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Early Life Socioeconomic Position and Risk of Deaths from Cardiovascular Diseases: An Application of Causal Mediation Analysis

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ABSTRACT

Objective: We aimed to quantify the mediating impact of adult social and behavioral mechanisms in the association between childhood socioeconomic position (SEP) and cardiovascular disease (CVD) mortality by employing a weighting approach to mediation analysis.

Design: Prospective cohort study.

Setting: Stockholm County, Sweden.

Participants: 19 720 individuals who participated in the Stockholm Public Health Cohort survey in 2002 and were older than 40 years.

Primary and secondary outcome measures: The primary outcome was CVD mortality. Non-CVD mortality was additionally analyzed for comparison.

Methods: Study subjects were followed in routine registers from 2002 until 2011 for mortality. Data on father's SEP and adult social and behavioral factors came from questionnaire survey. The inverse odds weighting method was used to estimate the total effect, the natural direct effect (NDE) and the natural indirect effect (NIE) in Poisson regression models. All results were adjusted for gender, age, and country of birth. Multiple imputation was used to handle missing data.

Results: The total effect of manual versus non-manual father's SEP on CVD mortality was estimated as an incidence rate ratio (IRR) of 1.29 (95% confidence interval [CI]: 1.13-1.48). The social and behavioral factors altogether mediated 44% (IRR^{NIE}: 1.11; 95% CI: 1.04-1.19) of the effect while the behavioral factors on their own mediated only 11% of the total effect. The association between father's SEP and non-CVD mortality was weaker (IRR 1.11; 95% CI: 1.00-1.24).

Conclusion: Adult social and behavioral factors partially mediated the early life social origin of CVD mortality. Future research employing the causal mediation framework should consider additional mediating factors for a fuller understanding of the mechanisms.

Keywords: childhood; inverse odds weights; mortality; life course; health behaviors.

Article Summary

Strengths and limitation of this study

- The study used, in a survival context, the inverse odds weighting approach that accommodates multiple mediators of mixed measurement scales and estimates valid mediation parameters regardless of exposure-mediator and mediator-mediator interactions.
- The study also utilized sequential causal mediation approach which is robust to the unmeasured common causes of two or more mediators.
- Multiple imputation technique was used to deal with biases potentially originating from systematic missing of data.
- The mediators were mostly self-reported and assessed at one point in time.

INTRODUCTION

Epidemiological studies consistently demonstrate an association between childhood socioeconomic position (SEP), often measured by parental occupation or education, and mortality later in life, especially mortality from cardiovascular diseases (CVD) (1–8). The association generally holds true for both men and women and across older and newer generations (1). Furthermore, the burden of CVD risk factors such as tobacco smoking, alcohol consumption, physical inactivity, and unhealthy diet has been found to be disproportionately distributed across different strata of the social hierarchies in childhood and adulthood, where the people with low SEP show more health-damaging behaviors than those with high SEP (4,5,9,10).

In life course epidemiology, two complementary models are proposed to explain the associations between social environment during childhood and risks of disease and mortality later in life: a pathway model and a critical period model. According to the former, early life circumstances affect health outcomes in adulthood by shaping later exposures operating at different stages across the life span (11,12). Social trajectories, such as education and employment, and the establishment of behavioral risk factors in adulthood such as smoking and alcohol drinking (8,13–15) constitute parts of the pathway framework.

The critical period model, on the other hand, predicts that poor circumstances early in life will be associated with increased risks of disease and mortality later in life even when educational attainment, adult SEP, and other risk factors have been accounted for. Evidence from several studies supports this hypothesis (8,16–19). Children born in disadvantaged families tend to be shorter than children from advantaged families and to develop higher diastolic blood pressure, higher cholesterol, and higher body mass index (BMI) as they grow up. These risk factors, in

turn, increase later-life mortality from stroke, heart diseases, and stomach cancer (13,14,17,20,21).

Typically, previous studies have examined underlying pathways by controlling for risk factors thought to mediate the association between exposure and health outcome (1,5,8,15). Findings in those studies may suffer from biases as they relied on regression models that tend to violate fundamental assumptions underlying causal mediation analyses and produce invalid estimates in certain settings (22–24). Potentially, a major source of bias is exposure-mediator interaction in the presence of which the traditional regression method fails to decompose the exposure effect (25–27). An important advance in mediation analysis came with Pearl's (28) counterfactual framework that effectively decomposes the total effect into the sum/product of the natural direct and indirect effects when an exposure-mediator interaction is at play. However, the existing counterfactual mediation techniques are still limited by the number and measurement scales of the mediators and are not generally suited to the multiple mediator and survival settings (22,29–31).

The current study has the ambition to overcome the afore-mentioned methodological limitations in quantifying the joint mediation effect of educational attainment, adult social class, and behavioral risk factors in the associations between social class in childhood and CVD mortality in adulthood in a population-based cohort in Stockholm, Sweden. To compare with CVD mortality, we also analyzed mortality from all causes except CVDs (henceforth non-CVD mortality) with a view to replicating the current evidence that the causes of CVD mortality, such as coronary heart diseases and stroke, are more strongly related to childhood socioeconomic conditions than other causes of deaths (16,17).

METHODS

Study population

The data were drawn from the Stockholm Public Health Cohort (SPHC), a population-based survey carried out by Statistics Sweden (32). In 2002, a postal questionnaire on health, risk factors, and social circumstances was sent out to 50 000 citizens living in the Stockholm County. The survey was based on an area-stratified random sample of men and women aged 18-84 years. Participants provided informed consent before filling out the self-administered questionnaire, including consent about the future register linkages. The response rate was 62%. We chose to exclude the participants who were younger than 40 years (n=11 308 individuals) since deaths resulting from CVD were not much common among them, leaving 19 720 individuals for the final analyses.

Measures

Outcomes

The two outcome measures were CVD mortality and non-CVD mortality. Data on mortality were derived from the Cause of Death Register. The study subjects were followed from July 1, 2002 until deaths or the end of the study on December 31, 2011 whichever occurred first. The World Health Organization's 10th Revision of the International Classification of Diseases (ICD) was used to define CVD mortality (ICD codes I00-I99). All other causes of death were classified as non-CVD mortality.

Exposure

The exposure was father's SEP measured by father's occupational social class. Data on father's occupation was retrospectively collected in the baseline survey in 2002. Based on the Swedish socioeconomic classification (33), Statistics Sweden coded the occupational

information into the following eight SEP categories: unskilled manual workers; skilled manual workers; non-manual workers at low level; non-manual workers at mid-level; non-manual workers at high level; self-employed; farmers; and unclassifiable. We dichotomized childhood SEP into non-manual SEP (low, mid, and high level non-manual workers) and manual SEP (unskilled and skilled manual workers) and treated the self-employed, farmers, and unclassified participants as missing observations.

Mediators

We have measured two distinct sets of mediators: i) the social mediators comprising participants' own education and adult SEP measured by own occupation; and ii) the behavioral mediators i.e., smoking, risky drinking, physical inactivity, diet, as well as BMI. Information on participants' own level of education was taken from Statistics Sweden. We classified education into three groups: low (primary schooling); medium (secondary schooling); and high (post-secondary/university education). Adult SEP was measured through the survey questionnaire where the participants were asked to report their current/previous occupation and tasks in as much detail as possible. The responses were used for classification of SEP made by Statistics Sweden: unskilled manual workers; skilled manual workers; non-manual workers at low level; non-manual workers at mid-level; non-manual workers at high level; and unclassifiable. We categorized adult SEP into three groups: non-manual SEP (low, mid, and high level non-manual workers), manual SEP (unskilled and skilled manual workers), and others (unclassifiable).

The measure of smoking was derived from two questions assessing current and former smoking respectively. Current smoking was defined as smoking tobacco daily during the survey and former smoking was defined as smoking tobacco daily for at least 6 months in the past. Participants were also asked to report the average amount of alcohol consumption per

week and the frequency of binge drinking. As in a previous study (9), we defined risky drinking as consumption of >168 grams of pure alcohol per week for men and >108 grams of pure alcohol per week for women, or consumption of alcohol equivalent to half bottle of spirits/two bottles of wine on a single occasion at least 1 time per month. Physical activity was measured by using the question "How much have you moved/exercised yourself physically in your leisure time during the past 12 months?" and was coded into 4 levels: active (at least 30 minutes of physical exercise >2 times per week with sweating); moderately active (i.e., at least 30 minutes of physical exercise 1 – 2 times per week with sweating e.g. running, swimming); slightly active (more than 2 hours of physical activity per week without sweating); and inactive (less than 2 hours per week). Diet was assessed by a question "How often do you consume fruits or berries?" and was coded into 3 categories: more than once a day; almost daily/a few times a week; and once a week or less. Body mass index (BMI) was calculated from self-reported height and weight and was conventionally defined as a ratio of weight in kilograms divided by height in meters squared. The BMI score was split into 4 groups: underweight (<18.5); normal weight (18.5 to <25); overweight (25 to <30); and obesity (≥30).

Control variables

The control variables used in the study were age (continuous), gender (men and women), and country of birth (Sweden, Nordic, and others). Whereas age and gender were register-based data and were considered as mediator-outcome confounders, country of birth was measured through the survey questionnaire and was considered as a confounder potentially affecting the exposure-outcome, exposure-mediator, and mediator-outcome relationships.

Analyses

We documented the overall distribution of the study variables and assessed the associations of social and behavioral risk factors with father's SEP by Pearson's chi-square test. Next, we examined the associations between potential mediators and mortality outcomes independent of the exposure. All statistical analyses were carried out in generalized linear models with Poisson family and log link function. Attained age was used as the primary time-scale. The underlying time-scale was finely split into years in order to let the mortality rates vary freely over time.

Mediation analysis was performed using the recently proposed Inverse Odds Weighting (IOW) method (29,30). It allowed us to decompose the total effect (TE) into the natural direct effect (NDE) and the natural indirect effect (NIE) without having to fit any model for the mediators. The inverse odds weights were obtained from a working model in which the exposure was regressed on all mediators of interest as well as covariates. Since these weights were used in the direct effect model in lieu of the mediators per se, the mediators should remain independent of the exposure. The purpose was to deactivate the potential pathways linking the exposure to the mediators and thus, to generate valid mediation parameters regardless of the presence of exposure-mediator interactions. The IOW analyses were carried out following the steps as detailed in eTable 1. Drawing on the sequential mediation approach (31), we estimated the joint mediation effect of education and adult SEP in the first step, followed by an estimation of the joint mediation effect of all mediators including the health behaviours in the next step. Within this approach, an ordering is assumed about the causal structure of the mediators to infer the magnitude of path specific mediation effects. Accordingly, we performed the mediation analysis assuming the behavioural mediators to be the causal descendants of the social mediators. For the purpose of comparison, we also used the traditional difference-in-coefficients method (34) to calculate the direct and indirect effects by controlling for the proposed mediators in the Poisson models.

We performed bootstrapping based on 1005 replications to derive the percentile, bias-corrected, and normal-based confidence intervals (CI) for all mediation parameters. We chose to report the percentile confidence intervals, as the percentile method has been demonstrated to be more powerful and valid than other methods in the multiple mediation context (35,36). The estimates were presented as incidence rate ratios (IRR) with 95% CIs. All analyses were undertaken for men and women combined as there was no evidence of effect modification by gender. Stata 15 was used for all analyses.

Missing data

The total proportion of missing observations in our data was 33% with a range from 0% to 22% across the study variables (eTable 2). We used multiple imputation by chained equations to handle the potential selection bias originating from missingness. Under the assumption of missing-at-random (eTable 3), we used Stata's "ice" command with 10 imputations. In addition to the variables from the analytic models, Nelson-Aalen estimate of the cumulative hazard function as well as a set of predictive auxiliary variables (e,g., civic status, country of birth, and self-rated health) were included in the imputation model (37). All statistical analyses were repeated using the 10 imputed data sets and the pooled estimates were reported.

RESULTS

The study results were based on 19 720 individuals (54% women) born during 1918-1962 and followed for mortality during 2002-2011. The mean age at baseline was 58.2 years (range 40 – 84) and the mean attained age at the end of follow up was 63.1 years (range 41–94). 82% of the study members were born in Sweden, 8% were born in other Nordic countries (Finland, Norway, Denmark, and Iceland) and 10% were born outside the Nordic region. During a mean follow-up of 9.06 years (range 0.37–9.50), a total of 2036 deaths occurred of which 751 (3.8%) were due to CVDs. More than half of the sample (54%) had fathers with manual

occupations. Table 1 shows the baseline characteristics of the sample both in the imputed data and in complete cases.

(Table 1 here)

Table 2 shows the distribution of the risk factors of CVD mortality by father's SEP. Results indicate that compared to offspring of non-manual fathers, offspring of manual fathers are themselves more likely to attain low education (17% versus 34%, p<0.001) and manual occupations (17% versus 38%, p<0.001) as adults. The degree of correlation of father's SEP with participants' own educational attainment and SEP in adulthood was 0.27 (p<0.001) and 0.13 (p<0.001) respectively. Similarly, the study subjects whose fathers had a manual occupation showed a more unhealthy behavioral risk profile in terms of smoking, risky alcohol drinking, physical inactivity, poor diet as well as overweight and obesity.

(Table 2 here)

In Table 3, we show the associations of each social and behavioral risk factor with CVD mortality and non-CVD mortality estimated on the IRR scale, adjusting for father's SEP and baseline covariates. Overall, all risk factors were found to be associated with both outcomes. However, the IRRs were generally lower in magnitude for non-CVD mortality than for CVD mortality, except for smoking and low BMI (underweight) which exerted apparently greater effects on non-CVD mortality. Moreover, overweight and obesity did not show any significant association with non-CVD mortality.

(Table 3 here)

The estimated total 'causal effect' as well as the direct and indirect effects of father's SEP on CVD and non-CVD mortality are shown in Table 4. Compared to father's non-manual SEP, manual SEP increased the risk of CVD mortality by 29% (IRR^{TE} 1.29; 95% CI: 1.13-1.47).

Formal tests did not yield any effect modification by age (p for interaction = 0.282) or gender (p for interaction = 0.167). Own education and SEP jointly mediated 33% (IRR^{NIE} 1.08; 95% CI: 1.03-1.14) of the total effect while the whole set of mediators including behavioral risk factors jointly mediated 44% (IRR^{NIE} 1.11; 95% CI: 1.05-1.17). Thus, the magnitude of the mediated effect by the behavioral factors independent of education and adult SEP was (44% - 33%)=11%. Moreover, father's SEP was associated with CVD mortality independent of the adult social and behavioral mediators (IRR^{NDE} 1.16; 95% CI: 1.01-1.33). On the other hand, the association between father's SEP and non-CVD mortality was relatively weak (IRR^{TE} 1.11; 95% CI: 1.00-1.24). The magnitude of the mediation was generally overestimated by the traditional mediation models when compared to the results from IOW-based models.

(Table 4 here)

DISCUSSION

The study results suggest that a difference does exist in the risk of adult CVD mortality by family social class and that this risk is more strongly pronounced than that of non-CVD mortality. Using the IOW method, our study further demonstrates that education and social class position in adulthood together with the behavioral risk factors and BMI accounts for less than half of the increased risk of CVD mortality. Existing literature investigating the magnitude of mediation has generated inconsistent evidence (8,14,15,18) which partially reflects the difference in methodological approaches and the measurement of the mediators.

