PostScript

LETTERS

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Smoking verification and the risk of myocardial infarction

We read the paper by Godtfredsen *et al* with interest.[1] The paper reported on the effect of smoking reduction on the incidence of myocardial infarction (MI) and found that although patients who stopped smoking had a decreased risk of MI, those who reportedly reduced their smoking did not. The conclusions drawn were that smoking reduction, rather than complete cessation, did not produce any benefit with regard a reduction of risk of MI.

The major drawback to this study is that the information about smoking was totally reliant on self reported smoking habit. There is abundant evidence that patients who smoke, when questioned about a smoking related illness, frequently under-report their cigarette consumption or deny smoking altogether. The more significant the effect smoking has, the greater the ''social desirability bias'', so increasing the likelihood of denial. To overcome this bias biochemical verification of smoking by measurement of nicotine metabolites, specifically cotinine, has become almost obligatory.

To improve the accuracy of information about smoking and to facilitate easier nicotine metabolite measurements we developed a six minute point of care test called SmokeScreen.[2] The easy to use colorimetric urine test can provide qualitative, semi-quantitative, and quantitative measurements of nicotine intake. Using this test we undertook an audit of smoking habits of 154 new patients attending a large inner city hospital cardiology outpatient clinic, comparing the test identification of smoking with self completed questionnaire of current smoking habit. The results identified 112 (72.7%) patients as non-smokers, 30 (19.5%) as confessed smokers, and 12 (7.8%) as ''smoking deceivers''.

We followed this with another study of the same population (n = 85, 33 smokers and 52 never-smokers) to examine the interaction of smoking and risk factors associated with coronary artery disease, as assessed by a biochemical screen and a blood count. Interestingly, none of the parameters measured in the biochemical screen, such as cholesterol, HDL and triglycerides, urea and electrolytes, and liver function tests were associated with smoking habit or quantitative assessment of nicotine intake. Whereas white blood cell count was significantly higher in smokers ($p = 0.002$), in particular, neutrophils ($p = 0.01$) and eosinophils ($p = 0.02$). Lymphocytes, monocytes, and basophiles were higher but failed to reach significance. Quantitative assessment of nicotine intake of the smokers further revealed a positive correlation with white blood cell count ($p = 0.0001$, neutrophils ($p = 0.001$), eosinophils ($p = 0.004$) and lymphocytes($p = 0.02$), with monocytes approaching significance ($p = 0.7$).

It would seem from this pilot study that smoking or the amount of tobacco consumed does not influence the biochemical risk factors for coronary artery disease, such as cholesterol and HDL. However, smoking does seem to increase many of the immune cells associated with both the formation and destabilisation of the atheromatous plaque. It would seem logical therefore that a reduction in nicotine intake would be accompanied by a reduced risk of MI, as supported by our quantitative findings. One reason for the poor association between smoking reduction and subsequent MI in the Godtfredsen *et al* study[1] may be the inaccuracy of self report. We suggest that identification of smokers with the point of care test is a more valuable method of smoking assessment. Coupling this test with subsequent advice on smoking cessation could have a significant impact on reducing a major risk factor associated with coronary artery disease and decrease cardiovascular events and mortality.

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2 **Cope GF**, Nayyar P, Holder R, *et al*. A simple near patient test for nicotine and its metabolites in urine to assess smoking habit. *Clin Chim Acta* 1996;**256**:135–49.

Authors' reply

We appreciate the comments from Cope and Battersby on our paper reporting the association between smoking cessation and smoking reduction and subsequent risk of myocardial infarction. Specifically, they propose that the lack of a beneficial effect of reduced smoking—in contrast with smoking cessation—could be attributable to inaccuracy (under-reporting) of the self reported tobacco consumption. In addition, they raise the important question of which measurement method most accurately reflects tobacco exposure in the individual smoker.

We agree that nowadays almost every study of smoking habits apply one or more measurements of biochemical marker of smoking in addition to self report. It is also correct that in our paper the study participants are divided into the different smoking categories on basis of self reported smoking and changes in smoking. However, as mentioned in the discussion, measurements of expired carbon monoxide (CO) and serum cotinine were undertaken in one of the follow up examinations. We found increasing levels of CO (table 2) and cotinine (not shown) with increasing self reported tobacco consumption, indicating that underreporting of smoking alone cannot explain our results, but clearly misclassification cannot be ruled out in this observational study. Furthermore, a previous review and meta-analysis[1] concluded that self reported smoking is an accurate measure of tobacco exposure in population based studies, whereas this is not the case in intervention and clinical studies. Our data were based on a sample of the general population; participants with known coronary heart disease before study entrance were excluded. In addition, information on smoking habits and changes in smoking were part of a large questionnaire initiated in the late 1970s and the 1980s, thus minimising the risk of ''social desirability bias'' in this study.

Cope and Battersby describe a pilot study using a urine cotinine test for measuring nicotine intake. There are various methods of validating tobacco intake including biochemical markers, and cotinine is one of the better because of its comparatively long half life and the possible linear relation with number of cigarettes smoked. However, cotinine is not very useful in smoking reduction studies as most of the participants in these trials are supplied with nicotine replacement medications. Interestingly, the intervention studies of smoking reduction all report that despite nicotine replacement the percentage decline in amount of tobacco is followed by a smaller decline in biochemical markers of smoking exposure.

