

Decomposing the educational gradient in allostatic load across European populations. What matters the most: differentials in exposure or in susceptibility?

Online supplementary methods, tables and figures

Details on the Oaxaca-Blinder decomposition

General description and overall decomposition

In our paper, we used the two-fold Oaxaca-Blinder decomposition [1-2] to disentangle the difference between the average value of a continuous outcome of two groups in the sum of two components, one interpretable in terms of differential exposure, and the other as differential susceptibility. For the purposes of our paper, the Oaxaca-Blinder decomposition offered two attractive features over other mediation analysis decomposition methods, i.e the possibility to look at multiple mediators at the same time, and the detailed decomposition presented in the main text (Table 2a and 2b). This latter is important to identify subgroups at risk for disproportionate allostatic load accumulation, allowing a better understanding of the aggregate differential susceptibility effect.

For people in the low (L) and in the high (H) educational groups, the mean of the Allostatic Load (AL) score can be expressed as a linear function of some characteristics (X; age, smoking and alcohol intake in our case) and can be estimated from linear regression models as:

$$\overline{AL}_L = \bar{X}_L \hat{\beta}_L \text{ and } \overline{AL}_H = \bar{X}_H \hat{\beta}_H$$

where the coefficients $\hat{\beta}_L$ and $\hat{\beta}_H$ represent the effect of X on AL in low and high educated subjects, respectively; and $\bar{X}_L$ and $\bar{X}_H$ represent the vector of mean values for X in each educational group.

Hence, the average difference in AL score between low and high educational classes becomes:

$$\Delta_{AL} = \overline{AL}_L - \overline{AL}_H = \bar{X}_L \hat{\beta}_L - \bar{X}_H \hat{\beta}_H$$

In the two-fold decomposition, we considered high educational group as the reference, i.e. we add and subtract the counterfactual quantity $\bar{X}_H \hat{\beta}_L$, which corresponds to the average AL score that could have been observed in the low educational class if the vector of mean values

of X was the same as in the high educational group. This quantity represents modelling policy-relevant counterfactual intervention scenarios where low-educational class exposure levels are brought to high-educational class levels.

The difference in mean AL score between low and high educational classes becomes:

$$\begin{aligned}\Delta_{AL} &= \overline{AL}_L - \overline{AL}_H = \bar{X}_L \hat{\beta}_L - \bar{X}_H \hat{\beta}_H + \bar{X}_H \hat{\beta}_L - \bar{X}_H \hat{\beta}_L = (\bar{X}_L - \bar{X}_H) \hat{\beta}_L + (\hat{\beta}_L - \hat{\beta}_H) \bar{X}_H \\ &= \widehat{DE} + \widehat{DS}\end{aligned}\quad (1)$$

We used the “oaxaca” command in STATA to estimate $\widehat{DE}$ and $\widehat{DS}$ [3]. The X matrix comprises age (in three groups), study center, smoking (in 5 groups) and alcohol (in 4 groups; see Table 1). In women, we used a three-class variable for alcohol, due to the very low prevalence of individuals drinking 5 or more drinks/day.

Detailed decomposition

Besides the total decomposition described in (1), we were interested into the detailed contribution of age, smoking and alcohol categories to $\widehat{DE}$ and $\widehat{DS}$. Since all variables are categorical, we used the Gardeazabal and Ugidos approach [4] (standard in the “oaxaca” command) to solve the identification problem, i.e. the fact that the $\widehat{DS}$ component changes according to the arbitrary choice of the reference category in the regression model. This approach restricts the coefficients for the single categories to sum to zero, that is, to express effects as deviations from the grand mean. In standard statistical software like SAS, this corresponds to a regression model with an effect coding parametrization.

The values of $\bar{X}_L \hat{\beta}_L$ and $\bar{X}_H \hat{\beta}_H$ used for the detailed Oaxaca-Blinder decomposition in Table 2a (men) and Table 2b (women) of the main text are presented as Supplementary Tables S5 (men) and S6 (women), respectively. For each i -th risk factor category, $\widehat{DE}_i = (\bar{x}_{L,i} - \bar{x}_{H,i}) \hat{\beta}_{L,i}$ and $\widehat{DS}_i = (\hat{\beta}_{L,i} - \hat{\beta}_{H,i}) \bar{x}_{H,i}$. The aggregate $\widehat{DE}$ in formula (1) is the sum of single contributions: $\widehat{DE} = \sum_i \widehat{DE}_i$. The aggregate $\widehat{DV}$ in formula (1) is $\widehat{DS} = \sum_i \widehat{DS}_i + (\hat{\beta}_{L,0} - \hat{\beta}_{H,0})$, where the last term is the difference in the intercepts, and represents a sort of “residual” difference due to “group membership”. Tables 2a and 2b report the aggregate $\widehat{DE}$ and $\sum_i \widehat{DS}_i$ for age, smoking and alcohol intake, while the contribution of the residual term is mentioned in the table footnotes.

