediation approach**

213 We fitted natural effect models, a class of marginal structural models directly parametrizing so-called
214 direct and indirect effects (and more generally, path-specific effects) expressed on their natural scale
215 (Lange et al., 2012). Under certain identifying conditions related to confounding (Steen et al., 2017)
216 (see Supplementary Material), such models have practical advantages of enabling simultaneous
217 estimation of natural direct and indirect effects, analysis of dichotomous outcomes (Lange et al.,
218 2012), estimation of joint indirect effects (e.g. effect of exposure on outcome mediated
219 simultaneously by a bloc of mediators) and fine-grained decompositions (path-specific indirect effects)
220 (Steen et al., 2017). Contrary to linear path analysis (Wright, 1934; MacKinnon and Dwyer, 1993),
221 marginal structural models allow estimation under a more general class of models including those
222 with mediators and/or outcome measured on a non-continuous scale (as in our study) and those
223 with an interaction between exposure and mediators (Robins et al., 2000; Vansteelandt et al., 2012;
224 VanderWeele et al., 2014).

225 For DAG₁ and DAG₃ only direct and joint indirect effects were estimated, as their identification is
226 not dependent on the true causal order of the mediators (VanderWeele and Vansteelandt, 2014).

227 For DAG₂ (see Figure B) joint indirect effect into two path-specific indirect effects (Steen et al.,
228 2017) were further broken down: 1) the effect mediated through highest attained education (
229 $S \rightarrow M_1 \rightarrow M_2 \rightarrow Y$ and $S \rightarrow M_1 \rightarrow Y$ in Figure B, that we denote as $S \rightarrow M_1 Y$); 2) the effect
230 mediated through individual's occupational position ($S \rightarrow M_2 \rightarrow Y$) and not through education.

231 All the aforementioned joint and path-specific effects matched parameters of natural effects models.

232 Those parameters were estimated via an approach based on counterfactual imputation (Steen et al.,

233 2017; Vansteelandt et al., 2012) (see Supplementary Material). The proportion mediated (PM) by a
234 bloc of mediators or through a path was derived by the ratio of the logarithms of the corresponding
235 natural indirect effect and the total effect odds ratios (ORs).

236 Estimated parameters of natural effects models appear to have a causal interpretation only when all
237 identifying conditions are satisfied (Glymour and Hamad, 2018, VanderWeele et al., 2014).

238 **Design of the study**

239 Adult occupational position and lifestyle behaviour was assessed at baseline for SKIPOGH and first
240 follow-up for CoLaus/PsyCoLaus, while C-reactive protein and financial difficulties were assessed at
241 follow-up for SKIPOGH and second follow-up for CoLaus/PsyCoLaus. This resulted in an average of
242 4.8 years of gap between the assessments of lifestyle factors and C-reactive protein. Between study
243 visits – baseline and follow-up in SKIPOGH, first follow-up and second follow-up in
244 CoLaus/PsyCoLaus – a total of 269 participants were lost (4.3%). Only participants attending both
245 visits were included in the analysis.

246 **Statistical analyses**

247 Analyses were run on pooled data of the two cohorts. For 69 individuals participating in both studies,
248 we only retained the SKIPOGH data collection. We excluded individuals with unknown ethnicity
249 (N=2 in CoLaus/PsyCoLaus) and missing CRP (N=12 (1.2%) in SKIPOGH, N=679 (14.1%) in
250 CoLaus/PsyCoLaus). A total of 5,152 participants were included in the analyses.

251 Father's occupational position, highest attained education and score of life-course disadvantaged SEPs
252 were modelled as ordered variables, hypothesizing a linear effect on the outcome.

253 We imputed missing data (all variables but age, gender, ethnicity, cohort and CRP) through
254 multivariate imputation by chained equations and by hypothesizing missingness at random (20
255 imputed data sets). Individuals with non-working fathers were excluded from each imputed data set.
256 Confidence intervals (95%) were estimated through percentiles from 1,000 bootstrap draws (with
257 replacement).

258 We performed sensitivity analyses for residual confounding, model specification and effects
259 modification (see Supplementary Material).

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263 **RESULTS**

264 **Characteristics of the population**

265 Summary statistics at each level of father's occupational position are reported in Table 1. Participants
266 with low paternal occupational position were older, had lower educational attainment and
267 occupational position, were more likely to experience financial hardship, to have higher BMI, to be
268 sedentary, to have high alcohol intake, and to have heightened inflammation than individuals with high
269 paternal occupational position.

270 **Mechanisms of childhood SEP inequalities**

271 Individuals with low father's occupational position (potentially counter to fact) had an OR of 1.51
272 [95% confidence interval (CI): 1.25, 1.84] for heightened inflammation in adulthood compared to
273 having (potentially counter to fact) high father's occupational position (Table 2). Socioeconomic
274 positions, financial hardship, and lifestyle factors in adult life (see Figure A) jointly mediated 59 [95%
275 CI: 34, 93]% of this effect. When only SEPs in adult life were considered as mediators (see Figure B),
276 they jointly mediated 33 [95% CI: 14, 69]%, the most important pathway being through education
277 since path-specific mediation via occupational position only mediated 3 [95% CI: -4, 13]% of the total
278 effect.

279 **Mechanisms of life-course SEP inequalities**

280 All life-course trajectories of socioeconomic position resulted in an increase of odds for heightened
281 inflammation in adulthood compared to a trajectory of high SEP across the life-course (Table 3). The
282 odds were the highest for individuals with a consistently low trajectory from childhood to adulthood,
283 and of similar size for the remaining other trajectories (intermediate to intermediate, downward, and
284 upward). The analysis of the accumulation score revealed that one-unit increment of disadvantaged
285 SEP at any life stage increased OR of 1.12 [95% CI: 1.08, 1.17] (not reported in Table 3). In particular,
286 this resulted in an OR of 2.27 [95% CI: 1.71, 2.98] for heightened inflammation in adulthood for
287 individuals with lowest life-course SEPs (low paternal occupational position, compulsory education
288 and low occupational position potentially counter to fact) compared to having highest life-course

289 SEPs (high paternal occupation, university education and high occupational position potentially
290 counter to fact) (see Table 3). Financial hardship and lifestyle factors in adult life jointly (see Figure C)
291 mediated 63 [95% CI: 44, 97]% of this effect.

292 **Sensitivity analyses**

293 Results were consistent with those reported in main analyses, and with a life-course SEPs effect
294 modification by sex (see Supplementary Material).

