Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement

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Abstract

Objective To examine the associations between a biomarker of overall passive exposure to tobacco smoke (serum cotinine concentration) and risk of coronary heart disease and stroke.
Design Prospective population based study in general practice (the British regional heart study).
Participants 4729 men in 18 towns who provided baseline blood samples (for cotinine assay) and a detailed smoking history in 1978-80.
Main outcome measure Major coronary heart disease and stroke events (fatal and non-fatal) during 20 years of follow up.
Results 2105 men who said they did not smoke and who had cotinine concentrations <14.1 ng/ml were divided into four equal sized groups on the basis of cotinine concentrations. Relative hazards (95% confidence intervals) for coronary heart disease in the second (0.8-1.4 ng/ml), third (1.5-2.7 ng/ml), and fourth (2.8-14.0 ng/ml) quarters of cotinine concentration compared with the first (≤ 0.7 ng/ml) were 1.45 (1.01 to 2.08), 1.49 (1.03 to 2.14), and 1.57 (1.08 to 2.28), respectively, after adjustment for established risk factors for coronary heart disease. Hazard ratios (for cotinine 0.8-14.0 *v* ≤ 0.7 ng/ml) were particularly increased during the first (3.73, 1.32 to 10.58) and second five year follow up periods (1.95, 1.09 to 3.48) compared with later periods. There was no consistent association between cotinine concentration and risk of stroke.
Conclusion Studies based on reports of smoking in a partner alone seem to underestimate the risks of exposure to passive smoking. Further prospective studies relating biomarkers of passive smoking to risk of coronary heart disease are needed.

Introduction

Meta-analyses examining the effect of living with a cigarette smoker on risk of coronary heart disease (CHD) among non-smokers have shown an overall increase in risk of about one quarter, after adjustment for potential confounding factors.[1 2] Passive smoking may also be related to risk of stroke.[3]

ELPS *This is the abridged version of an article that was posted on bmj.com on 30 June 2004: http://bmj.com/cgi/doi/10.1136/bmj.38146.427188.55*

Living with someone who smokes accounts for less than half of the variation in cotinine concentration among non-smokers[4] and does not take account of additional exposure in workplaces and in public places (particularly pubs and restaurants).[5] Biomarkers of passive exposure to smoking, particularly cotinine (a nicotine metabolite), can provide a summary measure of exposure from all these sources.[6] Although cotinine concentration in non-smokers has been strongly related to prevalent CHD,[7] there are no published reports of the prospective associations between serum cotinine concentration and risk of CHD and stroke in non-smokers. We examined these associations in the British regional heart study, a prospective study of cardiovascular disease in middle aged men, using retained baseline samples for retrospective measurement of cotinine.

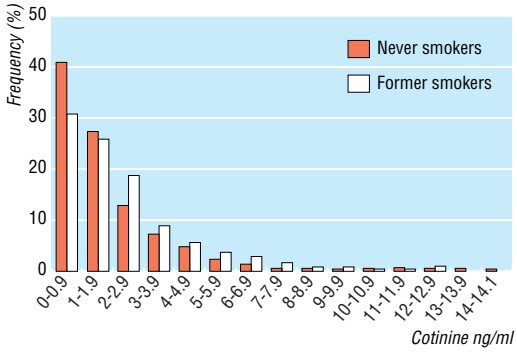

Fig 1 Distribution of serum cotinine concentrations among current non-smokers; lifelong non-smokers and former smokers are shown separately

Methods

The British regional heart study is a prospective study of cardiovascular disease in 7735 men aged 40-59 years in 24 towns (78% response rate).[8]

Baseline assessment—In 1978-80, research nurses administered a questionnaire on present and previous smoking habits (cigarettes, cigar, pipe), alcohol intake, physical activity, and medical history (including angina, myocardial infarction, stroke, and diabetes diagnosed by a doctor). Participants also completed a questionnaire on chest pain. Blood pressure, non-fasting total serum cholesterol concentration, and high density lipoprotein (HDL) cholesterol were measured. Serum samples were placed in long term storage at −20°C in the last 18 study towns. In 2001-2, these were thawed and cotinine concentration measured.[9]

Follow up—All men were followed up for all cause mortality and cardiovascular morbidity. Deaths were flagged by the NHS central registers. We obtained information on non-fatal CHD events and strokes from general practitioners' reports, and from regular reviews of patients' records every two years throughout follow up.[8] The analyses presented are based on all first major CHD or stroke events during the follow up period to December 2000, with an average follow up of 18.5 years for men who had no myocardial infarction or stroke (range 0.2-20.0 years).

