Short Report – Journal of Epidemiology and Community Health

Passive smoking assessed by salivary cotinine and self-report in relation to cause-specific mortality: 17 year follow-up of study participants in the UK Health and Lifestyle Survey

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Competing Interest: None declared.

Abstract

Background. Evidence that passive smoking is a risk factor for cardiovascular disease and selected cancers is largely derived from studies in which this exposure is self-reported. Objective assessment using biochemical techniques may yield a more accurate estimate of risk, although each approach has its strengths and weaknesses. We examined the association of salivary cotinine, a widely utilized biomarker for passive smoking, and self-reported passive smoking in the home, with mortality from all causes, cardiovascular disease and all cancers combined.

Methods. In 1992, investigators on the UK Health and Lifestyle Survey collected data on salivary cotinine, self-reported smoking (direct and passive), and a range of covariates in 3731 men and women aged 25 years and over. Mortality was ascertained using linkage to national death records.

Results. Analyses were based on 2523 individuals (1433 or 57% women) who classified themselves as non-smokers (never and former). Seventeen years of follow-up gave rise to 588 deaths (253 from cardiovascular disease and 146 from cancer). In men, hazard ratios (adjusted for a range of covariates which included socioeconomic position, alcohol intake, and disease history) for the association between cotinine levels (1.3-15.0 ng/ml vs. $\leq$0.3 ng/ml) and the various mortality outcomes were weak for total mortality (hazard ratio; 95% confidence interval: 1.22; 0.91-1.64) and cardiovascular disease (1.25; 0.78-1.99) and absent for all cancers combined (1.10; 0.61-2.00). Corresponding associations were generally stronger when self-reported passive smoking (some vs. none) was the exposure of interest: 1.53 (1.12-2.08), 1.88 (1.20-2.96), and 1.58 (0.85-2.93). The pattern of association for women in both sets of analyses was less consistent.

Conclusions. In men in the present study, compared with our biochemical marker of passive smoking, cotinine, mortality was generally more strongly associated with self-reported passive smoking.

Introduction

Position statements and systematic reviews conclude that passive smoking is a risk factor for cardiovascular disease and selected cancers.[1,2] Most of this evidence is derived from studies using self-reported passive smoking. Biochemical markers of passive smoking—carbon monoxide, carboxyhaemoglobin, nicotine, and cotinine—may lead to a more accurate estimate of its influence on health, although each method of measurement has its strengths and weaknesses. While cotinine particularly appears to offer high specificity and sensitivity,[3-5] very few studies have these data together with prospective measurement of health outcomes. Moreover, to our knowledge, simultaneous comparison of the association of self-reported and biochemical markers with disease risk is rare.[6] With data on both salivary cotinine and self-reported passive smoking, the Health and Lifestyle Survey provides an unusual opportunity to make such a comparison. With passive smoking being relatively common – although smoking is banned in public spaces in the UK, more than one third of people are exposed to passive smoking in the home[7] – quantification of its health impact continues to have value in informing public health policy.

Methods

The Health and Lifestyle Survey (HALS1) is a prospective cohort study of 9003 men and women initiated in 1984/1985.[8,9] The target population was UK-based adults (aged 18 years and older) randomly selected from Electoral Registers. In 1992, the second wave of the HALS study was conducted (HALS2) at which point cotinine measurements were introduced. For the purposes of the present analyses therefore, HALS2 represents 'baseline' data collection. Of the 6626 eligible HALS1 participants, 5352 (81%) were interviewed in HALS2. Ethical approval for the HALS surveys was received from the British Medical Association Ethical Committee before the initiation of each survey.[9]

Assessment of passive smoking

Interviews were conducted in the respondents' home by a research worker who administered a questionnaire that was used to enquire about demographic characteristics, direct smoking habits, chronic illnesses, and socioeconomic position.[9] The assessment of passive smoking was based on cotinine measurement and self-report. All study members were asked to place a dental roll in their mouths for 3-5 minutes until it was saturated with saliva. Having been stored in a specimen tube, the rolls were either immediately sent to the laboratory or frozen pending analyses. Cotinine concentration was measured by gas-liquid chromatography.[10] Concentrations below 0.10 ng/ml were undetectable and set to 0.05 ng/ml. The present analyses are restricted to adults who self-reported that they were former or never-smokers (current smokers were excluded). In agreement with other studies,[6,11] and based on the cotinine distribution in the present study, we created three cotinine groups; ≤0.3 (low exposure); 0.4-1.2 (medium); and 1.3-15.0 ng/ml (high). Respondents were also asked whether they lived with someone who currently smoked. Current non-smokers who answered positively were defined as self-reported passive smokers.

