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Smoking habit as a risk factor in tuberculosis: a case-control study

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ABSTRACT

Indonesia is fifth in the tuberculosis (TB) prevalence globally and this country is one of the largest tobacco producers. Smoking has been reported to be an important risk factor for TB and a reduction in smoking could be expected to have a significant impact on TB incidence and prevalence. However, studies from various countries yielded conflicting results. Our study aims to explore the association between smoking and TB in Indonesia as TB-endemic country. In two major cities of Indonesia, Jakarta and Bandung, a case-control study had been conducted. TB was diagnosed based on WHO criteria including clinical presentation, and chest X-ray (CXR) examination, and confirmed by microscopic detection of acid-fast bacilli in Ziehl-Nielsen stained sputum smears or by culture of *M. tuberculosis*. Newly diagnosed smear-positive pulmonary TB patients (n=802) and their spouses (n=253) or sex-matched neighborhood controls (n=534) were interviewed about their smoking habits. An extensive questionnaire was used to collect data about smoking habits of both patients and controls. Smoking categories were grouped into ever (for current/past smokers) and never. Our study result showed that smoking appears not to be strongly associated with TB (OR=0.99, 95% CI 0.76-1.31). The reasons for the effect heterogeneity remain to be elucidated as smoking is a lethal habit and should be well controlled. The need to incorporate tobacco cessation programs into TB treatment is strongly recommended to improve TB control.

Keywords: Smoking, tuberculosis, aged >15 years

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INTRODUCTION

With approximately 7-8 million new cases and 2-3 million deaths annually, tuberculosis (TB) is one of the leading infectious causes of death worldwide.[1] Although sufficiently high case detection and cure rates may ultimately eliminate transmission of the causative organism *M. tuberculosis*, this objective is currently out of reach due to difficulties of diagnosis, multi-drug resistance, treatment adherence, and the HIV pandemic.[2,3] New control tools, including better diagnostics, new drugs, and a more effective vaccine are therefore badly needed.

Another potential avenue for TB control is control of risk factors. Several risk factors for TB are known, either affecting the risk of infection, or the risk of developing disease after infection; including socio-economic factors (e.g. crowding), concomitant diseases and infections (e.g. diabetes mellitus, and HIV), and behavioral factors (e.g. smoking).[4] A strong association between tobacco smoking and TB has been found in several studies carried out in various countries. Meta-analysis of those studies concluded that smoking could be considered as an important risk factor for the development of TB.[5] There is also evidence that some of the sex differences in worldwide TB notification rates can be explained by sex differences in smoking.[6] Interestingly, a systematic review of studies in four countries: China, India, UK and USA, found associations between both the risk of TB infection and smoking, and between TB disease and smoking, suggesting that the latter association may be due to the increased risk of TB infection among smokers rather than an increased risk of TB disease.[7] The review included several high quality studies, carried out, *inter alia* in India, where the association appears to be particularly strong. For example, in a nested case-control study carried out in Tamil Nadu, India, a positive and dose-dependent relationship was identified with Odds Ratios (OR) being as high as 3.23 for the highest smoking category.[8] Possibly the largest ever study on this association was carried out by Gajalakshmi,[9] which positively identified smoking as a major risk factor for TB mortality in men in India. With an estimated relative risk of over 4, smoking would rank only second in strength among known risk factors for TB mortality after HIV infection, while in terms of population attributable fraction, it may even rank first. In the same study, from a separate population survey, slightly more moderate relative risk estimates were obtained for the effect of smoking on past or present prevalent TB. For cigarettes the prevalence ratio was 1.7 for <10 cigarettes/day and 2.6 for heavier smokers. For *bidis* (a cigarette rolled in the leaf of another plant, *temburni*) these prevalence ratios were 2.9 (< 15/day) and 4.5 (15/day or more) respectively. Other studies have also found a positive association between smoking and TB. For example, in a cohort study carried out in Hong Kong a highly significant effect (adjusted HR 2.87) of current smoking on pulmonary TB was found.[10] In a hospital-based case-control study carried out in Thailand again a strong positive relationship was found.[11] Smoking was similarly found to be a risk factor for TB in a study from South Africa,[12] although the strength of the effect (OR=1.61) was smaller than that found in either India or Hong Kong. This might, in part, be attributable to the design used in the South-African study, in which cases were deaths from smoking related conditions and controls deaths from *presumably* non-smoking related disorders.