The natural indirect effect accounting for 44% of the total effect of childhood SEP in our study represents the joint mediation effect carried forward by the social and behavioral candidates. We did not, however, estimate the contribution of individual mediators separately as it may not be an appropriate analytic strategy when the aim is to partition the exposure effect into direct and indirect effects. VanderWeele (22) cautions that the sum of the indirect

effects of each mediator may not add up to 100% when the mediators correlate with each other independent of the exposure.

There is no method available today that allows the fine decomposition of the total indirect effect into mediator specific direct and indirect effects. We have tried to partially address this complexity by estimating the path specific indirect effects using the sequential mediation approach (31). The sequential mediation required us to make the assumption that the social structural pathway comprising education and adult SEP precedes and impacts the behavioral mediators and not the other way round, although one may argue that the health behaviors are already shaped by family background and personality traits during childhood and adolescence. Our assumption is plausible given the finding that the social pathway explained a large proportion of the studied association (33%) whereas a relatively small proportion (11%) was explained by the addition of behavioral mediators. The findings from the sequential mediation analysis thus point to education and adult SEP as constituting a more powerful set of mediators than smoking, alcohol consumption, unhealthy diet, physical inactivity, and BMI taken together. A qualitatively similar conclusion has been drawn in recent studies examining the mediating roles of material and behavioral pathways (18,38).

We did also observe a substantial direct effect of childhood SEP on CVD mortality, i.e., an effect that remains after accounting for the socioeconomic indicators and health damaging behaviors measured in adulthood. This finding is in agreement with several earlier studies that documented an increased risk of CVD mortality associated with parental social background even when adulthood circumstances were held constant (8,39). However, the estimated natural direct effect in this study as well as in prior studies requires a cautious interpretation. A majority of the prior literature interpreted the direct effect as “critical period” effect, thereby defining it as a latent biological pathway unaffected by adult circumstances regardless of the number of adult risk factors considered. Given that we have considered a limited set of

social and behavioral mediators, there is room for additional unmeasured mediators or other potentially interlinked mediating pathways (e.g. health conditions in childhood) which, if taken into account, could possibly explain some of the 'direct' effect.

Similar to other causal mediation approaches, the mediation parameters obtained through the IOW approach rely on the sequential ignorability assumption. This assumption requires that there are no unmeasured confounders that affects the exposure-outcome, exposure-mediator, and mediator-outcome relationships, and that there are no unmeasured mediator-outcome confounders affected by the exposure. If the models were correctly specified and the no-confounding assumptions held, the IOW-based mediation parameters in our study deserve causal interpretations. Although the bias due to unmeasured confounding cannot be ruled out, the use of the IOW method has offered the current study an advantage over prior research in estimating causally interpretable parameters in the context of multi-mediators and exposure-mediator interactions in the presence of which the traditional mediation framework is often likely to generate biased results (22,40,41). The traditional mediation models presuppose that there are no exposure-mediator or mediator-mediator interactions, although this presupposition sounds unrealistic given the complexity of the social context within which diseases and health inequalities emerge. Ignoring interactions, even when the interaction terms are not statistically significant, potentially leads to biased conclusions (22). The main analytic challenge arises due to an exposure-mediator interaction which does not allow decomposing the total effect into direct and indirect effects. We overcame this analytic challenge with the IOW method which is agnostic to the inherent interaction structure in the data.

Limitations and strengths

In common with other weighting approaches, the IOW method works best when the exposure is binary. This led us to dichotomize father's occupation into manual and non-manual

occupations, thereby limiting the generalizability of the study findings to employees belonging to the labor market. Moreover, since the sample was drawn from the population living in the capital city in Sweden, it may not fully represent the general Swedish population. Given the age-heterogeneous sample, there is also a possibility of selection bias due to participation since the older participants were expected to experience relatively high rate of mortality in childhood. Such selective survival might result in a diminution of the magnitude of the total exposure effect in old ages (42). The survival bias, however, appears to be negligible since we found similar effects of childhood social class across younger and older age groups.

A further limitation is the subjective assessment of mediators, leading to potential mediator misclassification which is most likely when the mediator is dichotomized (23). The misclassification of a dichotomous mediator may result in an underestimation of the magnitude of the indirect effect and the consequent overestimation of the direct effect. Most of the mediators in our study contained multiple categories, which if misclassified, might have biased the direct/indirect effect estimates in either direction. A similar concern is the assessment of the mediators at one point in time which may have caused an underestimation of the indirect effects whereas repeated measures were previously shown to increase the proportion explained (43).

Despite these limitations, our study contributes to the growing body of counterfactual-based mediation literature by utilizing a novel method. Unlike the other counter-factual based mediation methods, the IOW method allowed us to implement causal mediation analysis in a survival setting as well as in the context of multiple mediators of mixed scales. An additional

strength is the use of sequential causal mediation analysis which is known to be robust to the unmeasured common causes of two or more mediators (31).

Implications and future research

The health consequences of socio-economic disadvantages experienced in childhood can be offset by intervening on adult social and lifestyle conditions to the extent that they mediate the disease risks associated with childhood disadvantages. The adult social and behavioral factors, however, do not entirely explain the link between childhood SEP and CVD mortality. Future research employing any causal mediation framework should go beyond the social and behavioral pathways and consider additional intervening factors related to, for instance, biological and psychosocial environment, for a fuller understanding of the mechanisms explaining the early life social origin of CVD mortality. Further methodological innovations are needed in order to gauge the unique ability of each mediator to explain the exposure effect in the presence of correlation between the mediators themselves.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Author Contributions

All authors took part in the design and conception of the study. Hossin performed statistical analyses and wrote the first draft of the manuscript with intellectual inputs from Falkstedt and Koupil. Falkstedt acquired the data and was responsible for the integrity of the data. Both Falkstedt and Koupil guided the analyses and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Ethical Standards

The study was approved by the Regional Ethical Review Board in Stockholm (no. 2013/2204-31/1).

Data Sharing Statement: The authors do not have permission to share the data. However, the data can be accessed through submitting a proposal to the Steering Committee at the Stockholm County Council, Sweden.

Tables

Table 1. Characteristics of the study sample (n=19720), the Stockholm Public Health Cohort

Characteristics	Unimputed data		Imputed Data
	n†	%	%
Gender			
Men	9075	46.3	46.3
Women	10539	53.7	53.7
Country of birth			
Sweden	16125	81.8	!
Nordic	1548	7.8	!
Other	2047	10.4	!
Father's SEP			
Nonmanual	9075	46.3	46.0
Manual	10539	53.7	54.0
Educational			
High	6559	33.4	33.4
Medium	7408	37.7	37.7
Low	5684	28.9	28.9
Adult SEP			
Nonmanual	11623	62.2	61.7
Manual	5532	29.6	30.3
Other	1519	8.1	8.0
Smoking			
Never smokers	9301	47.6	47.6
Current smokers	3548	18.1	18.2
Former smokers	6694	34.3	34.2
Risky alcohol			
No	14283	76.0	75.6
Yes	4509	24.0	24.4
Physical inactivity			
Active	2114	11.2	11.1
Moderately active	3819	20.1	19.9
Slightly active	9899	52.2	52.3
Inactive	3117	16.4	16.7
Diet (Fruits and			
More than once a	4253	22.0	22.0
Almost daily/a	12499	64.8	64.8
Once a week or	2547	13.2	13.2
Body Mass Index			
Underweight	254	1.3	1.3
Normal weight	9457	49.1	49.0
Overweight	7430	38.6	38.6
Obese	2119	11.0	11.1

†The numbers for certain variables do not add up to 19720 due to missing values.
!Indicates no missing values.
SD = Standard Deviation

Table 2. Distribution of social and behavioral risk factors by father's SEP (n=19720), the

Social and behavioral risk	Father's SEP		P value
	Non- %	Manual %	
Educational			<0.001
High	48.9	23.6	
Medium	33.9	42.7	
Low	17.2	33.6	
Adult SEP			<0.001
Nonmanual	74.2	55.1	
Manual	16.7	37.7	
Other	9.1	7.2	
Smoking			<0.001
Never smokers	48.6	45.3	
Current smokers	15.8	20.3	
Former smokers	35.6	34.4	
Risky alcohol			<0.001
No	80.8	74.9	
Yes	19.1	25.1	
Physical inactivity			<0.001
Active	12.4	10.1	
Moderately	22.9	19.1	
Slightly active	50.2	53.7	
Inactive	14.5	17.1	
Diet (Fruits and			<0.001
More than once a	23.1	21.4	
Almost daily/a	65.1	64.2	
Once a week or	11.8	14.3	
Body Mass Index			<0.001
Underweight	1.4	1.2	
Normal weight	53.9	45.6	
Overweight	35.6	40.7	
Obese	9.1	12.5	

Note: SEP =Socio-economic Position

Table 3. Associations of social and behavioral risk factors with CVD mortality and non-CVD mortality (n=19720), the Stockholm Public Health Cohort

Social and behavioral risk factors	CVD mortality (751 deaths)			Non-CVD mortality (1285 deaths)		
	No. of events	Crude rates (per 1000)	IRR (95% CI)*	No. of events	Crude rates (per 1000)	IRR (95% CI)*
Educational attainment						
High	66	1.0	1.00	191	3.0	1.00
Medium	153	2.1	1.51 (1.13-2.03)	349	4.9	1.34 (1.12-1.60)
Low	532	10.4	1.70 (1.27-2.27)	743	14.5	1.41 (1.17-1.70)
Adult SEP						
Nonmanual	361	3.2	1.00	688	6.2	1.00
Manual	284	5.4	1.42 (1.21-1.66)	420	8.0	1.18 (1.04-1.34)
Other	18	1.2	0.99 (0.61-1.59)	56	3.8	1.12 (0.85-1.47)
Smoking						
Never smokers	336	3.8	1.00	491	5.5	1.00
Current smokers	128	3.8	1.84 (1.50-2.27)	288	8.6	2.32 (2.00-2.69)
Former smokers	275	4.3	1.37 (1.16-1.61)	492	7.7	1.52 (1.34-1.73)
Risky alcohol drinking						
No	431	3.1	1.00	829	6.0	1.00
Yes	228	5.4	1.48 (1.26-1.74)	376	8.9	1.32 (1.16-1.49)
Physical inactivity						
Active	38	1.8	1.00	94	4.6	1.00
Moderately active	69	1.8	1.10 (0.75-1.62)	129	3.5	0.83 (0.64-1.09)
Slightly active	348	3.7	1.36 (0.98-1.89)	643	6.8	1.17 (0.95-1.46)
Inactive	233	8.2	2.87 (2.06-4.00)	320	11.3	1.94 (1.55-2.44)
Diet (Fruits and vegetables)						
More than once a day	112	2.7	1.00	215	5.2	1.00
Almost daily/a few times a week	516	4.3	1.41 (1.15-1.73)	836	7.0	1.23 (1.05-1.43)
Once a week or less	100	4.2	1.88 (1.43-2.46)	201	8.3	1.83 (1.50-2.22)
Body Mass Index						
Underweight	24	11.0	1.91 (1.24-2.95)	50	22.9	2.31 (1.70-3.13)

Normal weight	302	3.3	1.00	611	6.7	1.00
Overweight	286	4.0	1.21 (1.03-1.42)	440	6.2	0.89 (0.79-1.00)
Obese	102	5.1	1.70 (1.36-2.13)	149	7.4	1.13 (0.94-1.35)

*Adjusted for father's SEP, age, gender, and country of birth

Table 4. Mediation of the associations between father's SEP and CVD- and non-CVD mortality by education, adult SEP, and behavioral risk factors, the Stockholm Public Health Cohort (Both IOW and traditional methods were used) (n=19720)

	Father's SEP and CVD mortality	Father's SEP and non-CVD mortality
Mediation by education and adult SEP		
IOW Approach	IRR (95% CI[4])	IRR (95% CI[4])
Total effect[1]	1.29 (1.13-1.47)	1.11 (1.00-1.24)
Natural direct effect[2]	1.19 (1.03-1.35)	1.05 (0.94-1.17)
Natural indirect effect	1.08 (1.03-1.14)	1.06 (1.01-1.11)
Proportion mediated[5]	33%	56%
Traditional Approach		
Total effect[1]	1.29 (1.13-1.45)	1.11 (1.00-1.24)
Direct effect[3]	1.15 (1.00-1.30)	1.04 (0.93-1.15)
Indirect effect	1. 12 (1.07-1.17)	1.07 (1.03-1.10)
Proportion mediated[5]	48%	64%
Mediation by education, adult SEP+behavioral factors		
IOW Approach		
Total effect[1]	1.29 (1.13-1.47)	1.11 (1.00-1.24)
Natural direct effect[2]	1.16 (1.01-1.33)	1.05 (0.93-1.18)
Natural indirect effect	1.11 (1.05-1.17)	1.06 (1.01-1.10)
Proportion mediated[5]	44%	56%
Traditional Approach		
Total effect[1]	1.29 (1.13-1.45)	1.11 (1.00-1.24)
Direct effect[3]	1.13 (0.98-1.29)	1.05 (0.95-1.16)
Indirect effect	1.14 (1.09-1.20)	1.06 (1.01-1.11)
Proportion mediated[5]	54%	56%

Note: SEP = Socio-economic Position; CVD = Cardio-vascular Diseases; IRR = Incidence Rate Ratio; CI = Confidence Interval; IOW= Inverse Odds Weighting

[1]Adjusted for age, gender, and country of birth.

[2]Obtained by applying the inverse odds weights, in addition to adjusting for age, gender, and country of origin

[3]Adjusted for age, gender, country of origin, and the mediators of interest.

[4] Percentile-based bootstrap confidence intervals are reported.

[5]The proportion mediated was calculated using the formula: $\{IRR^{NDE} (IRR^{NIE} - 1)/(IRR^{NDE} * IRR^{NIE} -$

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Supplementary materials for online publication

1) eTable 1 shows the procedure of estimating mediation parameters using Inverse Odds Weighting Method.
2) eTable 2 shows the proportion of missing observations for each study variable.
3) eTable 3 shows the distribution of missing and complete data across the study variables.