Definition of baseline smoking status—Men were classified as "current non-smokers" at baseline if they reported that they did not smoke cigarettes, cigars, or a pipe and had a serum cotinine concentration <14.1 ng/ml.[10] Among these men, "lifelong non-smokers" were those who reported never having smoked cigarettes, cigars, or a pipe. For comparison purposes, "light active smokers" were men who reported smoking 1-9 cigarettes a day, irrespective of cotinine concentration.

Statistical methods—We used Cox proportional hazards models, stratified by town of residence, to examine the independent contribution of serum cotinine concentration to the risks of CHD and stroke. These produced relative hazards, adjusted for age and other

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Hazard ratios for cotinine group and risk of coronary heart disease (CHD) over 20 years of follow up

	Cotinine concentration (ng/ml)					
	≤0.7	0.8-1.4	1.5-2.7	2.8-14.0	Active smokers (1-9/day)	P value for trend*
All men						
Mean (SD) cotinine (ng/ml)	0.4 (0.2)	1.1 (0.2)	2.0 (0.4)	4.9 (2.1)	138.4 (149.3)	
No of participants	575	508	506	516	192	
No of events	61	74	81	92	34	
Person years	10 488	8966	8897	8823	3317	
CHD rate/1000 person years	5.82	8.25	9.10	10.43	10.25	
Hazard ratio (95% CI)†:						
Adjustment 1	1.00	1.50 (1.06 to 2.12)	1.56 (1.11 to 2.20)	1.61 (1.15 to 2.27)	1.65 (1.08 to 2.54)	0.001
Adjustment 2	1.00	1.47 (1.04 to 2.07)	1.43 (1.00 to 2.02)	1.46 (1.02 to 2.07)	1.60 (1.03 to 2.48)	0.008
Adjustment 3	1.00	1.45 (1.01 to 2.08)	1.49 (1.03 to 2.14)	1.57 (1.08 to 2.28)	1.66 (1.04 to 2.68)	0.001
Excluding former smokers						
Mean (SD) cotinine (ng/ml)	0.4 (0.2)	1.1 (0.2)	2.0 (0.4)	5.0 (2.4)	138.4 (149.3)	
No of participants	308	249	197	191	192	
No of events	31	27	25	28	34	
Person years	5752	4530	3519	3388	3317	
CHD rate/1000 person years	5.39	5.96	7.10	8.27	10.25	
Hazard ratio (95% CI)†:						
Adjustment 1	1.00	1.32 (0.78 to 2.25)	1.44 (0.83 to 2.50)	1.55 (0.90 to 2.69)	1.77 (1.07 to 2.96)	0.006
Adjustment 2	1.00	1.40 (0.82 to 2.39)	1.63 (0.93 to 2.86)	1.46 (0.83 to 2.56)	1.78 (1.07 to 2.99)	0.007
Adjustment 3	1.00	1.54 (0.88 to 2.69)	1.89 (1.05 to 3.39)	1.67 (0.91 to 3.07)	2.05 (1.14 to 3.69)	0.001

*From tests for linear trend between log (cotinine) concentration and CHD hazard across passive smoking groups.
†For CHD: adjustment 1 stratified by town and adjusted for age; adjustment 2 additionally adjusted for systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, FEV_1, height, and pre-existing CHD; adjustment 3 additionally adjusted for BMI, triglycerides, white cell count, diabetes, physical activity (none, occasional, light, moderate or more), alcohol intake (none/occasional, light/moderate, heavy), and social class (I, II, III non-manual, III manual, IV, V, and Armed Forces).

risk factors, for each quarter of the distribution of serum cotinine concentration compared with the lowest. We carried out overall tests of the association, fitting the continuous relation between log cotinine concentration and risk of CHD (see bmj.com). We fitted age, body mass index, height, systolic blood pressure, diastolic blood pressure, serum total cholesterol, high density lipoprotein cholesterol, white cell count, lung function (forced expiratory volume in one second (FEV_1)), and triglyceride concentration as continuous variables. Physical activity was fitted as a factor with four levels, alcohol intake with three levels, and social class with seven levels. History of cigarette smoking, pre-existing CHD, and diabetes were fitted as dichotomous variables.

