Francisco[17] which found that 17% of TB cases were due to smear negative transmission, Hernández-Garduño *et al* have included cases with extrapulmonary disease. They hypothesise that patients who appear to have extrapulmonary disease alone could be transmitting tubercle bacilli by previously undetected sputum smear negative transmission.

The methods used to ensure that apparent smear negative transmission could not have been caused by smear positive transmission appear rigorous. One theoretical confounding factor which the authors do not seem to have considered is the possibility that a smear negative patient at the time of diagnosis may have been smear positive earlier on in the disease. As the historical data suggest that 25–50% of untreated patients with pulmonary TB healed spontaneously, this remains a possibility. The finding that one sixth of the cases were due to smear negative transmission is remarkably similar to that of the earlier San Francisco study.[17] The fact that half of all patients with TB have never, to their knowledge, been in contact with a case of TB (so called ''casual transmission'') perhaps adds some weight to this evidence.[18]

If this is true, what are the implications for TB control? Firstly, it means that it is going to be much harder to eliminate TB in low prevalence settings than we had hoped. Secondly, we may have to revise our contact tracing procedures to include more extensive screening of contacts of smear negative cases, particularly if these may be immunocompromised in any way. Thirdly, the implication for the provision of adequate resources for TB control in low prevalence settings is made clearly in the paper by Ruddy *et al*.

CONCLUSIONS

The use of molecular methods for studying the epidemiology of TB is proving to be a two edged sword.[19] Unlike the dilemma of Pooh who found that the more he looked for Piglet in Piglet's house without finding him the more Piglet wasn't there,[20] the more we look at TB with this methodology the more we find it is there or, at least, is being transmitted with surprising efficiency. The implications for resources to improve TB control are evident. Unless we can convince our political masters that this is the case, we will have to stand by and watch as things get worse.

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Parental smoking

Effects of parental smoking on the respiratory health of adults

M N Upton

Further evidence that parental smoking may have long term effects into adulthood on the respiratory health of offspring

A paper on passive smoking by Cook and Strachan[1] published in a *Thorax* review series in 1999 reported odds ratios (OR) for childhood lower respiratory tract illnesses, respiratory symptoms, and middle ear disease of 1.2–1.6 for either parent smoking, the risks usually being higher in pre-school children than in children of school age. The review concluded that parental smoking was causally associated with impaired lung function in children, but found inconsistent evidence linking parental smoking to allergic sensitisation and suggested that evidence linking maternal smoking to bronchial hyperresponsiveness (BHR) may have arisen from publication bias.[1]

There is little information from follow up studies about the effect on adult health of exposure to parental smoking,[2 3] which is understandable given the logistical difficulties of following individuals for many decades from birth. In this issue of *Thorax* Svanes and colleagues take a short cut and report cross-sectional results from the European Community Respiratory Health Survey (ECRHS) linking recalled information about parental smoking to respiratory symptoms, asthma, forced expiratory volumes, and BHR in up to 18 688 adults aged 20–44 years from 37 centres in 17 countries.[4]

For men and women overall, maternal smoking was positively associated with wheeze (OR 1.12), with a composite variable of three or more asthma symptoms (OR 1.14), but not with current asthma. Because of the large sample, 95% confidence intervals were narrow and excluded unity despite excess risks of wheeze and asthma symptoms being low. The possibility that such weak effects may be due to

confounding should be considered, although similar sized effects were found in never smokers. Maternal smoking was associated with a forced expiratory volume in 1 second (FEV_1) 24 ml lower and ratio of FEV_1 to forced vital capacity (FEV_1/FVC) 0.5% lower, but not with differences in FVC or BHR. The effects of maternal smoking were greater in subjects whose mothers smoked in pregnancy but, as the authors acknowledge, this is an unreliable conclusion when exposure information is obtained by offspring recall. Overall, there was no effect of paternal smoking on any outcome.[4]

Several lines of evidence suggest that maternal smoking in pregnancy is a cause of childhood wheezing illness, especially transient early wheeze.[5 6] However, mothers who smoke in pregnancy almost invariably smoke afterwards, so it is difficult to separate a potential role for maternal smoking on a causal pathway leading to a wheeze related phenotype from its action as an environmental trigger. The finding by Svanes *et al* that maternal smoking may increase wheeze in never smokers, despite adjustment for current passive smoking, supports a causal link between maternal smoking and wheezing phenotype(s).

