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Objectively measured second hand smoke exposure and risk of cardiovascular disease: what is the mediating role of inflammatory and haemostatic factors?

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Abstract

Objectives—To examine the association between objectively measured second-hand-smoke (SHS) exposure and incident CVD death, and assess the extent to which this association can be explained through novel circulating markers of inflammation and haemostasis.

Background—Existing evidence suggests there is an association between SHS and cardiovascular disease (CVD) risk, although the mechanisms remain poorly understood.

Methods—In a prospective study of 13,443 participants living in England and Scotland [aged 53.5, (SD 12.6 yrs), 52.3% women] we measured salivary cotinine (an objective marker of SHS exposure) and novel CVD biomarkers (C-reactive protein, fibrinogen) at baseline.

Results—20.8% of the sample had high SHS exposure based on elevated levels of salivary cotinine (0.71 – 14.99 ng/mL). During a mean follow-up of 8 years, there were 1221 all-cause deaths and 364 CVD deaths. High SHS was associated with all-cause (age adjusted HR= 1.25, 95% CI, 1.02 – 1.53) and CVD death (age adjusted HR= 1.21, 95% CI, 0.85 – 1.73). High SHS was also associated with elevated CRP, which explained 48% of the association between SHS and CVD death. The excess risk of CVD associated with active smoking was exaggerated in relation to self report (age adjusted HR= 3.27, 95% CI, 2.48 – 4.31) compared with objective assessment (age adjusted HR= 2.44, 95% CI, 1.75 – 3.40).

Conclusion—Among a large representative sample of British adults we observed elevated levels of low grade inflammation in otherwise healthy participants exposed to high SHS, and this partly explained their elevated risk of CVD death.

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Keywords

cotinine; inflammation; nicotine; passive smoke; mortality; epidemiology

Recent studies that have utilised valid objective biochemical markers of second hand smoke (SHS) exposure have found associations with various cardiovascular disease (CVD) risk factors, including socio-economic deprivation, markers of inflammation, endothelial dysfunction, lipids, and glucose control.¹⁻⁴ To our knowledge, there are only two studies to date that have examined CVD mortality risk using objectively measured biomarkers of SHS exposure,^{4,5} although one of these studies⁵ utilised carboxyhaemoglobin concentration that is not a useful indicator of SHS.

Mechanisms explaining the association between SHS exposure and CHD risk have not been well examined. The suggestion that the association between SHS and CHD is not markedly attenuated by adjustment for conventional CVD risk factors, such as blood pressure, blood lipids, body mass index, and fasting glucose, raises the possibility that other, novel explanatory factors may be involved. The importance of low grade inflammation in the link between active smoking and CVD risk is increasingly recognised,^{6,7} but we are not aware of any existing study that has directly assessed the role of inflammatory and haemostatic markers in relation to SHS exposure.

In the present study, we examined the association between objectively measured SHS and incident CVD death and assessed the extent to which this association could be explained through two circulating markers of inflammation and haemostasis: C-reactive protein (CRP)⁸ and fibrinogen.⁹ We employed salivary cotinine as an objective indicator of nicotine exposure that is considered to be the gold standard measure.¹⁰

Methods

Study design and Participants

The Health Survey for England and Scottish Health Survey are annual, on-going repeated, cross-sectional, general population-based studies examining individuals living in households in each country.^{11,12} In the present sample we amalgamated data from both the Scottish Health Survey (1998, 2003), and Health Survey for England (1998, 1999, 2003, 2004). Consenting study members (94% in Health Surveys for England, 82.5% in Scottish Health Surveys) were linked to National Health Service mortality data. The final analytic sample consisted of 13,443 men and women aged over 35 and free of CVD or cancer (for sample selection, see Appendix). Study participants gave full informed consent and ethical approval was obtained from the London Research Ethics Council.

Assessment of direct and second hand smoke exposure

Data on self reported smoking were collected using standard methods^{11,12} and classified into three groups (current/ex-smoker/never). Exposure to SHS was assessed using salivary cotinine, which is a reliable and valid circulating biochemical marker of nicotine exposure.¹⁰ A dental roll saturated with participants' saliva was placed in a tube and later analysed using a Hewlett Packard hp5890 gas chromatograph (Hewlett Packard, Palo Alto, CA, USA), with a rapid-liquid chromatography technique (coefficient of variation [CV] <7%). In keeping with other analyses,^{1,4} participants reporting non-smoking status but with salivary cotinine > 15 ng/mL were re-categorised as smokers.