Evidence of the effects of reduced smoking on risk of coronary heart disease is limited. The few ongoing smoking reduction trials report favourable changes in blood analyses of parameters of arteriosclerosis up to two years after smoking reduction. Unfortunately, these studies have a very high ''drop out'' percentage, but it will be interesting to see the clinical results of a long term follow up in this type of ''risk reduction'' study.

In summary, we believe that the self reported smoking habits in our study are fairly precise. However, biochemical verification of smoking is necessary in intervention and clinical studies although there are no ideal markers of tobacco exposure specifically with respect to assessment of smoking reduction.

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Fibrinogen, social position, and risk of heart disease

The report by Jousilahti and colleagues adds to growing evidence of a consistent association between serum inflammatory markers—particularly fibrinogen—and social position.[1–3] These authors interpret their data as suggesting that the fibrinogen-social position link is not merely a reflection of the social patterning of prevalent disease, smoking, and obesity (all of which are associated with increased serum fibrinogen and lower social position) as a strong trend of increasing fibrinogen with decreasing social status survived statistical adjustment for these covariates. Fibrinogen, they conclude, is therefore a promising candidate for the ''missing link'' between social position and cardiovascular health.

The authors' reasoning implicitly accepts that fibrinogen is a cause of coronary heart disease (CHD). However, this runs contrary to recently published evidence using the principle of ''Mendelian randomisation'' (the situation where a particular genetic polymorphism influences exposure level of a putative disease risk factor, and should in turn be related to increased risk of disease if the risk factor is indeed a cause).[4 5] In fact we discussed this evidence in a recent commentary on psychosocial explanations of health inequalities.[6] Plasma fibrinogen concentrations are related to a polymorphism in the β-fibrinogen gene, with presence of the ''T'' allele being associated with higher levels. Among controls of a recent large case-control study, fibrinogen increased by 0.12 g/l per T allele present. Comparing cases with controls, a 0.12 g/l higher fibrinogen was associated with a relative risk of CHD of 1.20 (95% CI 1.13 to 1.26). If increased fibrinogen actually caused heart disease then a similar per allele relative risk of CHD should be seen. In fact the per-allele relative risk of CHD was 1.03 (0.96 to 1.10). People whose genotype would have subjected them to long term raised plasma fibrinogen experienced no substantial increased risk of heart disease, suggesting that observed associations between fibrinogen and CHD risk are not causal. This finding is in keeping with evidence from randomised controlled trials that suggests that drugs lowering fibrinogen do not decrease the risk of CHD.[7]

Fibrinogen probably predicts cardiovascular events because of reverse causation (atherosclerosis is an inflammatory condition and raises circulating fibrinogen concentrations) and because of confounding—smoking, abstaining from alcohol, not exercising and being poor are all associated with raised fibrinogen and themselves increase the risk—or are markers for factors that increase the risk—of cardiovascular disease.

The data presented by Jousilahti and colleagues illustrate how easy it is to misattribute causality to associations in social epidemiology. Many factors are socially patterned and thus appear as possible candidates for a causal role in the processes that generate any disease outcome that is also socially patterned.[6 8] Demonstrating apparent statistical independence of associations between such exposures and outcomes does little to infer their causal basis as it is often likely to reflect issues of residual confounding and measurement imprecision of correlated covariates.[9] Strategies such as randomised control trials and Mendelian randomisation can help untangle these issues. Where feasible, they should be more widely adopted in epidemiology.

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Air pollution and asthma in children

Lin and colleagues have published an interesting paper on asthma hospitalisation in children.[1] They concluded that the study showed positive relations between gaseous pollutants and asthma hospitalisation in children and that the effects of certain specific gaseous pollutants were found to vary in boys and girls. There are several issues that should be discussed before these conclusions can be confidently accepted.

The authors performed separate regression analyses for boys and girls, and compared the sexes by examining the odds ratios. Examination of their figure 1 suggests the possibility that differences between the sexes might be chance fluctuations. It has been recommended that statistical tests for interaction, which directly examine the strength of evidence for the treatment difference varying between subgroups, are the most useful approach for evaluating subgroup analyses.[2] The most simple hypothesis is that there is no difference in susceptibility between boys and girls. It would thus be helpful to know if these apparent differences are statistically significant.

Table 1 Distribution of the numbers of hospitalisations for asthma, 1992–99, among 94 children aged 6–12, in a cohort from the cities of Hamilton and Toronto, Ontario

Number of admissions	Number of children
1	73
2	10
3	5
4	4
8	1
12	1

A consideration in performing hypothesis tests is the standard error of the coefficients. The authors have treated all hospitalisation events as independent. It is probable, however, that some children were admitted to hospital more than once during the course of the study. I have compiled a cohort of some 108 000 people from primary care and respiratory practices in the cities of Hamilton and Toronto, Ontario (Toronto was the setting for the study by Lin *et al*). Hospitalisations for asthma, 1992–1999, were ascertained by linkage to the Provincial Hospital Discharge database. Ninety four children, aged 6–12, were hospitalised a total of 145 times, with a mean admission frequency of 1.5 times. Twenty two per cent of children were admitted more than once. Table 1 displays the distribution of numbers of asthma hospitalisations. The study of Lin *et al* is thus, in a sense, a repeated measures longitudinal study. Failure to take account of the non-independence of events will lead to underestimation of the standard errors and the possibility of inappropriate rejection of the null hypotheses of no effect of pollutants or no difference between the sexes.

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Authors' reply

We appreciate Dr Finkelstein's comments on our paper[1] regarding sex differences in effects