Does an estimated 10% excess risk of wheeze matter? The prevalence of maternal smoking varied widely in the ECRHS but was over 40% in Denmark, Iceland, and the English speaking centres.[4] We can estimate the population attributable risk (PAR) of adult wheeze due to maternal smoking in these latter centres to be 4–5%, which is the amount of wheeze that could be prevented if maternal smoking was abolished. Public health interventions that halved the prevalence of maternal smoking in these centres would therefore prevent about 2% of wheeze in adults aged 20–44, which seems modest, even allowing for possible underestimation of main effects by this study. This figure ignores the influence of parental smoking on the smoking behaviour of offspring,[7] although not all studies have found a link between smoking by parents and offspring.[8]

Before considering subgroup analyses, the strengths and weaknesses of the study should be considered. Strengths include precision of effect estimates from the large sample, standardisation across centres of exposures and outcomes, and the capacity to test for heterogeneity across multiple sociocultural settings. This last feature offers some safeguard that the associations in question are not confounded by unmeasured or poorly measured alternative risk factors, assuming that the confounding structure of known and unknown risk factors varies between populations. As with some other studies,[9–11] reliance on offspring reports of parental ''ever'' smoking is a weakness because this may be subject to differential (recall bias) and non-differential (random) error, and provides no information about the intensity, duration, or timing of exposure during early life and childhood.

The authors could not test the accuracy of recalled information about parental smoking in their study. However, it seems reasonable to assume that most adults can remember whether their mother or father had smoked regularly during their childhood. This is supported by unpublished findings from the Midspan family study[12] in which parents aged 45–64 reported their smoking habits in 1972–6 and adult offspring aged 30–59 answered a question about maternal smoking in 1996: ''From memory, did your mother ever smoke cigarettes regularly?'' The same enquiry was made about paternal smoking, both questions being similar to those in the ECRHS. In both studies nearly all participants responded positively or negatively about maternal (ECRHS 97%, Midspan 99%) and paternal (ECRHS 93%, Midspan 99%) smoking, despite being offered the opportunity of answering ''don't know'' (ECRHS) or ''not sure'' (Midspan). In the Midspan study there was good agreement between pre-recorded and recalled maternal smoking ($\kappa = 0.87$, $p<0.0001$) and paternal smoking ($\kappa = 0.70$, $p<0.0001$).

The latter study also illustrates the consequences of concatenating pre-recorded information about different intensities of current and former maternal smoking into a single binary variable—maternal ever smoking. Compared with adult offspring whose mothers were never smokers, offspring whose mothers were former smokers or current smokers of 1–14, 15–24, and ⩾25 cigarettes per day had FEV_1 differences of −44, −15, −108, −156 ml, respectively ($p<0.0001$ trend for never/current maternal smoking).[12] The difference in FEV_1 associated with maternal ever smoking was −67 ml (95% CI –106 to −28) using pre-recorded exposure and −61 ml (95% CI −99 to −23) using recalled exposure (M N Upton, unpublished finding). The main limitation when using recalled exposure therefore seems to be loss of dose-response. There is also a small degree of attenuation of effect, probably from non-differential error.

The estimate by Svanes *et al* for the effect of maternal smoking on adult FEV_1 (−24 ml) lies within the 95% confidence interval for the Midspan estimate using recalled exposure. It seems unlikely that such a small decrement would be relevant to the risk of COPD unless the FEV_1 deficit increases over time, perhaps by interacting with personal smoking. Svanes *et al* report that there were no significant interactions between maternal and personal smoking in their study, unlike findings in the Midspan family study where maternal and personal smoking synergised to increase airflow limitation.[13] Possible reasons for differences between the studies include the older age of Midspan subjects and perhaps a stronger exposure ''signal'' in Midspan because of the availability of pre-recorded information about the intensity of maternal smoking.

