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## Does smoking explain sex differences in the global tuberculosis epidemic?

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### SUMMARY

To date there has been no satisfactory explanation of the worldwide excess of tuberculosis (TB) notifications among adult males. We investigated the epidemiological basis for sex differences in TB notifications in high-burden countries using available group-level data. Multiple linear regression analysis was used to explore the ecological relationship between smoking and sex differences in TB notifications among high-burden countries. Cigarette consumption was a significant predictor of the sex ratio of TB notifications, and explained 33% of the variance in the sex ratio of TB notifications. Our findings suggest that smoking is an important modifiable factor which has a significant impact on the global epidemiology of TB, and emphasize the importance of tobacco control in countries with a high incidence of TB. This analysis provides support for the interpretation of sex differences in worldwide TB notification rates as indicative of true differences in the epidemiology of TB between males and females.

### INTRODUCTION

In almost every country in the world more male than female cases of tuberculosis (TB) are notified to the World Health Organization (WHO) each year [1], and globally there are 70% more male than female smear-positive TB notifications [2]. The consistency of the excess of TB notifications among males suggests that they represent epidemiological patterns of disease [1], however, the reasons for sex differences in notification rates is unclear [2].

Researchers have not determined whether the higher rate of TB notifications among males reflects a real higher incidence of disease among men, the under-detection or under-reporting of cases among women, or both [3]. The higher prevalence of

infection among males >15 years of age, despite comparability of the sensitivity of the tuberculin skin test in males and females, has been recognized as consistent with the higher incidence of TB among males, although this alone is not sufficient to account for the large difference in male and female notification rates [4].

Some explanations for the different rates of infection and disease in males and females include biological differences, such as differences in immunity [5]; differences in exposure to *Mycobacterium tuberculosis* associated with different social mixing patterns [4]; and differences in health-seeking behaviour which may lead to poorer detection of disease among females [6]. Research has not yet provided a satisfactory explanation of the impact of gender inequalities in accessing health care on reported sex ratios for TB or the reasons for the excess of male TB notifications [7], and there is a scarcity of epidemiological data to support the validity of competing theories.

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Smoking has been identified as one of a number of variables that may be associated with differences in the risk of TB according to sex [8], although there have been no aggregate-level studies which examine the association between smoking and sex differences in TB incidence. In many countries which have a high prevalence of TB, smokers are predominantly males. The prevalence of smoking among males in low- and middle-income countries is currently estimated to be 49%. Males in these countries are approximately six times more likely to smoke than females [9].

Smoking has been found to be a risk factor for infection and disease in numerous individual-level studies, although this evidence is not yet considered to be conclusive [10]. A recent case-control study of smoking and mortality in India, which was restricted to examining mortality among males due to the low rate of smoking among females, provides further support for the association between smoking and tuberculosis. This study found that 61% of urban adult male deaths from tuberculosis in India are attributable to smoking, and that smokers are approximately four times more likely to die of tuberculosis than non-smokers [11]. Two recent papers have also suggested that smoking may account for the observed sex differences in the incidence of TB [12, 13], with one study noting the concordance of the usual time of uptake of smoking in late adolescence with documented changes in tuberculin reactivity according to sex.

Although smoking has been identified as a risk factor for infection and disease at an individual level, the contribution of smoking to the distribution of disease across multiple high-burden settings has not been examined. We aimed to determine if smoking makes a significant contribution to sex differences in the distribution of TB among high-burden countries.

## METHODS

We performed a cross-sectional ecological analysis of the association between smoking and sex differences in TB notifications in 2001 using published country-level data. This analysis was limited to countries with a high burden of TB, as we hypothesized that an observable ecological correlation between TB notifications and smoking based on national notification data is contingent upon the chances of a sufficient overlap between the risk factor of smoking and exposure to *M. tuberculosis*.

Table 1. *The identification of countries that have high levels of cigarette consumption and HIV infection prevalence among the 22 World Health Organization-defined high-burden countries*

| Country            | Cigarette consumption > 2 cigarettes per adult ( $\geq 15$ years) per day | Prevalence of HIV infection among 15- to 49-year-olds > 2% |
|--------------------|---|--|
| India              | Yes   |  |
| China              | Yes   |  |
| Indonesia          | Yes   |  |
| Nigeria            |   | Yes  |
| Bangladesh         | Yes   |  |
| Ethiopia           |   | Yes  |
| Philippines        | Yes   |  |
| Pakistan           |   |  |
| South Africa       | Yes   | Yes  |
| Russian Federation | Yes   |  |
| DR Congo           |   | Yes  |
| Kenya              |   | Yes  |
| Viet Nam           | Yes   |  |
| UR                 |   | Yes  |
| Tanzania           |   |  |
| Brazil             | Yes   |  |
| Thailand           | Yes   |  |
| Uganda             |   | Yes  |
| Myanmar            | Yes   |  |
| Mozambique         |   | Yes  |
| Cambodia           |   | Yes  |
| Zimbabwe           |   | Yes  |
| Afghanistan        |   |  |