Assessment of covariates and mortality experience

Socioeconomic position was based on occupational social class as defined by the UK Registrar General's classification. Alcohol consumption (number of units per week) was ascertained from the self-reported amount of beer, cider, sherry, vermouth, wines, spirits, liqueurs, and other types of alcoholic drinks consumed in the previous week. Physical activity was denoted by time spent in a number of leisure time activities (keeping fit, sports, jogging, swimming, cycling etc.) during the past fortnight. We defined disease history as having any of the following conditions: coronary heart disease, cancer, or type 2 diabetes.

Using the National Health Service (NHS) Central Registry, 98% of study members were linked to mortality vital status. We classified mortality according to the *International Classification of*

Diseases (ICD, 9th revision) into all causes, cardiovascular disease (codes 390–460), and cancers from all sites combined (codes 140—209)

Statistical analyses

Having ascertained that the proportional hazards assumption had not been violated–the log-log-plot curves were approximately parallel–we used Cox proportional hazards regression[12] with calendar period as time scale to estimate the relationship between passive smoking using self-report or cotinine and risk of death from all causes, cardiovascular disease and cancer. Follow-up began at the date of the survey in 1992 and continued until date of death or June 30, 2009, whichever came first. Findings from a recent meta-analysis indicate that direct cigarette smoking was associated with a greater risk of coronary heart disease in women than men.[13] On the basis that the same observation might be made when passive smoking was the exposure of interest, men and women were analyzed separately.

Results

Out of 5352 participants in HALS2, 3731 (70%) had complete data (mean age 51.0 years; 2083 were female). Of these, 1321 (35.4 %) study members reported that they were never smokers, 1328 (35.6 %) former smokers, and 1028 (29.0 %) current smokers. The corresponding geometric means (IQR) for cotinine (ng/ml) were 0.69 (0.30-1.73), 0.95 (0.40-2.00), and 218.57 (191.15-423.68) in women; and 0.96 (0.40-2.30), 1.33 (0.50-3.20), and 279.05 (227.85-471.58) in men. Thus, while cotinine levels were similar in never and former smokers, they were markedly higher in current smokers.

Follow-up time among the 3731 full sample was 17.1 years (57,364 person-years), giving rise to 886 deaths from all causes, of which 359 were from cardiovascular disease and 245 from cancers. As anticipated, in women, self-reported current smokers relative to never-smokers experienced

markedly elevated rates of total (age-adjusted hazard ratio [HR]; 95% confidence interval [CI]: 2.45; 1.91-3.14), cardiovascular disease (2.27; 1.52-3.40), and cancer (2.78; 1.81-4.29) mortality. Corresponding results (95 % CI) for men were: 2.28 (1.70-3.06), 1.86 (1.16-2.99) and 3.39 (1.86-6.17).

The primary analytical sample was a combined group of 2582 never smokers or former smokers, the latter group not having smoked for one year or more. Using previously utilised thresholds,[14-15] the 59 participants who reported that they were non-smokers but nonetheless had cotinine levels at or above 15 ng/ml were excluded as they were regarded as current smokers. This resulted in an analytical sample of 2523 non-smokers (1314 never smokers, 1209 former smokers). During follow-up, 588 people died (253 from cardiovascular disease, 146 from all cancers combined). In Table 1 we show the associations between salivary cotinine level and the three mortality outcomes in these non-smoking study participants stratified by gender. There was some evidence of an age-adjusted elevated risk of total (men only) and cardiovascular disease mortality (men and women) in the highest cotinine group, although statistical significance at conventional levels was not evident in any of these analyses. Adjustment for a range of additional potential confounders (socioeconomic position, alcohol intake, physical activity, and disease history) did not appreciably change these effect estimates.

