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Exposure to Parental Smoking and Cardiac Structure and Function in Adulthood. The Cardiovascular Risk in Young Finns Study.

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Abstract

Background and aims: The relationship between childhood tobacco smoke exposure and cardiac structure and function in mid-life is unclear. We investigated the association between parental smoking with cardiac structure and function in adulthood.

Methods: 1,250 participants (56.5% female) from the Cardiovascular Risk in Young Finns Study who had data on parental smoking and/or serum cotinine, a biomarker of exposure to tobacco smoke, at baseline 1980 (age 3-18 years) and echocardiography performed in 2011. Parental smoking hygiene (i.e. smoking in the vicinity of children) was categorized by parental smoking and serum cotinine levels in offspring. Dimensions of left ventricle, diastolic and systolic function and cardiac remodeling were used as outcomes. Analyses were adjusted for sex, age, and covariates (BP, serum lipids, BMI, socioeconomic status, smoking (only in adulthood)) in childhood and adulthood.

Results: Parental smoking was not associated with systolic ~~function~~ or diastolic function in adulthood. Participants exposed to parental smoking (Odds Ratio [OR] 1.90, 95%CI 1.23-2.92), hygienic parental smoking (OR 1.74, 95%CI 1.12-2.71), and non-hygienic parental smoking (OR 1.88, 95%CI 1.02-3.45) had higher **odds** of concentric remodeling (relative wall thickness >85th sex-specific percentile without left ventricular hypertrophy). These associations attenuated after adjustment~~s~~ for child and adult covariates in **the** non-hygienic parental smoking group.

Conclusions: Exposed to parental smoking **in childhood was associated with a higher likelihood of** concentric remodeling and thicker left ventricular and interventricular septal wall in mid-life, **which** was not **improved** by **parents who smoked hygienically**. Parental smoking was not related to systolic and diastolic function in this relatively young population.

1 Introduction

Cardiovascular disease (CVD) is the main cause of death globally and the majority of these deaths are preventable[1]. Tobacco smoke is an important modifiable risk factor for CVD and atherosclerosis. Both active smoking and exposure to environmental tobacco smoke (or passive smoking) are associated with CVD[2] and with adverse changes in cardiac structure and left ventricle (LV) diastolic function which has been shown to associate with an increased incidence of heart failure[3].

Although implementation of strict tobacco policies have reduced smoking and exposure to secondhand **tobacco smoke**, there is increasing evidence that children exposed to parental smoking suffer long-term detrimental effects to their vascular health, independent of individual smoking habits and exposure to passive smoking later in life[4,5]. Exposure to parental smoking in childhood **might** increase the harmful effects of subsequent active smoking[6]. Furthermore, non-hygienic parental smoking (i.e. smoking in the presence of children) in childhood has been shown to increase **the** risk **of** carotid atherosclerotic plaque ~~later~~ in adulthood[7]. Moreover, acute and chronic exposure to passive smoking is known to impair LV systolic and diastolic function[3]. These dysfunctions may result from cardiac remodeling which is defined as molecular, cellular and/or interstitial changes that appear clinically as alterations in size, mass, geometry and function of the heart after injury[8]. Incidentally, 4-tiered (normal geometry, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy) classification of LV remodeling by relative LV wall thickness and LV mass can be used to assess risk for cardiovascular events in high risk patients[9]. However, the relationship between exposure to tobacco smoke and structure and function of the heart is not well understood.

The main aim of this study was to determine the association between parental smoking in childhood and cardiac structure and function in adulthood and whether hygienic smoking

modifies this effect. We used data from the Cardiovascular Risk in Young Finns Study, a population-based sample of individuals followed from childhood to adulthood for up to 31 years. We hypothesized that exposure to parental smoking in childhood/adolescence, especially those exposed to poor parental smoking hygiene, have worse cardiac structure and function in adulthood than those not exposed to parental smoking.

2 Methods

The Cardiovascular Risk in Young Finns Study is an ongoing longitudinal population-based study of cardiovascular risk factors from childhood to adulthood, conducted in five university hospitals in Finland (Helsinki, Kuopio, Oulu, Tampere, and Turku) and their rural surrounds. The baseline study was conducted in 1980 when 3,596 randomly selected children and adolescents aged 3, 6, 9, 12, 15 and 18 years participated. Since 1980 the cohort has been regularly followed-up in 3 to 9-year intervals. A detailed description of the cohort has been published previously[10]. Participants or their parents provided written informed consent and the study was approved by local ethics committees. Participants who had a) full data on parental smoking from 1980 or 1983 and serum cotinine levels from 1980 (n=1,678), and b) echocardiography performed in 2011 (n=1,491) were included in this study (n=1,250). Supplement Figure 1 **provides** a flow chart of the participants and non-participants.

Information on parental smoking was collected from self-report questionnaires in 1980 and 1983. Parents who indicated that they or their partner had ever smoked daily for at least 1 year were classified as “at least one smoking parent” in 1980 or 1983 shown to associate with measured serum cotinine in child offspring[7].

Fasting serum samples of the participants were collected in 1980 and stored at -20 °C without thawing and analyzed in 2014. A total of 1,999 participants had cotinine analyzed from childhood/adolescence. Serum cotinine concentration was quantified using two methods (described in supplemental content). For statistical analyses, participants were divided into 1) low (0-0.99ng/mL, n=1,448) and 2) elevated (≥1.00-<3ng/mL, n=232) serum cotinine groups[11].