Please see supplementary tables in a separate PDF file.

eAppendices

eTable 1. Procedure of estimating mediation parameters using IOW approach	
Step 1: The working model	An exposure model is run by regressing the exposure on all mediators and covariates using a logistic regression model.
Step 2: Create inverse odds weights	Based on the logistic regression model in step 1, inverse odds weights are created by taking the inverse of the predicted odds for each observation in the exposed group. The exposed and unexposed groups are then reweighted as follows: exposed = inverse odds, unexposed = 1.
Step 3: Total effect model	The total effect of the exposure, conditioning on potential confounders, is estimated by using the Poisson generalized linear model with a log link
Step 4: Direct effect model	The direct effect model is similar to the total effect model but additionally includes the inverse odds weights constructed from the mediators, instead of controlling for the mediators themselves.
Step 5: Compute indirect effect	Building on the traditional difference-in-coefficients approach, the indirect effect is obtained by subtracting the direct effect from the total effect.
Step 6: Estimate standard errors	The standard errors and CIs are obtained by bootstrapping the estimates.

eTable 2. Proportion of missing observations for each study variable, the Stockholm Public Health Cohort

Study variables	Missing	
	n	%
Age	0	0
Gender	106	0.5
Country of origin	0	0
Father's SEP*	4333	22.0
Educational attainment	69	0.4
Adult SEP	1046	5.3
Smoking	177	0.9
Risky alcohol drinking	928	4.7
Physical activity	771	3.9
Poor diet	421	2.1
Body mass index	460	2.3
Total	**6486**	**32.9**

*The missing observations represent farmers, self-employed and the unclassified.

eTable 3. Distribution of missing and complete data across the study variables, the Stockholm Public Health Cohort

Study variables*	Missing data	Complete data	P-value
N (%)	6486 (32.9)	13234 (67.1)	
Age, mean (SD)	61.2 (12.6)	56.7 (11.1)	<0.001
Gender			<0.01
Men	44.8	47.0	
Women	55.2	53.0	
Country of origin			<0.001
Sweden	74.1	85.5	
Nordic	10.1	6.7	
Other	15.7	7.8	
Father's SEP			<0.001
Nonmanual	41.8	47.5	
Manual	58.2	52.5	
Educational attainment			<0.001
High	25.0	37.4	
Medium	34.3	39.3	
Low	40.7	23.2	
Adult SEP			<0.001
Nonmanual	54.6	65.4	
Manual	37.8	26.3	
Other	7.6	8.3	
Smoking			<0.001
Never smokers	50.3	46.3	
Current smokers	18.7	17.9	
Former smokers	31.0	35.8	
Risky alcohol drinking			<0.001

No	69.4	78.8	
Yes	30.6	21.2	
Physical inactivity			<0.001
Active	10.7	11.3	
Moderately active	17.3	21.4	
Slightly active	52.0	52.4	
Inactive	20.0	14.9	
Diet (Fruits and vegetables)			0.075
More than once a day	21.2	22.4	
Almost daily/a few times a week	65.0	64.6	
Once a week or less	13.8	12.9	
Body Mass Index			<0.001
Underweight	1.6	1.2	
Normal weight	47.8	49.7	
Overweight	38.5	38.6	
Obese	12.1	10.5	

*T-test for age and chi-square test for all categorical variables

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6

	#6b	For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6-8
Bias	#9	Describe any efforts to address potential sources of bias	8-10
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8-10
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8-10
	#12b	Describe any methods used to examine subgroups and interactions	10
	#12c	Explain how missing data were addressed	10
	#12d	If applicable, explain how loss to follow-up was addressed	6
	#12e	Describe any sensitivity analyses	9
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	10
	#13b	Give reasons for non-participation at each stage	See note 1
	#13c	Consider use of a flow diagram	NA
Descriptive data	#14a	Give characteristics of study participants (eg demographic,	See note

		clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	2
	#14b	Indicate number of participants with missing data for each variable of interest	eTable 1
	#14c	Summarise follow-up time (eg, average and total amount)	10
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	See note 3
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	See note 4
	#16b	Report category boundaries when continuous variables were categorized	See note 5
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	See note 6
Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12-14
Generalisability	#21	Discuss the generalisability (external validity) of the study results	14
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

Author notes

1. Table 1, p.19
2. Table 1 and Table 2, pp.9-10
3. Table 3, p.21
4. Table 3 and Table 4, pp.21-22
5. Table 3, p.21
6. p.11; Table 4, p.22

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Title Page

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ABSTRACT

Objective: We aimed to quantify the mediating impact of adult social and behavioral mechanisms in the association between childhood socioeconomic position (SEP) and cardiovascular disease (CVD) mortality by employing a weighting approach to mediation analysis.

Design: Prospective cohort study.

Setting: Stockholm County, Sweden.

Participants: 19 720 individuals who participated in the Stockholm Public Health Cohort survey in 2002 and were older than 40 years.

Primary and secondary outcome measures: The primary outcome was CVD mortality. Non-CVD mortality was additionally analyzed for comparison.

Methods: Study subjects were followed in routine registers from 2002 until 2011 for mortality. Data on father's SEP and adult social and behavioral factors came from questionnaire survey. The inverse odds weighting method was used to estimate the total effect, the natural direct effect (NDE) and the natural indirect effect (NIE) in Poisson regression models. All results were adjusted for gender, age, country of birth, and marital status. Multiple imputation was used to handle missing data.

Results: The total effect of manual versus non-manual father's SEP on CVD mortality was estimated as an incidence rate ratio (IRR) of 1.24 (95% confidence interval [CI]: 1.09-1.41) and the social and behavioral factors altogether mediated 44% (IRR^{NIE}: 1.09; 95% CI: 1.04-1.14) of this effect. As for non-CVD mortality, father's manual SEP was associated with 1.15 fold excess risk (IRR: 1.15; 95% CI: 1.04-1.27) of which 42% (IRR^{NIE}: 1.06; 95% CI: 1.01-1.10) was explained by the whole set of mediators.

Conclusion: Adult social and behavioral factors had a considerable mediating effect on the early life social origin of mortality from CVDs and other causes. Future research employing causal mediation analysis may nevertheless have to consider additional factors for a fuller understanding of the mechanisms.

Keywords: childhood; inverse odds weights; mortality; life course; health behaviors.

Article Summary

Strengths and limitation of this study

- The study used, in a survival context, the inverse odds weighting approach that accommodates multiple mediators of any measurement scale and estimates valid mediation parameters regardless of exposure-mediator and mediator-mediator interactions.
- The use of multiple mediators en bloc means the study findings are robust to the unmeasured common causes of two or more mediators.
- Multiple imputation was used to deal with missing data.
- The mediators, however, were mostly self-reported and assessed at a single point in time.

INTRODUCTION

Epidemiological studies consistently demonstrate an association between childhood socioeconomic position (SEP), often measured by parental occupation or education, and mortality later in life, especially mortality from cardiovascular diseases (CVD) (1–8). The association generally holds true for both men and women and across older and newer generations (1). Furthermore, the burden of CVD risk factors in adulthood such as tobacco smoking, alcohol consumption, physical inactivity, unhealthy diet and body mass index (BMI) has been found to be disproportionately distributed across different strata of the social hierarchies in childhood and adulthood, where people with low SEP show more health-damaging behaviors than those with high SEP (4,5,9,10).

In life course epidemiology, two complementary models are proposed to explain the associations between social environment during childhood and risks of disease and mortality later in life: a pathway model and a critical period model. According to the former, early life circumstances affect health outcomes in adulthood by shaping later exposures operating at different stages across the life span (11,12). Thus, a large body of research have suggested that socioeconomic background in childhood affects adult CVDs and mortality by influencing social trajectories such as education and employment and acting through behavioral risk factors such as smoking and drinking (8,13–15). The critical period model, on the other hand, refers to a time period in life, particularly in early life, during which exposure to a risk factor may have an irreversible effect on subsequent health (16). In line with this hypothesis, several studies have shown that adverse social circumstances in childhood are associated with increased risks of adult CVDs, mortality, and other health outcomes independent of educational attainment, adult social position and other risk factors, implying a latent biological path unexplained by circumstances in adulthood (8,17–21).

Typically, previous studies have examined underlying pathways by controlling for risk factors thought to mediate the associations between exposures and health outcomes (1,5,8,15). The common statistical practice has been to fit and compare two regression models: one model without the mediators and another model adjusting for the mediators. The difference in estimates from the two models is interpreted as the mediated effect, i.e., the effect operating through the mediators. Findings in those studies may suffer from severe biases as they relied on traditional regression models that tend to violate some of the fundamental assumptions underlying causal mediation analyses. The recent literature on causal inference lists a set of strong assumptions important for the identification of direct and indirect effects: no unmeasured confounding of the exposure-outcome relationship, no unmeasured confounding of the mediator-outcome relationship, no unmeasured confounding of the exposure-mediator relationship, and no intermediate confounding i.e., confounding of the mediator-outcome relationship by a descendent of the exposure (22). These no-confounding assumptions must hold in order for the direct and indirect effects to be causally interpreted. Unfortunately, the mediator-outcome confounding has often been overlooked in the mediation literature based on the traditional regression approach (22–24).

Another major limitation is exposure-mediator interaction in the presence of which the traditional regression method fails to decompose the exposure effect (25–27). An important advance in mediation analysis came with Pearl's (28,29) mediation formula that effectively decomposes the total effect into the sum of the natural direct and indirect effects even when an exposure-mediator interaction is at play. Drawing on the Robins and Greenland's counterfactual framework (25), Pearl's mediation formula makes a causal contrast between two hypothetical worlds: every individual is exposed in one world while no individual is exposed in the other. In both worlds, the mediator is set to a value that each individual would naturally take in the absence of the exposure. The difference in the two hypothetical worlds is interpreted

as the natural direct effect. Similarly, the natural indirect effect is defined by fixing the exposure in both worlds while letting the mediator for each individual vary between the two worlds (28). Although theoretically appealing, the existing counterfactual mediation approach has limited utility since it is not generally suited to multi-categorical, multiple mediator and survival settings (22,30–32).

The current study has the ambition to overcome the afore-mentioned methodological limitations in quantifying the joint mediation effect of educational attainment, adult social class, and behavioral risk factors in the association between social class in childhood and CVD mortality in adulthood in a population-based cohort in Stockholm, Sweden. To compare with CVD mortality, we additionally analyzed mortality from all causes except CVDs (henceforth non-CVD mortality) with a view to replicating the current evidence that the causes of CVD mortality, such as coronary heart diseases and stroke, are more strongly related to adverse childhood experiences than other causes of death (17,18).

METHODS

Study population

The data were drawn from the Stockholm Public Health Cohort (SPHC), a population-based survey carried out by Statistics Sweden (33). In 2002, a postal questionnaire on health, risk factors, and social circumstances was sent out to 50 000 citizens living in the Stockholm County. The survey was based on an area-stratified random sample of men and women aged 18-84 years. Participants provided informed consent before filling out the self-administered questionnaire, and consent about the future register linkages was also obtained. The response rate was 62%. We chose to exclude the participants who were younger than 40 years (n=11 308 individuals) since deaths resulting from CVD were very rare among them (n=2) and the analysis was computationally demanding. Thus, a total of 19 720 individuals were left for analyses.

Participant involvement

None of the participants were involved in the development of the research question and assessment of the outcome measures, nor were they involved in the overall design and execution of the study. All participants in this study sample were de-identified and we have no possibility to disseminate the findings directly to them.

Measures

Outcomes

The two outcome measures were CVD mortality and non-CVD mortality. Data on mortality were derived from the Cause of Death Register. The study subjects were followed from July 1, 2002 until deaths or the end of the study on December 31, 2011 whichever occurred first. The World Health Organization's 10th Revision of the International Classification of Diseases (ICD) was used to define CVD mortality (ICD codes I00-I99). All other causes of death were classified as non-CVD mortality.

Exposure

The exposure was father's SEP measured by father's occupational social class. Data on father's occupation was retrospectively collected in the baseline survey in 2002. Based on the Swedish socioeconomic classification (34), Statistics Sweden coded the occupational information into the following eight categories: unskilled manual workers; skilled manual workers; non-manual workers at low level; non-manual workers at mid-level; non-manual workers at high level; self-employed; farmers; and unclassifiable. We treated the non-classified as missing observations and dichotomized the remaining categories into non-manual SEP (low, mid and high level non-manual workers, self-employed, and farmers) and manual SEP (unskilled and skilled manual workers). Since the self-employed and the farmers are in general considered to be advantaged in the Swedish socio-economic context (6), we chose to merge them into the non-manual group.

Mediators

We have used two distinct sets of mediators: i) the social mediators comprising participants' own education and adult SEP measured by own occupation; and ii) the behavioral mediators i.e., smoking, risky drinking, physical inactivity, diet as well as BMI. All mediators were assessed at baseline. We derived information on participants' level of education from Statistics Sweden and classified it into three groups: low (primary schooling); medium (secondary schooling); and high (post-secondary/university education). Adult SEP was measured through the survey questionnaire where the participants were asked to report their current/previous occupation and tasks in as much detail as possible. These responses were later used by Statistics Sweden for the Swedish socioeconomic classification: unskilled manual workers; skilled manual workers; non-manual workers at low level; non-manual workers at mid-level; non-manual workers at high level; and unclassifiable. We categorized adult SEP into three groups: non-manual SEP (low, mid and high level non-manual workers), manual SEP (unskilled and skilled manual workers), and others (unclassifiable).

The measure of smoking was derived from two questions assessing current and former smoking respectively. Current smoking was defined as smoking tobacco daily during the survey and former smoking was defined as smoking tobacco daily for at least 6 months in the past. Participants were also asked to report the average amount of alcohol consumption per week and the frequency of binge drinking. As in a previous study (9), we defined risky drinking as consumption of >168 grams of pure alcohol per week for men and >108 grams of pure alcohol per week for women (high consumption), or consumption of alcohol equivalent to half bottle of spirits/two bottles of wine on a single occasion at least 1 time per month (binge drinking). Physical activity was measured by using the question "How much have you moved/exercised yourself physically in your leisure time during the past 12 months?" and was coded into 4 levels: active (at least 30 minutes of physical exercise >2 times per week with sweating); moderately

active (i.e., at least 30 minutes of physical exercise 1 – 2 times per week with sweating e.g. running, swimming); slightly active (more than 2 hours of physical activity per week without sweating); and inactive (less than 2 hours per week). Diet was assessed by a question "How often do you consume fruits or berries?" and was coded into 3 categories: more than once a day; almost daily/a few times a week; and once a week or less. Body mass index (BMI) was calculated from self-reported height and weight and was conventionally defined as a ratio of weight in kilograms divided by height in meters squared. The BMI score was split into 4 groups: underweight (<18.5); normal weight (18.5 to <25); overweight (25 to <30); and obesity (≥30).

Covariates

The covariates used in the study were age (continuous), gender (men and women), country of birth (Sweden, Nordic, and others), and marital status (married and single/divorced/widowed) of the study subjects. Whereas age, gender and marital status were register-based data and were considered as mediator-outcome confounders, country of birth was measured through the survey questionnaire and was considered as a confounder potentially affecting the exposure-outcome, exposure-mediator and mediator-outcome relationships (Figure 1).

(Figure 1 about here)

Analyses

All analyses were conducted using Stata version 15. We first documented the overall distribution of the study variables and assessed the associations of social and behavioral risk factors with father's SEP by Pearson's chi-square test. Next, we examined the associations between potential mediators and mortality outcomes independent of the exposure. All statistical analyses were carried out in generalized linear models with Poisson family and log link function. Time since entry was used as the primary time-scale. Based on the participants' dates of entry into and exit from the study, we created "time of follow up" as another covariate to

take into account potential time confounding. The underlying time-scale was finely split into years in order to let the mortality rates vary freely over time.

Mediation analysis was performed using the recently proposed Inverse Odds Weighting (IOW) method (30,31,35). It is a counterfactual method that allowed us to decompose the total effect into natural direct and indirect effects without having to fit any model for the mediators. The inverse odds weights were obtained from a working model in which the exposure was regressed on all mediators of interest as well as covariates. Since these weights were used in the direct effect model in lieu of the mediators per se, the mediators remained independent of the exposure. The purpose was to deactivate the potential pathways linking the exposure to the mediators and thus generate valid mediation parameters regardless of the presence of exposure-mediator interactions. The IOW analyses were carried out following the steps and the Stata code as detailed in supplementary file 1.