295

296 **DISCUSSION**

297 Results indicated that individuals with a low paternal occupational position when they were children
298 had higher odds of heightened inflammation in adulthood compared to their more advantaged
299 counterparts. Socioeconomic positions, financial hardship and lifestyle factors in adult life jointly
300 mediated about 60% of that effect, while educational attainment alone mediated about 30%. Overall,
301 our findings supported an accumulating effect of disadvantaged socioeconomic positions along the
302 life-course on adult life heightened inflammation. About half of the effects of socioeconomic
303 exposures on heightened inflammation were not mediated by the examined risk factors.

304 Socioeconomic inequalities by paternal occupational position are in line with results reported from a
305 recent meta-analysis of five studies in four countries (Liu et al., 2017). The greater inequalities
306 observed in our study (OR = 1.51 vs 1.23) may be explained by cross-countries variations (one of
307 the studies run in New Zealand (Danese et al., 2009) reported an even higher odds ratio of 1.96),
308 and/or a different operationalization of the exposure (one of the studies run in the USA using
309 parental education (Shanahan et al., 2014) reported an odds ratio of 1.15).

310 The proportion of the effect of father's occupational position on heightened inflammation mediated
311 by the examined risk factors are consistent with results reported from a recent multi-cohort study
312 (N=23,008) (Berger et al., 2019), although CRP was modelled as a continuous variable, and mediation
313 was assessed through the adjustment-based method. In the study by Berger et al. (2019), lifestyle
314 factors attenuated the association of paternal occupational position to inflammatory levels of about
315 58%.

316 In our study, the marginal extra mediation accounted by adding adulthood lifestyle factors and
317 financial hardship to socioeconomic positions is substantive (59% vs 33%). This means that the
318 paternal occupational position -> adult financial hardship and lifestyle factors -> heightened
319 inflammation path is not entirely captured by the paternal occupational position -> adult
320 socioeconomic positions -> heightened inflammation path. Other unmeasured dimensions of
321 adulthood socioeconomic position such as assets or neighbour disadvantage may explain this marginal

322 additional mediation. For example, one investigation from the Health and Retirement Study reported
323 that the association of paternal education with obesity in adulthood was partly explained by
324 socioeconomic position in adulthood – i.e. education, income and wealth – and fully explained when
325 further accounting for neighbourhood disadvantage (Pavela, 2017). Alternatively, unexamined adverse
326 childhood experiences (ACE) such as physical neglect and domestic conflicts, or other early life
327 factors such as exposure to environmental toxics or poor nutrition during development might play a
328 mediating role. For example, a study from the 1958 British birth cohort reported that ACE were
329 associated to increased mid-life CRP levels and that lifestyle factors explained part of that association
330 independently from adulthood socioeconomic positions (Chen and Lacey, 2018).

331 The finding of the effect of different life-course SEP stages on heightened inflammation in adulthood
332 supports a chain of risk additive model as a mechanism operating in our observed population, in
333 agreement with other studies (Camelo et al., 2014; Liu et al., 2017; Tabassum et al., 2008). Given the
334 substantive indirect effect of adult SEPs, we did not find evidence for childhood SEP to be the only
335 (critical) determinant of inflammation in adulthood, in agreement with the former body of literature
336 (Liu et al., 2017). Furthermore, our findings did not support a social mobility model. Overall, our
337 results support neither the timing nor the change but the duration of exposure to low SEP across the
338 life-course contributes to heightened CRP levels in our population.

339 This is one of the first studies to investigate the mediating role of financial hardship and lifestyle
340 factors in adult life taken together with life-course SEPs. Financial hardship and lifestyle factors in
341 adult life mediated about 60% of that effect, supporting their important mechanistic role downstream
342 disadvantaged life-course SEPs. The remaining unexplained socioeconomic inequalities (or estimated
343 natural direct effects) prompt for complementary, not mutually exclusive explanations. Firstly,
344 biological embedding of those disadvantaged conditions, in particular early in life, could permanently
345 modify some biological parameters and so inflammatory pathways throughout the life-course (Berens
346 et al., 2017; Lupien et al., 2009). In this scenario, the critical period model could hold. Secondly,
347 other pathways not grasped by the examined mediators may as well operate to link early/life-course
348 SEPs and heightened inflammation in adulthood. For example, the whole impact of environmental

349 factors or job-related psychosocial stress was not examined here (Eddy et al., 2016; Esposito and
350 Giugliano, 2006; Thompson et al., 2015), although part of the effect of these factors may have been
351 taken into account by the assessed adulthood mediators. Finally, potential miss-classifications in
352 exposure and mediators may have led to biased estimates of direct and indirect effects
353 (VanderWeele et al., 2012).

354 We used a marker of inflammation measured at one time point only, so limiting the internal
355 consistency of results. Moreover, we focused on one biomarker of systemic inflammation, potentially
356 missing aspects of inflammatory processes not entirely captured by CRP (Castagné et al., 2016;
357 Davillas et al., 2017). Findings based on causal models DAG₂ and DAG₃ rely on the assumption the
358 lifestyle behaviours are downstream adult SEP, which may have been violated in some individuals.

359 Residual confounding due to either a varying time interval between assessment of exposures,
360 mediators and outcome or not included confounders may still be present and have biased our
361 estimates. Although we carefully included several confounding factors and ran sensitivity analyses, we
362 acknowledge that a mediation model based on nested counterfactuals rests on strong assumptions
363 about confounding (Robins and Greenland, 1992; VanderWeele and Vansteelandt, 2014; Vansteelandt
364 and Daniel, 2017). Triangulation of evidence from different studies and causal inference methods are
365 needed to strengthen our findings based on the inferred estimates (Vandenbrouke et al., 2016).

366 Compared to mediation analyses based on linear path analysis, our approach had the key strength of
367 relying upon a counterfactual framework for mediation estimation even when mediators and/or
368 outcomes were categorical and there was an interaction between exposure and mediators (Robins
369 and Greenland, 1992; VanderWeele et al., 2014). Additional advantages of our study are the inclusion
370 of multiple measures of socioeconomic and lifestyle factors, the life-course perspective and the path-
371 specific estimations. Moreover, our estimated joint indirect effects can be seen as a particular case of
372 randomized intervention analogues, whereby the socioeconomic exposure is left unchanged and the
373 mediator's distribution is manipulated as to be equalized between and among exposure levels
374 (Vansteelandt and Daniel, 2017). Under this conceptualization, our study suggests that interventions

375 to reduce socioeconomic inequalities in heightened inflammation could be performed by addressing
376 financial distress and unhealthy lifestyle among the socially disadvantaged groups of society.

377

378

379 **CONCLUSIONS**

380 Our study offers two main findings: i) the accumulation of disadvantaged socioeconomic positions
381 along the life-course pathway paternal occupational position -> education -> adult occupational
382 position is a mechanism underlying socioeconomic inequalities in adult heightened systemic
383 inflammation, and ii) financial hardship and lifestyle factors transmit about half the effect of
384 disadvantaged life-course socioeconomic exposures and some of the effect of low paternal
385 occupational position that propagates neither through education nor adult occupational position.
386 These findings can be generalized to other high-income countries with socioeconomic inequalities in
387 inflammatory levels and with distributions in the examined risk factors similar to those in
388 Switzerland.

