Previous tuberculosis infection associated with increased frequency of asthma and respiratory symptoms in a Nordic–Baltic multicentre population study

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Shareable abstract (@ERSpublications)
A history of TB infection, mostly before young adulthood, was associated with higher odds of having asthma and respiratory symptoms at age 50–75 years https://bit.ly/3G2gtPc

Cite this article as: Gyawali S, López-Cervantes JP, Jõgi NO, *et al*. Previous tuberculosis infection associated with increased frequency of asthma and respiratory symptoms in a Nordic–Baltic multicentre population study. *ERJ Open Res* 2023; 9: 00011-2023 [DOI: 10.1183/23120541.00011-2023].

Received: 5 Jan 2023
Accepted: 21 March 2023

Abstract

Background Tuberculosis (TB) infection induces profound local and systemic, immunological and inflammatory changes that could influence the development of other respiratory diseases; however, the association between TB and asthma is only partly understood. Our objective was to study the association of TB with asthma and respiratory symptoms in a Nordic–Baltic population-based study.

Methods We included data from the Respiratory Health in Northern Europe (RHINE) study, in which information on general characteristics, TB infection, asthma and asthma-like symptoms were collected using standardised postal questionnaires. Asthma was defined based on asthma medication usage and/or asthma attacks 12 months prior to the study, and/or by a report of ⩾three out of five respiratory symptoms in the last 12 months. Allergic/nonallergic asthma were defined as asthma with/without nasal allergy. The associations of TB with asthma outcomes were analysed using logistic regressions with adjustments for age, sex, smoking, body mass index and parental education.

Results We included 8379 study participants aged 50–75 years, 61 of whom reported having had TB. In adjusted analyses, participants with a history of TB had higher odds of asthma (OR 1.99, 95% CI 1.13–3.47). The associations were consistent for nonallergic asthma (OR 2.17, 95% CI 1.16–4.07), but not for allergic asthma (OR 1.20, 95% CI 0.53–2.71).

Conclusion We found that in a large Northern European population-based cohort, persons with a history of TB infection more frequently had asthma and asthma symptoms. We speculate that this may reflect long-term effects of TB, including direct damage to the airways and lungs, as well as inflammatory responses.

Introduction

Tuberculosis (TB) is a severe infectious disease caused mainly by *Mycobacterium tuberculosis*. TB still represents a major global health threat, especially in low- and middle-income countries, causing 1.5 million deaths worldwide in 2020 [1]. Asthma currently affects an estimated 300 million people worldwide, with around 250 000 deaths annually [2]. The tubercle bacilli enter the human body mainly *via*

the respiratory tract following inhalation of droplets [3], the lungs being the most commonly affected site [4]. However, bacilli may spread from the lungs to other body parts through the bloodstream, the lymphatic system or *via* direct extension [5].

Asthma is a chronic inflammatory disease of the airways with the common symptoms of wheezing, breathlessness, chest tightness and coughing [6]. The term "asthma" is considered an umbrella diagnosis for several diseases with distinct mechanistic pathways (endotypes) and variable clinical presentations (phenotypes). Phenotypes of asthma are defined based on observable combinations of clinical, biological and physiological characteristics [7]. When asthma is triggered by allergens, it is referred to as allergic asthma, while asthma that is not believed to be triggered by allergens is termed nonallergic asthma [8].

Pulmonary TB may cause lung damage and airflow obstruction by modifying parenchyma and scarring the lungs [9]. It has been suggested that the obstruction of airflow following TB infection is not only due to the scarring of parenchyma, but also to bronchiectasis and bronchial stenosis [10]. Such damage to the lungs is likely to increase the risk of asthma and other respiratory diseases following TB. On the other hand, the immunological response towards TB has been suggested to confer protection towards Th2-skewed reactions like in allergies. The literature on asthma after TB is inconsistent, as some studies indicate that TB may increase the risk of asthma, while others find an apparent protective effect [10–15]. One study states that it is not the polarisation but synergy between Th1 and Th2 responses that might protect against TB infection [11]. Owing to the limited and contradictory knowledge, we aimed to investigate the association of TB with subsequent asthma and respiratory symptoms in a large community-based study in the Northern European region.

