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Asthma, sinonasal disease, and the risk of active tuberculosis

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Abstract

Background: Although asthma is associated with impaired lung immunity, it is unclear whether asthma affects risk of active tuberculosis (TB). Since the upper and lower airways are immunologically related, sinonasal disease may also modify susceptibility to TB disease.

Objectives: To evaluate whether asthma and sinonasal disease prospectively modulate the risk of active TB in the Singapore Chinese Health Study.

Methods: In this population-based prospective cohort, we recruited 63,257 Chinese adults aged 45–74 years from 1993–1998 in Singapore, and conducted follow-up I interviews among 52,325 surviving participants from 1999–2004. Data on self-reported history of physician-diagnosed sinonasal disease was collected at baseline, and data on asthma and chronic bronchitis were collected at follow-up I interviews. Active TB cases were identified by linkage with the national TB notification registry through December 2014. Multivariable Cox proportional hazards regression models were used to estimate risk of active TB.

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Author contributions

WPK and JMY: designed the study. WPK and AZS: conducted statistical analysis. ACY, AZS and WPK: drafted the manuscript. JMY, WPK, CBEC and YTW: contributed to data acquisition and interpretation. WPK is the guarantor for this study, including its data and analysis. All authors provided critical intellectual input to the manuscript and approved the final manuscript.

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Results: During a mean follow-up of 17 years from recruitment, there were 1249 cases of active TB, and among them, 678 cases were diagnosed in the 12-year period from follow-up I interviews. We observed reduced risk of active TB in those with a history of asthma at follow-up I [hazard ratio (HR) 0.55, 95% confidence interval (CI) 0.32–0.93] or sinonasal disease at baseline (HR 0.59, 95% CI 0.36–0.95). Conversely, history of chronic bronchitis was not associated with risk of TB (HR 0.95, 95% CI 0.68–1.31).

Conclusions: Asthma or sinonasal disease may modulate immunological response to reduce incidence of active TB in the adult population.

Keywords

Asthma; Allergic rhinitis; tuberculosis; chronic bronchitis; rhinosinusitis

Introduction

Tuberculosis (TB) is one of the top 10 causes of death worldwide, with an estimated 23% of the world's population having latent infection and an incidence of 10.4 million active TB cases worldwide in the year 2015.^{1, 2} Approximately 10% of latently-infected adults develop active TB in their lifetime.³ Cigarette smoking, alcohol consumption, malnutrition, and diseases such as diabetes and immune-deficiency conditions have been identified as risk factors for active TB.⁴

Asthma increases the risk of pulmonary infections in general.⁵ Immunopathological features of asthma include secretion of type 2 cytokines, airway mucosal infiltration by Th2 cells, eosinophils and activated mast cells as well as increased mucous production,⁶ with increased susceptibility to microbial colonization and infection.^{7–9} Specifically with regards to TB, it has been hypothesized that while type 1 inflammation mediated by Th1 cells has been shown to be contributory to TB protection via interferon-gamma secretion and activation of macrophages, asthma shifts the Th1/Th2 inflammatory milieu in the airways towards a Th2 pattern, which may in turn be associated with decreased protection from mycobacterial infection.¹⁰

However, there is limited epidemiological data to support asthma as a risk factor for the development of active TB in human populations, with only one case-control study from the UK finding an adjusted odds ratio (OR) of 1.4 [95% confidence interval (CI): 1.0–2.0] for the relation between TB and a previous history of asthma.¹¹ On the contrary, several other studies evaluating the “hygiene hypothesis”—whether TB decreases the risk of developing allergic diseases—found an inverse relationship between TB rates and prevalence of asthma.^{12–14} Those studies were cross-sectional and could neither discern causal relationships, nor address the question of reverse causation, that is, whether asthma modifies susceptibility to TB. Therefore, a prospective study to clarify the temporality of the association between asthma and TB is essential.

