Parental tuberculosis as associated with offspring asthma and rhinitis: a Norwegian registry-based study

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Abstract

Background: Early life infections associate with asthma and allergies in a one-generation setting, while a link between parent's infection and offspring phenotype is hardly investigated. We aim to study the association of parental tuberculosis before conception of the offspring, with offspring asthma and rhinitis.

Methods: We included 2965 offspring born 1985-2004 registered in the Norwegian Prescription database, of 1790 parents born after 1960 with a history of tuberculosis, included in the Norwegian Tuberculosis registry. Offspring asthma (n=582) and rhinitis (n=929) were defined by diagnosis, type of medication and prescribed medication ≥1 year. Associations of parental tuberculosis ≤8 years, >8 years but before offspring's birth year, and after birth (reference category), with offspring asthma and rhinitis, were analysed using logistic regression.

Results: Asthma risk was higher in persons with parental tuberculosis in childhood (OR=1.73; 95%CI=1.20-2.50) or later preconception (1.38;1.00-1.91), than in persons with parental tuberculosis after offspring's birth; significant only in the maternal line (childhood 1.95;1.13-3.37; later preconception 1.74;1.08-2.80). Associations with rhinitis were not identified.

Conclusions: Parental childhood tuberculosis associated with higher asthma risk in future offspring. We speculate that tuberculosis impacts maternal immunity and dysregulate offspring type 2 immunity, and that tuberculosis-induced epigenetic reprograming of immune defence translates to offspring.

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Asthma and nasal allergies affect a large part of the world's population. It is estimated that asthma is the second most common chronic respiratory disease, with a prevalence of 3.6%[1]. Approximately 400 million people worldwide are estimated to have rhinitis[2]. The aetiology of these diseases is complex and interrelated, yet not completely understood[3]. A range of studies show that among the different factors influencing asthma and allergies, the early life environment may be of importance.

The role of infections for development of asthma and allergies have been investigated extensively[4,5]. A leading theory behind the increase in asthma following urbanisation is the "hygiene hypothesis" or "biodiversity hypothesis", suggesting allergies result from impaired immunological competence due to low microbial stimulation in early life[5,6]. On the other hand, some studies find that early life infections are associated with more asthma and allergies[4,7,8].

Tuberculosis (TB) is a bacterial infection that has followed humanity since ancient times. Today, it affects around 10 million people, with over one million annual fatalities. The interaction between *Mycobacterium tuberculosis* and the immune defence results in complex disease manifestations exemplified as the formation of granuloma harbouring a variety of immune cells[9,10].

The association between TB and asthma has been proposed to involve the Th1/Th2 paradigm, explaining an increased risk of allergies with declining TB prevalence[11,12]. Other studies find no association of TB or BCG vaccination with asthma/allergies, or even increased risk[13,14]. Reports of type 2 immunity associating with protection against *M. tuberculosis* have suggested that successful control of this infection could favour type 2 immune bias[15,16]. Importantly, although the field has been dominated by the view that interferon-γ-producing Th1 cells are the most central to TB protection, studies have failed to prove a correlation[17], leaving a blurred picture of T cell responses in TB.

Infections contribute to training of the immune system throughout life, and parental infections might possibly influence offspring immunity. A human study found that

parental seropositivity to the helminth *Toxocara* associates with increased asthma and allergy in offspring; the associations followed a sex-specific pattern indicative of epigenetic mechanisms for transfer of disease risk[18]. Recent murine studies found evidence that preconception infections impacted immunity in the next generation(s): preconception maternal helminth infection (cleared before mating), transferred protective immunity to offspring, mainly through nursing, which functionally persisted into adulthood[19]. Encouragingly, in this study, an infection *enhanced* immune competence in the next generation. Paternal effects have also been found; polymicrobial sepsis in mice was found to alter sperm methylome and reduce systemic and pulmonary immune responses in male offspring[20], and another study found that *Toxoplasma gondii* in mice altered sperm transcriptome and the behaviour of the pups[21].

Recent studies suggest that both the BCG vaccine and *M. tuberculosis* can cause epigenetic reprogramming of immune cells, both in the lung and the haematological compartment[22-24]. The effect is reflected both as DNA methylation and histone modifications. Importantly, two of these studies demonstrated a link to enhanced anti-mycobacterial activity[22, 24].

To the best of our knowledge, no studies have investigated whether TB in parents influences the risk of offspring asthma or allergies. The extensive immune remodelling, consequence of TB chronicity, could potentially result in transgenerational influence. In this study, we analyse a potential association between parental TB before conception and asthma/allergies in future offspring. For this purpose, we obtained data from excellent Norwegian registries with nationwide coverage, matching data from the population registry with registries of TB and prescribed medications.