Drawing on the sequential mediation approach (32), we estimated the joint mediation effect of education and adult SEP in the first step, followed by an estimation of the joint mediation effect of all mediators including the health behaviours in the next step. Within this approach, an ordering is assumed about the causal structure of the mediators to infer the magnitude of path specific mediation effects. Accordingly, we performed the sequential mediation analysis assuming the behavioural mediators to be the causal descendants of the social mediators. For the purpose of comparison, we also used the traditional difference-in-coefficients method (36) to calculate the direct and indirect effects by controlling for the proposed mediators in the Poisson models.

We performed bootstrapping based on 1000 replications to derive confidence intervals (CI) for all mediation parameters. We reported the percentile-based confidence intervals which have been demonstrated to be more powerful and valid than the bias corrected or normal-based CIs

in the multiple mediation context (37,38). The estimates were presented as incidence rate ratios (IRR) with 95% CIs. As there was no evidence of effect modification by gender, the main analyses were undertaken for men and women combined. Results from the gender-stratified analyses were moreover reported online in supplementary file 2. Sensitivity analyses were carried out to contrast the results from the full sample with those from the sample excluding the farmers (n=1156) and the self-employed (n=1147) from the non-manual group of fathers (Supplementary file 3).

Missing data

The total proportion of missing observations in our data was 23% with a range from 0% to 12% across the study variables (Supplementary file 4). We used multiple imputation by chained equations to handle the potential selection bias originating from missingness. Under the assumption of missing-at-random (Supplementary file 5), we used Stata's "ice" command to create 25 imputed datasets. In addition to the variables from the analytic models, Nelson-Aalen estimate of the cumulative hazard function as well as other available predictive auxiliary variables (e,g., self-rated health) were included in the imputation model (39). All statistical analyses were repeated using the 25 imputed data sets and the pooled estimates were reported.

RESULTS

The study results were based on 19 720 individuals (54% women) born during 1918-1962 and followed for mortality during 2002-2011. The mean age at baseline was 58.2 years (range 40 – 84) and the mean attained age at the end of follow up was 63.1 years (range 41–94). 82% of the study members were born in Sweden, 8% were born in other Nordic countries (Finland, Norway, Denmark, and Iceland) and 10% were born outside the Nordic region. During a mean follow-up of 9 years (range 0.37–9.50), a total of 2036 deaths occurred of which 751 were due to CVDs. The proportions of deaths from CVDs and non-CVDs in the sample were 3.8% and

6.5% respectively. Less than half of the sample (46%) had fathers with manual occupations. Table 1 shows the baseline characteristics of both the imputed sample and the sample with complete cases.

(Table 1 here)

Table 2 shows the distribution of the risk factors of CVD mortality by father's SEP. Results indicate that compared to offspring of non-manual fathers, offspring of manual fathers are themselves more likely to attain low education (23% versus 35%, p<0.001) and manual occupations (23% versus 39%, p<0.001) as adults. The degree of correlation of father's SEP with participants' own SEP in adulthood was 0.24 (p<0.001). Similarly, the study subjects whose fathers had a manual occupation showed a more unhealthy behavioral risk profile in terms of adult smoking, risky alcohol drinking, physical inactivity, poor diet as well as overweight and obesity.

(Table 2 here)

In Table 3, we show the associations of each social and behavioral risk factor with CVD mortality and non-CVD mortality estimated on the IRR scale, adjusting for father's SEP and baseline covariates. Overall, all risk factors were found to be associated with both outcomes. However, overweight and obesity did not exhibit any significant association with non-CVD mortality.

(Table 3 here)

The estimated total 'causal effect' as well as the direct and indirect effects of father's SEP on CVD and non-CVD mortality are shown in Table 4. Compared to father's non-manual SEP, manual SEP increased the risk of CVD mortality by 24% (IRR^{TE} 1.24; 95% CI: 1.09-1.41). Formal tests did not yield any effect modification by age (p-value for interaction = 0.391) or

gender (p-value for interaction = 0.419). Own education and SEP jointly mediated 29% (IRR^{NIE} 1.06; 95% CI: 1.01-1.11) of the total effect while the whole set of mediators including behavioral risk factors jointly mediated 44% (IRR^{NIE} 1.09; 95% CI: 1.04-1.14). Thus, the magnitude of the mediated effect by the behavioral factors independent of education and adult SEP was (44% - 29%) =15%. Moreover, father's SEP was associated with CVD mortality independent of the adult social mediators (IRR^{NDE} 1.17; 95% CI: 1.00-1.35). The gender-stratified results (supplementary file 2) further indicate that the total mediation effect was larger for women than for men (27% versus 64%).

With regard to non-CVD mortality, the effect of father's manual SEP was 1.15 times higher (95% CI: 1.04-1.27) compared to non-manual SEP. The effect mediated by all social and behavioral intermediates was equivalent to 42% (IRR^{NIE} 1.06: 95% CI: 1.01-1.10) whereas an effect equivalent to 38% (IRR^{NIE} 1.05: 95% CI: 1.02-1.09) was mediated by the two social intermediates, i.e., education and adult SEP. The magnitude of the mediation was generally overestimated by the traditional mediation models when compared to the results from IOW-based models, as evident from Table 4 as well as the online tables in supplementary file 2 and supplementary file 3.

(Table 4 here)

DISCUSSION

The results suggest that a difference by family social class does exist in the risks of both CVD mortality and non-CVD mortality, although the risk of non-CVD mortality tends to be less strong than that of CVD mortality. Using the IOW method, our study further demonstrates that education and social class position in adulthood together with the behavioral risk factors and BMI account for 44% of the increased risk of CVD mortality among the participants. Almost the same magnitude of mediation was observed in the association between childhood social

class and non-CVD mortality. The previous literature investigating the magnitude of mediation has generated inconsistent evidence (8,14,15,19) which partially reflects the difference in methodological approaches and the measurement of the mediators. The observed difference in mediation between men and women in the gender-specific analysis (supplementary file 2) needs to be verified in subsequent studies with larger numbers of CVD death.

The natural indirect effects accounting for over forty percent of the total effects of childhood SEP in our study represent the joint mediation effects carried forward by the social and behavioral risk factors. We did not, however, estimate the indirect effects of individual mediators separately as it may not be an appropriate analytic strategy when the mediators affect one another (22,32). We instead chose to estimate the path-specific indirect effects using the sequential mediation approach (32) which required us to make an additional assumption that the social structural pathway comprising education and adult SEP precedes and impacts the behavioral mediators, although one may argue that the health behaviors are already shaped by family background and personality traits during childhood and adolescence. The findings reveal that the social pathway explained large proportions of the studied associations whereas relatively small proportions were explained by the addition of behavioral mediators, i.e., 15% and 4% for CVD and non-CVD mortality respectively. The findings from the sequential mediation analysis thus point to education and adult SEP as constituting a more powerful set of mediators than smoking, alcohol consumption, unhealthy diet, physical inactivity, and BMI taken together. A qualitatively similar conclusion has been drawn in recent studies examining the mediating roles of material and behavioral pathways (19,40). Compared to non-CVD mortality, however, the behavioral factors turn out to be more important for CVD mortality.

We also observed a direct effect of childhood SEP on CVD mortality, i.e., an effect that remains after accounting for the socioeconomic indicators and health damaging behaviors measured in adulthood. This finding is in agreement with several earlier studies that documented an

increased risk of CVD mortality associated with parental social background even when adulthood circumstances were held constant (8,41). However, the estimated natural direct effect in this study as well as in prior studies requires a cautious interpretation. A majority of the prior literature interpreted the direct effect as a "critical period" effect, thereby defining it as a latent biological pathway unaffected by adult circumstances regardless of the number of adult risk factors considered. Given that we have considered a limited set of social and behavioral mediators, there is room for additional unmeasured mediators or other potentially interlinked mediating pathways (e.g. health conditions in childhood) which, if taken into account, could possibly explain some of the 'direct' effect.

Similar to other mediation approaches, the mediation parameters obtained through the IOW approach rely on the assumptions that there are no unmeasured confounders affecting the exposure-outcome, exposure-mediator and mediator-outcome relationships, and that there are no unmeasured mediator-outcome confounders affected by the exposure. If the models were correctly specified and the no-confounding assumptions held, the IOW-based mediation parameters in our study deserve causal interpretations. Although the bias due to unmeasured confounding cannot be ruled out, the use of the IOW method has offered the current study an advantage over prior research in estimating causally interpretable parameters in the context of multi-mediators and exposure-mediator interactions in the presence of which the traditional mediation framework is often likely to generate biased results (22,42,43).

The traditional regression models presuppose that there are no exposure-mediator or mediator-mediator interactions, although such a presupposition sounds unrealistic given the complexity of the contexts within which diseases and health inequalities emerge. Ignoring interactions, even when the interaction terms are not statistically significant, potentially leads to biased conclusions (22). The main analytic challenge arises due to an exposure-mediator interaction which does not allow decomposing the total effect into direct and indirect effects. We tried to

overcome this analytic challenge with the IOW method which is robust to the inherent interaction structure in the data (31). Similar to a previous study using the same method (35), the current study finds that the mediation parameters derived from the traditional regression models are not entirely compatible with those from the IOW models. A general inflation of the mediated effect has been found in traditional models. Since the traditional models require the assumption of no interaction, an inflation or diminution of the extent of mediation may depend on the directions and magnitudes of the underlying exposure-mediator and mediator-mediator interactions. In the absence of such interactions, however, the traditional regression approach to mediation can yield valid estimates.

Limitations and strengths

In common with other weighting approaches, the IOW method works best when the exposure is binary (31,32). This led us to dichotomize father's occupation into manual and non-manual occupations, with the possibility of exposure misclassification particularly due to the inclusion of the farmers and the self-employed in the non-manual group. The sensitivity analyses, however, do not suggest any major bias due to such exposure misclassification since the sample excluding the farmer and self-employed occupational categories produced pretty similar point estimates (Supplementary file 3). Moreover, since the sample was drawn from the population living in the capital city in Sweden, it may not fully represent the general Swedish population. Given the age-heterogeneous sample, there is also a possibility of selection bias due to participation since the older participants were expected to experience relatively high rate of mortality in childhood. Such selective survival might result in a diminution of the magnitude of the total exposure effect in old ages (44). The survival bias, however, appears to be negligible since we found similar effects of childhood social class across younger and older age groups.

Another concern is the assessment of the mediators at one point in time which may have caused an underestimation of the indirect effects whereas repeated measures of mediators were previously shown to increase the proportion explained (45). However, some of the studied mediators, education and adult SEP for example, are relatively stable over the life course and hence were unlikely to bias the results substantially. A further limitation is the subjective assessment of mediators with a possibility of mediator misclassification which is most likely when the mediator is dichotomized (23). The misclassification of a dichotomous mediator may result in an underestimation of the magnitude of the indirect effect and the consequent overestimation of the direct effect.

Despite these limitations, our study contributes to the growing body of counterfactual-based mediation studies in the context of life course epidemiology. Unlike the typical counter-factual based mediation method, the IOW method has allowed us to implement causal mediation analysis in a time-to-event context relatively easily and offered greater model flexibility in accommodating multiple mediators of mixed scales and relaxing the no-interaction assumptions. Furthermore, as multiple mediators are used en bloc in the IOW method, the estimated natural direct and indirect effects are robust to the unmeasured common causes of two or more mediators (32). This is not necessarily true, however, for the sequential mediation which does not eliminate the need to control for the common causes of two groups of mediators.

Implications and future research

The health consequences of socio-economic disadvantages experienced in childhood can be offset, in principle, by intervening in adult social and lifestyle conditions to the extent that they mediate the disease risks associated with childhood disadvantages. The adult social and behavioral factors, however, do not entirely explain the link between childhood SEP and CVD mortality. Future research employing any causal mediation framework should go beyond the

social and behavioral pathways and also consider undertaking gender-specific analysis for a fuller understanding of the mechanisms explaining the early life social origin of CVD mortality. Further methodological innovations are needed in order to gauge the unique ability of each mediator to explain the exposure effect in the presence of correlation between the mediators themselves.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Author Contributions

All authors took part in the design and conception of the study. Hossin performed statistical analyses and wrote the first draft of the manuscript with intellectual inputs from Falkstedt and Koupil. Falkstedt acquired the data and was responsible for the integrity of the data. Both Falkstedt and Koupil guided the analyses and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Ethical Standards

The study was approved by the Regional Ethical Review Board in Stockholm (no. 2013/2204-31/1).

Data Sharing Statement: The authors do not have permission to share the data. However, the data can be accessed through submitting a proposal to the Steering Committee at the Stockholm County Council, Sweden.

Tables

Table 1. Characteristics of the study sample (n=19720), the Stockholm Public Health Cohort

Characteristics	Unimputed data		Imputed Data
	n†	%	%
Gender			
Men	9075	46.3	46.3
Women	10539	53.7	53.7
Country of birth			
Sweden	16125	81.8	!
Nordic	1548	7.8	!
Other	2047	10.4	!
Marital status			
Married	11559	58.6	!
Single/divorced/widowed	8161	41.4	!
Father's SEP			
Nonmanual	9489	53.6	53.4
Manual	8201	46.4	46.6
Educational attainment			
High	6559	33.4	33.4
Medium	7408	37.7	37.7
Low	5684	28.9	28.9
Adult SEP			
Nonmanual	11623	62.2	61.7
Manual	5532	29.6	30.3
Other	1519	8.1	8.0
Smoking			
Never smokers	9301	47.6	47.6
Current smokers	3548	18.1	18.2
Former smokers	6694	34.3	34.2
Risky alcohol drinking			
No	14283	76.0	75.7
Yes	4509	24.0	24.43
Physical inactivity			
Active	2114	11.2	11.1
Moderately active	3819	20.1	19.9
Slightly active	9899	52.2	52.3
Inactive	3117	16.4	16.7
Diet (Fruits and berries)			
More than once a day	4253	22.0	22.0
Almost daily/a few times a	12499	64.8	64.8
Once a week or less	2547	13.2	13.2
Body Mass Index			
Underweight	254	1.3	1.3
Normal weight	9457	49.1	49.0
Overweight	7430	38.6	38.6
Obese	2119	11.0	11.1

†The numbers for certain variables do not add up to 19720 due to missing values.

