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Supplementary file

Supplementary File

I. Statistical Methods

IA. Details about multiplicative analysis

IB. Details about longitudinal analyses

II. Supplementary Tables

Supplementary Table 1

Supplementary Table 2

I. Statistical methods

IA. Multiplicative analysis

In order to assess the potential additive or multiplicative adverse effect of combination of bad behaviours (i.e. smoking and drinking intensity) at 17 years on aortic stiffness we generated a new variable with 3 categories: a) participants with low smoking and low-intensity drinking b) participants with intermediate smoking and intermediate drinking and c) participants classified as high intensity smokers and drinkers. Subsequently, we regressed this combined variable on PWV and adjusted for aforementioned confounders/predictors. Mean predicted increase in PWV for the “c” category of the combined variable was compared to relevant predicted changes in corresponding multivariable models for smoking frequency or drinking intensity alone. If the increase for the “c” category was \leq than the sum of increases for individual smoking or drinking the effect was considered additive. If the increase in the “c” category was $>$ than the sum of increases for individual smoking or drinking, the effect was considered multiplicative. In addition, a multiplicative combined effect of drinking and smoking behaviour was tested by introducing interaction terms (i.e. drinking frequency*smoking intensity) into the final adjusted model. Interaction terms were considered significant at $p < 0.1$. In case the interaction term or few individual categories of the combination between smoking and drinking pattern presented an interaction with PWV, a likelihood ratio test was implemented to assess the improvement of fit of the unrestricted model (with the interaction term) upon adding the interaction term in the restricted model (i.e. without the interaction term).

IB. Longitudinal analysis

Participants were grouped into five different patterns of longitudinal smoking behaviour: a) never smokers up to 17 years; b) smokers since 13 years c) smokers since 15 years d) smokers at 17 years and e) those who used to smoke at some point, but stopped smoking. A test for trend was implemented to assess differences in PWV between adolescents that never smoked (group a) and other groups. Additionally, all categories were compared to the reference group (a). A relevant analysis was performed for alcohol consumption across ages 13-17 years. The same approach to adjustment was used as for the cross-sectional analyses, but we further adjusted for

the height of participants, taking into account the different growth spurt for each adolescent across ages 13-17 years-

Multivariable models were built through an unbiased method of a priori variable selection, based on previous medical literature and conventional knowledge. In particular we adjusted the association of smoking and drinking behaviour with arterial stiffness for established CV risk factors (ie gender, age, family history of cardiovascular disease, LDL cholesterol, systolic blood pressure) and exposure variables which have previously been associated with increased CV risk and arterial stiffness (i.e. parental SES, high sensitivity CRP, physical activity and parental smoking).

Longitudinal data for smoking and drinking behaviour were assumed to be missing at random. Participants with and without longitudinal data on smoking and drinking habits did not differ substantially in anthropometric, biochemical and liver function indices as well as in risk factor distribution (Supplementary Table 1, 2).

II. Supplementary tables

Supplementary Table 1. Comparison of study's participants with and without available longitudinal data on smoking habits

	Longitudinal data not available (N=605)	Longitudinal data available (N=661)	P-Value
N (% males)	234(38.68)	191(28.90)	0.002
Socioeconomic status (I/V)%	15.47/8.68	12.39/11.69	0.206
Anthropometric			
Weight (kg)	65.5(12)	65.3(12.1)	0.816
Height (cm)	171(9)	170(8.48)	0.016
BMI (kg/m ²)	22.3(3.52)	22.6(3.73)	0.158
*Heart rate (beats/min)	64(57.8-71)	64.8(58.3-71.5)	0.433
Risk factors			
Passive smoking, n (%)	157(67.1)	180(27.2)	0.309
Family History of CAD, n (%)	38(16.2)	42(6.4)	0.786
*Physical activity, mins	447(364-564)	457(376-559)	0.573
SBP (mmHg)	116±9.4	115±9.1	0.224
DBP (mmHg)	63.5±5.84	63.9±5.67	0.181
Lipids			
Tchol (mmol/L)	3.79(0.69)	3.8(0.663)	0.803
LDL (mmol/L)	2.12(0.619)	2.11(0.614)	0.941
HDL (mmol/L)	1.28(0.303)	1.3(0.315)	0.334
*Triglycerides (mmol/L)	0.79(0.62-0.98)	0.79(0.6-1.02)	0.686
Inflammatory markers			
*CRP (mg/L)	0.625(0.31-1.4)	0.65(0.33-1.43)	0.576
Liver function			
*AST (U/L)	19.3(16.7-22.8)	19.1(16.5-22.2)	0.243
*ALT (U/L)	14.8(11.7-19.2)	14.9(11.7-18.9)	0.809
*GGT (U/L)	17(13-21)	16(13-22)	0.957

Comparisons between groups were performed by independent samples Student's T test or Mann-Whitney non-parametric test for continuous variables and chi squared test for categorical variables. Continuous variables are presented as mean(SD). Values for non-parametric variables (*) are presented as median(IQR).

Abbreviations: BMI: body mass index, CAD: coronary artery disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, Tchol: total cholesterol, LDL: low density lipoprotein, HDL: high density lipoprotein, CRP: c-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transpeptidase, SD: standard deviation, IQR: interquartile range

Supplementary Table 2. Comparison of study's participants with and without available longitudinal data on drinking habits

	Longitudinal data not available (N=243)	Longitudinal data available (N=1023)	P-Value
N (% males)	77(31.69)	348(34.02)	0.489
Socioeconomic status (I/V)%	8.33/14.7	15.13/9.23	0.001
Anthropometric			
Weight (kg)	65.5(12.1)	65.4(12.1)	0.949
Height (cm)	170(8.75)	171(8.75)	0.535
BMI (kg/m ²)	22.6(3.76)	22.5(3.6)	0.674
*Heart rate (beats/min)	65.1(58.5-72)	64.1(57.9-71)	0.075
Risk factors			
Passive smoking, n (%)	65(26.7)	272(26.6)	0.546
Family History of CAD, n (%)	17(7.0)	63(6.2)	0.828
*Physical activity, mins	460(364-541)	450(370-563)	0.999
SBP (mmHg)	116(9.8)	115(9.1)	0.379
DBP (mmHg)	64.1(5.58)	63.6(5.79)	0.298
Lipids			
Tchol (mmol/L)	3.78(0.635)	3.8(0.686)	0.703
LDL (mmol/L)	2.12(0.563)	2.12(0.628)	0.95
HDL (mmol/L)	1.29(.318)	1.29(0.307)	0.777
*Triglycerides (mmol/L)	0.75(0.61-0.98)	0.8(0.62-1)	0.211
Inflammatory markers			
*CRP (mg/L)	0.665(0.32-1.38)	0.615(0.32-1.42)	0.951
Liver function			
*AST (U/L)	19.3(16.5-21.9)	19.2(16.6-22.7)	0.637
*ALT (U/L)	14.7(11.9-19.7)	14.9(11.6-19)	0.648
*GGT (U/L)	16(13-20)	17(13-21)	0.262

Comparisons between groups were performed by independent samples Student's T test or Mann-Whitney non-parametric test for continuous variables and chi squared test for categorical variables. Continuous variables are presented as mean(SD). Values for non-parametric variables (*) are presented as median(IQR).

Abbreviations: BMI: body mass index, CAD: coronary artery disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, Tchol: total cholesterol, LDL: low density lipoprotein, HDL: high density lipoprotein, CRP: c-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transpeptidase, SD: standard deviation, IQR: interquartile range