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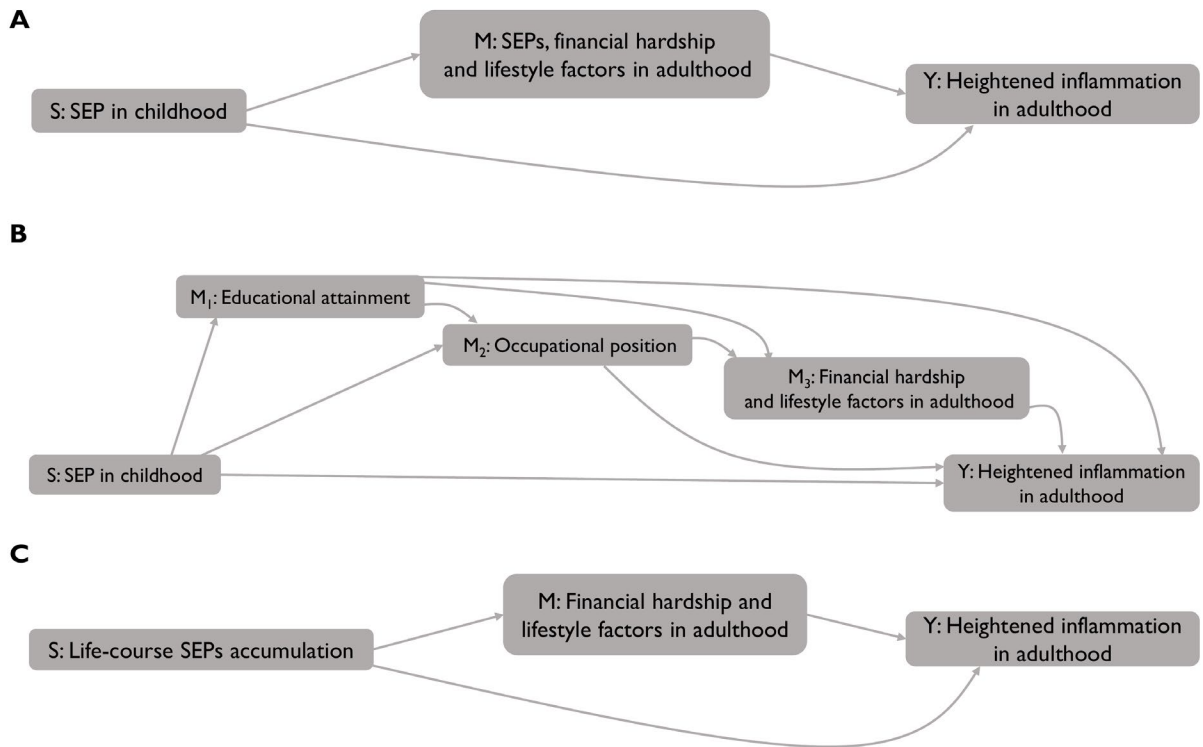
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581 **FIGURE I**



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583 **Causal models posited in the study.** Confounders (sex, ethnicity, age and cohort) are not drawn for the
 584 sake of simplicity. A) DAG₁ of the effect of socioeconomic position (SEP) in childhood (father’s occupational
 585 position or S) on adulthood heightened inflammation (Y). SEPs (individual’s educational attainment and
 586 occupational position), financial hardship, lifestyle factors (BMI, alcohol intake, smoking status, and physical
 587 inactivity) in adulthood are considered en-bloc mediators M. B) DAG₂ of the effect of childhood SEP on
 588 adulthood heightened inflammation through individual’s educational attainment (M₁), occupational position (M₂),
 589 and lifestyle behaviours and financial hardship in adulthood (M₃). C) DAG₃ of the effect of accumulation of life-
 590 course SEPs (paternal occupational position, individual’s educational attainment and occupational position or S)
 591 on adulthood heightened inflammation. Financial hardship and lifestyle factors in adulthood are considered en-
 592 bloc mediators.

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597 **TABLES**

598 **Table I.** Characteristics of the pooled populations according to levels of childhood socioeconomic exposure
 599 (N=4,707 after removing participants whose father's occupational position is unknown (N=404) and whose
 600 father was non-working (N=46)). Continuous characteristics are summarized through their mean and
 601 lower/upper quartiles. Categorical characteristics are summarized through their absolute and relative (%)
 602 prevalence. P values (rightmost column) for differences between levels of father's occupational position are
 603 obtained from a chi-squared test for categorical characteristics (χ^2 is the chi-squared statistics) and a linear
 604 model for continuous ones (T stands for t-statistics).

605

Father's occupational position / Characteristics	Low	Intermediate	High	P value
N	1341 (29%)	1990 (42%)	1376 (29%)	-
Age [years]	61 (52, 70)	60 (52, 71)	59 (51, 68)	0.0002 (T=3.7)
Sex	714 (53%)	1101 (55%)	737 (54%)	0.42 ($\chi^2=1.7$)
[woman/man]	627 (47%)	889 (45%)	639 (46%)	
Ethnicity	1270 (95%)	1882 (95%)	1273 (92%)	0.02 ($\chi^2=7.7$)
[white/other]	71 (5%)	108 (5%)	103 (8%)	
Highest attained education	264 (20%)	365 (19%)	43 (3%)	<2*10 ⁻¹⁶ ($\chi^2=722.5$)
[compulsory/vocational/	581 (44%)	819 (42%)	242 (18%)	
high-school/university]	186 (14%)	285 (15%)	256 (19%)	
	295 (22%)	488 (25%)	819 (60%)	
Occupational position	393 (30%)	484 (25%)	136 (10%)	<2*10 ⁻¹⁶ ($\chi^2=365.7$)
[low/intermediate/high/	590 (44%)	861 (44%)	645 (48%)	
not working]	116 (9%)	209 (11%)	385 (28%)	
	230 (17%)	385 (20%)	186 (14%)	
Financial difficulties	208 (16%)	292 (15%)	156 (12%)	0.002 ($\chi^2=12.5$)

