

Joint effects of alcohol use, smoking and body mass index as an explanation for the alcohol harm paradox: causal mediation analysis of eight cohort studies

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ABSTRACT

Background and aims Lower socio-economic status (SES) is associated with higher alcohol-related harm despite lower levels of alcohol use. Differential vulnerability due to joint effects of behavioural risk factors is one potential explanation for this 'alcohol harm paradox'. We analysed to what extent socio-economic inequalities in alcohol-mortality are mediated by alcohol, smoking and body mass index (BMI), and their joint effects with each other and with SES. **Design** Cohort study of eight health examination surveys (1978–2007) linked to mortality data. **Setting** Finland. **Participants** A total of 53 632 Finnish residents aged 25+ years. **Measurements** The primary outcome was alcohol-attributable mortality. We used income as an indicator of SES. We assessed the joint effects between income and mediators (alcohol use, smoking and BMI) and between the mediators, adjusting for socio-demographic indicators. We used causal mediation analysis to calculate the total, direct, indirect and mediated interactive effects using Aalen's additive hazards models. **Findings** During 1 085 839 person-years of follow-up, we identified 865 alcohol-attributable deaths. We found joint effects for income and alcohol use and income and smoking, resulting in 46.8 and 11.4 extra deaths due to the interaction per 10 000 person-years. No interactions were observed for income and BMI or between alcohol and other mediators. The lowest compared with the highest income quintile was associated with 5.5 additional alcohol deaths per 10 000 person-years (95% confidence interval = 3.7, 7.3) after adjusting for confounders. The proportion mediated by alcohol use was negative (−69.3%), consistent with the alcohol harm paradox. The proportion mediated by smoking and BMI and their additive interactions with income explained 18.1% of the total effect of income on alcohol-attributable mortality. **Conclusions** People of lower socio-economic status appear to be more vulnerable to the effects of alcohol use and smoking on alcohol-attributable mortality. Behavioural risk factors and their joint effects with income may explain part of the alcohol harm paradox.

Keywords Alcohol drinking, alcohol harm paradox, alcohol-related harm, causal mediation analysis, smoking, socio-economic factors.

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Submitted 4 May 2020; initial review completed 29 June 2020; final version accepted 23 December 2020

INTRODUCTION

Harmful alcohol use is a major public health challenge, leading to death and disability world-wide [1]. Lower socio-economic groups experience greater alcohol-related harm [2,3], despite reporting lower or similar levels of alcohol use compared with those of higher socio-economic status (SES) [4]. This discrepancy between alcohol

harm and consumption is known as the alcohol harm paradox [5–7].

The reasons for the alcohol harm paradox are still poorly understood. Differential vulnerability, e.g. due to joint effects of risk factors, is one potential explanation for this paradox [8]. Smoking and obesity are more prevalent in lower socio-economic groups [9–11], which could have synergistic negative effects with alcohol on the

incidence and prognosis of the most common causes of alcohol-attributable mortality [12].

Joint effects of alcohol and body mass index (BMI) have been shown for liver disease [13–16] and gastrointestinal cancers [17–19]. Common biological pathways mediating the impact of alcohol use and obesity on liver disease include oxidative stress, lipotoxicity, hepatocellular inflammation and fibrosis [16,20].

There is evidence of joint effects of smoking and alcohol use on liver enzymes [21] and disease [22], as well as on head and neck cancer [23,24], hepatocellular carcinoma [25] and pancreatic cancer [26]. However, no joint effects have been found for all-cause, cardiovascular and alcohol-related mortality [27,28]. In animal models, alcohol and nicotine interact to potentiate the rewarding effects on the dopamine reward pathway [29], providing a biological basis for comorbidity between alcohol use and smoking and the subsequent joint dependence observed in epidemiological studies [30].

Few studies have examined the role of behavioural risk factors as an explanation for the alcohol harm paradox [31,32]. These studies did not explore the joint effects between behavioural risk factors. In addition, they used traditional mediation analysis (i.e. the ‘change-in-estimate method’), comparing the change in the SES estimate after adjusting for smoking and/or BMI. This method, however, does not allow separation of the effects through the mediator (differential exposure) and through the joint effect between SES and the mediator (differential vulnerability). Disentangling differential exposure and differential vulnerability is important, as they have different policy implications [33].

Another limitation of traditional mediation analysis is that it cannot fully accommodate situations when the exposure (SES) and mediator interact, and have limitations when using non-linear exposures and mediators [34]. Given previous studies suggest a strong interaction between SES and alcohol use [31,35], we used novel methods in causal mediation analysis, which allows overcoming these limitations.

In this study we aim, first, to confirm the existence of joint (interactive) effects between SES and alcohol use; secondly, to examine whether joint effects exist between (a) SES, smoking and BMI and between (b) alcohol and smoking and BMI. Thirdly, assuming that we find evidence of additive interactions between behavioural risk factors and/or between the mediators, we aim to use novel causal mediation analysis to decompose the total effect of income on alcohol-attributable mortality into a direct effect of income on alcohol-attributable mortality, indirect effects through the mediators (differential exposure) and the joint effects of the mediators with income and between mediators (differential vulnerability). This decomposition allows us to quantify the extent to which socio-economic

inequalities in alcohol-attributable mortality are explained by behavioural risk factors and their joint effects with each other and with SES.

METHODS

We followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies [36]. A study protocol (76/2017) was submitted and approved by the Finnish Institute for Health and Welfare Biobank. The protocol is not publicly available, and therefore the results should be considered exploratory.

Setting and design

The design is a prospective cohort study of repeated cross-sectional national health examination surveys in Finland. The study populations were permanent residents in Finland from the Mini-Finland Survey 1978–80, six rounds of the National FINRISK Study from 1982 to 2007 and the Health 2000 Survey. We linked survey data to mortality data with the follow-up from baseline to December 2016 using the unique personal identifier assigned to all Finnish residents.