!Indicates no missing values.
SD = Standard Deviation

Table 2. Distribution of social and behavioral risk factors by father's SEP (n=19720), the Stockholm Public Health Cohort

Social and behavioral risk factors	Father's SEP		P value
	Non-manual	Manual	
	%	%	
Educational attainment			<0.001
High	42.9	22.8	
Medium	34.2	41.8	
Low	22.9	35.4	
Adult SEP			<0.001
Nonmanual	68.3	54.1	
Manual	22.7	38.8	
Other	9.0	7.1	
Smoking			<0.001
Never smokers	49.5	45.4	
Current smokers	16.1	20.5	
Former smokers	34.5	34.1	
Risky alcohol drinking			<0.001
No	77.8	73.4	
Yes	22.2	26.6	
Physical inactivity			<0.001
Active	12.0	10.0	
Moderately active	21.2	18.4	
Slightly active	51.1	53.7	
Inactive	15.6	17.8	
Diet (Fruits and berries)			<0.001
More than once a day	22.9	21.0	
Almost daily/a few times a week	65.1	64.3	
Once a week or less	12.0	14.6	
Body Mass Index			<0.001
Underweight	1.4	1.3	
Normal weight	52.4	45.2	
Overweight	36.6	40.8	
Obese	9.61	12.7	

Note: SEP =Socio-economic Position

Table 3. Associations of social and behavioral risk factors with CVD mortality and non-CVD mortality (n=20720), the Stockholm Public Health Cohort

Social and behavioral risk factors	CVD mortality (751 deaths)			Non-CVD mortality (1285 deaths)		
	No. of events	Crude rates (per 1000)	IRR (95% CI)*	No. of events	Crude rates (per 1000)	IRR (95% CI)*
Educational attainment						
High	66	1.1	1.00	191	3.1	1.00
Medium	153	2.3	1.53 (1.14-2.05)	349	5.1	1.34 (1.12-1.60)
Low	532	11.0	1.71 (1.27-2.29)	743	15.4	1.48 (1.22-1.79)
Adult SEP						
Nonmanual	361	3.4	1.00	688	6.5	1.00
Manual	284	5.7	1.34 (1.15-1.57)	420	8.5	1.15 (1.01-1.31)
Other	18	1.3	0.92 (0.57-1.48)	56	4.0	1.08 (0.82-1.42)
Smoking						
Never smokers	336	4.0	1.00	491	5.8	1.00
Current smokers	128	4.0	1.81 (1.48-2.22)	288	9.0	2.31 (1.99-2.67)
Former smokers	275	4.5	1.37 (1.17-1.61)	492	8.1	1.55 (1.37-1.75)
Risky alcohol drinking						
No	431	3.3	1.00	829	6.4	1.00
Yes	228	5.74	1.44 (1.22-1.71)	376	9.4	1.32 (1.17-1.49)
Physical inactivity						
Active	38	1.9	1.00	94	4.8	1.00
Moderately active	69	1.9	1.13 (0.76-1.68)	129	3.6	0.83 (0.64-1.09)
Slightly active	348	3.9	1.41 (1.02-1.95)	643	7.1	1.17 (0.94-1.45)
Inactive	233	8.7	3.00 (2.14-4.21)	320	11.9	1.99 (1.59-2.51)
Diet (Fruits and berries)						
More than once a day	112	2.9	1.00	215	5.5	1.00
Almost daily/a few times a week	516	4.6	1.39 (1.14-1.71)	836	7.4	1.25 (1.08-1.45)
Once a week or less	100	4.4	1.83 (1.39-2.41)	201	8.8	1.87 (1.54-2.27)
Body Mass Index						
Underweight	24	11.6	1.88 (1.23-2.86)	50	24.2	2.33 (1.72-3.14)

Normal weight	302	3.5	1.00	611	7.1	1.00
Overweight	286	4.2	1.20 (1.03-1.41)	440	6.5	0.89 (0.79-1.00)
Obese	102	5.3	1.66 (1.33-2.07)	149	7.8	1.11 (0.93-1.33)

*Adjusted for father's SEP, age, gender, country of birth, and marital status

Table 4. Mediation of the associations between father's SEP and CVD- and non-CVD mortality by social and behavioral risk factors, the Stockholm Public Health Cohort (Both IOW and traditional methods were used) (n=19720)

	CVD mortality	Non-CVD mortality
Mediation by education and adult SEP		
IOW Approach	IRR (95% CI[4])	IRR (95% CI[4])
Total effect[1]	1.24 (1.09-1.41)	1.15 (1.04-1.27)
Natural direct effect[2]	1.17 (1.00-1.35)	1.09 (0.96-1.21)
Natural indirect effect	1.06 (1.01-1.11)	1.05 (1.02-1.09)
Proportion mediated[5]	29%	38%
Traditional Approach		
Total effect[1]	1.24 (1.09-1.41)	1.15 (1.04-1.27)
Direct effect[3]	1.14 (0.99-1.32)	1.09 (0.96-1.21)
Indirect effect	1. 08 (1.05-1.12)	1.05 (1.03-1.08)
Proportion mediated[5]	39%	38%
Mediation by education, adult SEP + behavioral factors		
IOW Approach		
Total effect[1]	1.24 (1.09-1.41)	1.15 (1.04-1.27)
Natural direct effect[2]	1.13 (0.99-1.30)	1.09 (0.97-1.21)
Natural indirect effect	1.09 (1.04-1.14)	1.06 (1.01-1.10)
Proportion mediated[5]	44%	42%
Traditional Approach		
Total effect[1]	1.24 (1.09-1.41)	1.15 (1.04-1.27)
Direct effect[3]	1.10 (0.96-1.26)	1.08 (0.97-1.20)
Indirect effect	1. 13 (1.08-1.18)	1.07 (1.03-1.10)
Proportion mediated[5]	59%	49%

Note: SEP = Socio-economic Position; CVD = Cardio-vascular Diseases; IRR = Incidence Rate Ratio; CI = Confidence Interval; IOW= Inverse Odds Weighting

[1]Adjusted for age, gender, country of birth, and marital status

[2]Obtained by applying the inverse odds weights in addition to adjusting for age, gender, country of birth, and marital status

[3]Adjusted for age, gender, country of birth , marital status, and the mediators of interest.

[4] Percentile-based bootstrap confidence intervals are reported.

[5]The proportion mediated was calculated using the formula: $\{IRR^{NDE}(IRR^{NIE} - 1)/(IRR^{NDE}IRR^{NIE} - 1)\}*100$.

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Supplementary materials for online publication only

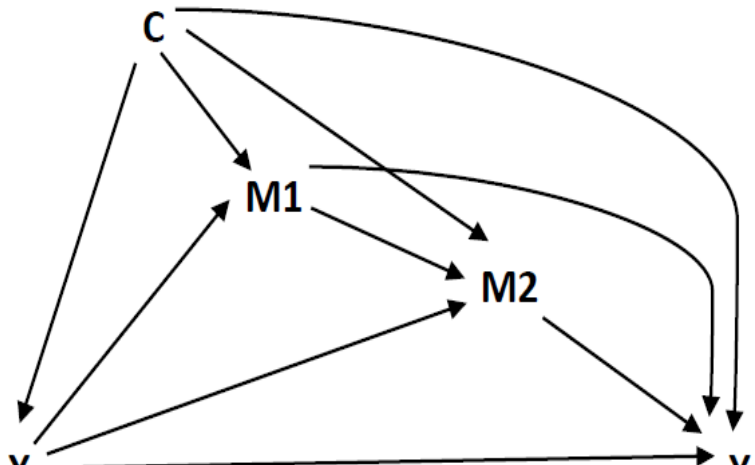
1) Supplementary file 1 displays the procedure and the Stata code for implementing the mediation analysis using inverse odds weights with multiple imputation
2) Supplementary 2 shows the gender-stratified mediation parameters.
3) Supplementary file 3 shows the sensitivity analysis contrasting the results from the full sample with those from the sample excluding the farmer and self-employed occupational categories from father's SEP.
4) Supplementary file 4 shows the proportion of missing observations for each study variable.
5) Supplementary file 5 shows the distribution of missing and complete case data across the study variables.

(Please see supplementary materials in separate PDF files.)

Figure legends

Figure 1: A simple causal diagram of the association between father's socioeconomic position and mortality.

X = father's socioeconomic position (Exposure); Y = cardiovascular mortality and mortality from causes other than cardiovascular diseases (Outcomes); M1 = own education and adult socioeconomic position (Social mediators); M2 = smoking, alcohol drinking, physical inactivity, poor diet, and body mass index (Behavioral mediators); C = country of birth, age, gender, marital status (Confounders).



Supplementary file 1

eTable 1. Procedure of estimating mediation parameters using IOW approach	
Step 1: The working model	An exposure model is run by regressing the exposure on all mediators and covariates using a logistic regression model.
Step 2: Create inverse odds weights	Based on the logistic regression model in step 1, inverse odds weights are created by taking the inverse of the predicted odds for each observation in the exposed group. The exposed and unexposed groups are then reweighted as follows: exposed = inverse odds, unexposed = 1.
Step 3: Total effect model	The total effect of the exposure, conditioning on potential confounders, is estimated by using the Poisson generalized linear model with a log link
Step 4: Direct effect model	The direct effect model is similar to the total effect model but additionally includes the inverse odds weights constructed from the mediators, instead of controlling for the mediators themselves.
Step 5: Compute indirect effect	Building on the traditional difference-in-coefficients approach, the indirect effect is obtained by subtracting the direct effect from the total effect.
Step 6: Estimate standard errors	The standard errors and CIs are obtained by bootstrapping.

Stata code for mediation analysis with inverse odds weights and imputed data

```
cd "\\kifs03.user.ki.se\k9_users$\zakhos\....."
use midata.dta, clear

*Prepare the data for survival analysis
mim, cat(manip) sortorder(zakirid): stset persontime, failure(cvdmort=1) scale(365.25) id(id)
stsplit fu, at(0(1)10) trim

* User-written program to estimate mediation parameters
capture program drop IOW
program IOW, rclass
capture drop loggodds predprob inverseodds weight_iow

*Step 1: run the exposure model
logit sei_father i.edulevel i.sei_own i.smoke alco_risky ib3.physact ib2.diet ib2.bmi_cat ///
fu i.origin age gender mstatus

*Step 2: create inverse odds weights
predict logodds, xb
gen predprob=exp(logodds)/(1+exp(logodds))
gen inverseodds=((1-predprob)/predprob)

gen weight_iow = 1 if sei_father==0
replace weight_iow = inverseodds if sei_father==1

*Step 3: Estimate the total effect (TE)
mim, storebv: glm _d sei_father fu i.origin age gender mstatus, family(poisson) ///
link(log) vce(cluster id) eform nolog base
matrix bb_TE= e(b)
scalar b_TE=bb_TE[1,1]
return scalar b_TE=bb_TE[1,1]

*Step 4:  Estimate the natural direct effect (NDE)
mim, storebv: glm _d sei_father fu i.origin age gender ///
mstatus [pweight= weight_iow], family(poisson) link(log) vce(cluster id) eform nolog base
matrix bb_NDE=e(b)
scalar b_NDE=bb_NDE[1,1]
return scalar b_NDE=bb_NDE[1,1]

*Step 5: calculate the natural indirect effect (NIE)
return scalar b_NIE=b_TE-b_NDE

end

*Step 6: bootstrap to get confidence intervals
bootstrap r(b_NIE) r(b_NDE) r(b_TE), cluster(id) seed(12345) reps(1000): IOW
estat bootstrap, all
```

Supplementary file 2

eTable 2. Gender-stratified mediation of the associations between father's SEP and CVD mortality by social and behavioral risk factors, The Stockholm Public Health Cohort

	Men (n=9075; 349 deaths)	**Women** (n=12 539; 390 deaths)
IOW Approach	IRR (95% CI[4])	IRR (95% CI[4])
Total effect[1]	1.32 (1.09-1.57)	1.17 (0.98-1.42)
Natural direct effect[2]	1.24 (1.00-1.52)	1.06 (0.86-1.31)
Natural indirect effect	1.07 (0.99-1.15)	1.10 (1.03-1.17)
Proportion mediated[5]	27%	64%
Traditional Approach		
Total effect[1]	1.32 (1.09-1.57)	1.17 (0.98-1.42)
Direct effect[3]	1.19 (0.97-1.43)	1.02 (0.84-1.25)
Indirect effect	1. 12 (1.04-1.20)	1.15 (1.07-1.22)
Proportion mediated[5]	48%	88%

Note: SEP = Socio-economic Position; CVD = Cardio-vascular Diseases; IRR = Incidence Rate Ratio; CI = Confidence Interval; IOW= Inverse Odds Weighting

[1]Adjusted for age, country of birth, and marital status.

[2]Obtained by applying the inverse odds weights, in addition to adjusting for age, country of birth, and marital status.

[3]Adjusted for age, country of birth, marital status, and the whole set of mediators.

[4] Percentile-based bootstrap confidence intervals are reported.

[5]The proportion mediated was calculated using the formula: $\{IRR^{NDE}(IRR^{NIE} - 1)/(IRR^{NDE} \times IRR^{NIE} - 1)\}*100$.

Supplementary file 3

eTable 3. Mediation of the associations between father's SEP and CVD mortality by social and behavioral risk factors after excluding the farmers and the self-employed from the group of nonmanual fathers, The Stockholm Public Health Cohort (n=17 417))

IOW Approach	**Mediation by education and adult SEP**	**Mediation by education, adult SEP + behavioral factors**
	IRR (95% CI[4])	IRR (95% CI[4])
Total effect[1]	1.23 (1.08-1.42)	1.23 (1.08-1.42)
Natural direct effect[2]	1.15 (0.97-1.40)	1.12 (0.96-1.32)
Natural indirect effect	1.06 (1.01-1.13)	1.10 (1.03-1.16)
Proportion mediated[5]	32%	48%
Traditional Approach		
Total effect[1]	1.23 (1.07-1.44)	1.23 (1.07-1.44)
Direct effect[3]	1.10 (0.94-1.33)	1.08 (0.93-1.27)
Indirect effect	1. 12 (1.07-1.17)	1.14 (1.08-1.21)
Proportion mediated[5]	57%	65%

Note: SEP = Socio-economic Position; CVD = Cardio-vascular Diseases; IRR = Incidence Rate Ratio; CI = Confidence Interval; IOW= Inverse Odds Weighting

[1]Adjusted for age, gender, country of birth, and marital status

[2]Obtained by applying the inverse odds weights, in addition to adjusting for age, gender, country of birth, and marital status

[3]Adjusted for age, gender, country of birth , marital status, and the mediators of interest.

[4] Percentile-based bootstrap confidence intervals are reported.

[5]The proportion mediated was calculated using the formula: $\{IRR^{NDE} (IRR^{NIE} - 1)/(IRR^{NDE} * IRR^{NIE} - 1)\}*100$.