We generated a variable of parental smoking hygiene that combined self-reports of parental smoking data from the baseline survey in 1980 with serum cotinine measurements[10]. Parental smoking hygiene was categorized as: 1) no parental smoking (children with non-smoking parents and low serum cotinine levels (29.4 %)); 2) hygienic parental smoking (children with at least one smoking parent and low serum cotinine levels (58.2%)); and 3) non-hygienic parental smoking (children with at least one smoking parent and a serum cotinine level ≥1 and < 3 ng/mL (12,4 %)) [11] 27 participants were excluded from analyses because they had measurable cotinine levels without self-reported parental smoking and 3 participants were excluded because they were missing information on parental smoking (supplement figure 1). Participants with cotinine levels of ≥3ng/ml were excluded from the analyses as they were assumed to be active smokers[12].

Covariates included questionnaire and anthropometric measures. Questionnaire measures gathered at baseline included childhood physical activity index, fruit and vegetable consumption and parent self-report of family annual income, which was considered as an indicator of socio-economic status (SES) and categorized as: 1) very low (<18,000 euros/year), 2) low (18,000–28,000 euros/year), 3) intermediate (28,001–38,000 euros/year), and 4) high (>38,000euros/year) income groups [11]. In case of missing information in 1980, data from the

first follow-up in 1983 was used. Adolescent smoking status was defined from baseline (1980) or the first follow-up (1983). Participants aged below 12 years were considered non-smokers. Physical activity index was calculated at baseline and due to separate questionnaires used for children (3-6 years of age) and older children (9-18 years of age) the values were standardized as previously described[13,14]. Participants' household annual income in the year 2011 was considered as an indicator of adulthood SES and was categorized as: 1) low (<21,680 euros/year), 2) intermediate (21,680–48,770 euros/year), and 3) high (>48,770 euros/year) income groups. In case of missing information in 2011, data from the previous follow-up in 2007 were used. Adult participants current daily smoking status was gathered at the year 2011 follow-up.

At baseline and all follow-up visits, weight was measured without shoes in light clothes with a digital Seca weighing scale to nearest kilogram (kg). A Seca stadiometer was used for height measurements and BMI was calculated as weight (kg) divided by height in meters squared (m^2). Baseline (1980) measurement was used as the primary indicator of childhood/adolescent BMI. In case of missing information, data from year 1983 follow-up was used. ~~For~~ Adulthood BMI ~~data~~ was derived from the latest follow-up study (2011). In case of missing information, data from the 2007 follow-up was used.

Fasting lipids were measured in the same laboratory at each follow-up with standard methods for serum total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides. Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald equation.

Brachial artery blood pressure was measured at baseline using an ultrasound device (Arteriosonde 1020, Roche) among participants aged 3 years, and using a standard mercury sphygmomanometer for participants aged ≥6 years at baseline. In case of missing

information, data from the 1983 follow-up was used. Adult blood pressure measurements were collected in the 2011 follow-up using a random-zero sphygmomanometer (Hawksley & Sons Ltd, Lancin, UK). All measurements were taken using a standardized method repeated 3 times on the right arm after the participant had been seated for 5 minutes with the average of the 3 measurements used.

Echocardiographic examinations were performed in 2011 according to American and European guidelines[15,16]. Transthoracic echocardiography was performed using a 3.5 MHz scanning frequency phased-array transducer (Sequoia 512, Acuson, CA, USA). Studies were saved in digital images which were all analyzed using the ComPACS 10.7.8 (MediMatic Solutions, Genova, Italy) analysis program by one reader blinded to subjects' details[17].

LV mass was calculated as previously described[18] and indexed LV mass was attained according to ~~subject's~~ participant height using the allometric power of 2.7 (indexed LV mass=LV mass/height$^{2.7}$) since this indexation has been shown to perform better among those with obesity[19]. Relative wall thickness was calculated and LV geometry groups were defined using sex-specific cut-off points[18]. Concentric remodeling was defined as high relative wall thickness (>85 percentile point) without LV hypertrophy. Eccentric hypertrophy was defined as LV hypertrophy without high relative wall thickness. Concentric hypertrophy was defined as LV hypertrophy with relative wall thickness. The intraclass correlation coefficients with the 5th and 95th percentile confidence intervals and coefficient of variance have been reported earlier along with the complete methodology for cardiac imaging and image analysis in the Young Finns Study[17]. Interventricular septal wall thickness and LV posterior wall thickness were measured from parasternal long-axis view in M-mode at end-diastole. LV diameter was measured from parasternal long-axis view in M-mode at end-diastole. LV ejection fraction

and ratios of E/e' and EA were calculated according to American and European guidelines[15,16]. Left atrium volume index was calculated in four-chamber apical view at end-systole and divided by body surface area using Du Bois formula (BSA = $0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$).

Baseline characteristics of the study population are reported as mean (SD) or median (25^{th} and 75^{th} percentiles, if skewed distributions) for continuous variables or as proportions for categorical variables.

For confirmation of participants' parental smoking exposure, we combined cotinine levels to questionnaire data for parental smoking hygiene variable. The relationship between parental smoking and serum cotinine measurement with continuous outcome variables was assessed using least squares means in generalized linear model adjusted with Tukey-Kramer approximation and for categorical outcome variables using logistic regression. Two models were created for the analyses; model 1 adjusted for sex and age, model 2 included model 1 covariates and additionally adjusted for childhood risk factors (systolic blood pressure, HDL-cholesterol, LDL-cholesterol, triglycerides, BMI, and family SES) and adult risk factors (BMI, systolic and diastolic blood pressure, HDL-cholesterol, LDL-cholesterol and triglycerides, participants own SES and own smoking status). We performed sensitivity analyses that excluded participants who reported they were current smokers in adolescence and that additionally adjusted for daily fruit and vegetable consumption and physical activity index in addition to those covariates included in model 2. We also conducted sensitivity analyses categorizing subgroups by age: 1) ≤6 years of age at baseline; 2) 15-18 years of age in baseline. Moreover, we analysed the data adjusted for age, sex, and adulthood alcohol intake (result are shown in supplemental content). To assess the degree of multicollinearity in the

multivariable analyses, we investigated variance inflation factors and found no highly collinear relationships (variance inflation factor always <2.9). All statistical analyses were performed using SAS version 9.4 and statistical significance was inferred at a two-tailed P-value <0.05.