Results

In the last 18 towns of the study, 5661 men took part (78% response rate). For 4729 of these we had data on history of smoking and blood samples for cotinine analysis. These men resembled the whole study population in reported smoking habits and risks of CHD and stroke. A total of 2158 men reported that they were current non-smokers, of whom 2105 (97.5%) had serum cotinine concentrations < 14.1 ng/ml. Of these, 945 men were classified as lifelong non-smokers, the remaining 1160 as former smokers. The cotinine distributions of these two groups (fig 1) were skewed, with a slightly higher geometric mean cotinine among former smokers than among lifelong non-smokers (1.49 *v* 1.18 ng/ml). Few men in either group had cotinine concentrations close to the 14.1 ng/ml cut off.

Serum cotinine and cardiovascular risk factors—Among current non-smokers, cotinine concentrations were not consistently related to age, total cholesterol concentration, physical activity score, or prevalent CHD but showed graded positive associations with mean body mass index, systolic and diastolic blood pressure, high density lipoprotein cholesterol, white cell count, and triglycerides (weakly) and positive associations with the prevalence of former smoking, heavy drinking, and manual occupation. Cotinine concentrations were inversely associated with FEV_1, prevalence of low alcohol intake, and residence in southern England. These associations were generally little affected when we excluded former smokers. Light active smokers had lower mean body mass index, diastolic blood pressure, and FEV_1 and a higher mean white cell count than men who did not smoke.

Serum cotinine concentration and CHD risk—We examined the association between quarters of the cotinine distribution and CHD hazard ratios among all 2105 current non-smokers using the complete follow up period (table). The risks in the upper three cotinine groups were markedly higher than the risk in the lowest group, with a relative hazard of 1.61 in the highest group in the simplest model, a hazard estimate similar to that of light active smokers. The association between cotinine concentration and CHD seemed graded and was not markedly affected by adjustment for other cardiovascular risk factors. When we examined the overall association between cotinine concentration and CHD, we found that a doubling of cotinine concentration was associated with a hazard increase of 16% (95% confidence interval 6% to 27%).

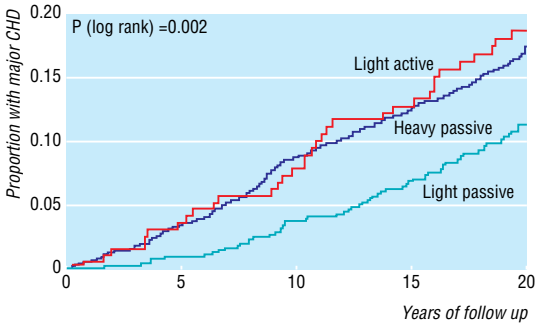

Fig 2 Proportion of men with major CHD by years of follow up in each smoking group. "Light passive" refers to lowest quarter of cotinine concentration among non-smokers (0-0.7 ng/ml), "heavy passive" to upper three quarters of cotinine concentration combined (0.8 to 14.0 ng/ml), "light active" to men smoking 1-9 cigarettes a day

Influence of follow up period—In a Kaplan-Meier plot showing the cumulative proportions of men with major CHD over time among three groups (light passive (lowest cotinine quarter), heavy passive (upper three cotinine quarters), and light active (1-9 cigarettes/day)) we found that the heavy passive and light active groups diverged rapidly from the light passive group during the first years of follow up but remained almost parallel during later years (fig 2). The corresponding hazard ratios for cotinine and risk of CHD in separate five year follow up periods were highest in the early years of follow up and declined with increasing duration of follow up (bmj.com). These patterns were little affected by adjustment for cardiovascular risk factors, and again the hazard ratios for the heavier passive smoking groups were comparable with those of light active smokers. Restriction of these analyses to lifelong non-smokers or to men with no evidence of pre-existing CHD had no material effect on the results.