Participants

Details on the national surveys used in this study can be found elsewhere [37–39]. Briefly, the Mini-Finland Survey (MFS1978–1980) was a nationally representative cross-sectional survey of people aged 30 years and older. The survey was based on a two-stage stratified clustered sampling design. The sampling frame was the Population Register of Statistics Finland, which includes people living in institutions and conscripts. Participants completed a questionnaire at home, which was reviewed by a trained nurse, followed by a health examination by trained nurses and physicians. Data were collected between 1978 and 1980. The participation rate was 90%. The number of participants with complete data analysed here was 7072 [37].

The National FINRISK Study (FINRISK) was a series of representative cross-sectional health surveys from different parts of Finland carried out every 5 years between 1972 and 2012. We used data from 1982 to 2007. The surveys used a stratified random sample design, taking the Population Register of Statistics Finland as the sampling frame. The survey covered three regions of Finland in 1982 and 1987 and five regions in subsequent years. The age range was 25–64 in FINRISK 1982–87 and gradually extended in different regions to 25–74 by 2007. Participants filled in a questionnaire at home, which was reviewed by a trained nurse, followed by a health examination by trained nurses. Participation rates ranged from 82 to 60%, with a

steady decline over time [38]. The number of participants with complete data was 40 400 [38].

The Health 2000 Survey (H2000) was a nationally representative cross-sectional health examination survey of people aged 30 years and older. The survey used a two-stage stratified clustered sampling design. The Population Register of Statistics Finland was used as a sampling frame. Participants underwent an interview at home by trained interviewers, completed a questionnaire at home and participated in a health examination by trained nurses and physicians. Data were collected in 2000–01. Participation rate was 83%. The number of participants with complete data was 6160 [39].

We used a structured protocol to produce comparable indicators for each of the health examination surveys. Details on this harmonization procedure can be found elsewhere [40].

Exposures

We used income as an indicator of SES. We defined income as the total household income per year divided by the number of consumption units (the first adult counts as 1 unit, other adults as 0.7 and children 0.5) and transformed the result into quintiles within surveys.

In sensitivity analyses, we used education as an indicator of SES. We categorized education into three levels (basic, secondary, tertiary) based on the highest educational degree obtained.

Mediators

We examined the role of alcohol use, smoking and BMI as mediators. We measured alcohol use by asking respondents about their average weekly consumption of beer and long drinks, wine and spirits. All surveys had almost identical questions. We converted the number of portions into grams of pure alcohol by multiplying by the average strength. Given the average strength of alcoholic beverages changed over time, we estimated these for each survey year using sales statistics. We created a categorical variable with the following categories drawing upon previous studies [32,41]: never and former drinkers, low intake (> 0 to < 84 g of ethanol per week), moderate intake (men 84 to < 252 g/week; women 84 to < 168 g/week) and high intake (men \geq 252 g/week; women \geq 168 g/week). In sensitivity analyses, we used heavy episodic drinking (HED) as an alternative indicator of alcohol use for a subsample (H2000, FINRISK 2002 and 2007, $n = 18\,475$). We defined HED as the consumption of more than five drinks per drinking occasion and categorized it into four groups: no HED, HED less than once a month, HED more than once a month but less

than once a week and HED once a week or more often (see Supporting information Appendix for details).

We assessed smoking using structured questions on smoking habits. We constructed a categorical variable: never smokers, ex-smokers and current smokers.

We calculated the BMI as the weight (in kg) divided by height (in m) squared. Weight and height were measured by trained nurses using standard methods. We modelled BMI as a categorical variable using the classification of the World Health Organization: < 18.5 underweight, 18.5–24.9 normal, 25–29.9 overweight, \geq 30 obesity [42].

Confounders

We controlled for sex, age at baseline, survey round and marital status as confounders. We defined marital status as those married or cohabiting versus those unmarried, widowed or divorced.

Outcome

The primary outcome was alcohol-attributable mortality (hereafter alcohol mortality). We defined alcohol-attributable mortality as deaths caused by any of the following International Classification of Disease (ICD) codes 100% attributable to alcohol (i.e. population-attributable fraction equal to 1), either as the underlying or a contributory cause of death: ICD-10 F10, G312, G4051, G621, G721, I426, K292, K70, K852, K860, O354 and X45 for accidental poisonings by alcohol; ICD-9: 291, 303, 3050A, 3575A, 4255A, 5353A, 5710A–5713X, 5770D–5770E, 5771C–5771D, 7607A, 7795A, 980; ICD-8: 291, 303, 5710, 577 (only for males) and 980. Contributory causes of death were available and used since 1987 [43].

Statistical methods

For all research questions, we used Aalen additive hazard models to estimate absolute effects and additive interactions [44]. Additive interactions have been argued to be of greater importance than multiplicative interactions for public health and clinical decision-making, as they represent directly the risk differences compared to interactions in multiplicative hazard models [45,46]. We considered a joint effect as a deviation from additivity of the absolute effects, i.e. that the combined effects of two variables are larger than the sum of their individual effects [45].

In additive hazard models, the hazard for the outcome for person i and age t is modelled as a linear function of the explanatory variables plus an unspecified baseline hazard [47]. The effect estimate is a hazard difference interpreted as the number of additional alcohol-attributable deaths per 10 000 person-years at risk in the specific category

compared with a reference category (e.g. highest versus lowest income quintile).

To respond to the first research question, we examined the existence of an income-alcohol additive interaction. For the second research question, we assessed interactions between income and other mediators (i.e. income–smoking and income–BMI) and between mediators (alcohol–smoking and alcohol–BMI). We fitted a model with income (S), the mediator (M) for person i and the interaction term (S × M) [44,47]:

$$\lambda_i(t) = \lambda_0 + \alpha_1 S_i + \alpha_2 M_i + \alpha_3 (S \times M)_i + \beta(t) L_i \quad (1)$$

The coefficients α_1 and α_2 are the separate additive effects; α_3 captures the additive interaction between them; and L_i denotes potential confounders [i.e. age (as time-scale), sex, survey round and marital status]. We also fitted mediator–mediator interactions by including both mediators and their product term. The different interactions were fitted in separate models. To simplify presentation, we restricted the comparison to the lowest versus the highest income quintile (21 440 participants) and compared the highest level of the mediator (high alcohol intake, current smoker and BMI ≥ 30) to the reference level (never or former drinker, never smoker and BMI between 18 and 25).