[yes/no]	1076 (84%)	1613 (85%)	1178 (88%)	
Heightened inflammation	276 (21%)	355 (18%)	196 (14%)	7.5×10^{-5} ($\chi^2=19.0$)
[yes/no]	1065 (79%)	1635 (82%)	1180 (86%)	
Smoking status	271 (22%)	386 (21%)	264 (21%)	0.67 ($\chi^2=2.4$)
[current/former/never smoker]	439 (35%)	659 (36%)	489 (38%)	
	529 (43%)	787 (43%)	532 (41%)	
Body mass index	220 (18%)	304 (16%)	136 (11%)	3.1×10^{-14} ($\chi^2=75.4$)
[obese/overweight/normal /underweight]	525 (42%)	699 (36%)	434 (34%)	
	482 (39%)	798 (46%)	686 (53%)	
	12 (1%)	32 (2%)	29 (2%)	
Alcohol intake	113 (9.1%)	140 (7.6%)	102 (8%)	3.2×10^{-5} ($\chi^2=26.0$)
[high/moderate/abstainer]	799 (64.5%)	1144 (62.2%)	896 (70%)	
	326 (26.3%)	555 (30.2%)	288 (22%)	
Physical activity	624 (56.4%)	867 (52.9%)	540 (47%)	1.7×10^{-5} ($\chi^2=21.9$)
[sedentary/active]	482 (43.6%)	772 (47.1%)	615 (53%)	
Prevalent diabetes	116 (9.3%)	139 (7.5%)	90 (7%)	0.07 ($\chi^2=5.3$)
[yes/no]	1129 (90.7%)	1708 (92.5%)	1200 (93%)	
History of stroke or coronary heart diseases	71 (6%)	114 (6%)	58 (5%)	0.13 ($\chi^2=4.1$)
[yes/no]	1173 (94%)	1729 (94%)	1228 (95%)	
Co-morbidities	172 (13%)	240 (12%)	140 (10%)	0.08 ($\chi^2=5.0$)
[yes/no]	1169 (87%)	1750 (88%)	1236 (90%)	

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612 **Table 2.** Odds ratio (OR) and 95% confidence intervals (CI) for the effects of low (vs high) paternal
 613 socioeconomic position on heightened inflammation in adulthood, estimated through the natural effect model.
 614 PM stands for proportion mediated (ratio of the indirect and total effect OR logarithm). The average
 615 population size across imputation and bootstrap draws was N=5,105.

Parameter estimates	OR [95% CI]
<i>Total effect of father's occupational position</i>	1.51 [1.25, 1.84]
Direct effect DAG ₁	1.18 [0.97, 1.46]
Joint indirect effect DAG ₁	1.27 [1.17, 1.39]; PM = 59 [34, 93]%
Direct effect DAG ₂	1.32 [1.07, 1.63]
Joint indirect effect DAG ₂	1.15 [1.07, 1.23]; PM = 33 [14, 69]%
Mediation through educational attainment <i>S</i> → <i>M</i> ₁ <i>Y</i>	PM = 30 [11, 64]%
Partial mediation through occupational position <i>S</i> → <i>M</i> ₂ → <i>Y</i>	PM = 3 [-4, 13]%

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625 **Table 3.** Odds ratio (OR) and 95% confidence intervals (CI) for associations of life-course occupational
626 positions trajectories and effects of highest (vs lowest) score of accumulation of life-course disadvantaged SEPs
627 on heightened inflammation in adulthood. The trajectories' ORs were estimated compared to individuals with
628 high father's occupational position and high individual occupational position. Highest score was defined by
629 having low father's occupational position, compulsory education, and low occupational position, while lowest
630 score by having high father's occupational position, university education and high occupational position. PM
631 stands for proportion mediated (ratio of the indirect and total effect OR logarithm). The average total
632 population size across imputation and bootstrap draws was N=4,170, of which N=406 were stable high, N=449
633 stable low, N=937 stable intermediate, N=973 upward, and N=1,405 downward.

Parameter estimates	OR [95% CI]
<i>Stable low life-course trajectory</i>	2.79 [1.98, 4.28]
<i>Stable intermediate life-course trajectory</i>	1.73 [1.22, 2.57]
<i>Upward life-course trajectory</i>	1.83 [1.32, 2.67]
<i>Downward life-course trajectory</i>	1.92 [1.39, 2.85]
<i>Total effect of accumulation score</i>	2.27 [1.71, 2.98]
Direct effect DAG ₃	1.35 [1.02, 1.80]
Joint indirect effect DAG ₃	1.68 [1.51, 1.89]; PM = 63 [44, 97]%

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643 **SUPPLEMENTARY TEXT**

644

645 **Study Populations**

646 Individual-participant data from two prospective Swiss cohort studies were used: the Swiss Kidney
647 Project on Genes in Hypertension (SKIPOGH) and the COhorte LAUSannoise (CoLaus/PsyCoLaus).

648 SKIPOGH. The SKIPOGH study was a multi-centre population-based study initiated in December
649 2009 to explore the genetic and environmental determinants of blood pressure (Alwan et al., 2014;
650 Ponte et al., 2014). Study participants were recruited in the cantons of Bern and Geneva and in the
651 city of Lausanne, Switzerland. Recruitment ended in April 2013 for the baseline assessment and
652 included 1,128 participants aged between 18 and 90. A follow-up survey on 1,033 individuals started
653 in October 2012 and was completed in December 2016. The SKIPOGH study was approved by the
654 ethical committees of Lausanne University Hospital, Geneva University Hospital and the University
655 Hospital of Bern.

656 CoLaus/PsyCoLaus. The CoLaus/PsyCoLaus study is an ongoing prospective cohort study assessing
657 the clinical, biological and genetic determinants of cardiovascular disease in the city of Lausanne,
658 Switzerland (Firmann et al., 2008). The initial survey was conducted between 2003 and 2006 and
659 included 6,733 participants aged between 35 and 75; the first follow-up survey was conducted 5.5
660 years afterwards and included 5,064 participants. The second follow-up assessment was carried out
661 between 2014 and 2017 and included 4,881 participants. The CoLaus/PsyCoLaus study was approved
662 by the ethical committee of the University of Lausanne.

663

664 **Measures**

665 Childhood socioeconomic position. In the follow-up of the SKIPOGH study and the second follow-
666 up of the CoLaus/PsyCoLaus study, participants were asked to report their father's profession when
667 they were children, and this was used as a proxy of socioeconomic position in early life. Answers
668 were mapped into four categories according to the European SocioEconomic Classification (ESEC)
669 scheme. We categorised occupational class into high (higher professionals and managers, higher
670 clerical, services, and sales workers (European socioeconomic class 1-3)), intermediate (small
671 employers and self-employed, farmers, lower supervisors and technicians, class 4-6), or low (lower
672 clerical, services, and sales workers, skilled workers, semi-skilled and unskilled workers, class 7-9)]
673 (Rose and Harrison, 2007). Finally, fathers who were reported to be retired or not working were
674 classed as not working.