Serum cotinine exposure and stroke—There was no strong association between cotinine concentration and stroke among non-smokers, either before or after adjustment for major cardiovascular risk factors (see bmj.com). Analyses based on lifelong non-smokers showed similar results.

Discussion

We believe this is the first published report to relate passive exposure to smoking, based on cotinine measurements, prospectively to the risks of CHD and stroke, although cotinine concentration among non-smokers has been related to prevalence of CHD.[7] Our study was conducted in a geographically and socially representative sample of middle aged men.[8] We were able to adjust for a wide range of potential confounding variables, and this had little effect on the results, in agreement with earlier reports.[1,2] A greater concern is the possibility that men in the higher cotinine groups were smoking cigarettes on an intermittent basis. However, study participants had no incentive to provide inaccurate information, there was close agreement between reported smoking and cotinine concentration, and the cotinine threshold was conservative and rarely approached, even among former smokers. In addition,

almost all surviving current non-smokers (99%) continued to report that they were non-smokers in responses to postal questionnaires five and 12 years later.

Passive smoking and CHD

Although the study was modest in size with limited precision, our results suggest that the relative risk of CHD associated with high levels of passive exposure to smoke is greater than that estimated for partner smoking alone, even at exposure levels of 20 cigarettes a day or more.[2] The similarity of relative risks among participants with substantial exposure to passive smoking and those who were light active smokers exposure is consistent with earlier findings.[1] The high relative risk associated with exposure to passive smoking in our study probably reflects the wide range of cotinine concentrations observed among non-smokers; the average concentrations of the lowest and highest cotinine quarters differed by almost 10-fold. This range seems considerably wider than that which might be expected from partner smoking alone, which in recent data has been associated with average increases in cotinine concentration of about 3.6-fold.[4] A 3.6 fold difference in cotinine concentration would, on the basis of the log cotinine-CHD association defined in the present study, be associated with a relative risk of CHD of about 1.32 (95% confidence interval 1.12 to 1.55)—a figure similar to the estimates of the effect of a partner smoking obtained in the earlier systematic reviews.[1 2]

The marked attenuation in the relative risks relating cotinine and CHD with increasing duration of follow up suggests that a single measurement of cotinine is a weak measure of the long term effects of passive smoking. In the present study population, a high initial cotinine concentration probably provides a systematic overestimate of the true longer term passive exposure to smoke, which has declined markedly in Britain during the follow up period—partly because of a declining prevalence of active smoking[11] and partly because passive exposure to smoke in public places and work places has declined.[12] In studies with a single assessment of exposure, analyses based on the first decade or so of follow up may well provide a better indication of true relative risks than those based on prolonged follow up.

As well as providing evidence that the relative risks associated with overall passive exposure to tobacco smoke are higher than those associated with partner smoking alone, the results indicate that important degrees of exposure to passive smoke were widespread in the present cohort, in which three quarters of non-smokers had an increased risk of CHD associated with increased exposure to cotinine. In contrast, the prevalences of partner smoking in studies of non-smoking men in earlier reports have often been well below 50%.[13 14] Taken in combination with the higher estimated relative risks, the high prevalence of exposure suggests that the contribution of passive smoking to the population attributable risk of CHD could be appreciable.

Passive smoking and stroke

Our results do not support the earlier suggestion from a retrospective case-control study that passive tobacco smoke exposure increases risk of stroke,[3] though the confidence intervals around the hazard estimates are wide. The lack of an apparent association between passive exposure to tobacco smoke and risk of stroke suggests that the association between passive smoking and CHD is specific and is not simply due to selection bias placing high risk participants in the higher cotinine groups.