However, not all studies yielded positive associations between smoking and TB. For example, in Chengdu, Szetchuan Province China, a positive association was identified, but only in association with alcohol consumption,[13] while, in a case-control study carried out in Malawi, no association at all was identified.[14] In view of the heterogeneity of results and the non-experimental nature of all studies, with the risk of confounding, combined with a lack of insight into the extent of publication bias, additional information on the association between smoking and TB would be valuable. As passive smoking was also found to constitute a risk factor, tobacco control could become one of the key pillars of TB control.[15] With an estimated incidence rate of 245/100.000 and a prevalence rate of 275/100.000, Indonesia harbors over 10% of TB cases worldwide, which makes this country rank third in terms of TB prevalence.[3] In order

to further explore the effect of tobacco smoking on TB in Indonesia as a TB-endemic country, we analyzed smoking data from a case-control study as part of a larger study on the immunogenetic basis of susceptibility to and disease manifestation of mycobacterial infections in Indonesia.

METHODS

Research design

A case-control study was carried out from March 2001 to December 2005 in two major cities of Indonesia, Jakarta and Bandung, as part of a larger study on the immunogenetic basis of susceptibility to and disease manifestation of mycobacterial infections in Indonesia, which is a collaborative study between Indonesian institutes in Jakarta and Bandung and the Netherlands.

Research subjects

A total of 1020 newly diagnosed smear positive active pulmonary TB patients aged >15 years from TB outpatient clinics were enrolled. TB patients were recruited from *Perkumpulan Pemberantasan Tuberkulosis Indonesia* (PPTI) in Jakarta and from a TB clinic of *Rumah Sakit Hasan Sadikin*. Briefly, TB was diagnosed based on WHO criteria including clinical presentation and chest X-ray (CXR) examination, and confirmed by microscopic detection of acid-fast bacilli in Ziehl-Nielsen stained sputum smears or by culture of *M. tuberculosis*. Free anti-TB drug treatment was provided to all patients, consisting of a standard regimen of isoniazide, rifampicin, pyrazinamide and ethambutol (2HRZE/4H3R3) according to guidelines of the national TB program. Treatment was supervised once weekly by directly observed treatment program. Active pulmonary TB patients with HIV-seropositive (n=10), concomitant diabetes mellitus (DM, n=153), other co-morbidity such as heart diseases (n=7), and those with missing smoking data (n=48), were excluded in this current study. DM in this study was excluded because it is strongly associated with TB as described previously elsewhere.[16]

In the same period, a total of 895 controls, including spouse controls and neighbor controls were recruited. Spouse controls were enrolled in view of the interest in passive smokers. Control neighbors were selected randomly from individuals in the same *Rukun Tetangga*, the smallest residential unit or compound system in Indonesia consisting of 15-30 households, and matched with patients of the same sex, age (+/- 10%), and socio-economic background. Controls were interviewed using the same standardized questionnaire, and subjected to physical and blood examination, and CXR scheme as TB cases. Controls were excluded when they showed signs and symptoms suggestive of active TB as seen in the CXR or had a history of anti-TB therapy (n=46), concomitant DM or other co-morbidities (n=30), were HIV-seropositive (n=3 of 238 tested controls), or had missing smoking data (n=29).

Data collection

In a part of an extensive questionnaire smoking habits were asked in both patients and controls. Further we grouped the smoking category into ever (i.e. current and past) vs. never, and the outcome variable into TB or control. Ever smoking was used, instead of current smoking, as TB patients may have quitted smoking because of their disease. Unfortunately, no information was available on the time when quitters stopped smoking.