675 Paternal occupational position is a commonly used indicator of socioeconomic positions in early life
676 (Galobardes et al., 2007) and is closely related to parental occupational position in the Swiss context
677 until the early 1970s. Indeed, according to census data (Swiss Federal Statistical Office), in 1970 the
678 percentage of non-working women living in a household with children (0-13 years) was 73%, and the
679 percentage of those working full time was 8%. Participants in our study were born on average in
680 1955, with 90% of participants being born by 1968.

681 Emerging adulthood socioeconomic position. Self-reported highest level of attained education was
682 used as a measure of emerging adulthood socioeconomic position. We categorised the variable into
683 university (university degree and any superior non-university training), high school (secondary
684 school), vocational (apprenticeship in CoLaus/PsyCoLaus and vocational training in SKIPOGH) or
685 mandatory or lower (mandatory school in CoLaus/PsyCoLaus and mandatory school or no diploma
686 in SKIPOGH). Information was collected at baseline for both population studies.

687 Adulthood socioeconomic position. Individual's last known occupational position in adulthood was
688 considered as a proxy for adulthood socioeconomic position. Categorization into four levels was
689 performed according to the same scheme as for father's occupational position. Non working

690 individuals were either self-identified housewives or unemployed. Information on current or past
691 occupational position were available at baseline of SKIPOGH and first follow-up of
692 CoLaus/PsyCoLaus. In order to minimize the missing job titles, we complemented that with
693 information on occupational position available at baseline for CoLaus/PsyCoLaus.

694 Life-course trajectories of socioeconomic positions. Father's and individual occupational position
695 were integrated to generate five life-course trajectories of socioeconomic positions. Individuals were
696 classified into stable high (high father's and individual's occupational position), downward (high
697 father's occupational position and intermediate or low individual's occupational position, or
698 intermediate father's occupational position and low individual's occupational position), upward (low
699 father's occupational position and intermediate or high individual's occupational position, or
700 intermediate father's occupational position and high individual's occupational position), stable
701 intermediate (intermediate father's and individual's occupational position) and stable low (low father's
702 and individual's occupational position).

703 Furthermore, a score of disadvantaged socioeconomic positions accumulating along the life-course
704 was computed. The score was operationalized by adding up the three levels of paternal occupational
705 position (not working fathers were excluded), the four levels of education and the three levels of
706 occupational position (not working individuals were excluded). That score ranged from 1 to 8, where
707 1 stood for participants who held a high occupational position, had university education and whose
708 father's occupational position was also high. Conversely, a value of 8 represented participants who
709 held a low occupational position, had compulsory education and whose father's occupational position
710 was low. Increasing values of the score represented an accumulating exposure to disadvantaged
711 socioeconomic conditions at any of the three life periods we investigated.

712 Financial hardship in adulthood. Financial difficulties in meeting basic needs as food, rent or health
713 insurance were self reported at first follow-up of SKIPOGH and second follow-up of
714 CoLaus/PsyCoLaus. Four answers were possible: i) "never happened"; ii) "not currently but this has
715 happened before"; iii) "yes, started less than a year ago"; iv) "yes, lasting several years". We
716 categorized them into two groups, defined as not having current financial difficulties (i or ii), or as
717 having current financial difficulties (iii or iv).

718 Lifestyle factors in adulthood. Self-reported smoking was classed into current, former, and never.
719 Alcohol consumption was measured in alcohol units weekly, and we categorized participants as
720 abstainers (0 units/week), moderate drinkers (1-21 units/week for men, 1-14 units/week for women),
721 or harmful drinkers (>21 units/week for men, >14 units/week for women). Height and weight were
722 measured using standard procedures; body mass index (BMI) was calculated as kg/m² and categorised
723 as underweight (<18.5), normal (18.5 to <25), overweight (25 to <30), or obese (≥30). Leisure
724 physical activity was measured with different questions in each study so we dichotomised it into
725 sedentary and active using population specific thresholds. In SKIPOGH, those reporting to not
726 practice sport on a regular basis were classified as sedentary, and those reporting to practice
727 regularly sport were classified as non-sedentary or active. In CoLaus/PsyCoLaus participants
728 expending more than 90% of daily energy expenditures in activities less intense than moderate or
729 high-intensity (defined by expending at least four times one's basal metabolic rate) were classified as
730 sedentary, and active otherwise (Bernstein et al., 1999). Lifestyle factors were collected at baseline in
731 SKIPOGH and first follow-up in CoLaus/PsyCoLaus.

732 Systemic inflammatory levels in adulthood. Inflammatory levels were assessed through the amount of
733 circulating C-reactive protein (CRP) in plasma at follow-up in SKIPOGH and second follow-up in
734 COLAUS. CRP is a sensitive marker of inflammatory levels and elevated amounts of CRP have been
735 associated with increased risk for several diseases (Emerging Risk Factors Collaboration et al., 2010).
736 In SKIPOGH, CRP was measured through standard immunoturbidimetry with different detection
737 limits depending on the center, 3mg/L being the highest. Most SKIPOGH participants (~60%) had
738 CRP values below the detection limits. In COLAUS, CRP was measured through high-sensitivity
739 immunoturbidimetry with a detection limit of 0.1 mg/L. We binarized CRP values by arbitrarily
740 defining heightened inflammation when CRP exceeded 3mg/L or 4mg/L.

741 Other. Age at follow-up for SKIPOGH and second follow-up for CoLaus/PsyCoLaus, sex, cohort and
742 ethnicity. For SKIPOGH, the cohort indicator included information about the three centres. Self-
743 reported ethnicity was dichotomized in being white or other. In SKIPOGH, no more detailed
744 information about non-white participants was collected.

745 Diabetes was defined as the presence of at least one of fasting glucose concentration ≥ 7 mmol/L or
746 self-reported medication for diabetes. History of stroke or coronary heart diseases (myocardial
747 infarction, heart failure, percutaneous coronary intervention or coronary artery bypass graft) was
748 self-reported. Diabetes, history of stroke and coronary heart diseases were measured at baseline in
749 SKIPOGH and first follow-up in CoLaus/PsyCoLaus. Individuals with diabetes, history of stroke or
750 coronary heart diseases and with a class III BMI (BMI ≥ 40) were dichotomized as having inflammation
751 related co-morbidities or not.

752 Table S1 reports prevalences and frequencies of all introduced characteristics in both population
753 studies.

754

755 **Counterfactual-based mediation framework**

756 We adopted a counterfactual mediation framework to disentangle direct and indirect effects of the
757 exposure(s) on the outcome, via multiple mediators. Contrary to traditional path analysis based on
758 parametric structural equation modelling, mediation analysis based on counterfactuals rely on formal
759 causal arguments and it allows path tracing even with binary outcomes, whereas the traditional path
760 analysis rely on stringent parametric constraints (MacKinnon and Dwyer, 1993). In this study,
761 marginal natural effect models, a class of marginal structural models for parametrizing and estimating
762 so-called direct and indirect effects (and more generally, path-specific effects) expressed on their
763 natural scale (Lange et al., 2012) were fitted.