There is a high prevalence of sinonasal disease among asthmatics.^{15–17} The most common phenotypes of sinonasal disease in asthma include allergic rhinitis and chronic rhinosinusitis, but other nonallergic forms such as entopy, nonallergic rhinitis with

eosinophilia syndrome, and neutrophilic phenotypes can also occur in asthma. Within this heterogeneity, concordance of inflammatory and histopathological features in the nasal and lower respiratory epithelium¹⁸ has been demonstrated. Treatment of comorbid sinonasal disease leads to improvement in asthma symptoms.¹⁹ This has led to the concept of “united airway disease”, where the upper and lower airways are viewed as a single entity,²⁰ forming a contiguous, united respiratory epithelial tract ultimately leading to the alveoli. According to this view, asthma and associated sinonasal disease represent different expressions of a common pathological process, such as allergy and mucosal inflammation.²¹ Although an inverse association between allergic rhinitis and infection with *Mycobacterium tuberculosis*^{22, 23} has been found in cross-sectional and case-control studies, the role of sinonasal disease in influencing the development of active TB disease has not been investigated prospectively.

Here, our aim was to determine whether asthma and sinonasal disease prospectively influenced the risk of developing active TB. Furthermore, because chronic bronchitis, a form of chronic obstructive pulmonary disease, is common in the general population and associated with the a predisposition to lower respiratory tract infection,^{24, 25} we also investigated whether chronic bronchitis was associated with the risk of developing active TB. We investigated this by utilising data from the Singapore Chinese Health Study, a large population cohort of middle-aged and older Chinese residing in Singapore. Participants of this cohort went through periods when TB was highly prevalent in the country a few decades ago, and those who had acquired latent TB infection in those early years would be at risk of disease reactivation at advanced age.²⁶

Methods

Study population

The Singapore Chinese Health Study is a prospective population-based cohort of 63,257 Chinese adults aged 45–74 years during recruited between April 1993 and December 1998.²⁷ Enrolled participants were citizens or permanent residents of Singapore residing in government housing estates, where about 86% of the Singapore resident population resided during the period of recruitment. We restricted the recruitment to the two major dialect groups of Chinese in Singapore - the Hokkiens who originated from the southern part of Fujian Province and the Cantonese who came from the central region of Guangdong Province.²⁷ Recruitment was initiated using a posted letter to invite potential participants to take part in the study. Study staff went door to door 5–7 days later to recruit participants for the study, if they met the inclusion criteria based on their ethnicity, age, dialect group, and residency status. Approximately 85% of the eligible subjects invited agreed to participate. Follow-up I of the study was conducted between 1999 and 2004 for 52,325 surviving cohort members via telephone interview. This study was approved by the Institutional Review Board at the National University of Singapore, and all study participants gave informed consent.

Exposure assessment

At recruitment, an in-person interview was conducted at each study participant's home by a trained interviewer with the use of a structured questionnaire. Data collected included demographics, lifetime use of tobacco, alcohol consumption, and history of physician-diagnosed medical conditions, including year of diagnosis. This included medical conditions such as sinonasal disease, diabetes and cancer. Usual diet over the past year was assessed using a semi-quantitative food-frequency questionnaire that included 165 commonly consumed food items in this population. The respondents were required to choose the portion size (small, medium, large) from provided photographs and select from 8 frequency categories (ranging from "never or hardly ever" to "two or more times a day"). The food-frequency questionnaire was subsequently validated using two 24-hour dietary recall interviews and a repeat administration of it among a subset of 810 cohort participants.²⁷ Information on the participant's weight, smoking status, alcohol intake and medical history were also updated during the follow-up I interview. The follow-up I interview additionally included questions that were not in the baseline interview to assess history of physician-diagnosed asthma and symptoms of chronic bronchitis, the latter defined according to American Thoracic Society 1995 consensus criteria²⁸ in use at the time of the study, i.e. as chronic productive cough for at least three months in each of two successive years in a patient in whom other causes of productive chronic cough have been excluded.

Ascertainment of TB cases

Active TB cases were identified by record linkage with the National TB Notification Registry²⁹ through 31 December 2014. Active TB cases were defined according to the 2013 revision of the World Health Organization definition and reporting framework for TB³⁰, which includes both "bacteriologically confirmed TB case" as well as "clinically diagnosed TB case", the latter defined as being diagnosed with active TB by a clinician and other medical practitioner and decision has been made to give the patient a full course of TB treatment, in the absence of bacteriologic confirmation. Under the Infectious Diseases Act in Singapore, notification of all active TB cases to the Ministry of Health within 72 hours is mandatory by law. All culture-positive TB patients in Singapore are also comprehensively captured in the National TB Notification Registry via electronic linkage with the two mycobacterial laboratories in Singapore²⁹. Follow-up of the cohort was made by regular linkage to the Singapore Registry of Births and Deaths to update vital status of cohort members. As of 31 December 2014, only 52 participants were known to be lost to follow-up for reasons such as migration out of Singapore.