Interpretation

From the interpretation viewpoint, given a positive Δ_{AL} , a positive (negative) $\widehat{DE}$ coefficient is the expected reduction (increase) in social gradient in AL score if low educated had, on average, the same levels of risk factors as more highly educated individuals. A positive (negative) $\widehat{DS}$ coefficient is the expected reduction (increase) in social gradient in AL score if the effect of risk factor on AL in low educated was the same as in more highly educated individuals.

Sensitivity analysis

To assess how confounding might have affected our DE/DS estimates, we performed a sensitivity analysis based on simulations. We simulated an unmeasured, continuous confounder U associated with one mediator (smoking, M) as well as with the outcome (allostatic load, AL). Simulations were carried out in our male sample, and under different scenarios based on the combination of values for the U-M correlation (from -0.2 to 0.2) and the U-AL correlation (from -0.40 to 0.40). We applied the OB decomposition including U, age and center as covariate, and estimated DE and DS for smoking, alcohol and their aggregated contribution. The average results over 50 simulation runs are displayed in two Supplementary Material figures, one for DE (Figure S2) and one for DS (Figure S3).

In the figures, the point labelled with “A” [U-M correlation and U-AL correlation = 0] corresponds to the observed estimate for DE (DS) in our study for men (as presented in Table 2a). The remaining points are representing a different simulation scenario (for U-M and U-AL correlation values). The point with the label “B” corresponds to a confounder U with a weak positive correlation with M of 0.1, and a weak positive correlation with AL of 0.1. Based on the paper by Ribeiro et al (5), such a confounder broadly corresponds to neighbourhood socio-economic deprivation. Thus, moving from “A” to “B” gives a sense of the amount of bias in our data due to having neglected a confounder with the same characteristics of neighbourhood deprivation.

The point with the label “C” corresponds to a confounder U with a moderate negative correlation with M of -0.2, and a moderate positive correlation with AL of 0.2. In our data,

such a confounder has the characteristics of age. Thus, moving from “A” to “C” gives a sense of the amount of bias in our data due to having neglected a confounder with the same characteristics of age.

From Figure S2, the DE component is sensitive to the sign and strength of the association between U and M. Thus, by having neglected a confounder with the same characteristics as neighbourhood socio-economic, we may have overestimated the DE component. Conversely, by having neglected a confounder with the same characteristics of age, we may have underestimated the DE component. Figure S3 instead suggests that the DS component is more sensitive to the strength of the association between U and AL, rather than to the correlation between U and M. For confounders with a strength similar to that of age or neighbourhood socio-economic status, the amount of bias is negligible (around 1% of the estimated value).

On line methods references:

1. Blinder A.S. 1973. Wage discrimination: reduced form and structural estimates. *Journal of Human Resources* 8: 436-455
2. Oaxaca R. 1973. Male-female wage differentials in urban labor markets. *International Economic Review* 14:693-709
3. Jann B. 2008 The Blinder-Oaxaca decomposition for linear regression models. *The Stata Journal*;8:453-479
4. Gardeazabal J and Ugidos A 2004. More on the identification in detailed wage decompositions. *Review of Economics and Statistics* 86: 1034-1036
5. Ribeiro AI, Fraga S, Kelly-Irving M, et al. Neighbourhood socioeconomic deprivation and allostatic load: a multi-cohort study. *Sci Rep.* 2019;9(1):8790.

Table S1: Characteristics of the surveyed populations, number of subjects, and percentage of subjects with complete data by educational class

Region	Population	No. of cohorts	Setting	Recruitment period	Part rates	Initial sample size†	Subjects with available data§			
							N	% by education		
								Low	Intermediate	High
Nordic Countries	Northern Sweden (Västerbotten\ Norrbotten Counties)°	6	U/R	1999-09	75%	7780	7162	93.6	91.8	90.7
	East Finland-FINRISK (North Karelia\Kuopio)	1	R	1997	75%	2686	2102	76.1	81.0	78.3
	West Finland-FINRISK (Helsinki\Turku\Loimaa)	1	U	1997	71%	2614	1782	69.3	68.5	67.5
The UK	Northern Ireland (PRIME-Belfast#)	1	U	1991-94	52%	2743	2090	76.7	73.8	78.0
	Scottish Heart Health Extended Cohorts (SHHEC)^	4	U/R	1984-95	70%	14364	12396	85.9	86.1	87.1
Central and South Europe	Germany (MONICA/KORA Augsburg)	1	U/R	1994-95	74%	3778	3447	91.1	93.4	89.8
	Northern Italy (Brianza)	3	U	1986-94	67%	3913	3398	86.8	88.5	85.8
	Southern Italy (Latina)‡	2	R	1993-96	56%	1759	1138	62.1	66.3	65.7
	Southern Italy (Moli-Sani)	1	U/R	2005-10	70%	20511	18376	87.9	89.1	91.1
	Spain (Catalonia)	1	U/R	1986-88	74%	2023	1866	92.8	92.8	91.3
All populations		21	-	-	-	62171	53757	86.2	86.2	87.0

Setting: U = Urban, R = Rural. Part rates: participation rates, computed from responders and invited in every survey of a given population. In case of re-examinations, participation is referred to the initial survey.