Methodology

Study design, settings and participants

Data were obtained using standardised questionnaires where participants provided information on general characteristics, habits and respiratory symptoms, as part of the Respiratory Health in Northern Europe study (RHINE, https://rhine.w.uib.no). This is a follow-up study in seven study centres in the Nordic–Baltic countries – Norway (Bergen), Denmark (Aarhus), Iceland (Reykjavik), Sweden (Umeå, Uppsala, and Gothenburg) and Estonia (Tartu) – of the population-based European Community Respiratory Health Survey (ECRHS, www.ecrhs.org) stage 1 performed in 1990–1994 [12]. Young adults aged 20 to 44 years were randomly selected from population registries in each study centre, and in the Nordic study centres the questionnaire samples were followed up in years 2000–2002 (RHINE II), 2010–2012 (RHINE III) and 2020–2022 (RHINE IV). The RHINE questionnaires on asthma, respiratory symptoms and general characteristics are harmonised with the ECRHS questionnaire, a widely used tool in epidemiological studies of asthma and respiratory health in adults [12].

In this paper we present cross-sectional analyses of data from the 4th study wave (RHINE IV) of the RHINE cohort study. Of the 8965 participants from the seven centres, 586 did not answer the question about TB and were excluded, leaving a total of 8379 participants to be included in the analyses.

Written consent was obtained from all the participants at each stage of the RHINE study, and each stage of the study was approved by the local ethical committee in each study centre.

Definition of exposure and outcomes

Exposure

Participants with TB were defined as people with a positive answer to the question, "Have you ever had tuberculosis?". Given that the question did not differentiate between active or latent TB, "TB" was used indistinctively for both. Based on the question, "When were you treated (for the first time) for tuberculosis?", the age of the participants when first treated for TB was calculated.

Outcomes

The respiratory outcomes were defined based on an affirmative answer to the questions presented in the supplementary data in supplementary table S1.

The asthma was defined based on an approach established by Pekkanen and Sunyer [13, 14]. 1) participants were considered to have asthma if they had given a positive answer to either of the questions, "Have you had an attack of asthma in the last 12 months?" or "Are you currently taking any medicine (including inhalers, aerosols, or tablets) for asthma?" (definition 1, current asthma medication/asthma attack). 2) The five self-reported asthma-like symptoms, wheezing, awoken with tightness in the chest, awoken with shortness of breath, awoken with an attack of cough and breathlessness (supplementary table S2),

were used to define an asthma symptom score, assigning one point to each question. Definition 2 thus consisted of having a symptoms score of ⩾3 points (⩾three asthma symptoms). 3) As per definition 3, participants were considered to have asthma if they met definitions 1 and/or 2 (current asthma and/or ⩾three asthma symptoms). We combined definitions 1 and 2 into one single variable to increase the sensitivity.

Furthermore, allergic asthma was defined as the aforementioned definitions of asthma/symptoms and a positive answer to the question, "Do you have any nasal allergies, including hay fever?". Similarly, nonallergic asthma was defined as having asthma without nasal allergy.

Statistical analyses

Potential confounders were assessed using a directed acyclic graph (figure 1) based on currently available evidence [15, 16]. The minimal adjustment set included age, sex, smoking, body mass index and parental education (as proxy for socioeconomic status).

First, we calculated the prevalence of respiratory outcomes among participants with and without TB infection. Further, we performed logistic regression analyses to study the crude and adjusted associations of TB with respiratory outcomes. The odds ratios (OR) with 95% confidence intervals (CI) were calculated for both unadjusted and adjusted models. The statistical analyses were performed using Stata/SE 17.0 (Stata Corp, College Station, TX, USA).