Statistical analysis

Participants with a history of active TB before date of recruitment, as recorded in the National TB Notification Registry, were excluded from our analysis ($n=3012$). As information on asthma and chronic bronchitis were collected only at follow-up I, analysis on these variables only included participants who completed the follow-up I interview. There were 60,245 participants included in the analyses on baseline sinonasal disease and 49,762 participants included in the analyses on asthma and chronic bronchitis. The Student's t-test (for continuous variables) and chi-square test (for categorical variables) were used to

compare the differences in distributions of characteristics between participants with and without the exposure of interest (sinonasal disease at baseline, asthma and chronic bronchitis at follow-up I) as well as between participants who developed active TB and participants who remained TB-free at the end of follow-up. Person-years of follow-up for each participant were calculated from the date of recruitment (for sinonasal disease) or follow-up I interview (for asthma and chronic bronchitis) to the date of diagnosis of active TB, death, lost-to-follow-up, or 31 December 2014, whichever occurred earlier.

Cox proportional hazards regression models were used to examine the associations between history of sinonasal disease at baseline, asthma and chronic bronchitis at follow-up I and the risk of active TB with adjustments for factors which have been reported to affect TB risk either in the literature or in our cohort.^{31–35} The strength of a given association was measured by the hazard ratio (HR) and its corresponding 95% CI. We built two models, a simpler Model 1 and a more comprehensive Model 2, so that the comparison of the change in risk estimates between the two models can offer an insight on the confounding effect of the additional covariates in Model 2. The first model was adjusted for age at baseline or follow-up I interview (years), year of interview (1993–1995, 1996–1998 for baseline; 1999–2001, 2002–2004 for follow-up I), gender, dialect group (Hokkien, Cantonese), level of education (no formal education, primary, secondary or above). The second model additionally adjusted for body mass index (kg/m²), history of diabetes, smoking status (never, former, current), alcohol intake (none, monthly, weekly, daily), tea intake (none, monthly, weekly, daily), total energy intake (kcal/day), and energy-adjusted intake of protein, cholesterol, marine omega-3, omega-6 fatty acids, vitamin A and vitamin C (quartiles).

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) statistical software package. All the *P*-values quoted were two-sided, and *P* < 0.05 was considered statistically significant.

Results

A total of 1249 incident cases of active TB were identified from recruitment to 31 December 2014, including 678 cases that occurred after the date of follow-up I interview (Figure 1). Approximately 91% of these active TB cases were pulmonary TB. The mean duration of follow-up from the date of recruitment until 31 December 2014 was 16.8 (SD 5.2) years, and that from follow-up I interview to 31 December 2014 was 12.2 (SD 3.3) years.

The prevalence of sinonasal disease, asthma and bronchitis was 2.7%, 4.4% and 4.7% respectively. Among participants who reported a baseline history of physician-diagnosed sinonasal disease, the majority (68.5%) had allergic rhinitis. Characteristics of participants by history of sinonasal disease at baseline, and by history of asthma or chronic bronchitis at follow-up I are shown in Table 1. Compared to their counterparts who did not report the conditions, those who reported physician-diagnosed sinonasal disease at baseline or asthma at follow-up I interviews were slightly younger, had higher education level, and were less likely to be current smokers. They also had higher dietary consumption of polyunsaturated fatty acids, namely omega-6 and omega-3 fatty acids, and Vitamin A. Those with sinonasal

disease had lower prevalence of diabetes compared to those without the disease, but the prevalence of diabetes was higher among those with asthma than those without. In the comparison between those with and without history of chronic bronchitis, those with the condition was more educated and, expectedly, more than twice as likely to be current smokers. They also had lower dietary consumption of polyunsaturated fatty acids, Vitamin A and Vitamin C. Age and prevalence of diabetes at follow-up I interviews were not significantly different between those with and without history of chronic bronchitis.