764 Let's nested counterfactuals $Y(s, M(s^*))$ denote the heightened inflammation that would have been
765 observed if exposure were set to high paternal occupational position or highest life-course SEPs (s)
766 and mediators M to the value it would have taken if exposure were set to low paternal occupational
767 position or lowest life-course SEPs (s^*). Denoting as C the set of confounders and hypothesizing no
768 product terms, in main analyses we posited the following natural effect model

$$769 \text{logit}[E\{Y(s, M(s^*))|C\}] = \beta_0 + \beta_1 s + \beta_2 s^* + \beta_3 C$$

770 From it, we can simultaneously estimate the natural direct effect odd ratio as

$$771 \frac{\text{odds}\{Y(s, M(s^*)) = 1 | C\}}{\text{odds}\{Y(s^*, M(s^*)) = 1 | C\}} = \exp\{\beta_1 (s - s^*)\}$$

772 and the natural indirect effect as

$$773 \frac{\text{odds}\{Y(s, M(s)) = 1 | C\}}{\text{odds}\{Y(s, M(s^*)) = 1 | C\}} = \exp\{\beta_2 (s - s^*)\}.$$

774 Their product measures the total effect $\text{odds}\{Y(s)=1|C\}/\text{odds}\{Y(s^*)=1|C\}$.

775 Under certain identifying conditions, natural effect models enable estimation of joint indirect effects
776 (e.g. effect of exposure on outcome mediated simultaneously by a bloc of mediators) and fine-grained
777 decompositions (path-specific indirect effects) (Steen et al., 2017a).

778 For DAG₁ and DAG₃ we estimated only direct and joint indirect effects, as their identification was
779 not dependent on the true causal order of the mediators (VanderWeele and Vansteelandt, 2014). In
780 other words, joint effects are robust to potential misspecifications of the causal order. This property
781 was useful in our case since the interrelations between financial hardship and lifestyle factors cannot
782 be determined unequivocally. Effects are identifiable if there are no unmeasured confounders of
783 exposure-outcome, exposure-mediators and mediators-outcome relations. Furthermore, contrary to

784 other types of path-specific effects, joint effects are identifiable under unmeasured confounding (not
785 induced by the exposure) among the mediators (Steen et al., 2017a). In DAG₁ the direct effect not
786 accounted for by educational attainment, occupational position, financial hardship and lifestyle factors
787 were taken as the effect on inflammation when changing individual's exposure from high to low
788 father's occupational position while keeping the value of the mediators at the level they had if
789 individuals were exposed to high father's occupational position. The joint indirect effect mediated by
790 all mediators taken together ($S \rightarrow M \rightarrow Y$, in Figure 1A) indicated the effect on heightened
791 inflammation when altering the levels of the mediators from levels observed if exposed to high
792 father's occupational position to levels that would have been observed at low father's occupational
793 position while otherwise remaining exposed to high father's occupational position. We mention that
794 joint indirect effects have an alternative interpretation, first proposed by VanderWeele and Robinson
795 (2014) in the context of non-modifiable exposures as ethnicity (VanderWeele and Robinson, 2014).
796 Within this conceptualization, the natural joint indirect effect might be interpreted as a particular
797 case of randomized intervention analogues, whereby the exposure is left unchanged and the
798 mediator's distribution is manipulated as to equalize it between the levels of exposure (VanderWeele
799 and Robinson, 2014; Vansteelandt and Daniel, 2017). Under the natural effect model estimation, this
800 equivalence holds if all identifying conditions mentioned above are satisfied.

801 Path-specific effects in DAG₂ (see Figure 1B) assessment was a two-step process. First, the total
802 effect of father's occupational position on adulthood heightened inflammation was broken down in
803 direct and joint indirect effects. Second, we further decomposed the joint indirect effect into two
804 path-specific indirect effects (Steen et al., 2017a): 1) the effect mediated through highest attained
805 education ($S \rightarrow M_1 \rightarrow M_2 \rightarrow Y$ and $S \rightarrow M_1 \rightarrow Y$ in Figure 1B, that we denote as $S \rightarrow M_1 Y$); 2) the
806 effect mediated directly through individual's occupational position ($S \rightarrow M_2 \rightarrow Y$) and not through
807 education. This further decomposition requires additional identifying assumptions, namely that there
808 is no unmeasured confounding among the pair of mediators and no confounders of the mediator-
809 outcome relations (either measured or unmeasured) are themselves affected by exposure.
810

811 All the aforementioned joint and path-specific effects corresponded to parameters of natural effects
812 models and were estimated via an imputation model of the nested counterfactuals (Vansteelandt et
813 al., 2014). This was performed in three steps by: i) fitting logistic regression models for heightened
814 inflammation with father's occupational position/accumulation score, the mediators and confounders
815 as explanatory variables; ii) imputing the counterfactual heightened inflammation for each
816 combination of unobserved (counterfactual) exposures and observed mediators levels; and iii) fitting
817 a logistic natural effect model for imputed heightened inflammation. In all cases, we specified models
818 for the outcome imputation to reflect the structure of the natural effects models (Vansteelandt et al.,
819 2014). Under the assumption of an outcome imputation model correctly specified and congenial with
820 the natural effect model (Vansteelandt et al., 2014), this estimation approach is appealing because it is
821 parsimonious in that it requires specifying only one model even in the presence of multiple
822 mediators. Furthermore, in empirical simulations it provided adequate estimates compared to inverse
823 probability and doubly robust estimators (Vansteelandt et al., 2014).

824 In main analyses, product terms between exposure and mediators on the multiplicative scale were
825 not included in the counterfactual imputation model based on weak evidence from likelihood ratio
826 tests (P value = 0.42, 0.55, 0.48 for DAG_{1,2,3} respectively). Product terms among mediators in DAG₂
827 were included based on likelihood ratio test (P value = 0.04). Product terms among mediators in
828 DAG_{1,3} could not be reliably estimated given their high numbers compared to the available
829 population size, consequently they were not included in the outcome imputation model.

830 Analyses were performed in R 3.5.1 (*medflex* (Steen et al., 2017b) for joint mediations, and in house
831 scripts for path-specific mediations).

832

833

834 **Sensitivity analyses**

835 We ran sensitivity analyses to investigate the stability of analyses upon a different choice of CRP cut-
836 off (4mg/L vs 3mg/L), removing participants with CRP>10mg/L or with co-morbidities. We removed
837 individuals with the aforementioned high CRP values by hypothesizing that they reflected short-term
838 immune responses due to current illness that might confound (possibly induced by life-course
839 accumulation of disadvantaged SEPs, DAG₃) the effect of adulthood financial hardship or lifestyle
840 factors on heightened inflammation. The same hypothesis underlies the removal of participants with
841 co-morbidities.