Supplementary file 4

eTable 4. Proportion of missing observations for each study variable, the Stockholm Public Health Cohort

	Missing	
Study variables	**n**	**%**
Age	0	0
Gender	106	0.5
Country of origin	0	0
Marital status	0	0
Father's SEP	2030	10.0
Educational attainment	69	0.4
Adult SEP	1046	5.3
Smoking	177	0.9
Risky alcohol drinking	928	4.7
Physical activity	771	3.9
Poor diet	421	2.1
Body mass index	460	2.3
Total	**4633**	**23.5**

Supplementary file 5

eTable 5. Distribution of missing and complete data across the study variables, the Stockholm Public Health Cohort

Study variables	Missing data[1]	Complete data[2]	P-value[3]
N (%)	4633 (23.5)	15087 (76.5)	
Age, mean (SD)	61.6 (13.1)	57.2 (11.2)	<0.001
Gender			<0.01
Men	44.9	46.7	
Women	55.1	53.3	
Country of origin			<0.001
Sweden	72.7	84.5	
Nordic	9.6	7.3	
Other	17.7	8.2	
Marital status			
Married	53.7	60.1	
Single/divorced/widowed	46.3	39.9	
Father's SEP			<0.001
Nonmanual	51.9	53.9	
Manual	48.1	46.1	
Educational attainment			<0.001
High	22.1	36.8	
Medium	33.7	38.9	
Low	44.2	24.3	
Adult SEP			<0.001
Nonmanual	53.0	64.4	
Manual	40.6	27.0	
Other	6.4	8.6	
Smoking			<0.001
Never smokers	50.3	46.8	
Current smokers	20.2	17.6	
Former smokers	29.5	35.6	
Risky alcohol drinking			<0.001
No	66.1	78.4	
Yes	33.9	21.6	
Physical inactivity			<0.001
Active	10.1	11.4	
Moderately active	15.8	21.3	
Slightly active	51.4	52.4	
Inactive	22.7	14.9	
Diet (Fruits and berries)			<0.001
More than once a day	19.0	22.9	
Almost daily/a few times a week	66.1	64.4	
Once a week or less	14.9	12.7	
Body Mass Index			<0.001
Underweight	2.0	1.1	
Normal weight	46.7	49.8	
Overweight	38.5	38.6	
Obese	12.8	10.5	

[1]The sample with data missing on any of the study variables. [2]The sample with complete data on all study variables. [3]T-test for age and chi-square test for all categorical variables

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-9*
Bias	9	Describe any efforts to address potential sources of bias	9-11
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7
		(b) Give reasons for non-participation at each stage	6-7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-9; Table 1 in p.20
		(b) Indicate number of participants with missing data for each variable of interest	eTable 4, suppl. 4
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 3 in p.23
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 in p.23
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	eTable 2 in suppl. 2 and eTable 3 in suppl.3
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Early Life Socioeconomic Position and Mortality from Cardiovascular Diseases: An Application of Causal Mediation Analysis in the Stockholm Public Health Cohort

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Title Page

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ABSTRACT

Objective: We aimed to quantify the mediating impact of adult social and behavioral mechanisms in the association between childhood socioeconomic position (SEP) and cardiovascular disease (CVD) mortality by employing a weighting approach to mediation analysis.

Design: Prospective cohort study.

Setting: Stockholm County, Sweden.

Participants: 19 720 individuals who participated in the Stockholm Public Health Cohort survey in 2002 and were older than 40 years.

Primary and secondary outcome measures: The primary outcome was CVD mortality. Non-CVD mortality was additionally analyzed for comparison.

Methods: Study subjects were followed in routine registers from 2002 until 2011 for mortality. Data on father's SEP and adult social and behavioral factors came from questionnaire survey. The inverse odds weighting method was used to estimate the total effect, the natural direct effect (NDE) and the natural indirect effect (NIE) in Poisson regression models. All results were adjusted for gender, age, country of birth, and marital status. Multiple imputation was used to handle missing data.

Results: The total effect of manual versus non-manual father's SEP on CVD mortality was estimated as an incidence rate ratio (IRR) of 1.24 (95% confidence interval [CI]: 1.09-1.41) When the social and behavioral factors were accounted for, the IRR for the NIE was 1.09 (95% CI: 1.04-1.14), suggesting a mediation of 44% of the total effect. As for non-CVD mortality, father's manual SEP was associated with 1.15 fold excess risk (IRR: 1.15; 95% CI: 1.04-1.27) of which the effect represented by the whole set of mediators was 1.06 (95% CI: 1.01-1.10).

Conclusion: Adult social and behavioral factors had a considerable mediating effect on the early life social origin of mortality from CVDs and other causes. Future research employing causal mediation analysis may nevertheless have to consider additional factors for a fuller understanding of the mechanisms.

Keywords: childhood; inverse odds weights; mortality; life course; health behaviors.

Article Summary

Strengths and limitation of this study

- The study used, in a survival context, the inverse odds weighting approach that accommodates multiple mediators of any measurement scale and estimates valid mediation parameters regardless of exposure-mediator and mediator-mediator interactions.
- The use of multiple mediators en bloc means the study findings are robust to the unmeasured common causes of two or more mediators.
- Multiple imputation was used to deal with missing data.
- The mediators, however, were mostly self-reported and assessed at a single point in time.

INTRODUCTION

Epidemiological studies consistently demonstrate an association between childhood socioeconomic position (SEP), often measured by parental occupation or education, and mortality later in life, especially mortality from cardiovascular diseases (CVD) (1–8). The association generally holds true for both men and women and across older and newer generations (1). Furthermore, the burden of CVD risk factors in adulthood such as tobacco smoking, alcohol consumption, physical inactivity, unhealthy diet and body mass index (BMI) has been found to be disproportionately distributed across different strata of the social hierarchies in childhood and adulthood, where people with low SEP show more health-damaging behaviors than those with high SEP (4,5,9,10).

In life course epidemiology, two complementary models are proposed to explain the associations between social environment during childhood and risks of disease and mortality later in life: a pathway model and a critical period model. According to the former, early life circumstances affect health outcomes in adulthood by shaping later exposures operating at different stages across the life span (11,12). Thus, a large body of research have suggested that socioeconomic background in childhood affects adult CVDs and mortality by influencing social trajectories such as education and employment and acting through behavioral risk factors such as smoking and drinking (8,13–15). The critical period model, on the other hand, refers to a time period in life, particularly in early life, during which exposure to a risk factor may have an irreversible effect on subsequent health (16). In line with this hypothesis, several studies have shown that adverse social circumstances in childhood are associated with increased risks of adult CVDs, mortality, and other health outcomes independent of educational attainment, adult social position and other risk factors, implying a latent biological path unexplained by circumstances in adulthood (8,17–21).

Typically, previous studies have examined underlying pathways by controlling for risk factors thought to mediate the associations between exposures and health outcomes (1,5,8,15). The common statistical practice has been to fit and compare two regression models: one model without the mediators and another model adjusting for the mediators. The difference in estimates from the two models is interpreted as the mediated effect, i.e., the effect operating through the mediators. Findings in those studies may suffer from severe biases as they relied on traditional regression models and often violated some of the fundamental assumptions underlying causal mediation analyses. The recent literature on causal inference lists a set of strong assumptions important for the identification of direct and indirect effects: no unmeasured confounding of the exposure-outcome relationship, no unmeasured confounding of the mediator-outcome relationship, no unmeasured confounding of the exposure-mediator relationship, and no intermediate confounding i.e., confounding of the mediator-outcome relationship by a descendent of the exposure (22). These no-confounding assumptions must hold in order for the direct and indirect effects to be causally interpreted. Unfortunately, the mediator-outcome confounding has often been overlooked in the mediation literature based on the traditional regression approach (22–24).

Another major limitation is exposure-mediator interaction in the presence of which the traditional regression method fails to decompose the exposure effect (25–27). An important advance in mediation analysis came with Pearl's (28,29) mediation formula that effectively decomposes the total effect into the sum of the natural direct and indirect effects even when an exposure-mediator interaction is at play. Drawing on the Robins and Greenland's counterfactual framework (25), Pearl's mediation formula makes a causal contrast between two hypothetical worlds: every individual is exposed in one world while no individual is exposed in the other. In both worlds, the mediator is set to a value that each individual would naturally take in the absence of the exposure. The difference in the two hypothetical worlds is interpreted

as the natural direct effect. Similarly, the natural indirect effect is defined by fixing the exposure in both worlds while letting the mediator for each individual vary between the two worlds (28). Although theoretically appealing, the existing counterfactual mediation approach has limited utility since it is not generally suited to multi-categorical, multiple mediator and survival settings (22,30–32).

The current study has the ambition to circumvent some of the afore-mentioned methodological limitations by applying a recently developed weighting approach to mediation analysis (30,31). The aim is to quantify the joint mediation effect of educational attainment, adult social class, and behavioral risk factors in the association between social class in childhood and CVD mortality in adulthood in a population-based cohort in Stockholm, Sweden. To compare with CVD mortality, we additionally analyzed mortality from all causes except CVDs (henceforth non-CVD mortality) with a view to replicating the current evidence that the causes of CVD mortality, such as coronary heart diseases and stroke, are more strongly related to adverse childhood experiences than other causes of death (17,18).

METHODS

Study population

The data were drawn from the Stockholm Public Health Cohort (SPHC), a population-based survey carried out by Statistics Sweden (33). In 2002, a postal questionnaire on health, risk factors, and social circumstances was sent out to 50 000 citizens living in the Stockholm County. The survey was based on an area-stratified random sample of men and women aged 18-84 years. Participants provided informed consent before filling out the self-administered questionnaire, and consent about the future register linkages was also obtained. The response rate was 62%. We chose to exclude the participants who were younger than 40 years (n=11 308

individuals) since deaths resulting from CVD were very rare among them (n=2) and the analysis was computationally demanding. Thus, a total of 19 720 individuals were left for analyses.

Participant involvement

None of the participants were involved in the development of the research question and assessment of the outcome measures, nor were they involved in the overall design and execution of the study. All participants in this study sample were de-identified and we have no possibility to disseminate the findings directly to them.

Measures

Outcomes

The two outcome measures were CVD mortality and non-CVD mortality. Data on mortality were derived from the Cause of Death Register. The study subjects were followed from July 1, 2002 until deaths or the end of the study on December 31, 2011 whichever occurred first. The World Health Organization's 10th Revision of the International Classification of Diseases (ICD) was used to define CVD mortality (ICD codes I00-I99). All other causes of death were classified as non-CVD mortality.

Exposure

The exposure was father's SEP measured by father's occupational social class. Data on father's occupation was retrospectively collected in the baseline survey in 2002. Based on the Swedish socioeconomic classification (34), Statistics Sweden coded the occupational information into the following eight categories: unskilled manual workers; skilled manual workers; non-manual workers at low level; non-manual workers at mid-level; non-manual workers at high level; self-employed; farmers; and unclassifiable. We treated the non-classified as missing observations and dichotomized the remaining categories into non-manual SEP (low, mid and high level non-manual workers, self-employed, and farmers) and manual SEP (unskilled and skilled manual

workers). Since the self-employed and the farmers are in general considered to be advantaged in the Swedish socio-economic context (6), we chose to merge them into the non-manual group.

Mediators

We have used two distinct sets of mediators: i) the social mediators comprising participants' own education and adult SEP measured by own occupation; and ii) the behavioral mediators i.e., smoking, risky drinking, physical inactivity, diet as well as BMI. All mediators were assessed at baseline. We derived information on participants' level of education from Statistics Sweden and classified it into three groups: low (primary schooling); medium (secondary schooling); and high (post-secondary/university education). Adult SEP was measured through the survey questionnaire where the participants were asked to report their current/previous occupation and tasks in as much detail as possible. These responses were later used by Statistics Sweden for the Swedish socioeconomic classification: unskilled manual workers; skilled manual workers; non-manual workers at low level; non-manual workers at mid-level; non-manual workers at high level; and unclassifiable. We categorized adult SEP into three groups: non-manual SEP (low, mid and high level non-manual workers), manual SEP (unskilled and skilled manual workers), and others (unclassifiable).

The measure of smoking was derived from two questions assessing current and former smoking respectively. Current smoking was defined as smoking tobacco daily during the survey and former smoking was defined as smoking tobacco daily for at least 6 months in the past. Participants were also asked to report the average amount of alcohol consumption per week and the frequency of binge drinking. As in a previous study (9), we defined risky drinking as consumption of >168 grams of pure alcohol per week for men and >108 grams of pure alcohol per week for women (high consumption), or consumption of alcohol equivalent to half bottle of spirits/two bottles of wine on a single occasion at least 1 time per month (binge drinking). Physical activity was measured by using the question "How much have you moved/exercised

yourself physically in your leisure time during the past 12 months?" and was coded into 4 levels: active (at least 30 minutes of physical exercise >2 times per week with sweating); moderately active (i.e., at least 30 minutes of physical exercise 1 – 2 times per week with sweating e.g. running, swimming); slightly active (more than 2 hours of physical activity per week without sweating); and inactive (less than 2 hours per week). Diet was assessed by a question "How often do you consume fruits or berries?" and was coded into 3 categories: more than once a day; almost daily/a few times a week; and once a week or less. Body mass index (BMI) was calculated from self-reported height and weight and was conventionally defined as a ratio of weight in kilograms divided by height in meters squared. The BMI score was split into 4 groups: underweight (<18.5); normal weight (18.5 to <25); overweight (25 to <30); and obesity (≥30).

Covariates

The covariates used in the study were age (continuous), gender (men and women), country of birth (Sweden, Nordic, and others), and marital status (married and single/divorced/widowed) of the study subjects. Whereas age, gender and marital status were register-based data and were considered as mediator-outcome confounders, country of birth was measured through the survey questionnaire and was considered as a confounder potentially affecting the exposure-outcome, exposure-mediator and mediator-outcome relationships (Figure 1).

(Figure 1 about here)

Analyses

All analyses were conducted using Stata version 15. We first documented the overall distribution of the study variables and assessed the associations of social and behavioral risk factors with father's SEP by Pearson's chi-square test. Next, we examined the associations between potential mediators and mortality outcomes independent of the exposure. All statistical analyses were carried out in generalized linear models with Poisson family and log link

function. Time since entry was used as the primary time-scale. Based on the participants' dates of entry into and exit from the study, we created "time of follow up" as another covariate to take into account potential time confounding. The underlying time-scale was finely split into years in order to let the mortality rates vary freely over time.

Mediation analysis was performed using the recently proposed Inverse Odds Weighting (IOW) method (30,31,35). It is a counterfactual method that allowed us to decompose the total effect into natural direct and indirect effects without having to fit any model for the mediators. The inverse odds weights were obtained from a working model in which the exposure was regressed on all mediators of interest as well as covariates. Since these weights were used in the direct effect model in lieu of the mediators per se, the mediators remained independent of the exposure. The purpose was to deactivate the potential pathways linking the exposure to the mediators and thus generate valid mediation parameters regardless of the presence of exposure-mediator interactions. The IOW analyses were carried out following the steps and the Stata code as detailed in supplementary file 1.

Drawing on the sequential mediation approach (32), we estimated the joint mediation effect of education and adult SEP in the first step, followed by an estimation of the joint mediation effect of all mediators including the health behaviours in the next step. Within this approach, an ordering is assumed about the causal structure of the mediators to infer the magnitude of path specific mediation effects. Accordingly, we performed the sequential mediation analysis assuming the behavioural mediators to be the causal descendants of the social mediators. For the purpose of comparison, we also used the traditional difference-in-coefficients method (36) to calculate the direct and indirect effects by controlling for the proposed mediators in the Poisson models.

We performed bootstrapping based on 1000 replications to derive confidence intervals (CI) for all mediation parameters. We reported the percentile-based confidence intervals as the percentile method has been demonstrated to be more powerful and valid than other methods in the multiple mediation context (37,38). The estimates were presented as incidence rate ratios (IRR) with 95% CIs. As there was no evidence of effect modification by gender, the main analyses were undertaken for men and women combined. Results from the gender-stratified analyses were moreover reported online in supplementary file 2. Sensitivity analyses were carried out to contrast the results from the full sample with those from the sample excluding the farmers (n=1156) and the self-employed (n=1147) from the non-manual group of fathers (Supplementary file 3).

Missing data

The total proportion of missing observations in our data was 23% with a range from 0% to 12% across the study variables (Supplementary file 4). We used multiple imputation by chained equations to handle the potential selection bias originating from missingness. Under the assumption of missing-at-random (Supplementary file 5), we used Stata's "ice" command to create 25 imputed datasets. In addition to the variables from the analytic models, Nelson-Aalen estimate of the cumulative hazard function as well as other available predictive auxiliary variables (e,g., self-rated health) were included in the imputation model (39). All statistical analyses were repeated using the 25 imputed data sets and the pooled estimates were reported.

