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

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ABSTRACT

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

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

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

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

INTRODUCTION

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

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

MATERIALS AND METHODS

Study Populations

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

Causal models and measures

The proposed causal structures underlying our study are shown in the directed acyclic graphs (DAGs) displayed in Figure 1. We based our causal modeling to evaluate path-specific mechanisms of socioeconomic inequalities in adulthood heightened inflammation (outcome). The first two causal models (Figure 1A,B) focus on inequalities driven by socioeconomic position experienced in childhood (exposure). The total effect of exposure is broken down into a non transmitted (direct effect) and transmitted (indirect effect) portion by examined intermediate mechanisms. In DAG_1 (Figure 1A) the indirect effect represents the joint mediated effect by adulthood SEPs (individual's highest educational attainment and occupational position), financial hardship and lifestyle factors (BMI, alcohol intake, smoking status, physical inactivity) en-bloc, and we do not posit any assumption on the causal order of the mediators. A null indirect effect in DAG_1 would support an early critical period model (Howe et al., 2016). In DAG_2 (Figure 1B), the indirect effect represents the joint mediated effects by both adulthood SEPs and we assumed i) education causes occupational position, a known temporal order, and ii) downstream risk factors of financial hardship and lifestyle factors are caused by those individual's SEPs (not displayed in DAG_2). By comparing the joint mediated effects in

154   DAG$_1$ vs DAG$_2$ we can understand whether financial hardship and lifestyle behaviour in adulthood

155   provide additional mediation compared to socioeconomic positions only. Furthermore, DAG$_2$

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 DAG$_2$ 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 DAG$_3$ (Figure 1C) we disantangled 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.

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 DAG_1 and DAG_3 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 DAG_2 (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 $S -> M_1 -> M_2 -> Y$ and $S -> M_1 -> Y$ in Figure B, that we denote as $S -> M_1Y$); 2) the effect

230 mediated through individual's occupational position ($S -> M_2 -> Y$) 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).

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.

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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RESULTS

Characteristics of the population

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

Mechanisms of childhood SEP inequalities

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

Mechanisms of life-course SEP inequalities

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

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DISCUSSION

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

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

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

In our study, the marginal extra mediation accounted by adding adulthood lifestyle factors and financial hardship to socioeconomic positions is substantive (59% vs 33%). This means that the paternal occupational position -> adult financial hardship and lifestyle factors -> heightened inflammation path is not entirely captured by the paternal occupational position -> adult socioeconomic positions -> heightened inflammation path. Other unmeasured dimensions of 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

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

We used a marker of inflammation measured at one time point only, so limiting the internal consistency of results. Moreover, we focused on one biomarker of systemic inflammation, potentially missing aspects of inflammatory processes not entirely captured by CRP (Castagné et al., 2016; Davillas et al., 2017). Findings based on causal models DAG_2 and DAG_3 rely on the assumption the lifestyle behaviours are downstream adult SEP, which may have been violated in some individuals.