°: 3 surveys with baseline visits in 1999, 2004 and 2009; and the 1999 re-examination of 3 additional surveys with original baseline visit in 1986, 1990 and 1994.

#: survey included into the PRIME study. The survey enrolled only men aged 49-60 years at baseline. ^: MONICA Glasgow, MONICA Edinburgh and Scottish Heart Health Study. ‡: re-examination of the original surveys recruited in 1983-87. †: 35-74 years old with data on education. §: data on Allostatic Load score and on covariates of interest

Table S2: Measurement details for the markers involved into the allostatic load score definition.

AL score marker	Where it was measured	Unit	Material	Measurement details
C-Reactive Protein	Local laboratory (lab) for Augsburg; centralized lab for the remaining populations	mg/L	Serum	-
Glucose	Local lab for Belfast; centralized lab for the remaining populations	mmol/L	Serum	Fasting status: Non-fasting specimens in the SHHEC study. Mixture of overnight fasting, 4-hour fasting and non-fasting samples in FINRISK study. Northern Sweden: Approximately 60% of all participants had an over-night fast, the remaining 40% at least 4 hours fasting. Overnight fasting observed in the remaining populations.
HbA1C	Local lab (available only for Augsburg, Brianza and Northern Sweden)	mmol/mol	Whole blood	Relevant for the KORA-Augsburg cohort only.
TC	Local lab for all the populations	mmol/L	Serum/ Plasma[1]	DQA available at: https://www.thl.fi/morgam/a/publications/qa/baseline/chol/cholqa.htm
HDL-C	Centralized lab for Northern Sweden; local lab for the remaining populations	mmol/L	Serum/ Plasma[1]	DQA available at: https://www.thl.fi/morgam/a/publications/qa/baseline/chol/cholqa.htm
Triglycerides	Centralized lab for Northern Sweden; local lab for the remaining populations	mmol/L	Serum/ Plasma[1]	DQA available at: https://www.thl.fi/morgam/a/publications/qa/baseline/chol/cholqa.htm Fasting status: Non-fasting specimens in the SHHEC study. Mixture of overnight fasting, 4-hour fasting and non-fasting samples in FINRISK study. Northern Sweden: Approximately 60% of all participants had an over-night fast, the remaining 40% at least 4 hours fasting. Overnight fasting observed in the remaining populations.
Blood pressure (systolic and diastolic)	Local measurement	mmHg	NA	Blood pressure was measured after 2-5 minutes rest while sitting, using a standard or random zero mercury sphygmomanometer or an automated oscillometric device. With the exception of Belfast (one measure only), two consecutive measurements were available, and the average was used as the study variable for systolic and diastolic blood pressure.
Body Mass Index	Local measurement of height and weight	Kg/m2	NA	We computed the Body Mass Index Quetelet index from measured height and weight.

Local: measurements performed locally by each population Centralized: measurements performed in the MORGAM/BiomarCaRE consortium laboratory. The laboratory was firstly located at the Johannes Gutenberg University, Mainz, and then moved at the University Heart Center, Hamburg. DQA = Data Quality Assessment [1]: plasma measure only for the Northern Ireland cohort

Table S3: Association between smoking and alcohol intake with allostatic load. Men (left) and women (right), 35-74 years old at baseline

	Men		Women	
	Change in AL (95%CI)	p-value^	Change in AL (95%CI)	p-value^
Smoking				
<i>Never smokers</i>	ref		ref	
<i>Former smokers</i>	0.68 (0.57; 0.79)		-0.09 (-0.23; 0.03)	
<i>1-10 cigs/day</i>	0.24 (0.04; 0.44)	<.0001	-0.59 (-0.76; -0.42)	<.0001
<i>11-20 cigs/day</i>	0.48 (0.33; 0.63)		0.23 (0.06; 0.39)	
<i>>20 cigs/day</i>	1.20 (0.99; 1.40)		1.13 (0.77; 1.49)	
Alcohol intake				
<i>0 (Teetotallers)</i>	0.11 (-0.02; 0.24)		0.64 (0.55; 0.74)	
<i>1-2 drinks/day</i>	ref		ref	
<i>3-4 drinks/day</i>	0.05 (-0.07; 0.17)	0.001	0.10 (-0.12; 0.32)	0.001
<i>5 or more</i>	0.49 (0.25; 0.72)		1.79 (0.17; 3.41)	

Change in AL estimated from gender-specific linear regression model adjusting for age, center, educational class.