Compared to participants who did not develop active TB, TB cases were older at recruitment, had lower body mass index, and were more likely to be men or to be ever-smokers. The proportions of TB cases with no formal education or at least secondary school education were both lower than for non-cases, hence, there was no clear direction of a lower proportion of TB cases with increasing level of education. TB cases also had higher prevalence of diabetes and regular alcohol consumption, but lower intake of protein, polyunsaturated fatty acids, vitamin A and vitamin C, compared with those who did not develop TB (Table 2).

Kaplan-Meier survival curves for TB disease-free progression over time among those with and without history of asthma, sinonasal disease or chronic bronchitis are shown in Online Repository E-Figure 1. The survival function was significantly higher in participants with history of asthma or sinonasal disease (log-rank $p=0.007$ and 0.002 respectively), but lower in participants with history of chronic bronchitis (log-rank $p=0.004$), compared to their respective counterparts without the disease. After full adjustment for confounders in Cox regression model 2 (Table 3), there was still statistically significant reduction in risk of active TB among participants with baseline history of sinonasal disease (HR 0.59, 95% CI 0.36–0.95) and among participants with history of asthma at follow-up I (HR 0.55, 95% CI 0.32–0.93) compared to participants who did not have the respective condition. In contrast, the association between history of chronic bronchitis at follow-up I and risk of active TB was attenuated and did not achieve statistical significance in the fully adjusted Cox regression model (HR 0.95, 95% CI 0.68–1.31). After excluding participants with a baseline history of sinonasal disease, the risk of active TB with history of asthma (HR 0.58, 95% CI 0.34–0.99) or chronic bronchitis (HR 0.99, 95% CI 0.72–1.37) at follow-up I remained similar. Among the 60,245 participants, 50,048 participated in follow-up I interviews. As a sensitivity analysis, we have repeated the analysis using time-dependent covariates in this subcohort for the variables that were updated at follow-up I, including smoking status, alcohol consumption, body mass index and diabetes status, for the analysis on sinonasal disease and TB risk, and the results remained similar; the HR (95% CI) was 0.64 (0.38–1.06). Further sensitivity analysis excluded participants who had a positive history of comorbid asthma and chronic bronchitis at follow-up I, and the risk of active TB among participants who reported only asthma was even lower (HR 0.37, 95% CI 0.18–0.74), while there remained no significant association among those who reported only chronic bronchitis (HR 0.88, 0.62–1.25).

Discussion

The present study prospectively examined the relationship between asthma, sinonasal disease and the incidence of active TB in a large population-based cohort. A history of physician-diagnosed asthma or sinonasal disease was found to be associated with reduced risk of incident active TB.

An inverse association between asthma or allergic rhinitis with TB had been demonstrated previously by a few cross-sectional studies. The International Study of Asthma and Allergies in Childhood surveyed 235,477 children worldwide and found that TB notification rates were inversely associated with prevalence of wheeze, asthma and allergic rhinoconjunctivitis,¹² a finding that was subsequently replicated.³⁶ A case-control study of smear-positive TB patients in three countries in West Africa found that a history of asthma was associated with decreased odds of TB.¹⁴ Similarly, atopic rhinitis defined on the basis of symptoms and skin prick test positivity to environmental allergens was associated a lower likelihood of positive tuberculin skin test in a cross-sectional study of 418 children.²³ The aforementioned studies were either cross-sectional or case-control studies. Cross-sectional studies are unable to infer temporal relationships between asthma/sinonasal disease and TB, whereas case-control studies are particularly prone to selection bias. However, their findings are consistent with ours and collectively support a protective effect of asthma/sinonasal disease on the development of active TB. To our knowledge, this is the first prospective study to demonstrate a protective association between history of asthma/sinonasal disease and TB risk.