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

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

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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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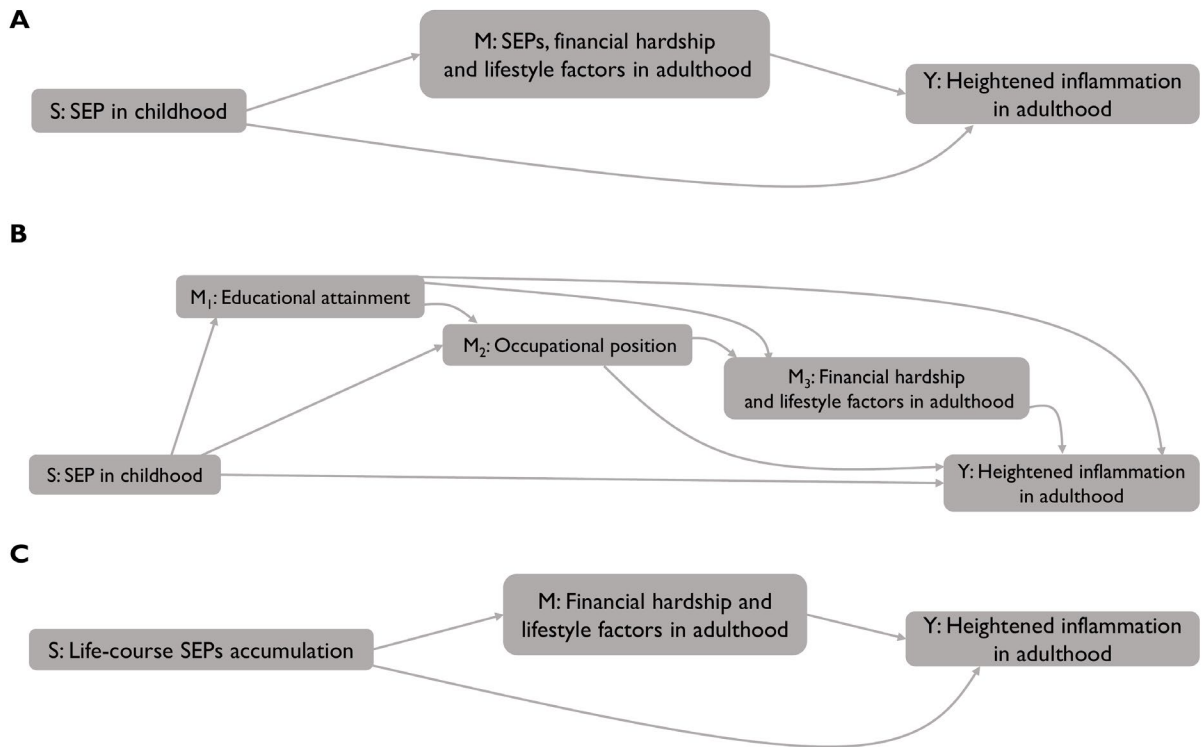566
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FIGURE 1

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Causal models posited in the study. Confounders (sex, ethnicity, age and cohort) are not drawn for the sake of simplicity. A) DAG_1 of the effect of socioeconomic position (SEP) in childhood (father's occupational position or S) on adulthood heightened inflammation (Y). SEPs (individual's educational attainment and occupational position), financial hardship, lifestyle factors (BMI, alcohol intake, smoking status, and physical inactivity) in adulthood are considered en-bloc mediators M. B) DAG_2 of the effect of childhood SEP on adulthood heightened inflammation through individual's educational attainment (M_1), occupational position (M_2), and lifestyle behaviours and financial hardship in adulthood (M_3). C) DAG_3 of the effect of accumulation of life-course SEPs (paternal occupational position, individual's educational attainment and occupational position or S) on adulthood heightened inflammation. Financial hardship and lifestyle factors in adulthood are considered en-bloc mediators.

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TABLES

Table 1. Characteristics of the pooled populations according to levels of childhood socioeconomic exposure (N=4,707 after removing participants whose father's occupational position is unknown (N=404) and whose father was non-working (N=46)). Continuous characteristics are summarized through their mean and lower/upper quartiles. Categorical characteristics are summarized through their absolute and relative (%) prevalence. P values (rightmost column) for differences between levels of father's occupational position are obtained from a chi-squared test for categorical characteristics (χ^2 is the chi-squared statistics) and a linear model for continuous ones (T stands for t-statistics).

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 [woman/man]	714 (53%) 627 (47%)	1101 (55%) 889 (45%)	737 (54%) 639 (46%)	0.42 (χ^2=1.7)
Ethnicity [white/other]	1270 (95%) 71 (5%)	1882 (95%) 108 (5%)	1273 (92%) 103 (8%)	0.02 (χ^2=7.7)
Highest attained education [compulsory/vocational/ high-school/university]	264 (20%) 581 (44%) 186 (14%) 295 (22%)	365 (19%) 819 (42%) 285 (15%) 488 (25%)	43 (3%) 242 (18%) 256 (19%) 819 (60%)	<2*10^{-16} (χ^2=722.5)
Occupational position [low/intermediate/high/ not working]	393 (30%) 590 (44%) 116 (9%) 230 (17%)	484 (25%) 861 (44%) 209 (11%) 385 (20%)	136 (10%) 645 (48%) 385 (28%) 186 (14%)	<2*10^{-16} (χ^2=365.7)
Financial difficulties	208 (16%)	292 (15%)	156 (12%)	0.002 (χ^2=12.5)