3 Results

Baseline characteristics of participants are show in **Table 1**. The total number of participants was 1,987 (54.2 % female) who had serum cotinine levels and parental smoking data available in childhood. Of these, 1,491 had at least one echocardiography measurement available. The mean age of participants was 42.2 years at the 2011 follow-up.

Associations between parental smoking with cardiac outcomes are shown in **Table 2**. We observed associations between parental smoking status with interventricular septal wall thickness (adjusted means, (95%CI): 7.29 (7.20-7.37) among participants with non-smoking parents vs. 7.39 (7.34-7.45) among participants with smoking parents, p=0.04) and LV posterior wall thickness (adjusted means + (95%CI): 7.22 (7.15-7.30) vs. 7.32 (7.26-7.37), p=0.045), but these were attenuated when further adjusted for childhood and adulthood covariates (adjusted means + (95%CI): 7.40 (7.29-7.51) vs. 7.48 (7.39-7.57), p=0.13 and 7.32 (7.22-7.42) vs. 7.37 (7.29-7.45), p=0.27, respectively). We observed no significant differences in the other echocardiography outcomes examined.

Associations between parental smoking hygiene and cardiac outcomes are shown in **Table 3**. We observed no significant differences in adult echocardiography variables according to parental smoking hygiene (all p>0.10).

Odds ratios between parental smoking, childhood serum cotinine levels, and parental smoking hygiene with cardiac remodeling are shown in **Table 4**. In analyses adjusted for age

and sex, participants exposed to parental smoking (OR 1.90, 95%CI 1.23-2.92), hygienic parental smoking (OR 1.74, 95%CI 1.12-2.71), and non-hygienic parental smoking (OR 1.88, 95%CI 1.02-3.45) had higher odds of concentric remodeling. The association between parental smoking and concentric remodeling persisted with adjustment for child and adult covariates (OR 1.72, 95%CI 1.09-2.70).

association between hygienic parental smoking and concentric remodeling remained following adjustment for childhood and adulthood risk factors (OR 1.61, 95%CI 1.01-2.56) whereas the association between non-hygienic parental smoking and concentric remodeling became non-significant ~~diluted~~ when adjusted for child and adult covariates.

The association between hygienic parental smoking and concentric hypertrophy was not statistically significant.

The evidence for associations between non-hygienic parental smoking and concentric hypertrophy were limited (n=2) in analyses adjusted for sex and age (OR 5.17, 95%CI 0.93-28.95) but additional adjustments for risk factors attenuated the association.

We observed no other associations between parental smoking or parental smoking hygiene and concentric or eccentric hypertrophy.

The association between childhood serum cotinine levels and cardiac outcomes are shown in **supplement table 1**. We observed no significant differences in adult echocardiography variables according to childhood serum cotinine level.

In sensitivity analyses, active smokers in adolescence were excluded and additional adjustments were made for daily fruit and vegetable consumption and childhood physical activity index with the results remaining essentially similar except the association between

non-hygienic parental smoking and concentric remodeling (OR 1.78, 95%CI 0.92-3.45) and concentric hypertrophy was diluted. We also conducted sensitivity analyses categorizing subgroups by age: 1) ≤6 years of age at baseline; 2) 15-18 years of age in baseline. The overall results in the fully adjusted models were consistent with those shown for the main results. Finally, we analysed the data adjusted for age, sex, and adulthood risk factors and these results are in line with our reported results and did not change the results.

4 Discussion

We hypothesized that parental smoking would be associated with adverse structural and functional cardiac changes, but we found no strong evidence of this. However, we observed an association between parental smoking in childhood with interventricular septal and LV posterior wall thickness in adulthood. Furthermore, parental smoking and smoking hygiene status were associated with concentric remodeling in adults.

To our knowledge this is the only longitudinal prospective study examining the association between exposure to parental smoking in childhood with the use of an objectively measured biomarker (serum cotinine) and echocardiography measurements performed in adulthood. While increased LV mass, a predecessor to cardiac remodeling, has been shown to associate with smoking in mid-life[20] and to exposure to secondhand smoke in rabbits[21], our results do not confirm this association. However, parental smoking was associated with increased thickness of interventricular septal and LV posterior walls, which may be predictive of future LV hypertrophy. As our participants are relatively young, the association to LV hypertrophy and function might become evident as they age. In line with previous studies, after adjusting for SES the association diluted[22]. In addition, it is known that exposure to secondhand

smoking in childhood can result in higher blood pressure[23], increased arterial stiffness[24], flow-mediated dilation impairment[4], and endothelial dysfunction, among others[25]. Combined, these factors might cause cardiac remodeling later in life by pressure overload[26].

Previous studies have found LV remodeling and higher age to associate with worse LV diastolic function which is often the first stage of heart failure[27]. Also, cardiovascular morbidity is higher among patients with concentric remodeling than in patients with normal geometry[28]. In our study, concentric remodeling (~~ie.~~ high relative wall thickness without LV hypertrophy) was associated with exposure to parental smoking and parental smoking hygiene.