^: Likelihood ratio chi-square test for heterogeneity (4 df for smoking, 3 df for alcohol intake)

Table S4: Details of the Oaxaca-Blinder Decomposition of the metabolic system sub-score difference between low and high education, for smoking and alcohol intake. Men, 35-74 years old at baseline

	Differential Exposure				Differential Susceptibility			
	Absolute ¹	95%CI		Relative [^] (%)	Absolute ²	95%CI		Relative [^] (%)
Smoking	0.010	-0.006	0.026	2.7	0.153	0.077	0.229	41.8
<i>Never smokers</i>	0.014	0.004	0.024	3.8	0.123	0.064	0.182	33.5
<i>Former smokers</i>	-0.004	-0.007	0.000	-1.0	0.066	0.011	0.121	17.9
<i>1-10 cigs/day</i>	-0.002	-0.005	0.000	-0.7	0.003	-0.012	0.019	0.8
<i>11-20 cigs/day</i>	-0.007	-0.015	0.001	-2.0	-0.024	-0.045	-0.003	-6.5
<i>>20 cigs/day</i>	0.010	0.003	0.016	2.6	-0.014	-0.027	-0.002	-3.9
Alcohol intake	-0.016	-0.031	-0.002	-4.5	0.101	0.005	0.197	27.5
<i>0 (Teetotallers)</i>	0.008	0.004	0.013	2.2	0.033	0.002	0.064	9.0
<i>1-2 drinks/day</i>	-0.011	-0.021	-0.002	-3.1	0.087	0.010	0.164	23.7
<i>3-4 drinks/day</i>	-0.006	-0.010	-0.002	-1.7	-0.011	-0.053	0.031	-3.1
<i>5 or more</i>	-0.007	-0.014	0.000	-1.9	-0.008	-0.016	0.000	-2.2
Aggregate contribution*	-0.007	-0.027	0.014	-1.8	0.254	0.137	0.371	69.3

[^]: Ratio between the absolute coefficient and the un-adjusted mean difference in AL score between low and high education [0.37; 95%CI: 0.29; 0.44].

*: The difference in educational class intercepts accounts for a residual 27%. Age and center account for 5.4%. All totaling 100%

1: a positive (negative) coefficient is the expected reduction (increase) in social gradient in AL score if low educated had on average, the same prevalence of risk factors as high educated men

2: a positive (negative) coefficient is the expected reduction (increase) in social gradient in AL score if the effect of risk factor on AL in low educated men was the same as in high educated men

In bold: results supporting statistical significance.

Table S5: Aggregate contribution of smoking and alcohol intake to the Oaxaca-Blinder Decomposition of Allostatic Load score (total and sub-scores) difference between low and intermediate education. Men (above) and women (below), 35-74 years old at baseline

		Differential Exposure			Differential Susceptibility		
	Δ ED (95%CI)	Absolute ¹	95%CI		Absolute ²	95%CI	
Men							
Cardiovascular system	-0.01 (-0.06; 0.05)	0.00	-0.01	0.01	-0.01	-0.07	0.06
Metabolic system	0.05 (-0.04; 0.13)	-0.01	-0.02	0.00	0.08	-0.02	0.19
Inflammation	0.02 (-0.01; 0.05)	0.02	0.01	0.02	0.01	-0.02	0.05
Allostatic Load score	0.06 (-0.06; 0.18)	0.01	-0.01	0.02	0.09	-0.05	0.24
Women							
Cardiovascular system	0.04 (-0.01; 0.10)	-0.02	-0.03	-0.01	0.03	-0.07	0.14
Metabolic system	0.34 (0.25; 0.43)	0.05	0.04	0.07	0.09	-0.07	0.26
Inflammation	0.08 (0.05; 0.11)	0.02	0.01	0.02	-0.02	-0.08	0.04
Allostatic Load score	0.47 (0.34; 0.60)	0.05	0.03	0.07	0.10	-0.14	0.35

1: a positive (negative) coefficient is the expected reduction (increase) in social gradient in AL score if low educated had on average, the same prevalence of risk factors as individuals in the intermediate education

2: a positive (negative) coefficient is the expected reduction (increase) in social gradient in AL score if the effect of risk factor on AL in low educated individuals was the same as in individuals in the intermediate education class

Cardiovascular system: systolic and diastolic BP

Metabolic system: Body Mass Index, Total cholesterol, HDL-cholesterol, triglycerides, glucose

Inflammation: CRP

Δ ED = un-adjusted mean difference in Allostatic Load score between low and high education, with 95% confidence intervals.

In bold: results supporting statistical significance.