Demographic and clinical variables

Computer-assisted personal interviewing modules assessed respondents' demographics, mental health status, history of disease, and health behaviours. In a separate visit, qualified nurses collected blood samples and measured seated blood pressure. Blood samples were analysed for CRP, fibrinogen, and total and HDL-cholesterol. The analysis of CRP levels from serum was performed using the N Latex high sensitivity CRP mono immunoassay on the Behring Nephelometer II analyser (CV <6%). Fibrinogen levels were determined using the Organon Teknika MDA 180 analyser, using a modification of the Clauss thrombin clotting method (CV <10%). Cholesterol and HDL cholesterol was measured using cholesterol oxidase assays on an Olympus 640 analyzer.

Mortality follow-up

Diagnoses for primary cause of death was recorded using the *International Classification of Diseases*, Ninth (ICD-9) and Tenth (ICD-10) Revisions. Cardiovascular disease codes were 390–459 for ICD-9 and I01-I99 for ICD-10.

Statistical analysis

Exposure to nicotine was categorised into four groups, representing 'low' SHS (Salivary cotinine ≤ 0.05 ng/mL), 'moderate' SHS (0.06 – 0.70 ng/mL), 'high' SHS (0.71 – 14.99 ng/mL) and 'current smoker' (based on self report or cotinine ≥ 15 ng/mL). This categorisation of SHS was based on previous evidence for health effects at this level of exposure.^{1,4} We used general linear models to examine the association between SHS and biological risk factors. The CRP data were log transformed in order to normalise the distribution. We used Cox proportional hazards models to compute hazard ratios (HR) with accompanying 95% confidence intervals (CIs) for the association between cotinine levels and CVD death/all cause-death. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure, although no appreciable violations were noted. In these analyses, calendar time (months) was the time scale. For participants that remained alive, the data were censored at 28th February 2008 in the Health Survey for England and 30th December 2008 in the Scottish Health Survey. There were no clear differences in our results between men and women, so the data were pooled and gender-adjusted. We fitted several mutually exclusive models (see Tables 3 and 4) and the percentage change in HR after multiple adjustments in comparison to the basic (age-adjusted) model was quantified as follows: $(HR_{\text{basic model}} - HR_{\text{adjusted}})/HR_{\text{basic model}} - 1) \times 100$.¹³ The 'non-smoking' group consisted of both never and ex-smokers although we conducted sensitivity analyses to examine associations among both groups separately. Statistical significance of $p < 0.05$ was employed throughout. All analyses were conducted using SPSS version 14.

Results

Characteristics

In the present sample, 28.7% of participants were classified as smokers and 20.8% had high SHS exposure based on levels of salivary cotinine. There was a dose-response relationship between self-reported smoking and cotinine values (Figure 1). Never smokers and ex-smokers did not differ significantly in levels of salivary cotinine. In comparison to those with lower SHS exposure, both smokers and participants with high SHS were younger, more likely to be male, come from lower social status groups, live in Scotland, and be less physically activity (Table 1). Levels of psychological distress were significantly elevated in smokers. Self-reported diabetes was not associated with smoking and only marginally with SHS exposure.

Correlations with inflammatory markers

Cigarette smoking was related to increased levels of fibrinogen, CRP, and lower HDL-cholesterol (Table 2). High SHS was associated with elevated CRP and blood pressure compared with low SHS. There were also significant associations of CRP and fibrinogen with age, female sex (for fibrinogen), lower physical activity and low social status/survey location (Appendix Table A1).

Cotinine and risk of CVD and all-cause death

Over an average follow up period of 8.0 years (range: 1 to 128 months) there were 1221 all-cause deaths and 364 CVD deaths. As anticipated, conventional risk factors were associated with CVD death (Appendix Table B1). In the total cohort, the association between SHS category and CVD did not reach conventional levels of statistical significance, although log cotinine, as a continuous variables, was associated with CVD (per unit increase; HR = 1.21, 95% CI, 1.15 – 1.25) (Table 3). When we restricted analyses to never-smokers, high SHS exposure was associated with over a 2-fold increased risk of CVD death (Table 3), although there was no association in ex-smokers (HR = 0.87, 95% CI, 0.55 – 1.36). Based on self-report, ex-smokers were at elevated risk of CVD compared with never (HR = 1.38, 95% CI, 1.07 – 1.78).