Ethical clearance

Written consent was obtained from all subjects, and the study protocol was approved by the ethical committees of the Medical Faculty, University of Indonesia, Jakarta and the Medical Faculty, University of Padjadjaran, Bandung.

Statistical analyses

As spouse controls were counter-matched for gender, and because in Bandung the information linking individual cases to controls was not adequately collected, we decided - for our main data analysis- to ignore the matching structure and to analyze the data using standard binary logistic regression, and to include the matching structure (Jakarta only) only as an auxiliary analysis using conditional logistic regression. The level of statistical significance was set at $p<0.05$.

RESULTS

Demographic data

In total, newly diagnosed smear-positive pulmonary TB patients (n=802) and their spouse (n=253) or sex-matched neighborhood controls (n=534) were analyzed, distributed in two cities (Jakarta and Bandung) as shown in Table 1. The mean age of all cases was 31.6 years ± s.d. 10.9 and 29.8 ± s.d. 10.6 for men and women, respectively. The mean age of all neighbor controls was 33.1 ± 12.0 years and 32.3 ± 11.4 years for men and women, respectively, while for all control spouses these numbers were 33.8 ± 11.7 years and 32.0 ± 10.2 years, respectively. Data from participants in Jakarta showed that BCG scar status in TB patients differed significantly from the control group, consisting of both neighbor and spouse controls (p=0.03; OR 0.75; CI 0.59-0.97, Table 1). The status of 'no BCG scar' does not mean that the participants never received BCG vaccination, as no medical record of BCG vaccination in the past was available. Table 2 shows the BCG scar and no BCG scar group in different age groups. Better medical recording for nation-wide vaccination is recommended to study the extent of protection afforded by BCG vaccination.

Table 1. Demographic data of the participants from two cities in Indonesia, Jakarta and Bandung

		Patients Pulmonary TB (n=802)	Controls		p	OR (95% CI)
			Neighbour (n=534)	Spouse (n=253)		
Place, n						
Jakarta		481	415	77		
Bandung		321	119	176		
Male, n (%)						
Jakarta		291 (60)	238 (57)	37 (48)		
Bandung		148 (46)	40 (34)	84 (48)		
Age, mean (SD)						
Jakarta		31.7 (10.8)	33.4 (11.6)	35.3 (11.8)		
Bandung		29.4 (11.3)	29.6 (11.6)	31.7 (10.3)		
BCG scar, n (%)						
Jakarta	Scar	193 (40.1)	199 (48.0)*	31 (40.3)*	0.03††	0.75 (0.59-0.97)
	No scar	288 (59.9)	214 (51.6)	45 (58.4)		
Bandung	Scar	150 (46.7)	51 (42.9)*,**	86 (48.9)*	0.249	
	No scar	171 (53.3)	57 (47.9)	72 (40.9)		
Smoking, n (%)						
Jakarta	Current/past	293 (60.9)	235(56.6)	43 (55.8)	0.162	
	Never	188 (39.1)	180 (43.4)	34 (44.2)		
Bandung	Current/past	148 (46.1)	55 (46.2)	82 (46.6)	0.934	

Note: *not all controls in Jakarta or Bandung have data on BCG scar. The number is only from the participants with BCG data; **neighbor controls were not equally recruited. †† Statistically significant ($p<0.05$) in Jakarta participants and in total number of analyses

Table 2. The distribution of BCG scar for age group among pulmonary TB patients and controls