High-burden countries were defined as the 22 high-burden countries in the WHO global TB control report based on 2001 data (Table 1) [14], and countries that had an estimated incidence of TB of  $\geq 300/100\,000$  population per year or an estimated prevalence of infection of >40% as identified by Dye and co-workers [15]. Multiple criteria were used to define high-burden countries to increase the number of countries included in the analysis and to provide a broad and inclusive definition of high-burden countries based on more than one data source. The majority (13) of the 22 countries considered to be high-burden in the most recent WHO global TB control report would have been included in this analysis based on the inclusion criteria applied to the estimates of Dye and co-workers, indicating a moderate degree of overlap between the inclusion criteria based on the two different data sources. The average estimated prevalence of infection for 1997

for the WHO-specified 22 high-burden countries was >38%, and the average estimated incidence of TB was >260/100 000 population per year.

The dependent variable in the analysis was the male to female ratio of smear-positive notification rates for persons aged  $\geq 15$  years. An age-standardized summary indicator for each country was derived by weighting the ratio of the reported age- and sex-specific smear-positive TB rates using a standardized world population structure [16]. Age- and sex-specific TB notification data for 2001 were available for 19 of the 22 WHO-identified high-burden countries [14], and data for the Philippines were available for 1998 [1]. TB notification data for Zimbabwe and Mozambique were not available within the previous 5 years, and these countries were excluded from the analysis.

Countries identified for inclusion in the analysis on the basis of Dye and co-workers' estimates [15] which were not WHO-specified high-burden countries were included if both TB notification data for 2001 and cigarette consumption data were available. Six countries identified using Dye et al.'s estimates as having a prevalence of infection >40% were included in the analysis (Haiti, Bolivia, Nepal, Mongolia, Peru and Morocco), and data were available for two additional countries that had an estimated incidence of TB of >300/100 000 (Malawi and Sierra Leone).

The main independent variable included in this analysis was annual adult (aged  $\geq 15$  years) *per capita* consumption of manufactured cigarettes for 1990–1992 [17]. Manufactured cigarettes are the main form of smoked tobacco in all regions of the world outside South Asia, and are replacing other forms of tobacco [18]. Estimates for South Asian countries included the consumption of local cigarettes (*bidis*) due to their high prevalence of use, and as such these data were considered to be the best indicator of tobacco consumption currently available. The increased risk of mortality from TB and other causes associated with smoking *bidis* in an Indian study [11] suggests that consumption of these local cigarettes should be included in the analysis. A cigarette consumption estimate for the Democratic Republic of Congo was unavailable from the above source, and was obtained from the Tobacco Atlas [19].

*Per capita* cigarette consumption was selected as the main indicator of tobacco exposure in this analysis. Data on smoking prevalence according to sex are likely to incorporate a greater level of uncertainty associated with different definitions of current