For the third research question, we used causal mediation analysis based on the potential outcomes framework to carry out a three-way decomposition of the total effect of income (i.e. lowest versus highest income quintile) on alcohol-attributable mortality [48–51]. Specifically, we employed a marginal structural approach method which allows for multiple mediators and income–mediator interactions [52]. The total effect of income on alcohol-attributable mortality (Fig. 1) was decomposed into three components [53,54]: (i) a pure direct effect (PDE) of income on alcohol-attributable mortality; (ii) a

pure indirect effect (PIE) through each mediator M (i.e. differential exposure) and (iii) a mediated interactive effect (INT_{med}) between the mediators and income (i.e. differential vulnerability). The proportion of the total effect of income on alcohol-attributable mortality mediated by each mediator is the sum of the pathways (ii) and (iii). The total effect (TE), which is equivalent to the association between income and alcohol-attributable mortality without mediators and adjusted for covariates (i.e. a minimally adjusted model) is the sum between direct, indirect and mediated interactive effects.

$$TE = PDE + PIE_{M_1} + INT_{med} M_1 + PIE_{M_2} + INT_{med} M_2 + PIE_{M_3} + INT_{med} M_3 \quad (2)$$

More details concerning the structural marginal method can be found in the Supporting information Appendix.

In all models, the time-scale was attained age. We used standard techniques to identify time-varying effects [45,55]. There was an indication of time-varying effects for sex, marital status and alcohol use. Therefore, we modelled sex and marital status as time-varying covariates. To obtain a coefficient, we used a survival model with constant invariant effects for alcohol use and ran sensitivity analyses for four age subgroups, where the time-invariant assumption was met (see Supporting information Appendix for details).

We carried out four sensitivity analyses: (1) stratified analyses by sex, (2) analyses using HED as an alternative indicator of alcohol use, (3) analyses using education as the SES indicator and (4) stratified analysis by duration of follow-up; and (5) stratified analyses by age subgroups. We used the *timereg* package [56] in R version 3.6.3 for all analyses [57]. The R markdown file can be found in the Supporting information Appendix.

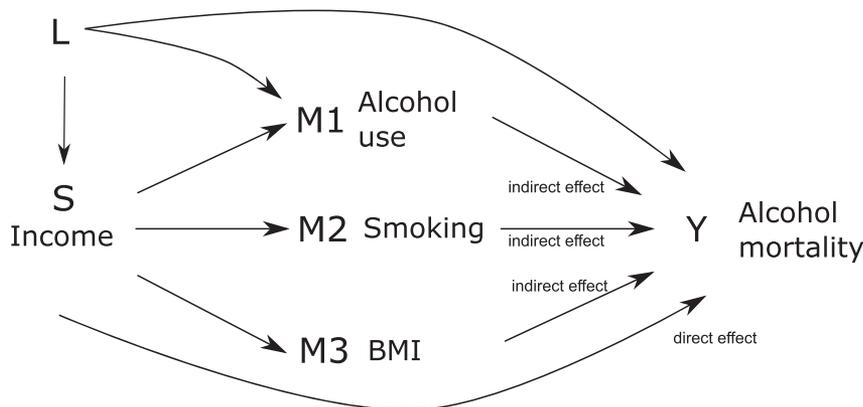


Figure 1 Causal diagram of the relations between income (S), mediators (M1 alcohol use, M2 smoking and M3 BMI), a vector of covariates (L age, sex, survey round and marital status) and the outcome, alcohol mortality (Y). Mediated interactive effects are not depicted in the causal diagram. The total effect is the sum of the direct effect and pure indirect effects and mediated interactive effects. For clarity, arrows between L and M2 and M3 are not drawn. BMI = body mass index

RESULTS

Baseline characteristics of the 53 632 participants can be found in Table 1. During 1 085 839 person-years and a mean follow-up of 20.3 years, we observed 865 alcohol-attributable deaths. Mean age at baseline was 47.9 years and 47.8% of participants were male. Participants in the lowest income quintile had much higher alcohol-attributable mortality than the highest income quintile (11.8 versus 6.9 alcohol-attributable deaths per 10 000 person-years). However, the prevalence of high alcohol intake was lower in the lowest income quintile (3.7%) than in the highest income quintile (7.0%). This indicates the existence of the alcohol harm paradox in our data.

Table 2 shows the results of testing for joint effects between income and behavioural risk factors. We observed joint effects between income and alcohol use and income and smoking. Joint effects of low income and high alcohol intake resulted in 46.8 additional alcohol-attributable deaths per 10 000 person-years [95% confidence interval (CI) = 25.0, 68.6]. Joint effects between low income and smoking resulted in 11.4 extra deaths due to interaction (95% CI = 5.8, 17.0). No

statistically significant interactions were observed between income and BMI or mediator–mediator interactions between alcohol and smoking or alcohol and BMI. Given that we did not find statistically significant mediator–mediator interactions, we did not include them in the causal mediation analysis.

We then proceeded to the causal mediation analysis that enables the decomposition of the total effect of income on alcohol-attributable mortality. The results are shown in Table 3. The total effect of income on alcohol-attributable mortality (i.e. lowest versus highest income quintile, equivalent to a minimally adjusted model) was 5.5 additional alcohol deaths per 10 000 person-years after adjusting for confounders (95% CI = 3.7, 7.3). The proportion mediated by alcohol use was negative (−69.3%), −22.1% of which was attributable to the indirect effect of income through alcohol use (differential exposure) and −47.2% to the mediated interactive effect of income and alcohol use (differential vulnerability). In other words, if a hypothetical intervention brought the level of alcohol use in the lowest income quintile to the level of the highest income quintile (i.e. to 7%), this would result in an increase of 69.3% in alcohol-attributable deaths among those in the lowest income quintile.