In the total cohort there was a significant association between SHS exposure and all cause mortality (Table 4). Although not reaching conventional levels of statistical significance we observed stronger associations in never-smokers (HR 1.33, 0.94 – 1.88), than in ex-smokers (HR 1.14, 0.89 – 1.48). The removal of 56 deaths within the first two years of follow up did not substantially alter these results.

Proportion of cotinine – CVD association explained by inflammatory markers

When we included all biological risk factors in the models for the total sample, the HR for high SHS and CVD death was attenuated by 48% (Table 3) and by 40% in the case of all cause mortality (Table 4). This effect was almost entirely explained by CRP since removal of other risk factors did not impact the result. When behavioural and psychosocial covariates (in addition to biological variables) were included in a fully adjusted model the point estimate was attenuated to the null. In the case of smoking, however, there remained an elevated risk despite full adjustments. When we focused on men and women who reported never smoking there remained over a two-fold increased risk of CVD death for high SHS that was minimally affected by adjustment for biological covariates. The excess risk was exactly 2-fold after full adjustment for all risk factors.

Discussion

The aim of the present study was to examine the association between objectively measured SHS and incident CVD death and the extent to which this association could be explained through novel (non-conventional) mechanisms. Firstly, there was an association of SHS exposure with all cause mortality and CVD death, which confirms results from two previous studies.^{4,5} We observed elevated levels of low-grade inflammation, indexed by CRP, in participants exposed to high SHS, and this partly explained the elevated risk of CVD and all-cause death associated with high SHS in the total cohort, but not in the sub-group of never smokers.

Previous studies on the association between SHS exposure and markers of inflammation and haemostasis have produced inconsistent findings. In a Greek population study, participants with a self-reported exposure to SHS on more than 3 days a week demonstrated elevated levels of CRP, fibrinogen, and white blood cell counts,¹⁴ and among Japanese women,

exposure to SHS outside the home was related to elevated fibrinogen.¹⁵ In studies that have employed objective measures of SHS, data from the Third National Health and Nutrition Examination Survey found associations of high SHS with fibrinogen but not CRP and white cell count,³ although the British Regional Heart Study demonstrated positive associations with all of these biomarkers, plus interleukin-6 and von Willebrand factor.¹

Previous studies based on self-reported SHS exposure have reported modest – typically 1.2 to 1.3-fold - increase in risk of CVD.¹⁶ A 1.4-fold increased risk was reported in a study utilising objective measures.⁴ Our data with a 1.2-fold excess risk for high SHS and CVD death in the total cohort is largely comparable with these figures, except for the associations in ‘never-smokers’ that is far larger than previous reports. In the case of ‘never-smokers’ there remained a two fold increased risk of CVD death for high SHS exposure after full adjustment for psychosocial, behavioural, and biological risk factors. In never smokers the associations of SHS with inflammatory and haemostatic risk factors were non-significant (data not shown), which is consistent with previous findings.¹ Thus, other mechanisms might be responsible for the excess risk of CVD. For example, experimental data suggests that SHS exposure can elicit acute endothelial dysfunction, although precise mechanisms remain unclear since the effects of SHS on the number and functional activity of circulating endothelial progenitor cells is inconsistent.^{17,18} This mechanism may account for the association of SHS with circulating markers of endothelial cell activation, such as von Willebrand factor.¹ Interestingly, there was no association between SHS exposure and CVD in ex-smokers. This might be partly explained by the fact ex-smokers already have heightened risk of CVD in comparison with never-smokers, thus SHS exposure may not add to existing risk. Indeed, inflammatory mediators like CRP are still significantly raised in ex-smokers up to 10 to 20 years after quitting,⁷ suggesting a persistent low-grade inflammatory response in former smokers. Former smokers may also be advised to quit because of existing health problems thus the associations may in part also be explained by reverse causation. Our data confirm the strong association between active smoking and CVD/all cause mortality,¹⁹ although the estimated effects were lower when using the objective indicator.