	Scar (n/%)	No Scar (n/%)
Pulmonary TB		
<20	27 (7.9)	48 (10.5)
20-30	143 (41.7)	226 (49.2)
30-40	98 (28.6)	87 (19.0)
40-50	54 (15.7)	59 (12.9)
>50	21 (6.1)	39 (8.5)
Control (neighbor)		
<20	28 (10.3)	30 (12)
20-30	115 (42.4)	77 (30.8)
30-40	44 (16.2)	69 (27.6)
40-50	49 (18.1)	54 (21.6)
>50	35 (12.9)	20 (8.0)
Control spouse		
<20	12 (10.3)	5 (4.3)
20-30	53 (45.3)	41 (35.0)
30-40	24 (20.5)	39 (33.3)
40-50	18 (15.4)	22 (18.8)
>50	10 (8.5)	10 (8.5)

Smoking data

Smoking categories were grouped into ever (for current/past smokers) and never. Notably, most of the males were smokers and most of the females were non smokers (Table 1). Surprisingly, no significant difference between pulmonary TB and control groups was found. This is different from global findings showing that smoking is a significant risk factor. Logistic regression of cases on age, age-squared, site (Jakarta or Bandung), sex, and ever smoking yielded no statistically significant association between any of the variables and TB, with an adjusted odds ratio (OR) for the association between TB and smoking of 0.99 (95% CI 0.76-1.31). Stepwise logistic regression with forward selection only yielded a (negative) statistically significant association between age and TB (data not shown). Repetition of the analysis with exclusion of spousal controls, to reduce the risk of over-matching (exposure to passive smoking, highly concordant TB infection) gave similar results with an OR of 0.93 (95% CI: 0.68-1.28). Re-analysis using conditional logistic regression to take the matching into account using only data from Jakarta again yielded no significant association between smoking and TB (data not shown). The distribution of smoking habits in TB patients and controls in Jakarta and Bandung, two major cities in Indonesia, is presented in Table 3.

Table 3. The distribution of smoking habits in male and female pulmonary TB patients, compared to neighbour and spouse controls in two major cities in Indonesia

Smoking Status		Patients Active Pulmonary TB n = 802 (%)	Controls		
			Neighbour Controls n = 534 (%)	Spouse Controls n = 253 (%)	
Jakarta					
Men	Never	29 (10.0)	31 (13.0)	5 (13.5)	p 0.99 *
	Current / Past	262 (90.0)	207 (87.0)	32 (86.5)	OR 0.99
Women	Never	159 (83.7)	149 (84.2)	29 (72.5)	
	Current / Past	31 (16.3)	28 (15.8)	11 (27.5)	(95% CI 0.76-1.31)
Bandung					
Men	Never	21 (14.2)	9 (22.5)	24 (28.6)	p 0.66**
	Current / Past	127 (85.8%)	31 (77.5)	60 (71.4)	OR 0.93
Women	Never	152 (87.9%)	55 (69.6)	70 (76.1)	
	Current / Past	21 (2.1%)	24 (30.4)	22 (23.9)	(95% CI 0.76-1.31)

Note. Smoking categories were grouped into ever for current/past smokers and never; * Logistic regression analysis of cases on site (Jakarta or Bandung), sex, and ever smoking, yielded no statistically significant association d TB; ** Repetition of the analysis with spousal controls excluded, to reduce the risk of over-matching OR (Odds Ratio).

DISCUSSION

Indonesia is one of the biggest tobacco producers in the world and smoking-at least among men is very common.[17] Indonesia has the third highest TB-prevalence worldwide after India and China, countries where smoking appears to be a strong risk factor.[18] If smoking would be a causal risk factor for TB in this high burden country as it appears to be in many other countries an enormous number of cases could be prevented through tobacco control.[19] In our present study in Indonesia, however, no significant positive association between smoking and TB was found. Thus, our data would seem to suggest that smoking is less of a risk factor for TB in Indonesia than in many other places in the world. Although the sample size of our study was only small compared to the studies in India and China, resulting in somewhat wide confidence intervals for effect parameters, our data seem to contradict a major effect of smoking on TB in this population.