Although both active smoking and exposure to chronic secondhand smoking in childhood have been linked with decreased LV diastolic function in Hispanics/Latinos[3], we found no association regarding parental smoking, serum cotinine levels or parental smoking hygiene status in our cohort. Potentially, this difference is due to younger age of our participants (42 years vs. 56 years of age).

While smoking is associated with higher risk of heart failure, a recent study found chronic exposure to secondhand smoking in childhood paradoxically increased LV ejection fraction[3]. Nevertheless, in our relatively young cohort, we found no association between parental smoking and LV ejection fraction or cardiac output.

The main strength of this study is its large study population and comprehensive data of lifestyle, biochemistry, and anthropometric measurements as well as socioeconomic information starting from childhood with over 30 years of follow-up. An apparent limitation of observational studies is that they are not able to establish causality, however it would be impossible to achieve a life-long trial on CVD progression in humans. Additional limitations include lack of data on prenatal parental smoking exposure which has been shown to have

long-lasting adverse effects to cardiovascular health. Furthermore, we were not able to evaluate change in the smoking hygiene over time. As some of the parents stopped regular smoking during the offspring's childhood. This could have diluted our findings. Moreover, young adults in the 1980s might have ~~had~~ been exposed to secondhand smoke outside of their family unit. However, we tried to minimize the effect of this by using cotinine levels in our study and excluded participants who had inconsistency between questionnaire data and cotinine levels. Therefore, the contrast between the results for serum cotinine and queried parental smoking suggests underestimation of smoking among the parents. In addition, we were not able to consider snus use in childhood as a potential confounder as data were not collected. Nevertheless, use of snus in youth in the 1980s was rare in Finland and has become more common among males only during the 1990s – though the rates remained relatively low (daily use of snus ~3 % in boys aged 16-18 years and <1 % in girls and women)[29]. Thus, use of snus is not likely to largely impact our results. In addition, individual variability in the rate of elimination of nicotine and cotinine could not be evaluated from our data and should be considered when interpreting our results. Non-participation at follow-up is inevitable in longitudinal studies. However, participation rates have been reasonably high, and participation has been dynamic, so that many participants lost to follow-up early in the study have returned at subsequent follow-ups[30]. Thus, the study population is likely representative of the original population[10,31]. Moreover, we understand that additional adjustments for Model 2 might have included factors which were perhaps mediating at least part of the association between the exposure and the outcome. In line, we have previously reported baseline risk factor levels to be essentially similar among participants and nonparticipants at subsequent follow-ups[32]. Furthermore, it is not possible to study the associations of parental smoking exposure on CVD as it develops gradually over decades and participants of YFS are

in their early midlife. Hence, none of the participants meet the clinical criteria of concentric hypertrophy. However, the cut-offs used allowed us to investigate associations between parental smoking and cardiac remodeling. We acknowledge that strict measures have been implemented on tobacco control in most developed countries since our cohort commenced in 1980 that has led to a substantial decline in daily smokers that might limit the generalizability of our findings. Public awareness of the adverse effects of secondhand smoking has subsequently increase but remains a problem in disadvantaged groups and those in low- and middle-income countries. Finally, our participants were an ethnically homogenous group of white Caucasians, which limits the generalizability of our results.

In conclusion, we found that exposure to parental smoking in childhood is associated with higher odds of concentric remodeling in later life and may also influence left ventricular wall diameters. Although these findings need to be replicated in other independent cohorts, we found exposure to parental smoking was not associated with higher likelihood of systolic or diastolic dysfunction in this relatively young study population.

Conflict of interest

The authors declared they do not have anything to disclose regarding no conflict of interest with respect to this manuscript.

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Author contributions

MD J. Pihlman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Jukka Pihlman, MD: conceptualization, investigation, formal analysis, software, data curation, validation, methodology, writing - original draft, writing - review and editing, visualization

Joel Nuotio, MD, PhD: conceptualization, writing - review and editing, supervision

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Table 1. Baseline (1980) and follow-up (2011) characteristics of study participants.

Year	Variable	Value
		1980
1980	N	1,250
	Male sex (%)	43.5
	Age (y)	10.6 (4.8)
	Family income (%)	
	<18,000 euros/year	25
	18,000–28,000 euros/year	29
	28,001–38,000 euros/year	23
	>38 000 euros/year	23
	HDL cholesterol (mmol/L)	1.57 (0.30)
	LDL cholesterol (mmol/L)	3.45 (0.82)
	Triglycerides (mmol/L)	0.65 (0.45, 0.77)
	Systolic blood pressure (mmHg)	113 (12)
	Diastolic blood pressure (mmHg)	69 (9)
	Body mass index (kg/m^2)	17.8 (3.0)
	Parental smoking (%)	70
	Fruit consumption (frequency/week)	6.3 (6.3, 9.5)
	Vegetable consumption (frequency/week)	6.3 (3.0, 9.5)
	Physical activity index	10 (8, 14)
	Active smoking (%)	15
	Cotinine (ng/ml)	0.13 (0.00, 1.33)
2011		
	Participants own income (%)	