The review by Cook and Strachan published in *Thorax* concluded that samples of at least 2000 were needed to detect effects of parental smoking in children, judged by the absence of publication bias in studies recruiting more than 2000 subjects.[1] According to this view, the study by Svanes *et al* should have sufficient power to detect effects of parental smoking in subgroups as large as this. However, this assumes not only that the effects of maternal smoking detected in children do not wane over time, but also that the signal-to-noise ratio of the main exposures (maternal or paternal smoking) match those in the studies of children included in the reviews. Both assumptions may be questioned, the latter because of the previously mentioned limitations around the assessment of parental smoking using offspring recall.

This may be a reason why some main effects in the subgroups in the study by Svanes *et al* did not reach conventional levels of statistical significance, despite large samples and similar point estimates. For example, the effect of maternal smoking on FEV_1 was similar in men (−22 ml) and women (−24 ml), whereas 95% confidence intervals included zero in men but not women. When the main effects are relatively weak, it is not surprising that 95% confidence intervals estimated using regression (or logistic regression) include zero (or unity) when the data are divided further. There was no evidence from heterogeneity tests that the effects of maternal smoking on symptoms or lung function differed between men and women. It is a pity that the ECRHS did not record forced expiratory flows because, in children, parental smoking has greater proportional effects on forced expiratory flows than on volumes[1 6] and such measurements may have increased the study's power, assuming that the decrements in question persist as offspring age.

In contrast to findings for maternal smoking, there was evidence that the

effect of paternal smoking differed between men and women, but only on the risk of wheeze (OR 1.13 for men, OR 0.95 for women, heterogeneity $p = 0.033$). Despite claims made to the contrary, there was little evidence that paternal smoking adversely affected lung function in men in the study by Svanes *et al* (table 4).[4] It is difficult to interpret the dose-response effect of number of parents smoking on lung function in the study, given the absence of effects of paternal smoking on lung function. Without information on the intensity of parental smoking, it is not possible to exclude the possibility that smoking intensity was higher in mothers whose partners smoked. It is also relevant that there was a similar size dose-response effect of number of parents smoking on FEV_1/FVC impairment in men and women. The authors suggest that their results are consistent with age windows of particular vulnerability that differ by sex. This is an attractive hypothesis,[6 14] but the only convincing sex differences in their data were effects of paternal smoking on wheeze in men only.

Another strength of the study is the objective evidence of atopy. Maternal smoking was associated more strongly with wheeze in non-atopic (OR = 1.23) than in atopic (OR = 1.04) subjects, a difference supported by heterogeneity tests. It is interesting that there appeared to be a greater effect of maternal smoking on wheeze in non-atopic subjects, without a correspondingly greater deficit in airflow limitation and without evidence of an effect of maternal smoking on BHR. It seems possible that there are a number of mechanisms underlying wheeze associated with maternal smoking. Although maternal smoking does not seem to have a large effect and impact on adult wheeze, it may perhaps be a tool to explore the pathogenesis of non-atopic asthma which is underdiagnosed[15] and under-researched,[16] yet has a large impact.

There is already substantial evidence that parental smoking, particularly maternal smoking, adversely affects the health of infants and children.[1 6] There is little need for further data to justify public health efforts to reduce the exposure of offspring to passive smoking before or after birth. The study by Svanes *et al*[4] adds to the evidence that parental smoking may have longstanding effects into adulthood on the respiratory health of offspring, and allows us to generalise evidence ''that something is going on'' from the limited studies that have so far been conducted in adults.[2 3 9–11 13] However, current evidence is insufficient to assess the clinical significance of the different effects reported in adults or to understand how exposure to maternal and paternal smoking at different times before and after birth integrates to cause longstanding changes in lung structure and function.

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