Shared immunological properties between upper and lower airways likely account for the observed risk reduction of TB in both asthma and sinonasal disease, but the exact immunological mechanisms conferring protection against TB are not known. Asthma is predominantly a Th2 inflammatory disease, as is allergic rhinitis which comprised the main phenotype of sinonasal disease in our study cohort. Th2 inflammation involves the release of cytokines IL-4, IL-5 and IL-13, and recruitment/activation of eosinophils. One possibility to explain the risk reduction of TB in both asthma and sinonasal disease is that eosinophils have a role in protection against TB. Although traditionally thought to be mainly mediating allergic and anti-helminthic responses, eosinophils have more recently been recognised to also have antibacterial and anti-mycobacterial actions.³⁷ Pulmonary eosinophilia has been reported to occur in pulmonary TB.³⁸ Eosinophils exhibit chemotaxis towards mycobacteria, are recruited to sites of granulomas, and can inhibit mycobacteria growth in a toll-like receptor-dependent manner via the action of alpha-defensins.³⁹ In addition, exposure to mycobacteria also triggers eosinophils to generate reactive oxygen species and the release of eosinophil granules,³⁹ which have been shown to have significant inhibitory activity against TB bacilli via mechanisms such as promoting cell wall lesions and lysis.^{40, 41} Eosinophilic airway inflammation occurring due to asthma and eosinophilic phenotypes of sinonasal disease may therefore augment eosinophil-mediated protective responses against mycobacteria, and explain the lower risk of active TB among individuals with a history of asthma and sinonasal disease. In this epidemiological study, we did not specifically delineate inflammatory phenotypes of asthma or sinonasal disease, but our data indicate that the majority of patients with sinonasal disease had allergic rhinitis and previous studies have

established that allergic rhinitis/allergic asthma due to house dust mite sensitization remains the most pervasive phenotype of asthma and rhinitis in Singapore.⁴² The focus of our investigation was on asthma and sinonasal disease as risk factors for TB, but we also examined whether TB risk was modified by chronic bronchitis, an obstructive lung disease which is immunopathologically distinct from asthma. This study found that, unlike asthma or sinonasal disease, chronic bronchitis was not associated with modified susceptibility to active TB. Airway inflammation in chronic bronchitis/COPD markedly differs from that of asthma,⁶ with the former characterized by mucosal infiltration of predominantly neutrophils and Th1 lymphocytes, whereas the latter is characterized by infiltration of eosinophils, mast cells, and Th2 lymphocytes. Differences in profile of inflammatory cytokines, chemokines and cells may explain the differential effect of these two chronic respiratory diseases, and may explain our observed associations.

The prevalence of physician-diagnosed asthma in this cohort was approximately 4.4%, which is comparable to 4.3–4.7% reported by another epidemiological study conducted in Singapore in 1994.⁴³ Prevalence of chronic bronchitis in our study was 4.6%, which is not dissimilar to COPD prevalence of approximately 6% reported elsewhere.⁴⁴ Approximately 60% of all notified TB cases in Singapore are bacteriologically confirmed (i.e. culture positive).⁴⁵ The incidence rate in the first 5 years of follow-up in the whole cohort was 1.27 per 1,000 person-years, and the incidence rate in the subsequent years in the whole cohort was 1.22 per 1,000 person-years. Hence, the incidence rate, though decreasing, was fairly stable, and consistent with national data of TB incidence among resident population in Singapore over this study period.⁴⁶

The strengths of our study include its prospective, longitudinal design with a mean follow-up of more than a decade, and adjusting for multiple variables that are known to be associated with TB, such as smoking, body mass index, history of diabetes, alcohol intake and dietary intake. Our study has several limitations. First, asthma was defined on the basis of self-reported history (albeit physician-diagnosed) in this study, whereas in current clinical practice, the diagnosis of asthma is ideally corroborated by supportive evidence such as demonstration of bronchial hyperresponsiveness, significant bronchodilator reversibility, or peak flow variability. However, these tests are logistically challenging to perform in the field and difficult to standardize in large-scale epidemiological studies, and it has been reported that the addition of bronchoprovocation testing does not improve diagnostic accuracy.^{47–49} Second, we were unable to assess the effect of inhaled corticosteroids, but the use of inhaled corticosteroids is likely to increase, rather than decrease, risk of TB.^{50–54} Third, socioeconomic status is an important determinant in the risk of active TB and is likely to affect access to healthcare for diagnosis of conditions like asthma, rhinitis and chronic bronchitis. Hence, we acknowledge that our adjustment for socioeconomic status by using highest level of education as a surrogate was also not optimal. Fourth, the study population included only Chinese participants and our findings may therefore not apply to other populations. For example, inflammatory mechanisms of chronic rhinosinusitis with nasal polyps varies depending on the population studied, being mainly eosinophilic in Caucasians but neutrophilic in Chinese populations.⁵⁵ In this study we were unable to assess different phenoendotypes of asthma/sinonasal disease in detail. The risk of TB in different populations and different inflammatory phenoendotypes of upper/lower airway disease