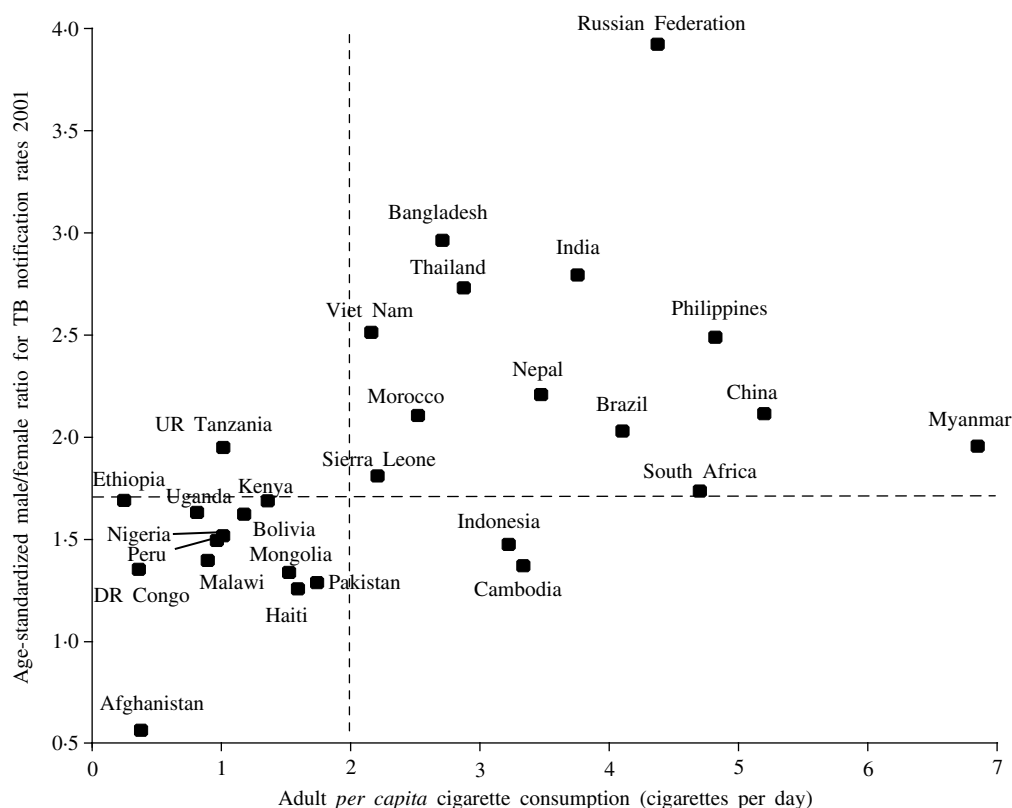
smoking and differences in survey methodologies between countries, and are less likely to be comparable between countries [18]. An indicator of the sex ratio of smokers was derived from reports of the prevalence of smoking among adult males and females [19], although these data were only available for 24 of the 28 countries included in the analysis.

A number of variables which may be important predictors of the sex ratio of TB notifications or potential group-level confounding factors were also included in the analysis. Indicators included adult (aged  $\geq 15$  years) *per capita* alcohol consumption (litres) for 2000 [20]; HIV prevalence in adults aged 15–49 years as of end 2001 [21], the estimated incidence of TB (all cases) [14], the TB case detection ratio (all cases) for 2001 [14], and *per capita* Gross Domestic Product (GDP) for 2000 or the most recent available estimate [22]. Adult *per capita* alcohol consumption data were unobtainable for Bangladesh and Afghanistan, and an estimate for 1999 for the Russian Federation was used due to the unavailability of more recent data. Missing data on HIV prevalence for Afghanistan and Myanmar were obtained from an alternate source [23]. An indicator of the sex ratio of HIV cases was computed as a ratio of data on the prevalence of HIV among men and women aged 15–24 years, although this was only available for 24 countries included in the analysis [21]. The use of HIV prevalence data for young adults to derive an indicator of the sex ratio of HIV cases is not ideal, however, we were unable to locate more comprehensive population data for the countries examined.

### Statistical analysis

Multiple linear regression analysis was used to determine the significant predictors of the sex ratio of notified TB cases. Backward elimination methods were used to derive the final model, and outliers, autocorrelation, collinearity, influential variables and model fit were evaluated [24, 25]. Pearson's correlation coefficients were used to describe correlations between the independent variables, and deviation scores were used for all independent variables in the analysis to minimize multicollinearity. A categorical analysis using logistic regression was also performed to quantify the odds of TB notifications in males exceeding that in females by  $\geq 70\%$  associated with a higher aggregate level of cigarette consumption.

The normality of all indicators was assessed prior to their use in regression analysis. The square root



**Fig.** Scatter plot of adult *per capita* cigarette consumption per day by the age-standardized sex ratio of TB notifications for 2001 in persons aged  $\geq 15$  years for 28 countries with a high burden of TB, showing reference lines for adult *per capita* consumption of 2 cigarettes per day and a 70% excess of male TB notifications over female notifications.

transformation was used to normalize the sex ratio of TB notifications, cigarette consumption, alcohol consumption, and the estimated incidence of TB. A natural logarithm was used to normalize HIV prevalence, smoking sex ratio and GDP, and an inverse transformation was used to normalize HIV sex ratio data. The assumption of linearity was met for all independent–dependent variable pairs.

## RESULTS

Cigarette consumption and HIV prevalence for the 22 WHO-defined high-burden countries are summarized in Table 1. Only two of these high-burden countries (Afghanistan and Pakistan) appear to have an absence of both of these risk factors for TB based on current published data.