Next, in the same group of non-smokers, we examined the association between self-reported passive smoking and mortality experience (Table 2). Using this method, passive smoking was reported by 179 (16.4 %) never- or former smoking men and by 276 (19.3 %) never- or former smoking women. As expected, cotinine levels (geometric means [IQR]) in women who reported passive exposure to cigarette smoke were higher (1.90 [1.10-4.00]) than those who did not report living with a smoker (0.56 [0.30-1.30], p-value for difference<0.001). Corresponding values in men were 3.24 (1.80-5.90) and 0.76 (0.40-1.80) (p-value for difference<0.001). In men, self-

Table 1. Hazard ratios (95% confidence intervals) for the relation of salivary cotinine (ng/ml) with cause-specific mortality risk among *non-smoking* men and women: the UK Health and Lifestyle Survey 2 (N=2523)

	All-cause mortality				Cardiovascular disease mortality				All cancer mortality		
	No. of deaths/no. at risk	Age-adjusted	Fully-adjusted[1]		No. of deaths/no. at risk	Age-adjusted	Fully-adjusted[1]		No. of deaths/no. at risk	Age-adjusted	Fully-adjusted[1]
Men (N=1090)											
≤0.3 ng/ml	85/220	1 (ref)	1		34/220	1	1		21/220	1	1
0.4-1.2	90/387	1.02 (0.76-1.38)	1.01 (0.75-1.36)		39/387	1.12 (0.71-1.79)	1.06 (0.66-1.69)		22/387	0.93 (0.51-1.70)	0.95 (0.52-1.75)
1.3-15.0	125/483	1.26 (0.95-1.67)	1.22 (0.91-1.64)		51/483	1.31 (0.84-2.05)	1.25 (0.78-1.99)		29/483	1.08 (0.61-1.92)	1.10 (0.61-2.00)
P for trend[2]		0.091	0.165			0.223	0.336			0.760	0.723
Women (N=1433)											
≤0.3 ng/ml	89/391	1	1		35/391	1	1		28/391	1	1
0.4-1.2	102/546	0.89 (0.67-1.18)	0.81 (0.61-1.09)		43/546	0.96 (0.62-1.50)	0.82 (0.52-1.30)		25/546	0.67 (0.39-1.15)	0.66 (0.38-1.14)
1.3-15.0	97/496	0.99 (0.75-1.33)	0.90 (0.67-1.22)		51/496	1.37 (0.89-2.12)	1.19 (0.76-1.87)		21/496	0.64 (0.36-1.13)	0.63 (0.35-1.13)
P-value for trend[2]		0.987	0.544			0.127	0.347			0.117	0.114

[1]Full adjustment is adjustment for: baseline age, socioeconomic position, alcohol intake, physical activity and a history of heart disease, cancer and diabetes.
[2]From Cox regression models of the linear associations between three categories of cotinine level and mortality in non-smokers.

Table 2. Hazards ratios (95% confidence intervals) for the relation of self-reported passive smoking with cause-specific mortality risk among *non-smoking* men and women: the UK Health and Lifestyle Survey 2 (N=2523)

	All-cause mortality				Cardiovascular disease mortality				All cancer mortality		
	No. of deaths/no. at risk	Age-adjusted	Fully-adjusted[1]		No. of deaths/no. at risk	Age-adjusted	Fully-adjusted[1]		No. of deaths/no. at risk	Age-adjusted	Fully-adjusted[1]
Men (N=1090)											
Non passive smokers	247/911	1 (ref)	1		98/911	1	1		59/911	1	1
Passive smokers	53/179	1.62 (1.20-2.19)	1.53 (1.12-2.08)		26/179	2.03 (1.31-3.15)	1.88 (1.20-2.96)		13/179	1.58 (0.86-2.90)	1.58 (0.85-2.93)
P-value for difference		0.002	0.007			0.002	0.006			0.143	0.150
Women (N=1433)											
Non passive smokers	255/1157	1	1		110/1157	1	1		66/1157	1	1
Passive smokers	33/276	0.99 (0.68-1.43)	0.96 (0.66-1.39)		19/276	1.58 (0.96-2.60)	1.55 (0.94-2.56)		8/276	0.72 (0.34-1.51)	0.72 (0.34-1.51)
P-value for difference		0.939	0.837			0.072	0.085			0.385	0.381

[1]Fully adjustment is adjustment for: baseline age, socioeconomic position, alcohol intake, physical activity and a history of heart disease, cancer and diabetes

reported passive smoking was associated with elevated rates of all three mortality endpoints to differing degrees of statistical significance. For women, only cardiovascular disease mortality rates were raised among passive smokers; again, statistical significance was not apparent. This pattern of association remained after multivariable adjustment.