should be the focus of future studies. We also lacked information on the status of Human Immunodeficiency Virus (HIV) infection among the participants, but with a very low prevalence (1278 per million population) of this condition in Singapore,⁵⁶ any confounding effect from not adjusting for HIV status in this cohort is likely to have negligible impact on the observed associations. Information on use of immunosuppressants was lacking in our study, but the use of systemic immunosuppressant that is sufficient to affect TB risk in a population-based cohort is unlikely to be high. Data on other confounders, including diet, were also based on retrospective self-report, which may be subject to measurement error. Finally, as in any observational studies, there could still be residual confounding of unknown or unmeasured factors on our observed association.

In conclusion, this population-based prospective cohort study demonstrated a protective effect of asthma and sinonasal disease on the incidence of active TB. Further studies are required to look into the mechanistic pathways to understand how these diseases contribute to reduce disease risk.

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Abbreviations

CI	confidence interval
COPD	chronic obstructive pulmonary disease
HIV	Human Immunodeficiency Virus
HR	hazard ratio
IL	interleukin
TB	tuberculosis
OR	odds ratio

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Highlight Box

1. **What is already known about this topic?** It is not known whether asthma or sinonasal disease modulates risk of developing active tuberculosis.
2. **What does this article add to our knowledge?** In this large cohort study of a middle- aged and older Chinese population residing in Singapore, a history of asthma or sinonasal disease was associated with reduced incidence of active tuberculosis.
3. **How does this study impact current management guidelines?** These findings challenge a common view that asthma increases susceptibility to infections, and highlights a possible role of eosinophils in antimycobacterial defence.

Figure 1.
Flow of the Singapore Chinese Health Study participants in this study

Online Repository E-Figure 1.

Kaplan-Meier curves for tuberculosis disease-free progression over time by history of A. sinonasal disease, B. asthma or C. chronic bronchitis. The log-rank test was used to compare Kaplan-Meier curves between participants with and without history of respective diseases.

Table 1:

Characteristics of participants by history of sinonasal disease at baseline, and by history of asthma or chronic bronchitis at follow-up I^a.

Characteristics	Sinonasal disease (assessed at Baseline, 1993–1998)			Asthma (assessed at Follow-up I, 1999–2004)			Chronic bronchitis (assessed at Follow-up I, 1999–2004)		
	No	Yes	P-value ^b	No	Yes	P-value ^b	No	Yes	P-value ^b
N (%)	58,610 (97.3)	1635 (2.7)		47,589 (95.6)	2173 (4.4)		47,436 (95.3)	2326 (4.7)	
Age, years ^a	56.4 ± 8.0	54.0 ± 7.4	<0.001	62.0 ± 7.9	61.6 ± 8	0.03	62.0 ± 7.9	62.2 ± 8.1	0.17
Body mass index ^a , kg/m ²	23.2 ± 3.3	22.9 ± 3.4	<0.001	23.2 ± 3.6	23.5 ± 3.9	<0.001	23.2 ± 3.6	23.3 ± 3.8	0.57
Gender			<0.001			0.27			<0.001
Men	25,107 (42.8)	807 (49.4)		19,689 (41.4)	873 (40.2)		19,141 (40.4)	1421 (61.1)	
Women	33,503 (57.2)	828 (50.6)		27,900 (58.6)	1300 (59.8)		28,295 (59.7)	905 (38.9)	
Dialect group			<0.001			0.01			0.33
Cantonese	27,024 (46.1)	953 (58.3)		23,150 (48.7)	996 (45.8)		23,040 (48.6)	1106 (47.6)	
Hokkien	31,586 (53.9)	682 (41.7)		24,439 (51.4)	1177 (54.2)		24,396 (51.4)	1220 (52.5)	
Level of education			<0.001			0.003			<0.001
No formal	16,394 (28.0)	216 (13.2)		12,378 (26.0)	525 (24.2)		12,458 (26.3)	445 (19.1)	
Primary	25,873 (44.1)	643 (39.3)		21,118 (44.4)	931 (42.8)		20,945 (44.2)	1104 (47.5)	
Secondary or above	16,343 (27.9)	776 (47.5)		14,093 (29.6)	717 (33.0)		14,033 (29.6)	777 (33.4)	
Smoking status			<0.001			<0.001			<0.001
Never	41,248 (70.4)	1184 (72.4)		33,263 (69.9)	1492 (68.7)		33,647 (70.9)	1108 (47.6)	
Former	6196 (10.6)	241 (14.7)		6984 (14.7)	385 (17.7)		6943 (14.6)	426 (18.3)	
Current	11,166 (19.1)	210 (12.8)		7342 (15.4)	296 (13.6)		6846 (14.4)	792 (34.1)	
Alcohol intake ^a			<0.001			0.02			<0.001
None	47,778 (81.5)	1272 (77.8)		38,620 (81.2)	1807 (83.2)		38,690 (81.6)	1737 (74.7)	
Monthly	4185 (7.1)	144 (8.8)		3559 (7.5)	156 (7.2)		3505 (7.4)	210 (9.0)	
Weekly	4666 (8.0)	170 (10.4)		3885 (8.2)	163 (7.5)		3807 (8.0)	241 (10.4)	
Daily	1981 (3.4)	49 (3.0)		1525 (3.2)	47 (2.2)		1434 (3.0)	138 (5.9)	
Tea intake			<0.001			<0.001			0.10
None	24,278 (41.4)	581 (35.5)		19,223 (40.4)	972 (44.7)		19,283 (40.7)	912 (39.2)	