[yes/no]	1076 (84%)	1613 (85%)	1178 (88%)	
Heightened inflammation	276 (21%)	355 (18%)	196 (14%)	$7.5*10^{-5}$ (χ^2=19.0)
[yes/no]	1065 (79%)	1635 (82%)	1180 (86%)	
Smoking status	271 (22%)	386 (21%)	264 (21%)	0.67 (χ^2=2.4)
[current/former/never	439 (35%)	659 (36%)	489 (38%)	
smoker]	529 (43%)	787 (43%)	532 (41%)	
Body mass index	220 (18%)	304 (16%)	136 (11%)	$3.1*10^{-14}$ (χ^2=75.4)
[obese/overweight/normal	525 (42%)	699 (36%)	434 (34%)	
/underweight]	482 (39%)	798 (46%)	686 (53%)	
	12 (1%)	32 (2%)	29 (2%)	
Alcohol intake	113 (9.1%)	140 (7.6%)	102 (8%)	$3.2*10^{-5}$ (χ^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%)	$1.7*10^{-5}$ (χ^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 (χ^2=5.3)
[yes/no]	1129 (90.7%)	1708 (92.5%)	1200 (93%)	
History of stroke or	71 (6%)	114 (6%)	58 (5%)	0.13 (χ^2=4.1)
coronary heart diseases	1173 (94%)	1729 (94%)	1228 (95%)	
[yes/no]				
Co-morbidities	172 (13%)	240 (12%)	140 (10%)	0.08 (χ^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]
Total effect of father's occupational position	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 $S -> M_1 Y$	PM = 30 [11, 64]%
Partial mediation through occupational position $S -> M_2 -> Y$	PM = 3 [-4, 13]%

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

Parameter estimates	OR [95% CI]
Stable low life-course trajectory	2.79 [1.98, 4.28]
Stable intermediate life-course trajectory	1.73 [1.22, 2.57]
Upward life-course trajectory	1.83 [1.32, 2.67]
Downward life-course trajectory	1.92 [1.39, 2.85]
Total effect of accumulation score	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]%

SUPPLEMENTARY TEXT

Study Populations

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

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

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

Measures

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

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

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

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

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

Life-course trajectories of socioeconomic positions. Father's and individual occupational position were integrated to generate five life-course trajectories of socioeconomic positions. Individuals were classified into stable high (high father's and individual's occupational position), downward (high father's occupational position and intermediate or low individual's occupational position, or intermediate father's occupational position and low individual's occupational position), upward (low father's occupational position and intermediate or high individual's occupational position, or intermediate father's occupational position and high individual's occupational position), stable intermediate (intermediate father's and individual's occupational position) and stable low (low father's and individual's occupational position).

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

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

Lifestyle factors in adulthood. Self-reported smoking was classed into current, former, and never. Alcohol consumption was measured in alcohol units weekly, and we categorised participants as abstainers (0 units/week), moderate drinkers (1-21 units/week for men, 1-14 units/week for women), or harmful drinkers (>21 units/week for men, >14 units/week for women). Height and weight were measured using standard procedures; body mass index (BMI) was calculated as kg/m^2 and categorised as underweight (<18.5), normal (18.5 to <25), overweight (25 to <30), or obese (≥30). Leisure physical activity was measured with different questions in each study so we dichotomised it into sedentary and active using population specific thresholds. In SKIPOGH, those reporting to not practice sport on a regular basis were classified as sedentary, and those reporting to practice regularly sport were classified as non-sedentary or active. In CoLaus/PsyCoLaus participants expending more than 90% of daily energy expenditures in activities less intense than moderate or high-intensity (defined by expending at least four times one's basal metabolic rate) were classified as sedentary, and active otherwise (Bernstein et al., 1999). Lifestyle factors were collected at baseline in SKIPOGH and first follow-up in CoLaus/PsyCoLaus.