842 Furthermore, we estimated joint indirect effects when adding co-morbidities as an additional
843 mediator in DAG_{1,2}, to evaluate whether the potential marginal extra mediation provided by adding
844 adulthood lifestyle factors and financial hardship (DAG₁) to socioeconomic positions (DAG₂) is
845 robust with respect to a potential confounder (possibly induced by father's occupational position).
846 We investigated mediation modifications by sex and ran analyses on complete data to check
847 consistency with results obtained via missing data imputation. Finally, to evaluate the chosen
848 specification of the natural effect model, we estimated joint and path-specific effects when adding a
849 product term between levels of counterfactual exposures in the natural effect model, and
850 exposure/mediators product terms in the outcome imputation models. Namely, we posited the
851 following natural effect model

852
$$\text{logit}[E\{Y(s, M(s^*))|C\}] = \beta_0 + \beta_1 s + \beta_2 s^* + \beta_3 s s^* + \beta_4 C$$

853 From it, we simultaneously estimated the natural pure direct effect odds ratio as

854
$$\frac{\text{odds}\{Y(s, M(s^*)) = 1 | C\}}{\text{odds}\{Y(s^*, M(s^*)) = 1 | C\}} = \exp\{\beta_1 (s - s^*)\}$$

855 and the natural total indirect effect odds ratio as

856
$$\frac{\text{odds}\{Y(s, M(s)) = 1 | C\}}{\text{odds}\{Y(s, M(s^*)) = 1 | C\}} = \exp\{(\beta_2 + \beta_3)(s - s^*)\}.$$

857

858 **Results.** Effect estimates were in the same direction and of similar magnitude to those reported in
859 main analysis when defining heightened inflammation as CRP>4mg/L (vs >3mg/L) (see Table S2),
860 when excluding participants with high values of CRP (>10mg/L) (see Table S3), or participants with
861 co-morbidities (see Table S4).

862 When adding co-morbidities as an additional mediator (Table S5), the marginal extra mediation of
863 childhood SEP inequalities accounted by adding adulthood lifestyle factors and financial hardship
864 (DAG₁) to socioeconomic positions (DAG₂) was similar to that reported in main analysis.

865 Analyses stratified by sex (Table S6) revealed that in women financial hardship and lifestyle factors
866 mediated life-course SEPs inequalities in heightened inflammation more than in men (72% vs 53%).
867 This is in line with previous research pointing to a sex disparity in the impact of life-course
868 socioeconomic positions on adult cardiovascular risk factors and diabetes (Murray et al., 2011; Smith
869 et al., 2011) and with a similar finding reported in the cross-sectional study by Camelo et al. (2014).

870 Estimation with complete data (N=3,699) provided results that were consistent with those reported
871 in main analysis (see Table S7), backing the adopted imputation procedure. Finally, natural effects
872 estimated with more complex models provided similar proportion mediated and effects compared to
873 those reported in main analysis (Table S8).

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982 **SUPPLEMENTARY TABLES**

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984

985 **Table S1.** Summary statistics for the SKIPOGH and CoLaus/PsyCoLaus populations. Continuous
 986 characteristics are summarized through their mean and lower/upper quartiles. Categorical characteristics are
 987 summarized through their absolute and relative (%) prevalence. The columns titled N report the number of
 988 individuals and the percentage of missing data if any.

989

Characteristics	SKIPOGH	N	CoLaus/PsyCoLaus	N
Sex	548 (53%)	1033	2689 (55%)	4881
[woman/man]	485 (47%)		2192 (45%)	
Age [years]	51 (36, 65)	1033	63 (54, 71)	4881
Ethnicity	1023 (99%)	1033	4495 (92%)	4879 (0.04%)
[white/other]	10 (1%)		384 (8%)	
Father's occupational position	266 (26%)	1008 (2%)	1229 (29%)	4247 (13%)
[low/intermediate/high/	493 (48%)		1708 (40%)	
not working]	245 (24%)		1268 (30%)	
	4 (0.4%)		42 (1%)	
Highest attained education	114 (12%)	966 (6%)	832 (17%)	4877 (0.1%)
[compulsory/vocational/	340 (35%)		1715 (36%)	
high-school/university]	153 (16%)		702 (15%)	
	359 (37%)		1557 (32%)	
Occupational position	171 (18%)	939 (9%)	1182 (24%)	4876 (0.1%)
[low/intermediate/high/	531 (57%)		1972 (40%)	
not working]	190 (20%)		632 (13%)	
	47 (5%)		1091 (22%)	
Financial difficulties	107 (11%)	1006 (3%)	671 (16%)	4238 (13%)
[yes/no]	899 (89%)		3567 (84%)	
Heightened inflammation	160 (16%)	1021 (1%)	781 (19%)	4198 (14%)
[yes/no]	861 (84%)		3417 (81%)	
Smoking status	232 (24%)	975 (6%)	882 (21%)	4289 (12%)
[current/former/never	306 (31%)		1632 (38%)	
smoker]	437 (45%)		1775 (41%)	
Body mass index	127 (13%)	982 (5%)	704 (16%)	4284 (12%)
[obese/overweight/normal/	308 (31%)		1664 (39%)	
underweight]	514 (52%)		1856 (43%)	
	33 (3%)		60 (1%)	
Alcohol intake	131 (14%)	961 (7%)	284 (7%)	4334 (11%)
[high/moderate/abstainer]	456 (47%)		2990 (69%)	
	374 (39%)		1060 (24%)	
Physical activity	365 (38%)	962 (7%)	2078 (57%)	3640 (25%)
[sedentary/active]	597 (62%)		1562 (43%)	
Prevalent diabetes	26 (3%)	981 (5%)	438 (10%)	4334 (11%)
[yes/no]	955 (97%)		3896 (89%)	
History of stroke or	25 (3%)	983 (5%)	305 (7%)	4303 (12%)
coronary heart diseases	958 (97%)		3998 (93%)	
[yes/no]				
Co-morbidities	50 (5%)	980 (5%)	687 (16%)	4277 (12%)
[yes/no]	930 (95%)		3590 (84%)	

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994 **Table S2.** Odds ratio (OR) and 95% confidence intervals (CI) for effects estimated through the natural effect
 995 model when participants with CRP>4 mg/L are declared with heightened inflammation. The average population
 996 size across imputation and bootstrap draws was N=5,105 and N=4,171 for the effects of father's occupational
 997 position (low vs high) and life-course accumulation of disadvantaged socioeconomic positions (highest vs lowest
 998 score), respectively. PM is proportion mediated (ratio of the indirect and total effect OR logarithm).