Table S6: Aggregate contribution of smoking and alcohol intake to the Oaxaca-Blinder Decomposition of Allostatic Load score difference between low and high education, in subgroups characterized by presence of obesity, elevated blood pressure, diabetes and cardiovascular disease. Men (above) and women (below), 35-74 years old at baseline

	N	ΔED (95%CI)	Differential Exposure				Differential Susceptibility			
			Absolute ¹	95%CI	Relative [^] (%)	Absolute ²	95%CI	Relative [^] (%)		
Men										
Obese	955	0.48 (-0.09; 1.05)	0.05	-0.09	0.19	11.3	0.15	-0.95	1.26	31.7
Elevated blood pressure	9959	0.45 (0.31; 0.59)	0.02	-0.02	0.05	3.5	0.23	0.02	0.44	51.1
Positive history of diabetes	4163	0.11 (-0.10; 0.32)	0.05	0.01	0.09	45.0	0.15	-0.17	0.47	132.5
Positive history of CVD	1156	0.84 (0.37; 1.31)	-0.11	-0.23	0.01	-12.8	1.11	0.09	2.13	131.9
Women										
Obese	730	2.34 (1.64; 3.04)	0.24	0.01	0.47	10.4	1.30	-0.43	3.04	55.7
Elevated blood pressure	8294	0.92 (0.76; 1.08)	0.07	0.03	0.11	7.8	0.15	-0.21	0.50	15.9
Positive history of diabetes	4842	0.39 (0.19; 0.59)	0.09	0.05	0.14	23.9	0.13	-0.31	0.56	32.0
Positive history of CVD	451	1.04 (0.17; 1.91)	-0.06	-0.31	0.18	-6.0	1.10	-1.26	3.46	105.6

1: a positive (negative) coefficient is the expected reduction (increase) in social gradient in AL score if low educated had on average, the same prevalence of risk factors as high educated individuals.

2: a positive (negative) coefficient is the expected reduction (increase) in social gradient in AL score if the effect of risk factor on AL in low educated individuals was the same as in high educated individuals.

Δ ED = un-adjusted mean difference in Allostatic Load score between low and high education.

[^]: Ratio between the absolute coefficient and the un-adjusted mean difference in AL score between low and high education (Δ ED)

In bold: results supporting statistical significance.

Table S7: Mean values ($\bar{X}$) and regression coefficients ($\hat{\beta}$) with standard errors used to derive the detailed Oaxaca-Blinder decomposition of allostatic load score in men (Table 2a in the main text)

	Low Education			High education			OBD coefficients	
	$\bar{X}_L$	$\hat{\beta}_L$	SE($\hat{\beta}_L$)	$\bar{X}_H$	$\hat{\beta}_H$	SE($\hat{\beta}_H$)	DE	DS
Mean AL score		0.2617			-0.4205			
Intercept	-	0.12	0.08	-	-0.189	0.090	-	0.31
Age								
35-44 years	0.24	-0.98	0.063	0.25	-1.214	0.062	0.006	0.059
45-54 years	0.31	0.20	0.06	0.35	0.282	0.056	-0.009	-0.030
55-74 years	0.45	0.78	0.05	0.40	0.933	0.055	0.039	-0.062
Study Center								
Northern Sweden	0.14	0.12	0.12	0.13	0.099	0.120	0.001	0.003
FINRISK	0.06	0.27	0.16	0.07	-0.114	0.143	-0.003	0.028
UK-Belfast	0.06	-0.21	0.16	0.08	-0.552	0.142	0.004	0.027
SHHEC	0.29	0.00	0.10	0.17	0.057	0.105	0.000	-0.009
MONICA/KORA	0.06	0.19	0.16	0.06	-0.031	0.154	0.000	0.014
Brianza	0.08	0.09	0.14	0.05	0.263	0.170	0.003	-0.008
Latina	0.01	-0.47	0.40	0.01	-0.071	0.365	0.001	-0.004
Moli-sani	0.27	0.09	0.10	0.40	0.084	0.085	-0.011	0.002
Catalonia	0.03	-0.08	0.22	0.03	0.264	0.200	0.000	-0.012
Smoking								
Never smokers	0.31	-0.35	0.08	0.40	-0.715	0.076	0.032	0.147
Former smokers	0.37	0.23	0.072	0.38	0.064	0.076	-0.004	0.065
1-10 cigs/day	0.07	-0.25	0.12	0.06	-0.547	0.134	-0.003	0.018
11-20 cigs/day	0.17	-0.11	0.09	0.11	0.120	0.108	-0.007	-0.025
>20 cigs/day	0.08	0.48	0.12	0.05	1.078	0.152	0.017	-0.028
Alcohol intake								
0 (Teetotallers)	0.21	-0.031	0.081	0.18	-0.143	0.096	-0.001	0.020
1-2 drinks/day	0.43	-0.08	0.07	0.53	-0.259	0.081	0.008	0.094
3-4 drinks/day	0.29	-0.16	0.07	0.27	-0.173	0.088	-0.005	0.002
5 or more	0.06	0.28	0.12	0.03	0.575	0.187	0.011	-0.008
Adj R-squared		0.04			0.06		-	-

Difference in mean AL score: $0.2617 - (-0.4205) = 0.6822$

Aggregate OBD components, smoking and alcohol: $\bar{DE} = \sum_i \widehat{DE}_i = (0.076 + 0.076 + \dots + 0.187) = 0.048$

; $\bar{DS} = \sum_i \widehat{DS}_i = (0.032 - 0.004 + \dots - 0.011) = 0.286$;