The present data were collected before the introduction of smoke free legislation in England and Scotland. The smoking ban appears to have already had a considerable impact on the health of the British population,²⁰ although we were unable to estimate the effects of this intervention in these analyses since follow up data on cotinine were not available. However, we would not expect that our results have been confounded by the smoking ban as our study includes only seven months of CVD deaths after the introduction of the ban (July 2007). Due to the lack of follow-up data on cotinine we were also unable to account for the effects of changes in smoking behaviour that are known to fluctuate over time. There was a large amount of missing data on alcohol intake and body mass index thus we were unable to account for these factors in our analyses. However, analyses in a smaller sub-sample of participants with available data on alcohol and body mass index suggested that the association between SHS exposure and CVD was not explained by these variables.

In summary, very few large scale, population-based studies have collected objective biochemical markers of SHS exposure with follow up data on mortality. Thus, we have presented novel data on the association between objectively measured SHS and incident CVD death in a nationally representative sample of British adults. We observed elevated levels of low grade inflammation in otherwise healthy participants exposed to high SHS, and this partly explained their elevated risk of CVD death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Median salivary cotinine levels in relation to self reported smoking status (cigarettes per day)

There was a dose-response relationship between self-reported smoking and cotinine values. Never smokers and ex-smokers did not differ significantly in levels of salivary cotinine.”

Table 1
Baseline characteristics of the study participants according to nicotine exposure (n=13,443)

Variable (sd)	Non-smoker (cotinine level; ng/mL)			Smoker (n=3859)	
	< 0.06 (n=1703)	0.06 – 0.70 (n=5089)	>0.70<15.0 (n=2793)		
Age (yrs)	55.6±13.5	54.2±12.9	53.7±12.5	50.8±11.4	<0.001
Sex (% men)	41.0	44.0	52.7	51.7	<0.001
Lower social status (% IV/V)	12.4	14.1	20.3	27.8	<0.001
Nationality (% Scottish)	49.3	55.0	57.6	61.0	<0.001
Psychological distress (%)	11.5	12.1	13.4	18.6	0.125
Weekly MVPA (% none)	50.6	48.5	55.1	63.3	<0.001
Doctor diagnosed diabetes (%)	2.9	2.4	3.3	2.3	0.06
					.52

MVPA, moderate-vigorous physical activity.

^a p-trend refers to trend across non-smokers,

^b p-trend refers to trend across whole sample.

Table 2

Association between second hand smoke exposure, smoking and CVD risk markers at baseline (n=13,443)

Exposure (cotinine level)	Fibrinogen β (95% CI)	log CRP β (95% CI)	Systolic BP β (95% CI)	HDL-C β (95% CI)
Low SHS (<0.06 ng/mL)	0 (Reference)	Reference	Reference	Reference
Medium SHS (0.06–0.7 ng/mL)	−0.01 (−0.04, 0.03)	0.002 (−0.04, 0.04)	−0.20 (−1.14, 0.73)	0.002 (−0.03, 0.03)
High SHS (0.71–14.99 ng/mL)	−0.01 (−0.03, 0.04)	0.08 (0.04, 0.13)	1.30 (0.26, 2.33)	0.006 (−0.02, 0.03)
Smokers (≥ 15 ng/mL)	0.30 (0.26, 0.34)	0.28 (0.24, 0.32)	−0.22 (−1.20, 0.76)	−0.08 (−0.10, −0.05)
p-trend	<0.001	<0.001	<0.001	<0.001

Models adjusted for age and sex. β -coefficients represent mean differences compared with reference group

CRP=C-reactive protein, BP = blood pressure, HDL-C=High density lipoprotein cholesterol

Table 3

Cox proportional hazards models of second hand smoke exposure, smoking and CVD mortality.