RESULTS

The study results were based on 19 720 individuals (54% women) born during 1918-1962 and followed for mortality during 2002-2011. The mean age at baseline was 58.2 years (range 40 – 84) and the mean attained age at the end of follow up was 63.1 years (range 41–94). 82% of the study members were born in Sweden, 8% were born in other Nordic countries (Finland,

Norway, Denmark, and Iceland) and 10% were born outside the Nordic region. During a mean follow-up of 9 years (range 0.37–9.50), a total of 2036 deaths occurred of which 751 were due to CVDs. The proportions of deaths from CVDs and non-CVDs in the sample were 3.8% and 6.5% respectively. Less than half of the sample (46%) had fathers with manual occupations. Table 1 shows the baseline characteristics of both the imputed sample and the sample with complete cases.

(Table 1 here)

Table 2 shows the distribution of the risk factors of CVD mortality by father's SEP. Results indicate that compared to offspring of non-manual fathers, offspring of manual fathers are themselves more likely to attain low education (23% versus 35%, $p<0.001$) and manual occupations (23% versus 39%, $p<0.001$) as adults. The degree of correlation of father's SEP with participants' own SEP in adulthood was 0.24 ($p<0.001$). Similarly, the study subjects whose fathers had a manual occupation showed a more unhealthy behavioral risk profile in terms of adult smoking, risky alcohol drinking, physical inactivity, poor diet as well as overweight and obesity.

(Table 2 here)

In Table 3, we show the associations of each social and behavioral risk factor with CVD mortality and non-CVD mortality estimated on the IRR scale, adjusting for father's SEP and baseline covariates. Overall, all risk factors were found to be associated with both outcomes. However, overweight and obesity did not exhibit any significant association with non-CVD mortality.

(Table 3 here)

The estimated total 'causal effect' as well as the direct and indirect effects of father's SEP on CVD and non-CVD mortality are shown in Table 4. Compared to father's non-manual SEP, manual SEP increased the risk of CVD mortality by 24% (IRR^{TE} 1.24; 95% CI: 1.09-1.41). Formal tests did not yield any effect modification by age (p-value for interaction = 0.391) or gender (p-value for interaction = 0.419). Own education and SEP jointly mediated 29% (IRR^{NIE} 1.06; 95% CI: 1.01-1.11) of the total effect while the whole set of mediators including behavioral risk factors jointly mediated 44% (IRR^{NIE} 1.09; 95% CI: 1.04-1.14). Thus, the magnitude of the mediated effect by the behavioral factors independent of education and adult SEP was (44% - 29%) =15%. Moreover, father's SEP was associated with CVD mortality independent of the adult social mediators (IRR^{NDE} 1.17; 95% CI: 1.00-1.35). The gender-stratified results (supplementary file 2) further indicate that the total mediation effect was larger for women than for men (27% versus 64%).

With regard to non-CVD mortality, the effect of father's manual SEP was 1.15 times higher (95% CI: 1.04-1.27) compared to non-manual SEP. The effect mediated by all social and behavioral intermediates was equivalent to 42% (IRR^{NIE} 1.06: 95% CI: 1.01-1.10) whereas an effect equivalent to 38% (IRR^{NIE} 1.05: 95% CI: 1.02-1.09) was mediated by the two social intermediates, i.e., education and adult SEP. The magnitude of the mediation was generally overestimated by the traditional mediation models when compared to the results from IOW-based models, as evident from Table 4 as well as the online tables in supplementary file 2 and supplementary file 3.

(Table 4 here)

DISCUSSION

The results suggest that a difference by family social class does exist in the risks of both CVD mortality and non-CVD mortality, although the risk of non-CVD mortality tends to be less

strong than that of CVD mortality. Using the IOW method, our study further demonstrates that education and social class position in adulthood together with the behavioral risk factors and BMI account for 44% of the increased risk of CVD mortality among the participants. Almost the same magnitude of mediation was observed in the association between childhood social class and non-CVD mortality. The previous literature investigating the magnitude of mediation has generated inconsistent evidence (8,14,15,19) which partially reflects the difference in methodological approaches and the measurement of the mediators. The observed difference in mediation between men and women in the gender-specific analysis (supplementary file 2) needs to be verified in subsequent studies with larger numbers of CVD death.

The natural indirect effects accounting for over forty percent of the total effects of childhood SEP in our study represent the joint mediation effects carried forward by the social and behavioral risk factors. We did not, however, estimate the indirect effects of individual mediators separately as it may not be an appropriate analytic strategy when the mediators affect one another (22,32). We instead chose to estimate the path-specific indirect effects using the sequential mediation approach (32) which required us to make an additional assumption that the social structural pathway comprising education and adult SEP precedes and impacts the behavioral mediators, although one may argue that the health behaviors are already shaped by family background and personality traits during childhood and adolescence. The findings reveal that the social pathway explained large proportions of the studied associations whereas relatively small proportions were explained by the addition of behavioral mediators, i.e., 15% and 4% for CVD and non-CVD mortality respectively. The findings from the sequential mediation analysis thus point to education and adult SEP as constituting a more powerful set of mediators than smoking, alcohol consumption, unhealthy diet, physical inactivity, and BMI taken together. A qualitatively similar conclusion has been drawn in recent studies examining

the mediating roles of material and behavioral pathways (19,40). Compared to non-CVD mortality, however, the behavioral factors turn out to be more important for CVD mortality.

We also observed a direct effect of childhood SEP on CVD mortality, i.e., an effect that remains after accounting for the socioeconomic indicators and health damaging behaviors measured in adulthood. This finding is in agreement with several earlier studies that documented an increased risk of CVD mortality associated with parental social background even when adulthood circumstances were held constant (8,41). However, the estimated natural direct effect in this study as well as in prior studies requires a cautious interpretation. A majority of the prior literature interpreted the direct effect as a "critical period" effect, thereby defining it as a latent biological pathway unaffected by adult circumstances regardless of the number of adult risk factors considered. Given that we have considered a limited set of social and behavioral mediators, there is room for additional unmeasured mediators or other potentially interlinked mediating pathways (e.g. health conditions in childhood) which, if taken into account, could possibly explain some of the 'direct' effect.

Similar to other mediation approaches, the mediation parameters obtained through the IOW approach rely on the assumptions that there are no unmeasured confounders affecting the exposure-outcome, exposure-mediator and mediator-outcome relationships, and that there are no unmeasured mediator-outcome confounders affected by the exposure. If the models were correctly specified and the no-confounding assumptions held, the IOW-based mediation parameters in our study deserve causal interpretations. Although the bias due to unmeasured confounding cannot be ruled out, the use of the IOW method has offered the current study an advantage over prior research in estimating causally interpretable parameters in the context of multi-mediators and exposure-mediator interactions in the presence of which the traditional mediation framework is often likely to generate biased results (22,42,43).

The traditional regression models presuppose that there are no exposure-mediator or mediator-mediator interactions, although such a presupposition sounds unrealistic given the complexity of the contexts within which diseases and health inequalities emerge. Ignoring interactions, even when the interaction terms are not statistically significant, potentially leads to biased conclusions (22). The main analytic challenge arises due to an exposure-mediator interaction which does not allow decomposing the total effect into direct and indirect effects. We tried to overcome this analytic challenge with the IOW method which is robust to the inherent interaction structure in the data (31). Similar to a previous study using the same method (35), the current study finds that the mediation parameters derived from the traditional regression models are not entirely compatible with those from the IOW models. A general inflation of the mediated effect has been found in traditional models. Since the traditional models require the assumption of no interaction, an inflation or diminution of the extent of mediation may depend on the directions and magnitudes of the underlying exposure-mediator and mediator-mediator interactions. In the absence of such interactions, however, the traditional regression approach to mediation can yield valid estimates.

Limitations and strengths

In common with other weighting approaches, the IOW method works best when the exposure is binary (31,32). This led us to dichotomize father's occupation into manual and non-manual occupations, with the possibility of exposure misclassification particularly due to the inclusion of the farmers and the self-employed in the non-manual group. The sensitivity analyses, however, do not suggest any major bias due to such exposure misclassification since the sample excluding the farmer and self-employed occupational categories produced pretty similar point estimates (Supplementary file 3). Moreover, since the sample was drawn from the population living in the capital city in Sweden, it may not fully represent the general Swedish population. Given the age-heterogeneous sample, there is also a possibility of selection bias due to

participation since the older participants were expected to experience relatively high rate of mortality in childhood. Such selective survival might result in a diminution of the magnitude of the total exposure effect in old ages (44). The survival bias, however, appears to be negligible since we found similar effects of childhood social class across younger and older age groups.

Another concern is the assessment of the mediators at one point in time which may have caused an underestimation of the indirect effects whereas repeated measures of mediators were previously shown to increase the proportion explained (45). However, some of the studied mediators, education and adult SEP for example, are relatively stable over the life course and hence were unlikely to bias the results substantially. A further limitation is the subjective assessment of mediators with a possibility of mediator misclassification which is most likely when the mediator is dichotomized (23). The misclassification of a dichotomous mediator may result in an underestimation of the magnitude of the indirect effect and the consequent overestimation of the direct effect.

Despite these limitations, our study contributes to the growing body of counterfactual-based mediation studies in the context of life course epidemiology. Unlike the typical counter-factual based mediation method, the IOW method has allowed us to implement causal mediation analysis in a time-to-event context relatively easily and offered greater model flexibility in accommodating multiple mediators of mixed scales and relaxing the no-interaction assumptions. Furthermore, as multiple mediators are used en bloc in the IOW method, the estimated natural direct and indirect effects are robust to the unmeasured common causes of two or more mediators (32). This is not necessarily true, however, for the sequential mediation which does not eliminate the need to control for the common causes of two groups of mediators.

Implications and future research

The health consequences of socio-economic disadvantages experienced in childhood can be offset, in principle, by intervening in adult social and lifestyle conditions to the extent that they mediate the disease risks associated with childhood disadvantages. The adult social and behavioral factors, however, do not entirely explain the link between childhood SEP and CVD mortality. Future research employing any causal mediation framework should go beyond the social and behavioral pathways and also consider undertaking gender-specific analysis for a fuller understanding of the mechanisms explaining the early life social origin of CVD mortality. Further methodological innovations are needed in order to gauge the unique ability of each mediator to explain the exposure effect in the presence of correlation between the mediators themselves.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Author Contributions

All authors took part in the design and conception of the study. Hossin performed statistical analyses and wrote the first draft of the manuscript with intellectual inputs from Falkstedt and Koupil. Falkstedt acquired the data and was responsible for the integrity of the data. Both Falkstedt and Koupil guided the analyses and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Ethical Standards

The study was approved by the Regional Ethical Review Board in Stockholm (no. 2013/2204-31/1).

Data Sharing Statement: The authors do not have permission to share the data. However, the data can be accessed through submitting a proposal to the Steering Committee at the Stockholm County Council, Sweden.

Tables

Table 1. Characteristics of the study sample (n=19720), the Stockholm Public Health Cohort

Characteristics	Unimputed data		Imputed Data
	n†	%	%
Gender			
Men	9075	46.3	46.3
Women	10539	53.7	53.7
Country of birth			
Sweden	16125	81.8	!
Nordic	1548	7.8	!
Other	2047	10.4	!
Marital status			
Married	11559	58.6	!
Single/divorced/widowed	8161	41.4	!
Father's SEP			
Nonmanual	9489	53.6	53.4
Manual	8201	46.4	46.6
Educational attainment			
High	6559	33.4	33.4
Medium	7408	37.7	37.7
Low	5684	28.9	28.9
Adult SEP			
Nonmanual	11623	62.2	61.7
Manual	5532	29.6	30.3
Other	1519	8.1	8.0
Smoking			
Never smokers	9301	47.6	47.6
Current smokers	3548	18.1	18.2
Former smokers	6694	34.3	34.2
Risky alcohol drinking			
No	14283	76.0	75.7
Yes	4509	24.0	24.43
Physical inactivity			
Active	2114	11.2	11.1
Moderately active	3819	20.1	19.9
Slightly active	9899	52.2	52.3
Inactive	3117	16.4	16.7
Diet (Fruits and berries)			
More than once a day	4253	22.0	22.0
Almost daily/a few times a	12499	64.8	64.8
Once a week or less	2547	13.2	13.2
Body Mass Index			
Underweight	254	1.3	1.3
Normal weight	9457	49.1	49.0
Overweight	7430	38.6	38.6
Obese	2119	11.0	11.1

†The numbers for certain variables do not add up to 19720 due to missing values.

!Indicates no missing values.
SD = Standard Deviation

Table 2. Distribution of social and behavioral risk factors by father's SEP (n=19720), the Stockholm Public Health Cohort

Social and behavioral risk factors	Father's SEP		P value
	Non-manual	Manual	
	%	%	
Educational attainment			<0.001
High	42.9	22.8	
Medium	34.2	41.8	
Low	22.9	35.4	
Adult SEP			<0.001
Nonmanual	68.3	54.1	
Manual	22.7	38.8	
Other	9.0	7.1	
Smoking			<0.001
Never smokers	49.5	45.4	
Current smokers	16.1	20.5	
Former smokers	34.5	34.1	
Risky alcohol drinking			<0.001
No	77.8	73.4	
Yes	22.2	26.6	
Physical inactivity			<0.001
Active	12.0	10.0	
Moderately active	21.2	18.4	
Slightly active	51.1	53.7	
Inactive	15.6	17.8	
Diet (Fruits and berries)			<0.001
More than once a day	22.9	21.0	
Almost daily/a few times a week	65.1	64.3	
Once a week or less	12.0	14.6	
Body Mass Index			<0.001
Underweight	1.4	1.3	
Normal weight	52.4	45.2	
Overweight	36.6	40.8	
Obese	9.61	12.7	

Note: SEP =Socio-economic Position

Table 3. Associations of social and behavioral risk factors with CVD mortality and non-CVD mortality (n=20720), the Stockholm Public Health Cohort

Social and behavioral risk factors	CVD mortality (751 deaths)			Non-CVD mortality (1285 deaths)		
	No. of events	Crude rates (per 1000)	IRR (95% CI)*	No. of events	Crude rates (per 1000)	IRR (95% CI)*
Educational attainment						
High	66	1.1	1.00	191	3.1	1.00
Medium	153	2.3	1.53 (1.14-2.05)	349	5.1	1.34 (1.12-1.60)
Low	532	11.0	1.71 (1.27-2.29)	743	15.4	1.48 (1.22-1.79)
Adult SEP						
Nonmanual	361	3.4	1.00	688	6.5	1.00
Manual	284	5.7	1.34 (1.15-1.57)	420	8.5	1.15 (1.01-1.31)
Other	18	1.3	0.92 (0.57-1.48)	56	4.0	1.08 (0.82-1.42)
Smoking						
Never smokers	336	4.0	1.00	491	5.8	1.00
Current smokers	128	4.0	1.81 (1.48-2.22)	288	9.0	2.31 (1.99-2.67)
Former smokers	275	4.5	1.37 (1.17-1.61)	492	8.1	1.55 (1.37-1.75)
Risky alcohol drinking						
No	431	3.3	1.00	829	6.4	1.00
Yes	228	5.74	1.44 (1.22-1.71)	376	9.4	1.32 (1.17-1.49)
Physical inactivity						
Active	38	1.9	1.00	94	4.8	1.00
Moderately active	69	1.9	1.13 (0.76-1.68)	129	3.6	0.83 (0.64-1.09)
Slightly active	348	3.9	1.41 (1.02-1.95)	643	7.1	1.17 (0.94-1.45)
Inactive	233	8.7	3.00 (2.14-4.21)	320	11.9	1.99 (1.59-2.51)
Diet (Fruits and berries)						
More than once a day	112	2.9	1.00	215	5.5	1.00
Almost daily/a few times a week	516	4.6	1.39 (1.14-1.71)	836	7.4	1.25 (1.08-1.45)
Once a week or less	100	4.4	1.83 (1.39-2.41)	201	8.8	1.87 (1.54-2.27)
Body Mass Index						
Underweight	24	11.6	1.88 (1.23-2.86)	50	24.2	2.33 (1.72-3.14)