Table 1 Baseline characteristics of 53 632 participants in eight cohort studies in Finland (1978–2007) by income quintile

	Income quintiles				
	Lowest	2nd quintile	3rd quintile	4th quintile	Highest
Total participants	10 999	10 974	10 377	10 871	10 411
Mean follow-up, years	18.8	19.3	20.8	21.5	20.9
Alcohol deaths, <i>n</i> (% of all)	244 (28.2)	165 (19.1)	153 (17.7)	152 (17.6)	151 (17.5)
Person-years	206 874	211 492	216 189	233 767	217 517
Death rate ^a	11.8	7.8	7.1	6.5	6.9
Mean age, years (SD)	50.6 (14.9)	49.7 (14.5)	45.7 (12.4)	45.4 (12.0)	47.4 (11.8)
Male, %	44.9	46.6	48.3	47.8	51.6
Alcohol intake					
Mean grams per week	40 (101.2)	45.3 (88.7)	52.6 (93.8)	60.1 (95.4)	75.3 (111.2)
Never and former drinkers, %	57.1	46.8	39.1	33.5	26.4
Low intake, %	29.5	36.5	40.9	43.2	44.5
Moderate intake, %	9.7	13.1	15.9	18.5	22.1
High intake, %	3.7	3.6	4.1	4.8	7
Smoking					
Never smoker, %	54.5	52.7	51.9	52.3	53.8
Ex-smoker, %	18.4	21.5	22.3	21.9	22.7
Current smoker, %	27.1	25.8	25.8	25.8	23.5
Body mass index					
Underweight, %	1.1	0.9	0.7	0.8	0.7
Normal weight, %	36.6	38.2	41.5	43.9	43.5
Overweight, %	37.8	40.0	40.5	39.6	40.5
Obese, %	24.5	20.9	17.2	15.8	15.3
Marital status					
Single, divorced or widowed, %	36.9	31.3	13.7	24.3	24.7

^aDeath rate is per 10 000 person-years. SD = standard deviation.

Table 2 Income–mediator (M) and mediator–mediator additive interactions on alcohol-attributable mortality using Aalen hazard models

Minimally adjusted model plus:	Category	Additional alcohol-attributable deaths per 10 000 person-years	95% CI
Income, alcohol use and interaction term	Lowest versus highest income quintile	0.9	−1.1, 2.8
	High alcohol intake versus never or former drinker	23.1	14.2, 31.8
	Interaction lowest income × high alcohol intake	46.8	25.0, 68.6
Income, smoking and interaction term	Lowest versus highest income quintile	1.2	−0.3, 2.7
	Current smoker versus never smoker	7.7	4.3, 11.0
	Interaction lowest income × current smoker	11.4	5.8, 17.0
Income, BMI and interaction term	Lowest versus highest income quintile	6.6	4.0, 9.2
	Obese versus normal weight	4.1	−0.02, 8.1
	Interaction lowest income × obese	−4.2	−9.8, 1.4
Alcohol use, smoking and interaction term	High alcohol intake versus never or former drinker	28.6	18.0, 39.2
	Current smoker versus never smoker	6.9	4.7, 9.1
	Interaction high alcohol intake × current smoker	12.3	−1.3, 25.9
Alcohol use, BMI and interaction term	High alcohol intake versus never or former drinker	38	28.4, 47.6
	Obese versus normal weight	1.1	−0.6, 2.8
	Interaction high alcohol intake × obese	−0.7	−18.1, 16.7

Data are estimates of the number of additional alcohol-attributable deaths per 10 000 person-years and 95% confidence intervals (CI). Comparison levels: income: lowest versus highest income quintile, alcohol: high alcohol intake (men ≥ 252 g/week; women ≥ 168 g/week) versus never or former drinker; smoking: current smoker versus never smoker; body mass index (BMI): obese (> 30 kg/m²) versus normal weight (18.5–30 kg/m²). ^aMinimally adjusted model is adjusted for age (as time-scale), sex, survey round and marital status.

Table 3 Total, direct, indirect and mediated interactive effects of income on alcohol-attributable mortality after adjusting for covariates

	Additional alcohol-attributable deaths per 10 000 person-years (95% CI)	Proportion explained (%) (95% CI) ^a
Total effect of income ^b	5.5 (3.7, 7.3)	100
Direct effect of income	8.3 (6.0, 10.6)	151.3 (133.5, 177.7)
Indirect effect of income, combined	−2.8 (−3.8, −1.8)	−51.3 (−85.0, −30.9)
Indirect effect, through alcohol use	−1.2 (−2.0, −0.4)	−22.1 (−43.0, −7.3)
Mediated interactive effect, through alcohol use ^c	−2.6 (−3.8, −1.4)	−47.2 (−72.2, −27.3)
Indirect effect, through smoking	0.5 (0.3, 0.7)	9.2 (4.8, 16.2)
Mediated interactive effect, through smoking ^d	0.5 (0.1, 0.8)	8.4 (1.7, 15)
Indirect effect, through BMI	0.4 (0.1, 0.8)	7.9 (1.5, 16.9)
Mediated interactive effect, through BMI ^e	−0.4 (−0.9, 0.1)	−7.4 (−18.9, 1.4)

Model is a marginal structural Aalen additive hazard model adjusted for age (as time-scale), sex, marital status and survey round. ^aProportion explained is the ratio between the effect and the total effect × 100. ^bTotal effect is the sum of direct, individual indirect and mediated interactive effects. ^cMediated through income × alcohol interaction. ^dMediated through income × smoking interaction. ^eMediated through income × body mass index (BMI) interaction.

The proportion mediated by smoking and BMI was 18.1%, 9.2% of which was attributable to the indirect effect of smoking (differential exposure) and 8.4% to the mediated interactive effect of smoking (differential vulnerability). The indirect and mediated effects of obesity were of opposite signs and cancelled each other. All in all, the combined indirect and mediated interactive effect of all three mediators was negative, resulting in −2.8 additional

deaths per 10 000 person-years (95% CI = −3.8, −1.8), which partially masked the direct effect of income on alcohol-attributable mortality (8.3 additional deaths per 10 000 person-years, 95% CI = 6.0, 10.6).