Residual and confounders (age, center): $(\hat{\beta}_{L,0} - \hat{\beta}_{H,0}) + \sum_{age} (\bar{X}_{L,age=i} - \bar{X}_{H,age=i}) * \hat{\beta}_{L,age=i} +$

$\sum_{age} (\hat{\beta}_{L,age=i} - \hat{\beta}_{H,age=i}) * \bar{X}_{H,age=i} + \sum_{center} (\bar{X}_{L,center=j} - \bar{X}_{H,center=j}) * \hat{\beta}_{L,center=j} +$

$\sum_{center} (\hat{\beta}_{L,center=j} - \hat{\beta}_{H,center=j}) * \bar{X}_{H,center=j} = 0.348$

Overall OBD: $0.048 + 0.286 + 0.348 = 0.6822$

Table S8: Mean values ($\bar{X}$) and regression coefficients ($\hat{\beta}$) with standard errors used to derive the detailed Oaxaca-Blinder decomposition of allostatic load score in women (Table 2b in the main text)

	Low Education			High education			OBD coefficients	
	$\bar{X}_L$	$\hat{\beta}_L$	SE($\hat{\beta}_L$)	$\bar{X}_H$	$\hat{\beta}_H$	SE($\hat{\beta}_H$)	DE	DS
Mean AL score		0.6646			-0.8553			
Intercept	-	0.29	0.08	-	-0.913	0.098	-	1.20
Age								
35-44 years	0.25	-2.29	0.061	0.29	-2.437	0.059	0.082	0.043
45-54 years	0.35	0.06	0.06	0.34	0.051	0.057	0.001	0.002
55-74 years	0.39	2.23	0.06	0.37	2.386	0.057	0.047	-0.057
Study Center								
Northern Sweden	0.12	-0.28	0.12	0.14	-0.188	0.111	0.004	-0.013
FINRISK	0.06	0.23	0.15	0.08	0.293	0.136	-0.005	-0.005
SHHEC	0.32	0.12	0.09	0.18	0.053	0.102	0.018	0.012
MONICA/KORA	0.06	-0.26	0.15	0.06	-0.251	0.148	0.001	-0.001
Brianza	0.08	0.25	0.13	0.06	-0.034	0.159	0.006	0.016
Latina	0.03	-0.67	0.22	0.03	-0.670	0.203	0.004	0.000
Moli-sani	0.30	0.30	0.09	0.42	0.117	0.078	-0.036	0.079
Catalonia	0.03	0.30	0.22	0.04	0.678	0.184	-0.004	-0.015
Smoking								
Never smokers	0.59	-0.03	0.08	0.59	-0.208	0.098	0.000	0.103
Former smokers	0.14	-0.12	0.103	0.22	-0.241	0.111	0.009	0.026
1-10 cigs/day	0.10	-0.75	0.12	0.10	-0.568	0.133	0.000	-0.017
11-20 cigs/day	0.14	0.00	0.10	0.08	0.208	0.139	0.000	-0.017
>20 cigs/day	0.03	0.90	0.19	0.01	0.808	0.309	0.016	0.001
Alcohol intake								
0 (Teetotallers)	0.50	0.353	0.075	0.39	0.398	0.074	0.037	-0.017
1-2 drinks/day	0.46	-0.30	0.08	0.55	-0.227	0.072	0.029	-0.040
3+ drinks/day	0.05	-0.05	0.13	0.06	-0.172	0.119	0.000	0.006
Adj R-squared		0.18			0.20		-	-

Difference in mean AL score: $0.6646 - (-0.8553) = 1.5199$

Aggregate OBD components, smoking and alcohol: $\widehat{DE} = \sum_i \widehat{DE}_i = (0.098 + 0.111 + \dots + 0.119) = 0.092$

; $\widehat{DS} = \sum_i \widehat{DS}_i = (0.000 + 0.009 + \dots + 0.000) = 0.044$;

Residual and confounders (age, center): $(\hat{\beta}_{L,0} - \hat{\beta}_{H,0}) + \sum_{age} (\bar{X}_{L,age=i} - \bar{X}_{H,age=i}) * \hat{\beta}_{L,age=i} +$

$\sum_{age} (\hat{\beta}_{L,age=i} - \hat{\beta}_{H,age=i}) * \bar{X}_{H,age=i} + \sum_{center} (\bar{X}_{L,center=j} - \bar{X}_{H,center=j}) * \hat{\beta}_{L,center=j} +$

$\sum_{center} (\hat{\beta}_{L,center=j} - \hat{\beta}_{H,center=j}) * \bar{X}_{H,center=j} = 1.384$

Overall OBD: $0.092 + 0.044 + 1.38 = 1.5199$

Figure S1: Distribution of Allostatic Load score by population and gender.