< 21 680 euros/year	15
21 680 - 48 770 euros/year	62
> 48 770 euros/year	23
HDL cholesterol (mmol/L)	1.32 (0.33)
LDL cholesterol (mmol/L)	3.25 (0.83)
Triglycerides (mmol/L)	1.31 (0.75, 1.56)
Systolic blood pressure (mmHg)	118 (14)
Diastolic blood pressure (mmHg)	75 (11)
Body mass index (kg/m^2)	26.5 (5.0)
Serum glucose levels (mmol/l)	5.4 (1.1)
Own adult smoking (%)	20.1
LV mass ($g/m^{2.7}$)	30.6 (6.5)
Intraseptal wall end-diastolic thickness (mm)	7.32 (0.92)
LV Posterior wall all end-diastolic thickness (mm)	7.23 (0.87)
E/e'-ratio	4.81 (1.02)
E/A-ratio	1.56 (0.40)
LAVI	22.5 (6.4)
LV end-diastolic diameter (mm)	49.5 (4.7)
Ejection fraction (%)	58.5 (3.5)
Cardiac output (l/min)	4.7 (1.2)
Cardiac remodeling (%)	
Normal geometry	73
Concentric hypertrophy	2
Concentric remodeling	12
Eccentric hypertrophy	13

HDL=high-density lipoprotein; LDL=low-density lipoprotein; LV=left ventricle; LAVI=left atrium volume index. Data are mean (SD) or median (25th, 75th percentile) for continuous variables and percentages for categorical variables.

Table 2. Effect estimates and their 95% confidence intervals (CI) for adult outcome variables according to parental smoking status.

Model		No parental smoking			≥1 parent smoking				
	Adult outcome	Effect estimate	95% CI	n	Effect estimate	95% CI	n	*p*	n
1									
	LV Mass (g/m$^{2.7}$)	30.45	(29.79 - 31.10)	361	30.92	(30.48 - 31.35)	839	0.23	1200
	Interventricular septal wall (mm)$_a$	7.29	(7.20 - 7.37)	362	7.39	(7.34 - 7.45)	842	0.04	1204
	Posterior wall (mm)$_a$	7.22	(7.15 - 7.30)	362	7.32	(7.26 - 7.37)	841	0.05	1203
	E/e'	4.75	(4.65 - 4.85)	369	4.80	(4.73 - 4.86)	844	0.49	1217
	E/A	1.55	(1.51 - 1.59)	372	1.56	(1.54 - 1.59)	861	0.72	1233
	LAVI	22.81	(22.15 - 23.47)	360	22.63	(22.19 - 23.06)	846	0.64	1206
	LV (mm)$_a$	52.0	(51.6 - 52.5)	363	52.0	(51.7 - 52.3)	842	0.86	1205
	EF (%)	58.3	(57.9 - 58.7)	365	58.4	(58.2 - 58.7)	853	0.62	1218
	Cardiac output (l/min)	4.68	(4.56 - 4.80)	345	4.78	(4.70 - 4.86)	813	0.17	1158
2									
	LV Mass (g/m$^{2.7}$)	31.35	(30.56 - 32.13)	330	31.34	(30.73 - 31.95)	771	0.99	1101
	Interventricular septal wall (mm)$_a$	7.40	(7.29 - 7.51)	330	7.48	(7.39 - 7.57)	773	0.13	1103
	Posterior wall (mm)$_a$	7.32	(7.22 - 7.42)	330	7.37	(7.29 - 7.45)	772	0.27	1102

E/e'	4.83	(4.69 - 4.96)	336	4.82	(4.72 - 4.93)	778	0.93	1114
E/A	1.55	(1.49 - 1.60)	340	1.57	(1.53 - 1.61)	787	0.29	1127
LAVI	23.15	(22.25 - 24.04)	329	22.79	(22.10 - 23.48)	777	0.39	1106
LV (mm) [a]	52.0	(51.4 - 52.6)	331	51.9	(51.4 - 52.4)	772	0.46	1103
EF (%)	58.3	(57.8 - 58.8)	333	58.4	(58.0 - 58.8)	781	0.64	1114
Cardiac output (l/min)	4.76	(4.61 - 4.90)	315	4.77	(4.66 - 4.88)	748	0.85	1063

[a] End-diastolic diameter. LV=left ventricular; EF=ejection fraction; LAVI=left atrium volume index; E/e'=ratio of early mitral inflow velocity and mitral annular early diastolic velocity; E/A ratio of peak velocity blood flow from left ventricular relaxation in early diastole to peak velocity flow in late diastole caused by atrial contraction. Adjusted Model 1 included sex and age. Adjusted model 2 included Model 1 covariates plus childhood SES (household annual income) and childhood risk factors (LDL-cholesterol, HDL- cholesterol, triglycerides, systolic blood pressure, and body mass index), adult SES (annual income) and adult risk factors (LDL-cholesterol, HDL- cholesterol, triglycerides, systolic blood pressure, body mass index and own smoking status).

Table 3. Effect estimates and their 95% confidence intervals (CI) for adult outcome variables according to parental smoking hygiene.