Results

The general characteristics of the study population related to TB status are presented in table 1. The analyses included 8379 participants born between 1945 and 1973, 61 of whom reported TB. Among those who reported having had TB, 63.9% were females and 45.9% answered that they have never smoked. The corresponding numbers for the participants who did not report having ever had TB were 52.9% females and 52.3% never-smokers.

Most of the participants reporting TB were treated before the year 1989. In addition, 33 study participants with TB had undergone TB treatment before 15 years of age, and 44 were younger than 25 years old when they were first treated for TB (table 2).

Overall, participants who reported TB had a higher prevalence of all respiratory outcomes (table 3). ∼36% of participants who reported TB had wheezing compared to 19.5% among those without TB. Likewise, 36.1% of participants with TB reported current asthma medication/asthma attack and/or ⩾3 asthma symptoms compared to 20.8% among those without TB.

The associations of TB with respiratory symptoms and asthma are presented in table 4. TB was associated with increased odds of several asthma outcomes. The odds of self-reported wheezing was 2.3 times higher among those who reported TB compared to those who did not, and this association remained significant after adjustment for confounders (OR 2.01; 95% CI 1.13–3.6). TB was associated with higher odds for asthma as per all three definitions of asthma (OR 1.61; 95% CI 0.83–3.10, OR 2.34; 95% CI 1.30–4.21 and OR 1.99; 95% CI 1.33–3.47 as per definitions 1, 2 and 3, respectively).

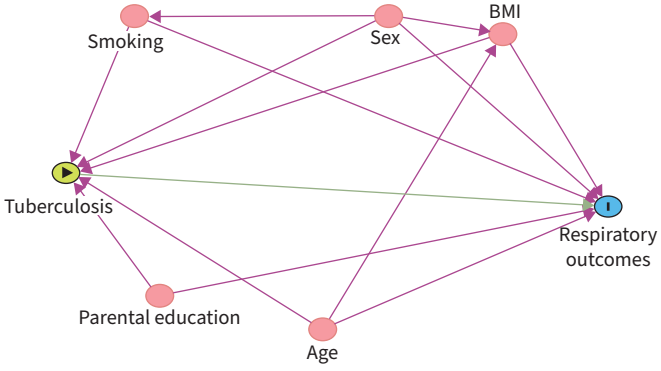

FIGURE 1 Direct acyclic graph linking the tuberculosis infection (exposure) to respiratory outcomes (outcome). BMI: body mass index.

TABLE 1 Basic characteristics of participants of a Nordic–Baltic general population study according to tuberculosis (TB) status

	With TB	Without TB	Total
Participants n	61	8318	8379
Sex			
Male	22 (36.1)	3917 (47.1)	3939 (47.0)
Female	39 (63.9)	4401 (52.9)	4440 (53.0)
Birth year range	1946–1971	1945–1973	1945–1973
Age years	64.9±7.4	62.4±7.1	62.4±7.1
Smoking			
Never-smoker	28 (45.9)	4354 (52.3)	4382 (52.3)
Current smoker	10 (16.4)	745 (9.0)	755 (9.0)
Ex-smoker	23 (37.7)	3219 (38.7)	3242 (38.7)
Parental education (any of the parents)			
Primary school	21 (34.4)	3125 (37.6)	3146 (37.6)
Secondary school	21 (34.4)	2332 (28.0)	2353 (28.1)
College or university	8 (13.1)	1558 (18.7)	1566 (18.7)
Do not know of both	11 (18.0)	1303 (15.7)	1314 (15.7)
Height cm	169.7±11.5	172.8±9.4	172.8±9.4
Weight kg	80.0±17.9	80.4±16.7	80.4±16.7
BMI kg·m^{-2}	27.9±6.9	26.8±4.6	26.8±4.7

Data are presented as n (%) or mean±SD unless indicated otherwise. BMI: body mass index.

Our results indicate a positive association between TB and nonallergic asthma (table 5) with OR 2.13 (95% CI 0.99–4.67) as per definition 1, OR 2.11 (95% CI 1.07–4.19) as per definition 2 and OR 2.17 (95% CI 1.16–4.07) as per definition 3. While the adjusted association was not statistically significant for the first asthma definition, the point estimate does not differ much from the point estimates of the associations with other definitions. We thus consider the result consistent for all three definitions of asthma.