Normal weight	302	3.5	1.00	611	7.1	1.00
Overweight	286	4.2	1.20 (1.03-1.41)	440	6.5	0.89 (0.79-1.00)
Obese	102	5.3	1.66 (1.33-2.07)	149	7.8	1.11 (0.93-1.33)

*Adjusted for father's SEP, age, gender, country of birth, and marital status

Table 4. Mediation of the associations between father's SEP and CVD- and non-CVD mortality by social and behavioral risk factors, the Stockholm Public Health Cohort (Both IOW and traditional methods were used) (n=19720)

	CVD mortality	Non-CVD mortality
Mediation by education and adult SEP		
IOW Approach	IRR (95% CI[4])	IRR (95% CI[4])
Total effect[1]	1.24 (1.09-1.41)	1.15 (1.04-1.27)
Natural direct effect[2]	1.17 (1.00-1.35)	1.09 (0.96-1.21)
Natural indirect effect	1.06 (1.01-1.11)	1.05 (1.02-1.09)
Proportion mediated[5]	29%	38%
Traditional Approach		
Total effect[1]	1.24 (1.09-1.41)	1.15 (1.04-1.27)
Direct effect[3]	1.14 (0.99-1.32)	1.09 (0.96-1.21)
Indirect effect	1. 08 (1.05-1.12)	1.05 (1.03-1.08)
Proportion mediated[5]	39%	38%
Mediation by education, adult SEP + behavioral factors		
IOW Approach		
Total effect[1]	1.24 (1.09-1.41)	1.15 (1.04-1.27)
Natural direct effect[2]	1.13 (0.99-1.30)	1.09 (0.97-1.21)
Natural indirect effect	1.09 (1.04-1.14)	1.06 (1.01-1.10)
Proportion mediated[5]	44%	42%
Traditional Approach		
Total effect[1]	1.24 (1.09-1.41)	1.15 (1.04-1.27)
Direct effect[3]	1.10 (0.96-1.26)	1.08 (0.97-1.20)
Indirect effect	1. 13 (1.08-1.18)	1.07 (1.03-1.10)
Proportion mediated[5]	59%	49%

Note: SEP = Socio-economic Position; CVD = Cardio-vascular Diseases; IRR = Incidence Rate Ratio; CI = Confidence Interval; IOW= Inverse Odds Weighting

[1]Adjusted for age, gender, country of birth, and marital status

[2]Obtained by applying the inverse odds weights in addition to adjusting for age, gender, country of birth, and marital status

[3]Adjusted for age, gender, country of birth , marital status, and the mediators of interest.

[4] Percentile-based bootstrap confidence intervals are reported.

[5]The proportion mediated was calculated using the formula: $\{IRR^{NDE}(IRR^{NIE} - 1)/(IRR^{NDE}IRR^{NIE} - 1)\}*100$.

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Supplementary materials for online publication only

1) Supplementary file 1 displays the procedure and the Stata code for implementing the mediation analysis using inverse odds weights with multiple imputation
2) Supplementary 2 shows the gender-stratified mediation parameters.
3) Supplementary file 3 shows the sensitivity analysis contrasting the results from the full sample with those from the sample excluding the farmer and self-employed occupational categories from father's SEP.
4) Supplementary file 4 shows the proportion of missing observations for each study variable.
5) Supplementary file 5 shows the distribution of missing and complete case data across the study variables.

(Please see supplementary materials in separate PDF files.)

Figure legends

Figure 1: A simple causal diagram of the association between father's socioeconomic position and mortality. Social mediators = own education and adult socioeconomic position; Behavioral mediators = smoking, alcohol drinking, physical inactivity, poor diet, and body mass index; Confounders = country of birth, age, gender, marital status.

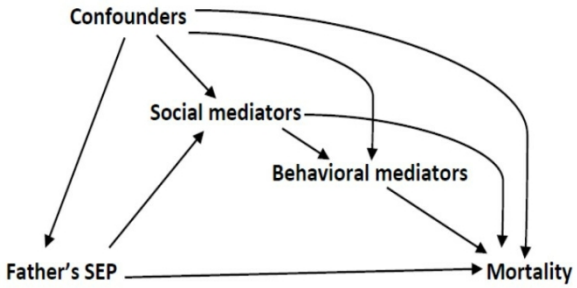

Figure 1: A simple causal diagram of the association between father's socioeconomic position and mortality. Social mediators = own education and adult socioeconomic position; Behavioral mediators = smoking, alcohol drinking, physical inactivity, poor diet, and body mass index; Confounders = country of birth, age, gender, marital status.

108x60mm (300 x 300 DPI)

Supplementary file 1

eTable 1. Procedure of estimating mediation parameters using IOW approach	
Step 1: The working model	An exposure model is run by regressing the exposure on all mediators and covariates using a logistic regression model.
Step 2: Create inverse odds weights	Based on the logistic regression model in step 1, inverse odds weights are created by taking the inverse of the predicted odds for each observation in the exposed group. The exposed and unexposed groups are then reweighted as follows: exposed = inverse odds, unexposed = 1.
Step 3: Total effect model	The total effect of the exposure, conditioning on potential confounders, is estimated by using the Poisson generalized linear model with a log link
Step 4: Direct effect model	The direct effect model is similar to the total effect model but additionally includes the inverse odds weights constructed from the mediators, instead of controlling for the mediators themselves.
Step 5: Compute indirect effect	Building on the traditional difference-in-coefficients approach, the indirect effect is obtained by subtracting the direct effect from the total effect.
Step 6: Estimate standard errors	The standard errors and CIs are obtained by bootstrapping.

Stata code for mediation analysis with inverse odds weights and imputed data

```
cd "\\kifs03.user.ki.se\k9_users$\zakhos\....."
use midata.dta, clear

*Prepare the data for survival analysis
mim, cat(manip) sortorder(zakirid): stset persontime, failure(cvdmort=1) scale(365.25) id(id)
stsplit fu, at(0(1)10) trim

* User-written program to estimate mediation parameters
capture program drop IOW
program IOW, rclass
capture drop loggodds predprob inverseodds weight_iow

*Step 1: run the exposure model
logit sei_father i.edulevel i.sei_own i.smoke alco_risky ib3.physact ib2.diet ib2.bmi_cat ///
fu i.origin age gender mstatus

*Step 2: create inverse odds weights
predict logodds, xb
gen predprob=exp(logodds)/(1+exp(logodds))
gen inverseodds=((1-predprob)/predprob)

gen weight_iow = 1 if sei_father==0
replace weight_iow = inverseodds if sei_father==1

*Step 3: Estimate the total effect (TE)
mim, storebv: glm _d sei_father fu i.origin age gender mstatus, family(poisson) ///
link(log) vce(cluster id) eform nolog base
matrix bb_TE= e(b)
scalar b_TE=bb_TE[1,1]
return scalar b_TE=bb_TE[1,1]

*Step 4:  Estimate the natural direct effect (NDE)
mim, storebv: glm _d sei_father fu i.origin age gender ///
mstatus [pweight= weight_iow], family(poisson) link(log) vce(cluster id) eform nolog base
matrix bb_NDE=e(b)
scalar b_NDE=bb_NDE[1,1]
return scalar b_NDE=bb_NDE[1,1]

*Step 5: calculate the natural indirect effect (NIE)
return scalar b_NIE=b_TE-b_NDE

end

*Step 6: bootstrap to get confidence intervals
bootstrap r(b_NIE) r(b_NDE) r(b_TE), cluster(id) seed(12345) reps(1000): IOW
estat bootstrap, all
```

Supplementary file 2

eTable 2. Gender-stratified mediation of the associations between father's SEP and CVD mortality by social and behavioral risk factors, The Stockholm Public Health Cohort

	Men (n=9075; 349 deaths)	**Women** (n=12 539; 390 deaths)
IOW Approach	IRR (95% CI[4])	IRR (95% CI[4])
Total effect[1]	1.32 (1.09-1.57)	1.17 (0.98-1.42)
Natural direct effect[2]	1.24 (1.00-1.52)	1.06 (0.86-1.31)
Natural indirect effect	1.07 (0.99-1.15)	1.10 (1.03-1.17)
Proportion mediated[5]	27%	64%
Traditional Approach		
Total effect[1]	1.32 (1.09-1.57)	1.17 (0.98-1.42)
Direct effect[3]	1.19 (0.97-1.43)	1.02 (0.84-1.25)
Indirect effect	1. 12 (1.04-1.20)	1.15 (1.07-1.22)
Proportion mediated[5]	48%	88%

Note: SEP = Socio-economic Position; CVD = Cardio-vascular Diseases; IRR = Incidence Rate Ratio; CI = Confidence Interval; IOW= Inverse Odds Weighting

[1]Adjusted for age, country of birth, and marital status.

[2]Obtained by applying the inverse odds weights, in addition to adjusting for age, country of birth, and marital status.

[3]Adjusted for age, country of birth, marital status, and the whole set of mediators.

[4] Percentile-based bootstrap confidence intervals are reported.

[5]The proportion mediated was calculated using the formula: $\{IRR^{NDE}(IRR^{NIE} - 1)/(IRR^{NDE} \times IRR^{NIE} - 1)\}*100$.

Supplementary file 3

eTable 3. Mediation of the associations between father's SEP and CVD mortality by social and behavioral risk factors after excluding the farmers and the self-employed from the group of nonmanual fathers, The Stockholm Public Health Cohort (n=17 417))

IOW Approach	**Mediation by education and adult SEP**	**Mediation by education, adult SEP + behavioral factors**
	IRR (95% CI[4])	IRR (95% CI[4])
Total effect[1]	1.23 (1.08-1.42)	1.23 (1.08-1.42)
Natural direct effect[2]	1.15 (0.97-1.40)	1.12 (0.96-1.32)
Natural indirect effect	1.06 (1.01-1.13)	1.10 (1.03-1.16)
Proportion mediated[5]	32%	48%
Traditional Approach		
Total effect[1]	1.23 (1.07-1.44)	1.23 (1.07-1.44)
Direct effect[3]	1.10 (0.94-1.33)	1.08 (0.93-1.27)
Indirect effect	1. 12 (1.07-1.17)	1.14 (1.08-1.21)
Proportion mediated[5]	57%	65%

Note: SEP = Socio-economic Position; CVD = Cardio-vascular Diseases; IRR = Incidence Rate Ratio; CI = Confidence Interval; IOW= Inverse Odds Weighting

[1]Adjusted for age, gender, country of birth, and marital status

[2]Obtained by applying the inverse odds weights, in addition to adjusting for age, gender, country of birth, and marital status

[3]Adjusted for age, gender, country of birth , marital status, and the mediators of interest.

[4] Percentile-based bootstrap confidence intervals are reported.

[5]The proportion mediated was calculated using the formula: $\{IRR^{NDE} (IRR^{NIE} - 1)/(IRR^{NDE} * IRR^{NIE} - 1)\}*100$.

Supplementary file 4

eTable 4. Proportion of missing observations for each study variable, the Stockholm Public Health Cohort

	Missing	
Study variables	**n**	**%**
Age	0	0
Gender	106	0.5
Country of origin	0	0
Marital status	0	0
Father's SEP	2030	10.0
Educational attainment	69	0.4
Adult SEP	1046	5.3
Smoking	177	0.9
Risky alcohol drinking	928	4.7
Physical activity	771	3.9
Poor diet	421	2.1
Body mass index	460	2.3
Total	**4633**	**23.5**

Supplementary file 5

eTable 5. Distribution of missing and complete data across the study variables, the Stockholm Public Health Cohort

Study variables	Missing data[1]	Complete data[2]	P-value[3]
N (%)	4633 (23.5)	15087 (76.5)	
Age, mean (SD)	61.6 (13.1)	57.2 (11.2)	<0.001
Gender			<0.01
Men	44.9	46.7	
Women	55.1	53.3	
Country of origin			<0.001
Sweden	72.7	84.5	
Nordic	9.6	7.3	
Other	17.7	8.2	
Marital status			
Married	53.7	60.1	
Single/divorced/widowed	46.3	39.9	
Father's SEP			<0.001
Nonmanual	51.9	53.9	
Manual	48.1	46.1	
Educational attainment			<0.001
High	22.1	36.8	
Medium	33.7	38.9	
Low	44.2	24.3	
Adult SEP			<0.001
Nonmanual	53.0	64.4	
Manual	40.6	27.0	
Other	6.4	8.6	
Smoking			<0.001
Never smokers	50.3	46.8	
Current smokers	20.2	17.6	
Former smokers	29.5	35.6	
Risky alcohol drinking			<0.001
No	66.1	78.4	
Yes	33.9	21.6	
Physical inactivity			<0.001
Active	10.1	11.4	
Moderately active	15.8	21.3	
Slightly active	51.4	52.4	
Inactive	22.7	14.9	
Diet (Fruits and berries)			<0.001
More than once a day	19.0	22.9	
Almost daily/a few times a week	66.1	64.4	
Once a week or less	14.9	12.7	
Body Mass Index			<0.001
Underweight	2.0	1.1	
Normal weight	46.7	49.8	
Overweight	38.5	38.6	
Obese	12.8	10.5	

[1]The sample with data missing on any of the study variables. [2]The sample with complete data on all study variables. [3]T-test for age and chi-square test for all categorical variables

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-9*
Bias	9	Describe any efforts to address potential sources of bias	9-11
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7
		(b) Give reasons for non-participation at each stage	6-7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-9; Table 1 in p.20
		(b) Indicate number of participants with missing data for each variable of interest	eTable 4, suppl. 4
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 3 in p.23
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 in p.23
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	eTable 2 in suppl. 2 and eTable 3 in suppl.3
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Correction: *Early life socioeconomic position and mortality from cardiovascular diseases: an application of causal mediation analysis in the Stockholm Public Health Cohort*

Hossin MZ, Koupil I, Falkstedt D. Early life socioeconomic position and mortality from cardiovascular diseases: an application of causal mediation analysis in the Stockholm Public Health Cohort. *BMJ Open* 2019;**9:**e026258. doi: 10.1136/bmjopen-2018-026258.

This article was previously published with errors. Figure 1 and reference 22 have been updated.

BMJ Open 2021;**11**:e026258corr1. doi:10.1136/bmjopen-2018-026258corr1