Characteristics	Sinonasal disease (assessed at Baseline, 1993–1998)			Asthma (assessed at Follow-up I, 1999–2004)			Chronic bronchitis (assessed at Follow-up I, 1999–2004)		
	No	Yes	<i>P</i> -value ^b	No	Yes	<i>P</i> -value ^b	No	Yes	<i>P</i> -value ^b
Monthly	7063 (12.1)	212 (13.0)		5846 (12.3)	253 (11.6)		5837 (12.3)	262 (11.3)	
Weekly	14,240 (24.3)	465 (28.4)		11,779 (24.8)	535 (24.6)		11,703 (24.7)	611 (26.3)	
Daily	13,029 (22.2)	377 (23.1)		10,741 (22.6)	413 (19.0)		10,613 (22.4)	541 (23.3)	
History of diabetes ^a	5279 (9.0)	122 (7.5)	0.03	6491 (13.6)	348 (16.0)	0.002	6517 (13.7)	322 (13.8)	0.89
Total energy intake, kcal/day	1549±563	1667±570	<0.001	1561±562	1571 ± 550	0.43	1556±558	1689± 611	<0.001
Protein, g/day	59.2 ± 10.0	60.4 ± 10	<0.001	59.3 ± 9.9	60.3 ± 9.9	<0.001	59.3 ± 9.9	59.1 ± 10.6	0.28
Cholesterol, mg/day	173.0 ± 74.3	183.4 ± 80.3	<0.001	172.7 ± 73.2	178.0 ± 71.9	0.001	172.7 ± 72.8	178.5 ± 79.1	<0.001
Polyunsaturated fatty acid, g/day ^c	8.88 ± 3.37	9.44 ± 3.83	<0.001	8.95 ± 3.41	9.09 ± 3.45	0.06	8.97 ± 3.41	8.63 ± 3.46	<0.001
Vitamin A, IU/day	5122 ± 2972	5652 ± 3489	<0.001	5216 ± 3003	5365 ± 3221	0.02	5239 ± 3001	4891 ± 3237	<0.001
Vitamin C, mg/day	103.1 ± 131	132.8 ± 189	<0.001	105.9 ± 134	107.1 ± 140	0.68	106.3 ± 134	98.5 ± 140.3	0.009

^aInformation on age, body mass index, smoking status, alcohol consumption and history of diabetes for the analysis on sinonasal disease was collected at baseline interviews, and the same information for the analysis on asthma or chronic bronchitis was collected at follow-up I interviews. Information on all the other variables in this Table was collected at baseline interviews.