Discussion

This is one of the first large population-based studies addressing the association of TB infection with asthma and respiratory symptoms in a low TB incidence setting, namely a Nordic–Baltic population. We found that a history of TB infection, mostly before young adulthood, was associated with higher odds of having asthma and respiratory symptoms at age 50–75 years. The associations were consistent across

TABLE 2 Distribution of study participants with tuberculosis (TB) by year and age when they were treated for TB (n=61 out of 8379)

Year treated for TB	
1950–1959	19
1960–1969	8
1970–1979	10
1980–1989	8
1990–1999	4
2000–2010	5
2010–	2
No information	5
Age at treatment years	
0–5	18
6–10	10
11–15	5
16–20	3
21–25	8
26–40	6
Above 40	6
No information	5

TABLE 3 Respiratory outcomes according to tuberculosis (TB) status

	With TB	Without TB
Participants n	61	8318
Wheezing[#]	22 (36.0)	1621 (19.5)
Wheezing with shortness of breath[#]	15 (24.5)	932 (11.2)
Wheezing without cold[#]	16 (26.2)	1185 (14.2)
Awoken with tightness in chest[#]	16 (26.2)	949 (11.41)
Awoken with shortness of breath[#]	7 (11.5)	450 (5.4)
Awoken with an attack of cough[#]	29 (47.5)	2052 (24.7)
Shortness of breath when active[#]	40 (65.6)	4318 (51.9)
Difficulty breathing when walking on ground level[#]	27 (44.3)	1783 (21.6)
Breathlessness[#]	14 (22.3)	692 (6.3)
Shortness of breath while walking[#]	9 (15.0)	270 (3.3)
Phlegm[#]	17 (28.3)	1273 (15.6)
Nasal allergies	19 (31.7)	2236 (27.1)
Asthma definition 1 (current asthma medication/asthma attack)	12 (19.7)	991 (11.9)
Asthma definition 2 (⩾3 asthma symptoms)	19 (31.1)	1245 (14.9)
Asthma definition 3 (current asthma and/or ⩾3 asthma symptoms)	22 (36.1)	1733 (20.8)

Data are presented as n (%). [#]: in the last 12 months.

different definitions of asthma and symptom-based outcomes. The association was strong and consistent for nonallergic asthma, while our analyses could not identify any association with allergic asthma.

Several studies support our findings regarding more respiratory symptoms and/or asthma after TB. A study conducted in India found that out of 69 patients with TB and asthma, 70% developed asthma after TB infection [17]. A multinational population-based cross-sectional study conducted in 19 sites, as well as a cross-sectional study conducted in India, found a positive association between TB and obstructive pulmonary diseases [10, 18]. One study conducted in Brazil reported reduced pulmonary function after the treatment of pulmonary TB [19]. In contrast, a study carried out in Sudan to estimate the prevalence of asthma among TB patients concluded that TB infection was associated with a lower prevalence of asthma [20]. Nonetheless, this analysis did not differentiate between allergic and nonallergic asthma.

Our study is one of the few available that analysed the association between TB infection and respiratory outcomes in a low TB incidence setting. Relatedly, a case–control study conducted in the USA found that a group with active TB had a higher risk of pulmonary impairment compared to a group with latent TB infection [21]. Similarly, a cross-sectional study in Finland showed a positive association between previous TB infections and airways obstruction [22]. A recent cohort study conducted among immigrants in Canada reported a two-fold higher risk of airways diseases in patients with a history of pulmonary TB compared to controls [15].