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

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

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

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

Counterfactual-based mediation framework

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

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

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

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

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

and the natural indirect effect as

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

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

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

For DAG$_1$ and DAG$_3$ we estimated only direct and joint indirect effects, as their identification was not dependent on the true causal order of the mediators (VanderWeele and Vansteelandt, 2014). In other words, joint effects are robust to potential misspecifications of the causal order. This property was useful in our case since the interrelations between financial hardship and lifestyle factors cannot be determined unequivocally. Effects are identifiable if there are no unmeasured confounders of 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 DAG_1 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 ($S -> M -> Y$, 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 DAG_2 (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   (
806 $S -> M_1 -> M_2 -> Y$ and $S -> M_1 -> Y$ in Figure 1B, that we denote as $S -> M_1 Y$); 2) the
807 effect mediated directly through individual's occupational position ($S -> M_2 -> Y$) and not through
808 education. This further decomposition requires additional identifying assumptions, namely that there
809 is no unmeasured confounding among the pair of mediators and no confounders of the mediator-
810 outcome relations (either measured or unmeasured) are themselves affected by exposure.

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 DAG_2
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).

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Sensitivity analyses

We ran sensitivity analyses to investigate the stability of analyses upon a different choice of CRP cut-off (4mg/L vs 3mg/L), removing participants with CRP>10mg/L or with co-morbidities. We removed individuals with the aforementioned high CRP values by hypothesizing that they reflected short-term immune responses due to current illness that might confound (possibly induced by life-course accumulation of disadvantaged SEPs, DAG_3) the effect of adulthood financial hardship or lifestyle factors on heightened inflammation. The same hypothesis underlies the removal of participants with co-morbidities.

Furthermore, we estimated joint indirect effects when adding co-morbidities as an additional mediator in $DAG_{1,2}$, to evaluate whether the potential marginal extra mediation provided by adding adulthood lifestyle factors and financial hardship (DAG_1) to socioeconomic positions (DAG_2) is robust with respect to a potential confounder (possibly induced by father's occupational position). We investigated mediation modifications by sex and ran analyses on complete data to check consistency with results obtained via missing data imputation. Finally, to evaluate the chosen specification of the natural effect model, we estimated joint and path-specific effects when adding a product term between levels of counterfactual exposures in the natural effect model, and exposure/mediators product terms in the outcome imputation models. Namely, we posited the following natural effect model

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

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

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

and the natural total indirect effect odds ratio as

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

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

When adding co-morbidities as an additional mediator (Table S5), the marginal extra mediation of childhood SEP inequalities accounted by adding adulthood lifestyle factors and financial hardship (DAG_1) to socioeconomic positions (DAG_2) was similar to that reported in main analysis.

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

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

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SUPPLEMENTARY TABLES

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

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

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

Parameter estimates	OR [95% CI]
Total effect of father's occupational position	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 $S -> M_1 Y$	PM = 19 [4, 40]%
Partial mediation through occupational position $S -> M_2 -> Y$	PM = 3 [-2, 12]%
Total effect of accumulation score	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]%

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

Parameter estimates	OR [95% CI]
Total effect of accumulation score	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]%

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

Parameter estimates	OR [95% CI]
Total effect of accumulation score	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]%

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

Parameter estimates	OR [95% CI]
Total effect of father's occupational position	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]%

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

Parameter estimates	Women OR [95% CI]	Men OR [95% CI]
Total effect of accumulation score	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]%

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

Parameter estimates	OR [95% CI]
Total effect of father's occupational position	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]%

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]
Total effect of father's occupational position	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 $S -> M_1Y$	PM = 28 [3, 66]%
Partial mediation through occupational position $S -> M_2 -> Y$	PM = 4 [-7, 20]%
Total effect of accumulation score	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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