There was a high degree of association between a number of independent variables considered in this analysis. *Per capita* GDP was moderately positively correlated with *per capita* cigarette consumption ( $r=0.61$ ,  $P=0.001$ ) and case detection rate ( $r=0.48$ ,  $P=0.01$ ), reflecting higher cigarette consumption and case detection rates in countries with higher *per capita*

GDP. The estimated incidence of TB was moderately positively associated with HIV prevalence ( $r=0.61$ ,  $P=0.001$ ) and (inverse) HIV sex ratio ( $r=0.79$ ,  $P<0.001$ ) suggesting a higher prevalence of HIV and a predominance of HIV among females in countries with a high estimated incidence of TB.

The ability of each independent variable to predict the sex ratio of smear-positive TB notifications was initially examined using individual linear regression models. Only adult *per capita* cigarette consumption ( $P=0.001$ ) and *per capita* GDP ( $P=0.01$ ) were significant predictors of the sex ratio of smear-positive TB notifications, explaining 33% and 22% of the variance in the sex ratio of smear-positive TB notifications respectively.

The association between adult *per capita* cigarette consumption and the sex ratio of smear-positive TB notifications for high-burden countries is displayed in the Figure. Adult *per capita* alcohol consumption was not a significant predictor of the sex ratio of smear-positive TB notifications ( $P=0.14$ ) and was not significantly associated with adult *per capita* cigarette consumption ( $P=0.91$ ). The significant association between *per capita* GDP and the sex ratio

Table 2. Multiple linear regression analysis of the predictors of the sex ratio of TB notifications ( $n=28$ )

| Independent variables  | Partial regression coefficient ( $B$ ) | Standard error of $B$ | Standardized regression coefficient ( $\beta$ ) | $t^*$ | $P$ value |
|------------------------|--|-----------------------|---|-------|-----------|
| Cigarette consumption† | 0.25                                   | 0.07                  | 0.58  | 3.60  | 0.001     |
| Constant               | 1.36                                   | 0.04                  |   | 35.9  | <0.001    |

Model  $R^2=0.33$ , Adjusted  $R^2=0.31$ ,  $F(1, 26)=12.93$ ,  $P=0.001$ .

\* The  $t$  statistic tests the hypothesis that a population regression coefficient is zero.

† Square root of adult *per capita* cigarette consumption per day.

of smear-positive TB notifications ( $r=0.47$ ,  $P=0.01$ ) became non-significant after controlling for adult *per capita* cigarette consumption ( $r=0.18$ ,  $P=0.38$ ).

Using multivariate linear regression analysis we found that adult *per capita* cigarette consumption was the only significant predictor of the sex ratio of smear-positive TB notifications irrespective of the method used to derive the model. The addition of interaction terms to the model did not produce a significant change in the model  $F$  statistic or a significant contribution to the model. The inclusion of *per capita* GDP in the final model (Table 2) did not result in any improvement in the adjusted  $R^2$  of the model or any significant change in the regression coefficient for *per capita* cigarette consumption or its precision (data not shown). Regression standardized residuals were approximately normally distributed and plots indicated that errors were generally homoskedastic.

As is likely with models based on a small number of observations, regression fit indicators demonstrated that several observations had a reasonable degree of influence on the model fit. As there is no specific rationale justifying the exclusion of the influential observations identified, a number of models were fitted with the influential observations excluded. Exclusion of five influential observations based on a high Cook's  $D$  statistic or standardized DfFit statistic (Russian Federation, Myanmar, Afghanistan, Bangladesh and Cambodia) did not significantly influence the model fit [ $R^2=0.35$ , Adjusted  $R^2=0.32$ ,  $F(1, 21)=11.27$ ,  $P=0.003$ ] or change the outcome of the analysis.

Compared with countries that had a *per capita* cigarette consumption of  $\leq 2$  cigarettes/day, countries that had a *per capita* cigarette consumption of  $>2$  cigarettes/day were 78 times more likely to have TB notifications among males exceed those among females by  $\geq 70\%$  (95% CI 6.2–974.6).

## DISCUSSION

Cigarette consumption explained a significant proportion of the variance in the sex distribution of TB case notifications among the 28 high-burden countries studied. There is growing evidence for an individual-level association between smoking, infection with *M. tuberculosis* and TB [10–13], and this is the first group-level analysis which suggests that smoking has the capacity to explain a significant proportion of the observed sex differences in the global epidemiology of TB. Our findings suggest that the reported sex differences in TB notification rates and the incidence of smear-positive TB reflect true differences in the epidemiology of TB, and indicate the significant impact that smoking is having on the global TB epidemic.