The question is how to explain this apparent heterogeneity in the effect of smoking. First, our study was not specifically designed to study this association, and smoking habits were not elicited in great detail, also no attempt was made to independently verify information. Second, misclassification of smoking status may have biased the odds ratios towards unity. Another explanation may be overmatching in our study. Some of the controls in this study were spouses, and smoking in spouses may be correlated, especially if passive smoking would have a similar effect as smoking itself. A study in China showed that passive smoking accounted for 13.7% of active TB and for 18.5% of culture-positive TB;[15] however, in our study only a minority of the controls were spouses and exclusion of spouse controls did not affect our conclusions. A fourth possibility may be that the heterogeneity in the effect of smoking is real, due to differences in exposures resulting from smoking. For example, the type of tobacco smoked may differ, which could lead to different exposure to, and uptake of, various chemical substances and elements such as iron.[20] Smoking habits differ markedly between countries. In India, for example, many people smoke (unfiltered) *bidis*, whereas in Indonesia *kretek* (unfiltered, cloves containing) cigarettes are common.[17] Cloves are known to have disinfecting properties, and may have immuno-modulatory effects as well.[21] Also the average amount of tobacco smoked may differ among countries. Fifth, either the associations between smoking and TB in other places may have been due to confounding, or conversely our failure to find an association may be due to confounding by an unmeasured variable.

In Indonesia most men smoke, but most women do not. This makes men who do not smoke, or women who do, somewhat exceptional, and the reason for not smoking by men, for instance, may be health related. Smoking may be associated with other risk factors for TB, and these associations may differ among countries, which makes it notoriously difficult to rule out or adjust for confounding. For example, it is well known that in many populations smoking and alcohol consumption are positively correlated.[22] Unfortunately, we have no data on alcohol consumption to explore whether there are any interactions with alcohol consumption, but in view of the fact that the majority of Indonesian population are Muslims, this is probably low. Other associations may exist, for example, it is still disputed whether the association between smoking and cervical cancer which has been observed in different populations is causal or due to confounding by sexual behavior.[23] Similarly disputed is the protective effect of smoking on Alzheimer's disease.[23,24] However, confounding can also mask true associations, which might explain our failure to find an association.

One may use Hill's (minimal) criteria to explore the plausibility of causality.[25] The association between tobacco and TB clearly

meets several of these criteria. For example, an association is highly plausible given that tobacco smoking affects the lungs, and is also known to have many effects on the human immune system and increases the risk of several other infections as well.[26,27] Several studies, such as the two studies cited above carried out in India, also clearly identify a dose-response relationship, again strongly supporting a causal relationship. Another important criterion is consistency, i.e. whether the result can be replicated in different settings or using different methodologies. Here the support for a causal relationship between tobacco and TB appears somewhat less positive in view of the negative or mixed findings from Malawi, Chengdu and Indonesia.

Case-control studies and other non-experimental studies have many potential biases.[28] In addition, there exists the possibility of publication bias, as studies identifying smoking as a risk factor would have greater potential public health impact than those that did not.[19] Whether this indeed occurs is uncertain, since no registers of epidemiological studies exist as they do for clinical trials. Nevertheless, large-scale studies such as the one carried out in India are unlikely to go unreported even when the results would show no association. Obviously, no clinical trial to establish experimentally the effect of tobacco smoking on TB is possible, though experiments *in vivo* and *in vitro* with primary human alveolar macrophages exposed to cigarette smoke extract, nicotine, or acrolein showed an increased burden of intracellular *M. tuberculosis*.[29]

CONCLUSION

TB is a multifactorial disorder. Our finding showed that smoking appears not to be strongly associated with TB in Indonesia. This inconsistency in smoking and TB findings needs to be further explored as it may provide insight into both the noxious effects of tobacco smoking and the pathogenesis of TB. It has little bearing on public health policy, however, since smoking is a lethal habit and should be controlled by all reasonable means. The need to actively incorporate tobacco cessation programs into TB services is strongly recommended to improve TB control.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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