TABLE 4 Association of tuberculosis infection with the odds of respiratory symptoms and asthmatic condition

	Crude		Adjusted[#]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Wheezing	2.33 (1.37–3.94)	0.002	2.01 (1.13–3.6)	0.017
Wheezing with shortness of breath	1.78 (0.69–4.61)	0.235	1.74 (0.67–4.57)	0.254
Wheezing without cold	1.42 (0.47–4.29)	0.527	1.36 (0.45–4.12)	0.584
Awoken with tightness in chest	2.76 (1.55–4.90)	0.001	2.71 (1.49–4.93)	0.001
Awoken with attack of cough	2.76 (1.67–4.58)	0.000	2.59 (1.52–4.41)	0.000
Difficulty breathing when walking on ground level	2.88 (1.73–4.78)	0.000	2.43 (1.36–4.35)	0.003
Shortness of breath when active	1.76 (1.03–2.99)	0.030	1.62 (0.92–2.85)	0.089
Phlegm	2.14 (1.22–3.77)	0.008	1.69 (0.92–3.11)	0.088
Asthma definition 1 (current asthma medication/asthma attack)	1.81 (0.95–3.41)	0.067	1.61 (0.83–3.10)	0.154
Asthma definition 2 (⩾3 asthma symptoms)	2.57 (1.49–4.43)	0.001	2.34 (1.30–4.21)	0.005
Asthma definition 3 (current asthma and/or ⩾3 asthma symptoms)	2.14 (1.27–3.62)	0.004	1.99 (1.13–3.47)	0.016

[#]: adjusted for age, sex, smoking, education and body mass index.

TABLE 5 Association between tuberculosis infection and the odds of allergic and nonallergic asthma

	Allergic (with hay fever)				Nonallergic (without hay fever)			
	Crude		Adjusted[#]		Crude		Adjusted[#]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Asthma definition 1 (current asthma medication/asthma attack)	1.03 (0.37–2.87)	0.944	0.97 (0.34–2.73)	0.962	2.61 (1.23–5.53)	0.012	2.13 (0.99–4.67)	0.05
Asthma definition 2 (⩾3 asthma symptoms)	2.01 (0.91–4.43)	0.085	1.78 (0.78–4.08)	0.173	2.56 (1.35–4.82)	0.004	2.11 (1.07–4.19)	0.032
Asthma definition 3 (current asthma and/or ⩾3 asthma symptoms)	1.27 (0.57–2.80)	0.553	1.20 (0.53–2.71)	0.652	2.55 (1.42–4.58)	0.002	2.17 (1.16–4.07)	0.015

[#]: adjusted for age, sex, smoking, education and body mass index.

The exact mechanisms that could cause obstructive pulmonary disease following TB infection are still under investigation, and several hypotheses have been presented [23]. Most literature agrees that the host immune response and host–pathogen interaction may damage the lungs by distortion of the airway, reduced elasticity, damage to bronchial walls, and impairment to the lung parenchyma and vasculature which may cause chronic airflow obstruction [24].

Some literature finds that TB might have an inverse relationship with allergic asthma [25, 26]. Decreased risk of allergic asthma following TB infection is explained by the hygiene hypothesis, suggesting that the decrease in infectious diseases in developed countries could be important for immunological competence and therefore contribute to the increase in allergic and autoimmune diseases [27, 28]. Our analysis did not observe any association of TB with allergic asthma and thus does not provide evidence to support this hypothesis.

Some researchers suggest that children receiving BCG vaccination may develop fewer allergic diseases later in life [29, 30]. In the Nordic countries, the vaccination policy of routine BCG vaccination was replaced by selective vaccination after 1975 [31]. As all participants of the present study were born between 1945 and 1971, it is likely that practically all have received BCG vaccination. Unfortunately, we do not have data on BCG vaccination and cannot contribute to this topic.

The present study has several strengths. To the best of our knowledge, this is the first study to address the association of TB infection with respiratory symptoms and asthmatic conditions in participants from the Nordic–Baltic region in a single study. Importantly, the assessment of the participants was done by using a standardised questionnaire. Further, we included population-based study samples from different study centres, which reduced the risk of confounding by socioeconomic factors which differ between the study centres.