^b*P*-values for comparisons between those with and without history of each disease were computed by Student's *t*-test (continuous variables) and chi-square test (categorical variables).

^cIncludes omega-3 and omega-6 fatty acids.

Table 2:

Characteristics of participants according to incident active tuberculosis

Characteristics	Tuberculosis		<i>P</i> -value ^a
	No	Yes	
N (%)	58,996	1249	
Age at baseline interview, years	56.3 ± 8.0	59.3 ± 7.9	<0.001
Body mass index, kg/m ²	23.2 ± 3.3	22.2 ± 3.5	<0.001
Gender			<0.001
Men	24,999 (42.4)	915 (73.3)	
Women	33,997 (57.6)	334 (26.7)	
Dialect group			0.02
Cantonese	27,438 (46.5)	539 (43.2)	
Hokkien	31,558 (53.5)	710 (56.9)	
Level of education			<0.001
No formal education	16,302 (27.6)	308 (24.7)	
Primary school	25,849 (43.8)	667 (53.4)	
Secondary school or above	16,845 (28.6)	274 (21.9)	
Smoking status			<0.001
Never	41898 (71.0)	534 (42.8)	
Former	6262 (10.6)	175 (14.0)	
Current	10836 (18.4)	540 (43.2)	
Alcohol intake			<0.001
None	48,106 (81.5)	944 (75.6)	
Monthly	4237 (7.2)	92 (7.4)	
Weekly	4720 (8.0)	116 (9.3)	
Daily	1933 (3.3)	97 (7.8)	
Tea intake			0.33
None	24,328 (41.2)	531 (42.5)	
Monthly	7120 (12.1)	155 (12.4)	
Weekly	14,428 (24.5)	277 (22.2)	
Daily	13,120 (22.2)	286 (22.9)	
History of diabetes	5226 (8.9)	175 (14.0)	<0.001
Total energy intake, kcal/day	1551 ± 564	1601 ± 574	0.002
Energy-adjusted intake Protein, g/day	59.2 ± 9.9	57.6 ± 10.5	<0.001
Cholesterol, mg/day	173.2 ± 74.3	175.2 ± 84.3	0.42
Marine omega-3 fatty acid, g/day	0.32 ± 0.16	0.30 ± 0.16	<0.001
Omega-6 fatty acid, g/day	8.0 ± 3.2	7.3 ± 3.1	<0.001
Vitamin A, IU/day	5152 ± 2990	4413 ± 2806	<0.001
Vitamin C, mg/day	104.2 ± 133	87.5 ± 121	<0.001

^a *P*-values were computed by Student's *t*-test (continuous variables) or chi-square test (categorical variables).

Table 3:

History of medical conditions at baseline (1993–1998) and follow-up I (1999–2004) in relation to risk of active tuberculosis (TB), the Singapore Chinese Health Study

	TB Cases	Person-years	HR (95% CI) ^a	HR (95% CI) ^b
Sinonasal disease at baseline				
Sinonasal disease absent	1232	984,578	1.00	1.00
Sinonasal disease present	17	28,112	0.55 (0.34–0.88)	0.59 (0.36–0.95)
Asthma at follow-up I				
Asthma absent	663	580,633	1.00	1.00
Asthma present	15	26,269	0.54 (0.32–0.90)	0.55 (0.32–0.93)
Chronic bronchitis at follow-up I				
Chronic bronchitis absent	632	579,601	1.00	1.00
Chronic bronchitis present	46	27,301	1.19 (0.88–1.61)	0.95 (0.68–1.31)

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aModel 1 adjusted for age at baseline or follow-up I interview (years), year of interview (1993–1995, 1996–1998 for baseline; 1999–2001, 2002–2004 for follow-up I), gender, dialect group (Hokkien, Cantonese), level of education (no formal education, primary, secondary or above).

^bModel 2 additionally adjusted for body mass index (kg/m²), history of diabetes, smoking status (never, former, current), alcohol intake (none, monthly, weekly, daily), tea intake (none, monthly, weekly, daily), total energy intake (kcal/day), energy-adjusted intake of protein, cholesterol, marine n-3, n-6 fatty acids, vitamin A, vitamin C (quartiles).