Global TB control strategies have placed little emphasis on addressing modifiable lifestyle factors which contribute to the TB epidemic. Although the degree of increased individual-level susceptibility to *M. tuberculosis* infection and disease associated with smoking is many times lower than that associated with HIV infection, the high prevalence of smoking in many countries with a high prevalence of TB means that smoking has a significant impact on the sex ratio of TB notification rates at a population level. In contrast, despite the considerable increase in TB incidence associated with the HIV epidemic, this has been associated with only a minor shift in the sex ratio of notified TB cases [26].

The association between smoking and sex differences in TB notifications found in this study may be conservative. Estimates of cigarette consumption are likely to be associated with a significant degree of uncertainty, and TB notification data from high-incidence countries are a potentially limited indicator of the actual distribution of disease in these populations. TB notification data are also indicative of factors determining case detection rates, and are



influenced by country-specific reporting practices. Despite limitations in the representativeness of TB notification data and its comparability across countries, there is evidence that sex differences in TB notification data are largely due to gender differences in the prevalence of TB [26], supporting the validity of TB notification data.

We have been unable to identify an uncontrolled confounder which could account for the significant association between cigarette consumption and the sex ratio of smear-positive TB notifications at an ecological level. Although the findings of individual-level studies are supportive of our conclusions, we cannot exclude the possibility that cigarette smoking is related to an indicator not considered in this analysis. More precise epidemiological data on the individual and joint distributions of TB and tobacco consumption as well as the potential confounders of the association between these variables are required to confirm this relationship and improve the precision of the estimates of effect.

A further limitation in this analysis is the time delay between the assessment of the main indicators of smoking and sex differences in TB notifications due to the unavailability of recent comprehensive tobacco consumption data. While we could have used earlier TB notification data in the analysis, the most recent TB data are more complete and are likely to be of a higher quality. Although we expect a delay between smoking exposures and the impairment of respiratory defence mechanisms [27, 28] to a degree which may be associated with an increased risk of TB, we are uncertain of the exact time period required.

Even after allowing for an underestimation of the effect of smoking on the sex ratio of TB notifications due to data considerations, much of the variance in the sex ratio of TB notifications remains unexplained. As such our findings do not preclude the significant influence of other factors on the sex distribution of TB. A number of additional factors which are likely to have an important impact on the sex distribution of notified TB cases were unable to be controlled in this analysis. Country-specific disease distribution and transmission patterns may have a strong influence on the incidence of TB in population subgroups. The high rate of TB in prisons in the Russian Federation [29] is likely to be associated with an increased risk of disease among males. Prevalent treatment-seeking behaviours and deficiencies in case notification among some provider groups may also have a considerable influence on the epidemiological properties

of national notification data. Evidence suggests that a significant proportion of male TB cases in Afghanistan may be omitted from the national statistics due to the tendency of men to use private sector health services [30]. Accounting for factors such as these may increase the association between smoking and the sex ratio of TB notifications.

An important factor sustaining suspicion of the possible under-notification of women who have TB as an explanation for sex differences in TB notifications, particularly in passive-case finding contexts [8], is the possibility that there is an increased risk of TB among young adult women. Much of the evidence supporting the existence of an elevated risk of TB among young adult women is derived from studies of TB epidemics in the mid-1900s [8]. A lack of support for an increased risk of TB among young adult women in a more recent study [31], as well as the recent finding that women are less likely to test sputum smear-positive for TB [6] indicate that the increased rate of TB previously found among young adult women may have been related to gender differences in risk factors for infection and disease at that time. Alternatively, an increase in the risk of TB among males, in part attributable to smoking, could be obscuring this previously detected effect.

Although ecological studies are limited in their inability to infer findings to the individual level, and findings should not be directly generalized to individual-level relationships, ecological factors that can predict variation in the distribution of disease constitute important targets for group-level interventions. Our findings suggest that significant gains in global TB control would be associated with the modification of smoking behaviour in high-prevalence settings, and support the strengthening of population-level interventions which are aimed at decreasing tobacco consumption. The inclusion of tobacco-control strategies within TB prevention and control programmes should enhance the effectiveness of current initiatives. The association of smoking with an often highly stigmatized disease may also facilitate behaviour change and a reduction in the growing rates of tobacco-related morbidity and mortality in developing countries.

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## DECLARATION OF INTEREST

None.

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