Asthma has been defined in a range of different ways over the years. A strength of our study is that we investigated the association of TB with asthma defined in several ways, based on the ECRHS questionnaire [13, 15]. The questionnaires and definitions developed by ECRHS are widely used as operational definitions in epidemiological studies of asthma. The different definitions of asthma represent different epidemiological tools that capture various aspects of the disease. Typically, ECRHS defines asthma as an attack of shortness of breath, an attack of asthma or the use of asthma medication. Symptoms are important in defining asthma, and using asthma symptom scores rather than diagnosed asthma increases the power of the study [13]. Definition 1 in this study may be relatively specific, but there is a chance of introducing doctor bias. Definition 2 is based on respiratory symptoms, which could be more sensitive but less specific than definition 1, and less influenced by doctor bias. According to Sunyer *et al.* [14], the use of an asthma symptoms score based on a combination of questions on asthma is valid when analysing asthma in epidemiological studies. Definition 3 defines asthma from both the patients' and doctors' views and is more sensitive than either of the previous definitions because some patients are so well treated that they have very few symptoms. Consistency of the results across the different definitions strengthens the inference that the results may be due to biological mechanisms rather than misclassification bias.

Undeniably, there are certain limitations to this study. One limitation of the study is the cross-sectional study design, and therefore potential challenges related to the timeline. Table 2 shows how most of the participants had TB before 1990. Further, asthma was defined based on current use of asthma medication and asthma symptoms during the last 12 months, and no participant with TB reported childhood asthma (see supplementary table S3). The defined asthma outcomes are thus assumed to have occurred after TB;

however, the possibility that asthma onset preceded TB in some cases and that asthma thus could have been worsened rather than induced by TB cannot be discarded.

Further, as there were few participants reporting TB, we observed relatively broad confidence intervals to the estimates. Moreover, because of the small number of cases, we had to limit our sub-analysis. The follow-up response rate after 20 years of follow-up was about 53% in the RHINE study. Reassuringly regarding loss to follow-up, in an analysis of the RHINE study, Johannessen *et al*. [32] found that disease prevalence was slightly affected by the loss to follow-up, whereas exposure–outcome associations were not affected. The use of self-reported information may lead to information bias, and there may be recall bias regarding TB, asthma and allergies. The questions on TB have not been validated, while the questions on asthma, allergies and respiratory symptoms are from the widely used epidemiological tool of the ECRHS questionnaire. It is a limitation of our study that we did not have lung function measurements. Without lung function measurements, COPD may sometimes be misdiagnosed as asthma due to partly overlapping symptoms. Therefore, some participants in our study who were classified as having asthma may actually have had COPD. This limitation could have affected our findings, as there is a previously recognised association between COPD and TB [23]. Social desirability bias may have occurred as it has been described that individuals with a history of TB may answer negatively to questions about having had the disease [33]. It is likely that misclassification bias in our study would be non-differential, as it is not likely that misclassification of TB would be systematic with regard to asthmatic symptoms [34]. Non-differential misclassification would imply that the actual association of TB with asthma and respiratory symptoms might be stronger than observed.

The findings from the current study suggest that history of TB could possibly influence development of asthma and asthma-like symptoms, supporting a need for follow-up of TB patients after the completion of treatment. It is alarming that 36% of TB patients reported an asthma-related outcome at the age of 50–75 years. In addition, the study also suggests that unifying efforts to mitigate the burden of TB worldwide may also help reduce the prevalence of asthma and respiratory symptoms.

Conclusion

We found that in a large Northern European population-based cohort, persons with a history of TB infection more often had asthma and respiratory symptoms, in particular nonallergic asthma symptoms at age 50–74 years, as compared to persons without a history of TB infection. We speculate that this may reflect the long-term effects of TB, including direct damage to the airways and lungs, as well as inflammatory responses. Further mechanistic and epidemiological studies would be important to elucidate the mechanism underlying these associations and to strengthen the knowledge for targeted intervention efforts.

Provenance: Submitted article, peer reviewed.

Conflict of interest: The research team declares no conflict of interest.

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