		No parental smoking			Hygienic parental smoking			Non-hygienic parental smoking				
Model	Adult outcome	Effect estimate	95% CI	n	Effect estimate	95% CI	n	Effect estimate	95% CI	*n*	*p*	n
1												
	LV Mass (g/m$^{2.7}$)	30.46	(29.79 - 31.13)	339	30.96	(30.48 - 31.44)	649	30.74	(29.71 - 31.76)	145	0.48	1178
	Interventricular septal wall (mm)$_a$	7.30	(7.21 - 7.38)	340	7.39	(7.33 - 7.45)	697	7.40	(7.27 - 7.53)	145	0.19	1182
	Posterior wall (mm)$_a$	7.22	(7.14 - 7.30)	340	7.31	(7.26 - 7.37)	696	7.33	(7.20 - 7.45)	145	0.11	1181
	E/e'	4.75	(4.64 - 4.85)	346	4.78	(4.71 - 4.86)	700	4.86	(4.71 - 5.02)	148	0.48	1194
	E/A	1.55	(1.51 - 1.59)	349	1.56	(1.53 - 1.59)	711	1.58	(1.52 - 1.64)	150	0.75	1210
	LAVI	22.74	(22.07 - 23.41)	338	22.72	(22.24 - 23.19)	700	22.17	(21.15 - 23.20)	146	0.61	1184
	LV (mm)$_a$	52.0	(51.5 - 52.5)	340	52.1	(51.7 – 52.4)	696	51.5	(50.8 - 52.3)	146	0.44	1182
	EF (%)	58.2	(57.9 - 58.6)	342	58.4	(58.1 - 58.7)	706	58.5	(57.9 - 59.1)	147	0.74	1195
	Cardiac output (l/min)	4.66	(4.53 - 4.78)	323	4.77	(4.68 - 4.85)	673	4.83	(4.65 - 5.02)	140	0.21	1136
2												
	LV Mass (g/m$^{2.7}$)	31.36	(30.57 - 32.16)	311	31.60	(30.96 - 32.24)	641	30.67	(29.65 - 31.70)	130	0.22	1082
	Interventricular septal wall (mm)$_a$	7.41	(7.30 - 7.52)	311	7.50	(7.41 - 7.59)	643	7.43	(7.28 - 7.57)	130	0.19	1084
	Posterior wall (mm)$_a$	7.30	(7.20 - 7.41)	311	7.38	(7.30 - 7.46)	642	7.33	(7.20 - 7.46)	130	0.28	1083

E/e'	4.82	(4.69 - 4.96)	316	4.82	(4.71 - 4.94)	646	4.83	(4.65 - 5.01)	132	1.00	1094
E/A	1.54	(1.49 - 1.60)	320	1.56	(1.52 - 1.61)	654	1.59	(1.53 - 1.66)	133	0.40	1107
LAVI	23.03	(22.13 - 23.94)	309	22.79	(22.06 - 23.52)	646	22.45	(21.28 - 23.61)	131	0.67	1086
LV (mm)[a]	51.9	(51.3 - 52.5)	311	51.9	(51.5 - 52.4)	642	51.3	(50.5 - 52.0)	130	0.30	1083
EF (%)	58.2	(57.7 - 58.7)	313	58.4	(58.0 - 58.8)	650	58.4	(57.8 - 59.1)	131	0.78	1094
Cardiac output (l/min)	4.75	(4.60 - 4.90)	296	4.78	(4.66 - 4.90)	622	4.72	(4.53 - 4.91)	126	0.79	1044

[a] End-diastolic diameter. LV=left ventricular; EF=ejection fraction; LAVI=left atrium volume index; E/e'=ratio of early mitral inflow velocity and mitral annular early diastolic velocity; E/A ratio of peak velocity blood flow from left ventricular relaxation in early diastole to peak velocity flow in late diastole caused by atrial contraction. Adjusted Model 1 included sex and age. Adjusted model 2 included Model 1 covariates plus childhood SES (household annual income) and childhood risk factors (LDL-cholesterol, HDL- cholesterol, triglycerides, systolic blood pressure, and body mass index), adult SES (annual income) and adult risk factors (LDL-cholesterol, HDL- cholesterol, triglycerides, systolic blood pressure, body mass index and own smoking status).

Table 4. Adjusted odds ratio (OR) and 95% confidence intervals (CI) for adult cardiac remodeling according to different measures of child exposure to passive smoking.

		Normal geometry		Concentric hypertrophy			Concentric remodeling				Eccentric hypertrophy						
Model	Child exposure variable		n	OR	95% CI	*p*	n	OR	95% CI	*p*	n	OR	95% CI	*p*	*n*	*p* all	n all
1																	
	Parental smoking	Reference	874	2.85	(0.83 - 9.75)	0.10	22	1.90	(1.23 - 2.92)	0.004	144	1.13	(0.78 - 1.64)	0.53	159	0.01	1199
	Cotinine levels	Reference	875	1.91	(0.69 - 5.33)	0.22	22	1.06	(0.64 - 1.76)	0.82	144	0.85	(0.51 - 1.44)	0.55	161	0.56	1202
	Hygienic smoking	Reference	752	3.70	(0.84 - 16.35)	0.09	17	1.74	(1.12 - 2.71)	0.01	123	1.15	(0.78 - 1.70)	0.49	140	0.10	1177
	Non-hygienic smoking	Reference	263	5.17	(0.93 - 28.95)	0.06	2	1.88	(1.02 - 3.45)	0.04	29	0.88	(0.46 - 1.68)	0.70	44		
2																	
	Parental smoking	Reference	801	2.13	(0.59 - 7.66)	0.25	20	1.72	(1.09 - 2.70)	0.02	134	1.06	(0.71 - 1.57)	0.79	146	0.09	1101
	Cotinine levels	Reference	801	1.35	(0.40 - 4.62)	0.63	20	0.98	(0.57 - 1.70)	0.95	134	0.67	(0.37 - 1.22)	0.19	146	0.56	1101
	Hygienic smoking	Reference	690	3.01	(0.64 - 14.11)	0.16	16	1.61	(1.01 - 2.56)	0.046	115	1.13	(0.75 - 1.72)	0.56	131	0.23	1082
	Non-hygienic smoking	Reference	241	2.68	(0.39 - 18.35)	0.32	2	1.62	(0.83 - 3.14)	0.15	28	0.68	(0.33 - 1.40)	0.30	40		

Reference for parental smoking: no parental smoking, for cotinine levels: <1ng/ml, and for smoking hygiene: no parental smoking and no measured cotinine in serum. Adjusted Model 1 included sex and age. Adjusted model 2 included Model 1 covariates plus childhood SES (household annual income) and childhood risk factors (LDL-cholesterol, HDL- cholesterol, triglycerides, systolic blood pressure, and body mass

index), adult SES (annual income) and adult risk factors (LDL-cholesterol, HDL- cholesterol, triglycerides, systolic blood pressure, body mass index and own smoking status).