We observed similar patterns in analyses stratified by sex (Supporting information, Table S1), but the effect sizes for women were much smaller. The total effect of low income on alcohol-attributable mortality was 0.5 in women

(95% CI = -1.4, 2.5) and 14.1 in men (95% CI = 9.3, 18.8). The indirect effect was negative for both men and women and masked the direct effect on alcohol-attributable mortality. In a subsample of cohorts with HED measure, we did not observe important differences using HED instead of volume of alcohol use (Supporting information, Table S2). Other sensitivity analyses were consistent with our main analyses and did not change our conclusions (Supporting information, Tables S3–S5).

DISCUSSION

Our study aimed to quantify the extent to which socio-economic inequalities in alcohol mortality are mediated by alcohol, smoking and BMI and their additive income–mediator and mediator–mediator interactions. We confirmed the presence of the alcohol harm paradox and showed the existence of joint effects between the lowest income quintile, on one hand, and alcohol and smoking on the other hand, reflecting differential vulnerability to alcohol use and smoking in people in the lowest socio-economic groups. In contrast, there were no statistically significant interactions between alcohol, smoking and BMI. The causal mediation analysis showed that the proportion explained by smoking, BMI and their additive interactions with income was a relatively small proportion of the total effect of income on alcohol mortality.

Comparison with previous studies

We found evidence of joint effects between SES and alcohol and SES and smoking on alcohol-attributable mortality and no joint effects for SES–BMI. Previous studies have only explored interactions between SES and alcohol use using composite endpoints (i.e. alcohol morbidity and mortality) as outcomes. Our results are in line with a Danish cohort study, which found an additive interaction of similar magnitude between education and alcohol use [55]. In a Scottish cohort study, Katikireddi *et al.* found evidence of a multiplicative interaction between SES and alcohol use [31]. Another study in Scotland did not find interactions between smoking and alcohol on alcohol-attributable causes, although the authors suggested that the statistical power was insufficient due to a lower number of events [27].

We did not find evidence of interactions between alcohol–smoking and alcohol–BMI. In the case of alcohol–smoking, this may have been due to insufficient statistical power, as the confidence intervals were mainly compatible with an additive interaction.

Our causal mediation analysis showed a negative proportion mediated by alcohol use. The interpretation of this negative indirect effect and mediated interactive effect can

be best understood in terms of a hypothetical intervention that would bring the levels of alcohol use to those of the highest income quintile [58,59]. In our case, alcohol use in the lowest income group would increase considerably and their alcohol-attributable mortality would thereby be estimated to increase by almost 70%. Previous studies have observed an increase in the hazard ratio after adjusting for covariates in a nested Cox model. In the study discussed above, Katikireddi *et al.* found an increase in the hazard ratio after adjusting for alcohol use when using income or area-based deprivation, but not education and social class as socio-economic indicators [31]. Similarly, a Swedish study found a very small attenuation in the hazard ratio after adjusting for volume of alcohol use [32]. These findings are equivalent to a negative total indirect effect (PIE + INT_{med}), although in our study we were able to distinguish the proportion explained by the differential exposure and vulnerability (PIE and INT_{med}, respectively).

We found an additive interaction between income and smoking and a positive mediated proportion of the impact of income on alcohol-attributable mortality mediated by smoking. Both aforementioned studies observed attenuations of the hazard ratios after adjusting for smoking [32] and smoking and BMI, but they did not explicitly study interactions between alcohol or SES and these risk factors [31]. Given alcohol use is a necessary cause of alcohol attributable mortality (i.e. the event cannot occur in the absence of alcohol use), the observed mediated effect of smoking on alcohol-attributable mortality could be due to unmeasured harmful drinking, as alcohol use and smoking strongly correlate, or to combined effects that were not captured by the interaction between alcohol and smoking [60].

Strengths and limitations

Major strengths of our study include the large pooled health examination survey data; a relatively high participation rate and a sampling frame that includes people living in institutions and conscripts, which reduces selection bias, and a low risk of misclassification bias in the outcome, as death certificates in Finland are scrutinized rigorously; 31.4% certified with an autopsy [61,62]. The study capitalized on the rapidly evolving literature on causal mediation analysis with survival outcomes [63,64], allowing us to quantify the contribution of each behavioural risk factor and the mediated interactive effect.

Limitations include that, first, we measured risk behaviours at one time-point only. Behaviours may have changed, especially for older surveys with longer follow-up times. Sensitivity analyses using different follow-up times suggested that changes in alcohol use and other risk factors do not greatly impact upon our results. Secondly, we have assumed that SES precedes the

behavioural risk factors, which is explicit in Fig. 1. However, as our data are based on cross-sectional population surveys, we cannot disentangle the temporal precedence of SES and behavioural risk factors. Thirdly, we accounted for drinking patterns only in a subsample and combined never and former drinkers into a single category. The subsample gave similar results, and based on previous research using the same data set the impact of accounting for never and former drinkers on socio-economic differences is likely to be small [40]. Fourthly, we cannot exclude the possibility that the accuracy of our alcohol use estimate differs between SES categories. Fifthly, we used complete case analysis for the data analysis, as we considered multiple imputation unfeasible given the analytical and computational complexity of the analyses. As a result, we excluded 11.1% of the analytical sample, which could potentially bias the estimates.

Finally, the results of the causal mediation analysis are valid under restrictive assumptions of no income–mediator or mediator–outcome confounding [65]. Even though we adjusted for major confounders some residual confounding is likely, e.g. due to adverse childhood experiences [54,66]. The method used assumes that pathways between mediators are not intertwined (i.e. mediators do not affect each other), which was not the case in our data. Further, despite recent methodological developments, Aalen hazard models in the R program's *timereg* package cannot account for complex survey designs, and methods to incorporate time-varying effects are still under development.