In sensitivity analyses, additional adjustment for smoking history (never and former smoking), educational level, marital status, body mass index, and systolic blood pressure had no marked impact on the effect estimates. We also conducted some subgroup analyses. To address the problem that individuals who report being former smokers may oscillate between cessation and re-initiation,[16] and to facilitate comparison with some studies where the focus has been never-smokers, [14,17-19] we repeated analyses in never-smokers only. Numbers were markedly lower in this group (N=1314; 218 deaths during follow-up) leading to lower statistical stability. The associations between cotinine level and mortality outcomes were generally of the same magnitude as in the afore-described analyses except for cardiovascular disease-mortality among women, which was more strongly associated with cotinine level among never smokers than among all non-smokers (tables available upon request).

Discussion

Our main findings were that cotinine level, our biomarker of passive smoking, was weakly related to mortality among non-smokers in the present cohort study. In contrast, when the exposure was derived from self-report, the passive smoking—mortality relationship was stronger and more consistent, most notably among men. Investigators utilising subjective measures of passive smoking status have found an increased risk of mortality, with hazard ratios typically ranging from 1.1 to 1.7, although this varies according to cause of death, age, sex, and type and intensity of passive smoking.[17-20] Our results for self-reported passive smoking and mortality from all-causes,

cardiovascular disease and cancer broadly fall within this range, particularly in analyses of men. That we did not find evidence of an association between cotinine and cardiovascular disease mortality is not unique.[6,21]

Self-reported passive smoking may be an overall measure of habitual exposure, although, in this study, only in one domain – the home – with participants not asked about exposure in the workplace or elsewhere. By contrast, while cotinine may capture exposure in all contexts, it has a half-life of 20 hours so will only index passive smoking exposure in the very recent past. It is also the case that there is some individual variability in nicotine metabolism and elimination.[4,5]

HALS2 has a series of strengths. The participants in HALS2 were compared with those of the 1991 census, and the distribution of the HALS2 population by age and region was similar to that seen in the 1991 census. This suggests a reasonable degree of generalizability of our results. Further, in a prior comparison of baseline risk factor–mortality associations, in people who participated in the resurvey and those who did not, effect estimates were similar indicating that selection bias at least based on the baseline sample had not occured.[22] Moreover, known risk factor– cardiovascular disease associations (for obesity, raised blood pressure, amongst others) are also evident in HALS,[22] as were the usual effects for direct smoking reported herein. This gives us some confidence in the more novel results for passive smoking reported herein.

Our study is of course not without its shortcomings. The self-report passive smoking variable was dichotomous and as such we could not examine dose-response relationships with the mortality outcomes. Passive smoking, together with other exposure and covariate data, was captured on a single (baseline) occasion which may have resulted in some degree of misclassification as these variables will have changed during follow-up. However, a high proportion of the HALS participants had stable smoking habits over the seven years between surveys, with 88.2 % of never-

smoking men and 84.1 % of never-smoking women in HALS1 being so classified in HALS2. Similarly high stability was apparent for former and current smokers (results not shown). Finally, while recognizing that because direct smoking is not linked to every cancer phenotype there is no good reason to expect passive smoking to be, low numbers nonetheless meant we had to utilise all cancers combined as a single outcome.

In conclusion, in the present study, mortality outcomes were generally more strongly associated with self-reported passive smoking than salivary cotinine.

What is already known on this subject?

- Evidence for the deleterious health impact of passive smoking is accumulating.
- With these data almost exclusively based on self-assessed passive smoking, we report on rare analyses of the relation of cotinine, a biomarker of passive smoking, with mortality risk.

What does this study add?

- In men, we found stronger effects for mortality in relation to self-reported passive smoking compared with salivary cotinine.

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