Supplement table 1. Effect estimates and their 95% confidence intervals (CI) for adult outcome variables according to childhood serum cotinine levels.

Model		Cotinine ≥0, <1 (ng/ml)			Cotinine ≥1, <3 (ng/ml)				
	Adult outcome	Effect estimate	95% CI	n	Effect estimate	95% CI	n	*p*	n
1									
	LV Mass ($g/m^{2.7}$)	30.80	(30.41 - 31.19)	1036	30.66	(29.71 - 31.62)	167	0.80	1203
	Interventricular septal wall $(mm)_a$	7.36	(7.31 - 7.41)	1040	7.36	(7.24 - 7.48)	167	0.98	1207
	Posterior wall $(mm)_a$	7.28	(7.24 - 7.33)	1039	7.32	(7.21 - 7.43)	167	0.53	1206
	E/e'	4.77	(4.71 - 4.83)	1049	4.86	(4.72 - 5.01)	171	0.26	1220
	E/A	1.55	(1.53 - 1.58)	1063	1.58	(1.52 - 1.63)	173	0.46	1236
	LAVI	22.74	(22.35 - 23.13)	1041	22.39	(21.43 - 23.35)	168	0.51	1209
	LV $(mm)_a$	52.0	(51.8 - 52.3)	1039	51.7	(51.0 - 52.3)	169	0.34	1208
	EF (%)	58.3	(58.1 - 58.6)	1051	58.6	(58.1 - 59.1)	170	0.42	1221
	Cardiac output (l/min)	4.73	(4.66 - 4.80)	999	4.85	(4.68 - 5.03)	162	0.20	1161
2									
	LV Mass ($g/m^{2.7}$)	31.49	(30.88 - 32.09)	952	30.71	(29.73 - 31.69)	149	0.12	1101

Interventricular septal wall (mm)[a]	7.47	(7.39 - 7.56)	954	7.41	(7.28 - 7.55)	149	0.41	1103
Posterior wall (mm)[a]	7.36	(7.28 - 7.43)	953	7.34	(7.22 - 7.47)	149	0.84	1102
E/e'	4.82	(4.72 - 4.93)	962	4.82	(4.65 - 4.99)	152	0.99	1114
E/A	1.56	(1.52 - 1.60)	974	1.59	(1.53 - 1.66)	153	0.30	1127
LAVI	22.93	(22.24 - 23.61)	955	22.67	(21.56 - 23.78)	151	0.65	1106
LV (mm)[a]	51.9	(51.4 - 52.4)	965	51.3	(50.6 - 52.1)	151	0.12	1103
EF (%)	58.3	(58.0 - 58.7)	963	58.5	(57.9 - 59.1)	151	0.59	1114
Cardiac output (l/min)	4.77	(4.66 - 4.88)	918	4.73	(4.55 - 4.91)	145	0.64	1063

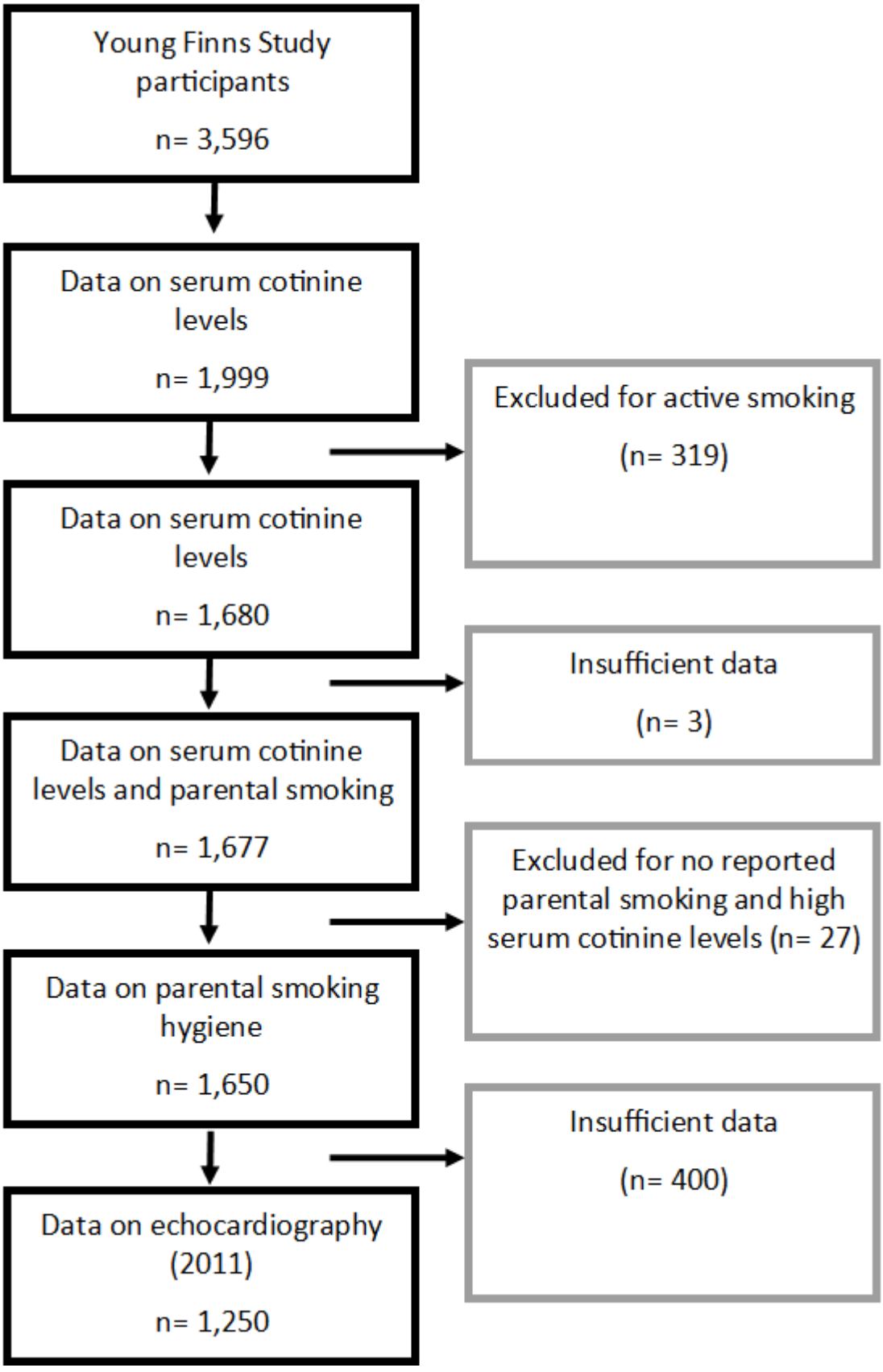
[a] End-diastolic diameter. LV=left ventricular; EF=ejection fraction; LAVI=left atrium volume index. Adjusted Model 1 included sex and age. Adjusted model 2 included Model 1 covariates plus childhood SES (household annual income) and childhood risk factors (LDL-cholesterol, HDL-cholesterol, triglycerides, systolic blood pressure, and body mass index), adult SES (annual income) and adult risk factors (LDL-cholesterol, HDL-cholesterol, triglycerides, systolic blood pressure, body mass index and own smoking status).