Public health implications

The public health implications of our study are twofold. First, the results on interactions show that people in the lowest socio-economic groups are more vulnerable to the effects of alcohol and smokers are also more vulnerable to die from alcohol-attributable causes. Cost-effective universal alcohol and tobacco policies can yield greater benefits to lower socio-economic groups, especially pricing policies [67,68]. Targeted policies to low-income settings could include reducing alcohol and tobacco availability and marketing, together with policies to increase coverage of brief alcohol interventions [69]. Secondly, these results reinforce the need for action on social, commercial, political and environmental determinants of health to address differential vulnerability, rather than focusing solely upon health behaviours [70,71].

CONCLUSIONS

People of lower SES are more vulnerable to the effects of alcohol use and smoking on alcohol-attributable mortality. The indirect effects of alcohol use, smoking and BMI and the joint effects between SES–alcohol and SES–smoking explained a relatively small fraction of the total effect of SES

on alcohol mortality. Future research should explore the role of other mediators, such as access to health care and psychological stress, and include longitudinal data to account for time-dependent effects.

Declaration of interests

None.

Acknowledgements

This work was supported by the Finnish Foundation for Alcohol Studies, Juho Vainio Foundation and the University of Helsinki's Doctoral Programme in Population Health. The authors are thankful to Anne Juolevi, Tuija Jääskeläinen and Harri Rissanen for assistance in obtaining access to the data sets and to Tuomo Nieminen and Jonas Sundman for help with the virtual access to Linux cluster. We are also thankful to Niina Markkula and Victoria Whitaker for comments on an earlier draft of the manuscript.

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References

1. Global Burden of Disease (GBD). 2016 Alcohol Collaborators Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet* 2018; **392**: 1015–35.
2. Probst C., Roerecke M., Behrendt S., Rehm J. Gender differences in socioeconomic inequality of alcohol-attributable mortality: a systematic review and meta-analysis. *Drug Alcohol Rev* 2015; **34**: 267–77.
3. Mackenbach J. P., Kulhanova I., Bopp M., Borrell C., Deboosere P., Kovacs K., et al. Inequalities in alcohol-related mortality in 17 European countries: a retrospective analysis of mortality registers. *PLOS Med* 2015; **12**: e1001909.
4. Peña S., Mäkelä P., Valdivia G., Helakorpi S., Markkula N., Margozzini P., et al. Socioeconomic inequalities in alcohol consumption in Chile and Finland. *Drug Alcohol Depend* 2017; **173**: 24–30.
5. Sadler S., Angus C., Gavens L., Gillespie D., Holmes J., Hamilton J., et al. Understanding the alcohol harm paradox: an analysis of sex- and condition-specific hospital admissions