What is already known on this topic

Passive smoking (generally defined as living with someone who smokes) is associated with an increase in risk of coronary heart disease risk of 25-30%

Passive smoking may also increase the risk of stroke, though information is limited

Living with someone who smokes is not the only relevant source of passive smoking, but few studies have taken account of all sources of exposure by relating biomarkers such as cotinine to disease outcomes

What this study adds

Higher concentrations of serum cotinine among non-smokers are associated with an excess risk of coronary heart disease of about 50-60%, but show little association to risk of stroke

Risks associated with passive smoking are widespread among non-smokers in this study population

The association between serum cotinine concentration and coronary heart disease seems to decline with time since assessment of exposure, suggesting that studies examining the association of passive smoking to coronary heart disease over long follow up periods may have underestimated the true strength of association

Conclusion

High overall exposure to passive smoking seems to be associated with a greater excess risk of CHD than partner smoking and is widespread in non-smokers, suggesting that the effects of passive smoking may have been underestimated in earlier studies. Our results add to the weight of evidence suggesting that exposure to passive smoking is a public health hazard and should be minimised.

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Competing interests: None declared.

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Acquisition of *Helicobacter pylori* infection after outbreaks of gastroenteritis: prospective cohort survey in institutionalised young people

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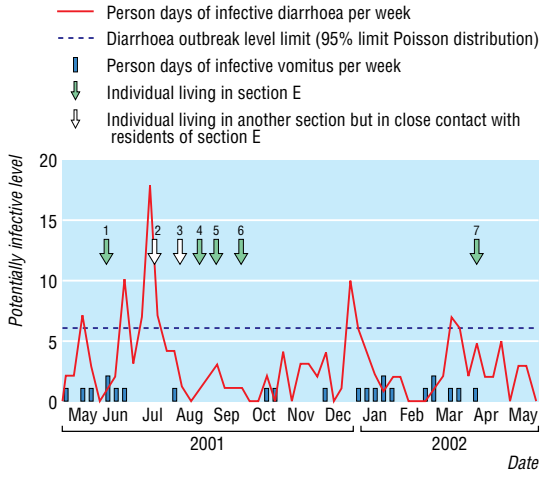
The exact mode of spread of *Helicobacter pylori* is still unknown. Transmission during transit disorders of the gastrointestinal tract has been suggested, although there is no evidence to date of transmission during outbreaks of gastroenteritis.[1–3] We determined whether gastroenteritis in young people infected with *H pylori* can lead to acquisition of the bacterium by peers.

Participants, methods, and results

Our study took place in a French institution for neurologically handicapped children and adolescents. The young people had been institutionalised for several years and resided across five housing sections (A to E). We included all 112 residents in May 2001. *H pylori* infection present at the outset of the study was detected by using the non-invasive HpSA stool antigen test (Meridian; 91% sensitivity and 93% specificity).[4] Stool samples were stored and transported at 4°C within 48 hours and then frozen. The residents were monitored for one year. Events and clinical data were recorded daily by nurses. Gastroenteritis was defined as a sudden outbreak of liquid stools in more than two residents concurrently. For each patient with *H pylori* infection, we defined one day of potentially infective diarrhoea or vomiting as that when at least one liquid stool or vomitus was emitted. Stool samples were collected every week for each resident who was free of infection at the study outset, and at the end of the study we compared the last sample with the first sample. When conversion was observed, we identified the oldest positive stool sample collected from that patient during follow up.



Relation between new cases of *Helicobacter pylori* infection and exposure to infective diarrhoea and vomitus in housing section E

The prevalence of *H pylori* infection was high; 47 of the 112 residents (42%) were positive for *H pylori* at the study outset. Seven of the 65 residents who were initially negative for *H pylori* showed conversion during follow up (figure). Five of the seven young people lived in section E, and our records showed that the two other residents had frequent contacts with the infected patients from section E during physiotherapy and entertainment sessions. Vomitus was rare in all sections. The frequency of diarrhoeal stools from the infected patients varied across sections; residents of sections A and B had 475 and 338 person days of potentially infective diarrhoea over the year, respectively. Acute diarrhoea was rare in these sections, and no outbreaks of gastroenteritis were recorded. A lower frequency of diarrhoeal stools was observed in sections C, D, and E; 34, 104, and 164 person days of potentially infective diarrhoea over the year, respectively. The frequency was always low in sections C and D, where no outbreaks of gastroenteritis were