Exposure	Event/N	Age adjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Fully adjusted HR (95% CI)
All	364/13,443					
Low SHS	52/1703	1.00 (reference)	1.00	1.00	1.00	1.00
Medium SHS	114/5088	0.89 (0.64 – 1.23)	0.88 (0.63 – 1.22)	0.85 (0.61 – 1.18)	0.88 (0.64 – 1.23)	0.86 (0.62 – 1.19)
High SHS	73/2793	1.21 (0.85 – 1.73)	1.08 (0.75 – 1.54)	1.00 (0.69 – 1.43)	1.11 (0.77 – 1.58)	0.97 (0.68 – 1.40)
Smokers	125/3859	2.44 (1.75 – 3.40)	2.12 (1.52 – 2.97)	2.03 (1.45 – 2.85)	2.04 (1.46 – 2.86)	1.74 (1.24 – 2.46)
Log cotinine (per unit)		1.21 (1.15 – 1.25)	1.18 (1.13 – 1.23)	1.17 (1.12 – 1.23)	1.16 (1.12 – 1.22)	1.14 (1.09 – 1.19)
Never-smokers	96/5,500					
Low SHS	15/1025	1.00	1.00	1.00	1.00	1.00
Medium SHS	49/3024	1.28 (0.72 – 2.28)	1.28 (0.71 – 2.28)	1.28 (0.71 – 2.29)	1.35 (0.75 – 2.42)	1.33 (0.74 – 2.39)
High SHS	32/1455	2.22 (1.20 – 4.12)	2.02 (1.09 – 3.75)	1.98 (1.05 – 3.72)	2.22 (1.19 – 4.15)	2.00 (1.06 – 3.78)
Log cotinine (per unit)		1.72 (1.21 – 2.44)	1.62 (1.13 – 2.32)	1.60 (1.11 – 2.30)	1.69 (1.18 – 2.42)	1.60 (1.11 – 2.31)

All models mutually exclusive of one another

Model 1 (behavioural): adjusted for age, sex, moderate-vigorous physical activity (none, up to 3/wk, >3/week)

Model 2 (psychosocial): adjusted for age, sex, social status (I/II professional/intermediate, III skilled non-manual/manual, IV/V part skilled/unskilled), survey location (England, Scotland), psychological distress (GHQ-12 < or ≥ 4).

Model 3 (biological): adjusted for age, sex, log C-reactive protein, fibrinogen, HDL-cholesterol, systolic blood pressure

Table 4

Cox proportional hazards models of second hand smoke exposure, smoking and all cause mortality.

Exposure	Event/N	Age adjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Fully adjusted HR (95% CI)
All	1221/13,443					
Low SHS	153/1703	1.00	1.00	1.00	1.00	1.00
Medium SHS	349/5088	0.89 (0.74 – 1.08)	0.88 (0.73 – 1.07)	0.85 (0.70 – 1.03)	0.89 (0.74 – 1.08)	0.86 (0.71 – 1.05)
High SHS	233/2793	1.25 (1.02 – 1.53)	1.15 (0.94 – 1.42)	1.07 (0.87 – 1.31)	1.15 (0.93 – 1.41)	1.03 (0.83 – 1.27)
Smokers	487/3859	2.89 (2.40 – 3.48)	2.60 (2.16 – 3.14)	2.44 (2.02 – 2.95)	2.52 (2.09 – 3.04)	2.19 (1.81 – 2.65)
Log cotinine (per unit)		1.23 (1.21 – 1.26)	1.21 (1.19 – 1.24)	1.21 (1.18 – 1.24)	1.21 (1.18 – 1.21)	1.18 (1.16 – 1.21)
Never-smokers	273/5,500					
Low SHS	56/1025	1.00	1.00	1.00	1.00	1.00
Medium SHS	142/3024	0.97 (0.71 – 1.32)	0.96 (0.70 – 1.31)	0.94 (0.69 – 1.28)	1.00 (0.73 – 1.36)	0.98 (0.71 – 1.33)
High SHS	75/1455	1.33 (0.94 – 1.88)	1.26 (0.89 – 1.79)	1.24 (0.87 – 1.77)	1.31 (0.92 – 1.86)	1.27 (0.89 – 1.81)
Log cotinine (per unit)		1.26 (0.99 – 1.60)	1.21 (0.95 – 1.55)	1.21 (0.95 – 1.55)	1.24 (0.97 – 1.58)	1.21 (0.95 – 1.55)

All models mutually exclusive of one another

Model 1 (behavioural): adjusted for age, sex, moderate-vigorous physical activity (none, up to 3/wk, >3/week)

Model 2 (psychosocial): adjusted for age, sex, social status (I/II, III, IV/V), survey location (England, Scotland), psychological distress (GHQ-12 < or ≥ 4).

Model 3 (biological): adjusted for age, sex, log C-reactive protein, fibrinogen, HDL-cholesterol, systolic blood pressure