- by socio-economic group for alcohol-associated conditions in England. *Addiction* 2017; **112**: 808–17.
6. Beard E., Brown J., West R., Angus C., Brennan A., Holmes J., *et al.* Deconstructing the alcohol harm paradox: a population based survey of adults in England. *PLOS ONE* 2016; **11**: e0160666.
 7. Lewer D., Meier P., Beard E., Boniface S., Kaner E. Unravelling the alcohol harm paradox: a population-based study of social gradients across very heavy drinking thresholds. *BMC Public Health* 2016; **16**: 599.
 8. Bellis M. A., Hughes K., Nicholls J., Sheron N., Gilmore I., Jones L. The alcohol harm paradox: using a national survey to explore how alcohol may disproportionately impact health in deprived individuals. *BMC Public Health* 2016; **16**: 111.
 9. Sydén L., Landberg J. The contribution of alcohol use and other lifestyle factors to socioeconomic differences in all-cause mortality in a Swedish cohort. *Drug Alcohol Rev* 2017; **36**: 691–700.
 10. Stringhini S., Sabia S., Shipley M., Brunner E., Nabi H., Kivimaki M., *et al.* Association of socioeconomic position with health behaviors and mortality. *JAMA* 2010; **303**: 1159–66.
 11. Harper S., Lynch J. Trends in socioeconomic inequalities in adult health behaviors among U.S. states, 1990–2004. *Public Health Rep* 2007; **122**: 177–89.
 12. Probst C., Kilian C., Sanchez S., Lange S., Rehm J. The role of alcohol use and drinking patterns in socioeconomic inequalities in mortality: a systematic review. *Lancet Public Health* 2020; **5**: e324–e332.
 13. Carter A. R., Borges M.-C., Benn M., Tybjaerg-Hansen A., Davey S. G., Nordestgaard B. G., *et al.* Combined association of body mass index and alcohol consumption with biomarkers for liver injury and incidence of liver disease: a Mendelian randomization study. *JAMA Netw Open* 2019; **2**: e190305–e190305.
 14. Lau K., Baumeister S. E., Lieb W., Meffert P. J., Lerch M. M., Mayerle J., *et al.* The combined effects of alcohol consumption and body mass index on hepatic steatosis in a general population sample of European men and women. *Aliment Pharmacol Ther* 2015; **41**: 467–76.
 15. Hart C. L., Morrison D. S., Batty G. D., Mitchell R. J., Davey Smith G. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. *BMJ* 2010; **340**: c1240.
 16. Boyle M., Masson S., Anstee Q. M. The bidirectional impacts of alcohol consumption and the metabolic syndrome: cofactors for progressive fatty liver disease. *J Hepatol* 2018; **68**: 251–67.
 17. Yi S.-W., Hong J.-S., Yi J.-J., Ohrr H. Impact of alcohol consumption and body mass index on mortality from nonneoplastic liver diseases, upper aerodigestive tract cancers, and alcohol use disorders in Korean older middle-aged men: prospective cohort study. *Medicine* 2016; **95**: e4876–e4876.
 18. Loomba R., Yang H.-I., Su J., Brenner D., Barrett-Connor E., Iloeje U., *et al.* Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. *Am J Epidemiol* 2013; **177**: 333–42.
 19. Zhao J., Zhu Y., Wang P. P., West R., Buehler S., Sun Z., *et al.* Interaction between alcohol drinking and obesity in relation to colorectal cancer risk: a case-control study in Newfoundland and Labrador, Canada. *BMC Public Health* 2012; **12**: 94.
 20. Mahli A., Hellerbrand C. Alcohol and obesity: a dangerous association for fatty liver disease. *Dig Dis* 2016; **34**: 32–9.
 21. Park E. Y., Lim M. K., Oh J.-K., Cho H., Bae M. J., Yun E. H., *et al.* Independent and supra-additive effects of alcohol consumption, cigarette smoking, and metabolic syndrome on the elevation of serum liver enzyme levels. *PLOS ONE* 2013; **8**: e63439.
 22. Liu P., Xu Y., Tang Y., Du M., Yu X., Sun J., *et al.* Independent and joint effects of moderate alcohol consumption and smoking on the risks of non-alcoholic fatty liver disease in elderly Chinese men. *PLOS ONE* 2017; **12**: e0181497.
 23. Dal M. L., Torelli N., Biancotto E., Di Maso M., Gini A., Franchin G., *et al.* Combined effect of tobacco smoking and alcohol drinking in the risk of head and neck cancers: a re-analysis of case-control studies using bi-dimensional spline models. *Eur J Epidemiol* 2016; **31**: 385–93.
 24. Maasland D. H., van den Brandt P. A., Kremer B., Goldbohm R. A., Schouten L. J. Alcohol consumption, cigarette smoking and the risk of subtypes of head-neck cancer: results from the Netherlands cohort study. *BMC Cancer* 2014; **14**: 187.
 25. Kuper H., Tzonou A., Kaklamani E., Hsieh C.-C., Lagiou P., Adami H.-O., *et al.* Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. *Int J Cancer* 2000; **85**: 498–502.
 26. La Torre G., Sferrazza A., Gualano M. R., De Waure C., Clemente G., De Rose A. M., *et al.* Investigating the synergistic interaction of diabetes, tobacco smoking, alcohol consumption, and hypercholesterolemia on the risk of pancreatic cancer: a case-control study in Italy. *Biomed Res Int* 2014; **2014**: 481019–481019.
 27. Hart C. L., Davey S. G., Gruer L., Watt G. C. The combined effect of smoking tobacco and drinking alcohol on cause-specific mortality: a 30 year cohort study. *BMC Public Health* 2010; **10**: 789.
 28. Xu W.-H., Zhang X.-L., Gao Y.-T., Xiang Y.-B., Gao L.-F., Zheng W., *et al.* Joint effect of cigarette smoking and alcohol consumption on mortality. *Prev Med* 2007; **45**: 313–9.
 29. Hurley L. L., Taylor R. E., Tizabi Y. Positive and negative effects of alcohol and nicotine and their interactions: a mechanistic review. *Neurotox Res* 2012; **21**: 57–69.
 30. Dawson D. A. Drinking as a risk factor for sustained smoking. *Drug Alcohol Depend* 2000; **59**: 235–49.
 31. Katikireddi S. V., Whitley E., Lewsey J., Gray L., Leyland A. H. Socioeconomic status as an effect modifier of alcohol consumption and harm: analysis of linked cohort data. *Lancet Public Health* 2017; **2**: e267–e276.
 32. Sydén L., Sidorchuk A., Mäkelä P., Landberg J. The contribution of alcohol use and other behavioural, material and social factors to socio-economic differences in alcohol-related disorders in a Swedish cohort. *Addiction* 2017; **112**: 1920–30.
 33. Hussein M., Diez Roux A. V., Mujahid M. S., Hastert T. A., Kershaw K. N., Bertoni A. G., *et al.* Unequal exposure or unequal vulnerability? Contributions of neighborhood conditions and cardiovascular risk factors to socioeconomic inequality in incident cardiovascular disease in the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2017; **187**: 1424–37.
 34. Valeri L., Vanderweele T. J. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods* 2013; **18**: 137–50.
 35. Christensen H. N., Diderichsen E., Hvidtfeldt U. A., Lange T., Andersen P. K., Osler M., *et al.* Joint effect of alcohol consumption and educational level on alcohol-related medical events:

- a Danish register-based cohort study. *Epidemiology* 2017; **28**: 872–9.
36. Von Elm E., Altman D. G., Egger M., Pocock S. J., Gøtzsche P. C., Vandenbroucke J. P., et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; **61**: 344–9.
 37. Knekt P., Rissanen H., Järvinen R., Heliövaara M. Cohort profile: the Finnish Mobile clinic health surveys FMC, FMCf and MFS. *Int J Epidemiol* 2017; **46**: 1760.
 38. Borodulin K., Tolonen H., Jousilahti P., Jula A., Juolevi A., Koskinen S., et al. Cohort profile: the national FINRISK study. *Int J Epidemiol* 2017; **47**: 696696–NaN–696i.
 39. Heistaro S. *Methodology Report: Health 2000 Survey*. Helsinki, Finland: National Public Health Institute; 2008.
 40. Peña S., Mäkelä P., Härkönen T., Heliövaara M., Gunnar T., Männistö S., et al. Measurement error as an explanation for the alcohol harm paradox: analysis of eight cohort studies. *Int J Epidemiol* 2020; 10.1093/ije/dyaa113.
 41. Smyth A., Teo K. K., Rangarajan S., O'donnell M., Zhang X., Rana P., et al. Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: a prospective cohort study. *Lancet* 2015; **386**: 1945–54.
 42. World Health Organization (WHO) Physical status: the use and interpretation of anthropometry. Report of a WHO expert committee. *Tech Rep Ser* 1995; **854**: 1–452.
 43. Statistics Finland. Quality Description: Causes of death 2018. 2018. Available at: http://www.stat.fi/til/ksyyt/2018/ksyyt_2018_2019-12-16_jaa_001_en.html (accessed 1 May 2020).
 44. McKeague I. W., Sasieni P. D. A partly parametric additive risk model. *Biometrika* 1994; **81**: 501–14.
 45. Rod N. H., Lange T., Andersen I., Marott J. L., Diderichsen F. Additive interaction in survival analysis: use of the additive hazards model. *Epidemiology* 2012; **23**: 733–7.
 46. Vandenbroucke J. P., Von Elm E., Altman D. G., Gøtzsche P. C., Mulrow C. D., Pocock S. J., et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *PLOS Med* 2007; **4**: e297.
 47. Aalen O., Scheike T. H. Aalen's Additive Regression Model. In: Armitage P., Colton T., editors. *Encyclopedia of Biostatistics*. Hoboken, NJ: Wiley & Sons; 2005; 1–6.
 48. Robins J. M., Hernán M. Á., Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; **11**: 550–60.
 49. Vanderweele T. J. Causal mediation analysis with survival data. *Epidemiology* 2011; **22**: 582–5.
 50. Lange T., Hansen J. V. Direct and indirect effects in a survival context. *Epidemiology* 2011; **22**: 575–81.
 51. Huang Y.-T., Yang H.-I. Causal mediation analysis of survival outcome with multiple mediators. *Epidemiology* 2017; **28**: 370–8.
 52. Lange T., Rasmussen M., Thygesen L. C. Assessing natural direct and indirect effects through multiple pathways. *Am J Epidemiol* 2013; **179**: 513–8.
 53. Vanderweele T. J. A three-way decomposition of a Total effect into direct, indirect, and interactive effects. *Epidemiology* 2013; **24**: 224–32.
 54. Nordahl H., Lange T., Osler M., Diderichsen E., Andersen I., Prescott E., et al. Education and cause-specific mortality: the mediating role of differential exposure and vulnerability to behavioral risk factors. *Epidemiology* 2014; **25**: 389–96.
 55. Nordahl H., Diderichsen E., Hvidtfeldt U. A., Lange T., Andersen P. K., Osler M., et al. Joint effect of alcohol consumption and educational level on alcohol-related medical events: a Danish register-based cohort study. *Epidemiology* 2017; **28**: 872–9.
 56. Scheike T. H., Martinussen T. *Dynamic Regression Models for Survival Data*. New York: Springer; 2006.
 57. R Core Team R: *A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2020.
 58. Diderichsen E., Hallqvist J., Whitehead M. Differential vulnerability and susceptibility: how to make use of recent development in our understanding of mediation and interaction to tackle health inequalities. *Int J Epidemiol* 2018; **48**: 268–74.
 59. Mutlu U., Ikram M. A., Ikram M. K. Clinical interpretation of negative mediated interaction. *Int J Epidemiol* 2018; **48**: 1286–93.
 60. Härkönen J., Aalto M., Suvisaari J., Lintonen T., Mäki-Opas T., Peña S., et al. Predictors of persistence of risky drinking in adults: an 11-year follow-up study. *Eur Addict Res* 2017; **23**: 231–7.
 61. Lehti V., Gissler M., Markkula N., Suvisaari J. Mortality and causes of death among the migrant population of Finland in 2011–13. *Eur J Public Health* 2017; **27**: 117–23.
 62. Statistics Finland. Autopsies and other means to determine cause of death by ground for investigating the cause of death, age, information and year. 2019. Available at: http://pxnet2.stat.fi/PXWeb/pxweb/en/StatFin/StatFin_ter_ksyyt/statfin_ksyyt_pxt_11c1.px/table/tableViewLayout1/ (accessed 21 May 2019).
 63. Lapointe-Shaw L., Bouck Z., Howell N. A., Lange T., Orchanian-Cheff A., Austin P. C., et al. Mediation analysis with a time-to-event outcome: a review of use and reporting in healthcare research. *BMC Med Res Methodol* 2018; **18**: 118.
 64. Lange T., Hansen K. W., Sørensen R., Galatius S. Applied mediation analyses: a review and tutorial. *Epidemiol health* 2017; **39**: e2017035–e2017035.
 65. Vanderweele T. J. Mediation analysis: a Practitioner's guide. *Annu Rev Public Health* 2016; **37**: 17–32.
 66. Kestilä L., Martelin T., Rahkonen O., Joutsenniemi K., Pirkola S., Poikolainen K., et al. Childhood and current determinants of heavy drinking in early adulthood. *Alcohol Alcohol* 2008; **43**: 460–9.
 67. Callinan S., Room R., Dietze P. Alcohol price policies as an instrument of health equity: differential effects of tax and minimum price measures. *Alcohol Alcohol* 2015; **50**: 629–30.
 68. Sassi F., Belloni A., Mirelman A. J., Suhrcke M., Thomas A., Salti N., et al. Equity impacts of price policies to promote healthy behaviours. *Lancet* 2018; **391**: 2059–70.
 69. Mulia N., Schmidt L. A., Ye Y., Greenfield T. K. Preventing disparities in alcohol screening and brief intervention: the need to move beyond primary care. *Alcohol Clin Exp Res* 2011; **35**: 1557–60.
 70. Donkin A., Goldblatt P., Allen J., Nathanson V., Marmot M. Global action on the social determinants of health. *BMJ Glob Health* 2017; **3**: e000603–e000603.
 71. Loring B. *Alcohol and Inequities: Guidance for Addressing Inequities in Alcohol-Related Harm*. Geneva, Switzerland: World Health Organization; 2014.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Total, direct, indirect and mediated interactive effects of income on alcohol-attributable mortality with mediators after adjusting for covariates in 53 632 participants in eight cohort studies in Finland, stratified by sex.

Table S2 Total, direct, indirect and mediated interactive effects of income on alcohol-attributable mortality with mediators after adjusting for covariates, using HED as an alternative measure of alcohol use.

Table S3 Total, direct, indirect and mediated interactive effects of educational level on alcohol-attributable mortality

with mediators after adjusting for covariates in 55 980 participants in eight cohort studies in Finland

Table S4 Total, direct, indirect and mediated interactive effects of income on alcohol-attributable mortality with mediators after adjusting for covariates in 53 632 participants in eight cohort studies in Finland, stratified by duration of follow-up

Table S5 Total, direct, indirect and mediated interactive effects of income on alcohol-attributable mortality with mediators after adjusting for covariates in 53 632 participants in eight cohort studies in Finland, stratified by age subgroups.

R code for submitted manuscript.