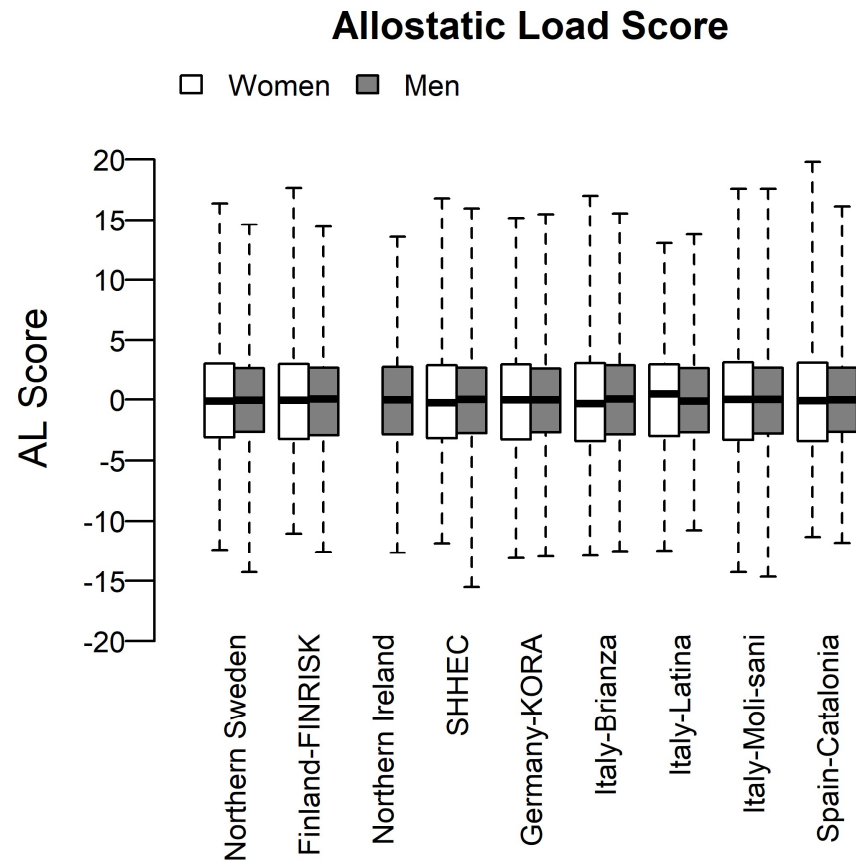
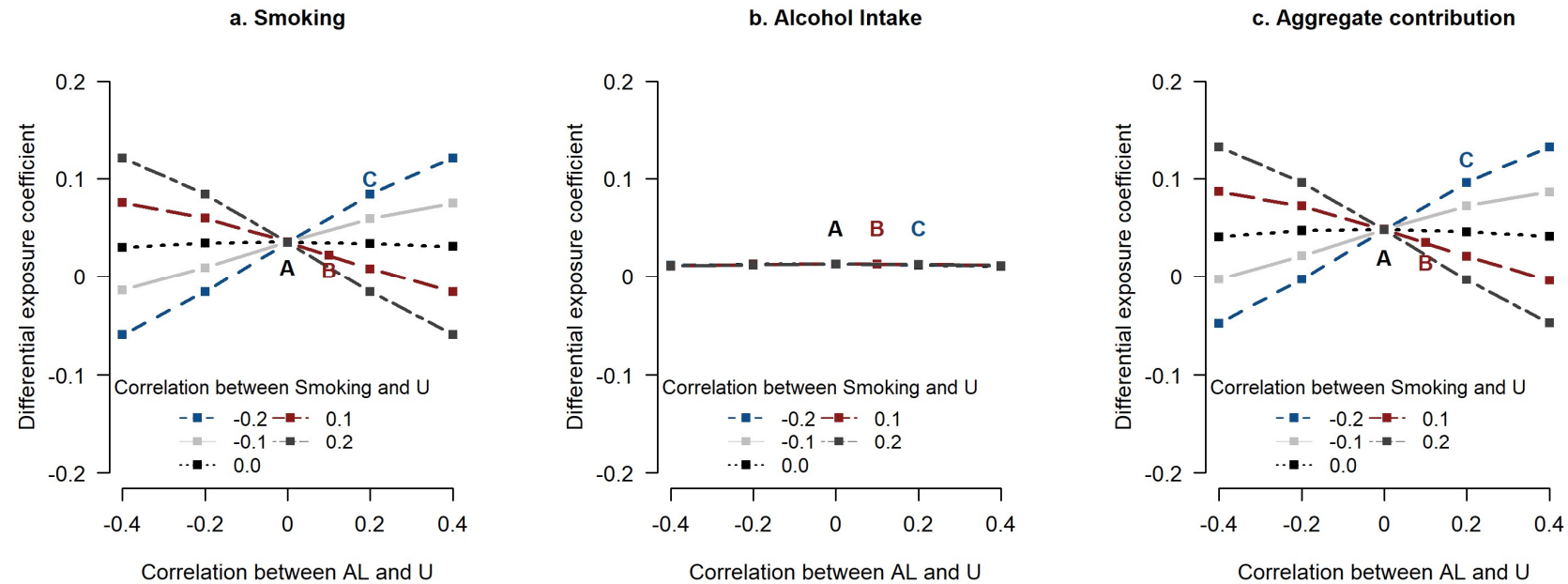