Parameter estimates	OR [95% CI]
<i>Total effect of father's occupational position</i>	1.8 [1.4, 2.3]
Direct effect DAG ₁	1.4 [1.1, 1.8]
Joint indirect effect DAG ₁	1.3 [1.1, 1.4]; PM = 42 [21, 77]%
Direct effect DAG ₂	1.6 [1.2, 2.0]
Joint indirect effect DAG ₂	1.1 [1.0, 1.2]; PM = 22 [8, 47]%
Mediation through educational attainment <i>S</i> → <i>M</i> ₁ <i>Y</i>	PM = 19 [4, 40]%
Partial mediation through occupational position <i>S</i> → <i>M</i> ₂ → <i>Y</i>	PM = 3 [-2, 12]%
<i>Total effect of accumulation score</i>	2.8 [2.0, 4.1]
Direct effect DAG ₃	1.6 [1.2, 2.4]
Joint indirect effect DAG ₃	1.7 [1.5, 2.0]; PM = 53 [37, 79]%

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1001 **Table S3.** Odds ratio (OR) and 95% confidence intervals (CI) for effects estimated through the natural effect
 1002 model when participants with high values of CRP (>10 mg/L) are excluded. The average population size across
 1003 imputation and bootstrap draws was N=4,081 for the effect of life-course accumulation of disadvantaged
 1004 socioeconomic positions (highest vs lowest score). PM is proportion mediated (ratio of the indirect and total
 1005 effect OR logarithm).

Parameter estimates	OR [95% CI]
<i>Total effect of accumulation score</i>	2.1 [1.7, 2.9]
Direct effect DAG ₃	1.3 [1.0, 1.8]
Joint indirect effect DAG ₃	1.6 [1.5, 1.8]; PM = 66 [45, 93]%

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1008 **Table S4.** Odds ratio (OR) and 95% confidence intervals (CI) for the effect of life-course accumulation of
 1009 disadvantaged socioeconomic positions (highest vs lowest score) on heightened inflammation in adulthood
 1010 estimated through the natural effect model when participants with co-morbidities were removed. The average
 1011 population size across imputation and bootstrap draws was N=3,701. PM is proportion mediated (ratio of the
 1012 indirect and total effect OR logarithm).

Parameter estimates	OR [95% CI]
<i>Total effect of accumulation score</i>	2.6 [1.8, 3.5]
Direct effect DAG ₃	1.6 [1.1, 2.1]
Joint indirect effect DAG ₃	1.6 [1.5, 1.8]; PM = 53 [37, 82]%

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1019 **Table S5.** Odds ratio (OR) and 95% confidence intervals (CI) for the effect of father's occupational position
 1020 (low vs high) on heightened inflammation in adulthood estimated through the natural effect model when co-
 1021 morbidities were added as an additional mediator. The average population size across imputation and bootstrap
 1022 draws was N=5,105. PM is proportion mediated (ratio of the indirect and total effect OR logarithm).

Parameter estimates	OR [95% CI]
<i>Total effect of father's occupational position</i>	1.5 [1.3, 1.8]
Direct effect DAG ₁	1.2 [1.0, 1.4]
Joint indirect effect DAG ₁	1.3 [1.2, 1.4]; PM = 57 [36, 87]%
Direct effect DAG ₂	1.3 [1.1, 1.6]
Joint indirect effect DAG ₂	1.1 [1.1, 1.2]; PM = 32 [17, 71]%

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 1024 **Table S6.** Odds ratio (OR) and 95% confidence intervals (CI) for the sex specific effect of the life-course
 1025 accumulation of disadvantaged socioeconomic positions (highest vs lowest score) on adulthood heightened
 1026 inflammation estimated through the natural effect model. The average population size across imputation and
 1027 bootstrap draws was N=2,121 and N=2,049 for women and men respectively. PM is proportion mediated
 1028 (ratio of the indirect and total effect OR logarithm).

Parameter estimates	Women OR [95% CI]	Men OR [95% CI]
<i>Total effect of accumulation score</i>	2.7 [2.0, 4.0]	2.0 [1.5, 3.1]
Direct effect DAG ₃	1.3 [1.0, 2.0]	1.4 [1.0, 2.2]
Joint indirect effect DAG ₃	2.0 [1.7, 2.4]; PM = 72 [49, 97]%	1.5 [1.3, 1.7]; PM = 53 [28, 89]%

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 1031 **Table S7.** Odds ratio (OR) and 95% confidence intervals (CI) for the effect (low vs high) of father's
 1032 occupational position and adulthood heightened inflammation estimated through the natural effect model with
 1033 complete data (N=3,699). PM is proportion mediated (ratio of the indirect and total effect OR logarithm).

Parameter estimates	OR [95% CI]
<i>Total effect of father's occupational position</i>	1.6 [1.3, 2.1]
Direct effect DAG ₁	1.3 [1.0, 1.6]
Joint indirect effect DAG ₁	1.3 [1.2, 1.4]; PM = 53 [30, 90]%

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1041 **Table S8.** Odds ratio (OR) and 95% confidence intervals (CI) for effects estimated through the natural effect
 1042 model specified with a product term between levels of counterfactual exposure. The ORs were estimated with
 1043 an outcome imputation model specified with product terms between exposure and mediators on the
 1044 multiplicative scale. The average population size across imputation and bootstrap draws was N=5,105 and
 1045 N=4,171 for the effects of father's occupational position (low vs high) and life-course accumulation of
 1046 disadvantaged socioeconomic positions (highest vs lowest score), respectively. PM is proportion mediated
 1047 (ratio of the indirect and total effect OR logarithm).

Parameter estimates	OR [95% CI]
<i>Total effect of father's occupational position</i>	1.5 [1.3, 1.8]
Pure direct effect DAG ₁	1.2 [1.0, 1.5]
Joint total indirect effect DAG ₁	1.2 [1.1, 1.4]; PM = 50 [23, 83]%
Pure direct effect DAG ₂	1.3 [1.1, 1.7]
Joint total indirect effect DAG ₂	1.1 [1.0, 1.2]; PM = 32 [3, 71]%
Mediation through educational attainment <i>S</i> → <i>M</i> ₁ <i>Y</i>	PM = 28 [3, 66]%
Partial mediation through occupational position <i>S</i> → <i>M</i> ₂ → <i>Y</i>	PM = 4 [-7, 20]%
<i>Total effect of accumulation score</i>	2.3 [1.7, 3.0]
Pure direct effect DAG ₃	1.4 [1.0, 1.9]
Joint total indirect effect DAG ₃	1.6 [1.4, 1.9]; PM = 59 [38, 93]%

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