Supplemental Table 2. Adjusted odds ratio (OR) and 95% confidence intervals (CI) for adult cardiac remodeling comparing child exposure between hygienic or non-hygienic smoking.

		Normal geometry	Concentric hypertrophy				Concentric remodeling				Eccentric hypertrophy					
Model	Child exposure variable		n	OR	95% CI	*p*	n	OR	95% CI	*p*	n	OR	95% CI	*p*	*n*	*p* all
1																
	Hygienic smoking	Reference	489		Reference		15		Reference		94		Reference		96	
	Non-hygienic smoking	Reference	104	1.35	(0.43 - 4.21)	0.61	4	1.05	(0.62 - 1.77)	0.86	21	0.82	(0.46 - 1.46)	0.50	16	
2																
	Hygienic smoking	Reference	449		Reference		14		Reference		87		Reference		91	
	Non-hygienic smoking	Reference	96	0.83	(0.20 - 3.41)	0.80	3	0.99	(0.56 - 1.76)	0.97	19	0.58	(0.30 - 1.14)	0.11	12	

Reference for parental smoking: no parental smoking, for cotinine levels: <1ng/ml, and for smoking hygiene: no parental smoking and no measured cotinine in serum. Adjusted Model 1 included sex and age. Adjusted model 2 included Model 1 covariates plus childhood SES (household annual income) and childhood risk factors (LDL-cholesterol, HDL- cholesterol, triglycerides, systolic blood pressure, and body mass index), adult SES (annual income) and adult risk factors (LDL-cholesterol, HDL- cholesterol, triglycerides, systolic blood pressure, body mass index and own smoking status).

Supplement figure 1. Flow chart of participant selection into the study.



Supplemental

Methods

First, serum cotinine was extracted into dichloroethane by the method of Feyerabend and Russell[1] with the concentrated extract measured by means of gas-liquid chromatography, and with a quantitation limit at 0.16ng/mL (n=1,668)[2]. Second, 0.5ng isotope labelled internal standard for cotinine was added to the 0.1mL serum sample. Serum sample was extracted with dichloromethane and determined by LC-MS/MS with quantitation limit at 0.10ng/mL (n=1,301). Subsequently, the mean of both cotinine measurements was calculated for each participant (mean value was used for 970 participants). In case of missing information on either measurement, the one available measure was used instead of a mean of two measures.

Advanced cardiac remodeling or cardiomyopathy is associated with various mutations. The considerable genetic heterogeneity suggests that there are multiple pathways that lead to changes in heart structure and function. However, our study population is representative of the whole population and heredity probably does not impact the results in a significant way.

Previous studies have shown an association between alcohol intake and cardiac remodeling[3]. When adjusted for age, sex, and adulthood alcohol intake, association between parental smoking hygiene and concentric remodeling among those exposed to hygienic parental smoking persisted ((OR 1.67, 95%CI 1.03-2.57) when compared to the original result (OR 1.74, 95%CI 1.12-2.71)). However, association between non-hygienic parental smoking and concentric remodeling was diluted (OR 1.641, 95%CI 0.87-3.10) when compared to the original result (OR 1.88, 95%CI 1.02-3.45)).
In the fully adjusted model, additionally adjustment for adult alcohol intake diluted the association between exposure to hygienic parental smoking and concentric remodeling (OR 1.45, 95%CI 0.91-2.33) when compared to the original result (OR 1.61, 95%CI 1.01-2.56)).

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