Figure S2: Sensitivity analysis for the *differential exposure* component

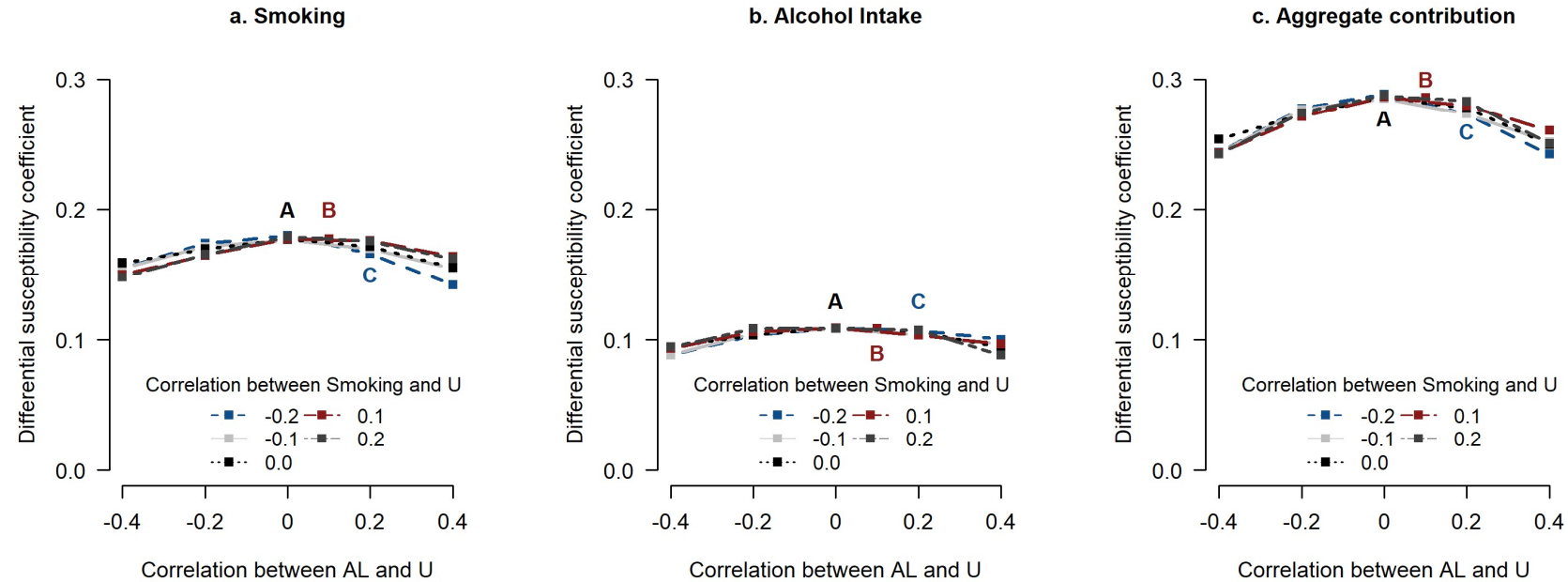


The point labelled with “A” is the observed estimate for DE in our study for men (as presented in Table 2a). The remaining points are representing a different simulation scenario (for U-M and U-AL correlation values).

The point with the label “B” corresponds to a confounder U with a weak positive correlation with M, and a weak positive correlation with AL. Based on the paper by Ribeiro et al (5), such a confounder broadly corresponds to neighborhood socio-economic deprivation. Thus, moving from “A” to “B” gives a sense of the amount of bias in our data due to having neglected a confounder with the same characteristics of neighborhood deprivation.

The point with the label “C” corresponds to a confounder U with a moderate negative correlation with M, and a moderate positive correlation with AL. In our data, such a confounder has the characteristics of age. Thus, moving from “A” to “C” gives a sense of the amount of bias in our data due to having neglected a confounder with the same characteristics of age.

Figure S3: Sensitivity analysis for the *differential susceptibility* component



The point labelled with “A” is the observed estimate for DS in our study for men (as presented in Table 2a). The remaining points are representing a different simulation scenario (for U-M and U-AL correlation values).

The point with the label “B” corresponds to a confounder U with a weak positive correlation with M, and a weak positive correlation with AL. Based on the paper by Ribeiro et al (5), such a confounder broadly corresponds to neighborhood socio-economic deprivation. Thus, moving from “A” to “B” gives a sense of the amount of bias in our data due to having neglected a confounder with the same characteristics of neighborhood deprivation.

The point with the label “C” corresponds to a confounder U with a moderate negative correlation with M, and a moderate positive correlation with AL. In our data, such a confounder has the characteristics of age. Thus, moving from “A” to “C” gives a sense of the amount of bias in our data due to having neglected a confounder with the same characteristics of age.