METHODS

Study design and study population

A registry-based, retrospective, two-generation study cohort was generated by match of several Norwegian registries: the *Norwegian Tuberculosis Registry* (NTR or referred to

as the *tuberculosis registry*) contains exhaustive information about TB diagnosis and treatment. It was established in 1962, and later included in the *Norwegian Surveillance System for Communicable Diseases* (MSIS) which collects information from physicians and hospitals around Norway on notifiable infectious diseases. The *National Population Registry* (NPR or referred to as the *population registry*), contains general demographic information of all Norwegian inhabitants and uniquely identifies each person. The *Norwegian Prescription Database* (NorPD, or referred to as the *prescription registry*) was established in 2004 and contains information on all prescription dispensing at outpatient pharmacies, prescribed by physicians in primary and specialist health care.

All the subjects included in the TB registry from 1962 to 2010 were initially identified. Using a unique personal identification number, they were matched to the population registry to obtain data about family relationships and descendance, thereby identifying a two-generation study population consisting of all persons diagnosed with TB and their offspring. The identification numbers of this two-generation study population were again matched, first, with the tuberculosis registry to get detailed information regarding TB infection for both generations, secondly, with the prescription registry to acquire information on medications prescribed for asthma and allergies (Anatomical Therapeutic Chemical Classification System [ATC] codes R01 and R03) for both generations. Figure 1 depicts the process of matching and establishing the database.

A total of 24426 subjects (females= 9970; males=14456) were included in the tuberculosis registry during the period 1962-2010. Family linkage identified 18619 *offspring* from 10300 *parents* (one parent with TB), and 949 offspring who had two parents with TB. Regarding the prescription registry, 16 057 offspring had information of one or more prescription related to the specified ATC codes, duration of treatment and diagnosis. The final study sample was restricted to offspring-parent pairs with one parent per offspring, offspring born between 1985 and 2004 and alive at the establishment of the dataset in 2020 (n=2965), with parents born after 1960 (n=1790).

Ethics

This study was approved by the Norwegian regional medical research ethics committee (REK 2017/2101); informed consents were not required as the data were anonymized.

Exposure

Parental age at diagnosis of TB was classified in three categories: 1) parental childhood TB ≤8 years; 2) parental TB after age 8 years and before offspring's birth year; and 3) parental TB after offspring's birth year. The first two categories represent preconception time windows, the third category was the reference category (there is no literature suggesting that shared environment could give both parental TB and offspring asthma). In addition, parental TB in these three-time windows was analysed regarding location of disease manifestation – pulmonary and extra-pulmonary.

Outcomes

The health outcomes in offspring were assessed using data from the prescription registry. Asthma and rhinitis were defined based on three criteria: 1) ATC codes corresponding to R01 (nasal preparations) and/or R03 (drugs for obstructive airway diseases); 2) the International Classification of Diseases (ICD) and/or International Classification of Primary Care (ICPC) codes for asthma and/or rhinitis; and 3) duration of prescribed medications for one year or more.

Covariates and stratified analyses

Potential confounders were evaluated using directed acyclic graph (DAG), however, no adjusting variables were identified in this assessment. Information about parental socioeconomic status and smoking habits, which could possibly have been considered confounders, was not available. Analyses were performed separately in the male and female lines and further stratified by offspring sex, because sex-specific patterns are biologically plausible in transfer of information across generations. Analyses were further stratified by parental migrant status and organ affected, as prevalence of asthma/allergies and differential immune response secondary to TB location could possibly modify potential associations. Finally, the statistical significance for interactions

with the parent's migrant status, organ affected by TB and offspring's sex were evaluated separately in the maternal and paternal lines.

Statistical analysis

We performed logistic regression analyses to investigate associations between parental TB and offspring asthma and rhinitis. Considering offspring were clustered as families (siblings), we present values from multilevel analyses. We executed sensitivity analysis by stratification by possible modifying factors, sex and parental migrant status. The analyses were performed using the statistical package Stata 17.0 (StataCorp, College Station, TX).

RESULTS

The median age of the offspring population was 17 years, ranging from 6 to 35 years and 50% of the offspring were female (Table 1). Asthma and rhinitis, defined as having the appropriate diagnosis plus relevant medication for one year or more, were present in 20% and 31% of the offspring, respectively; 8.6% filled the criteria for both diagnoses. These 2965 offspring (with only one parent with TB) were the offspring of altogether 1790 parents with a history of TB (mean age at diagnosis, 23.7 years). Of these parents, 630 had TB diagnosed before they were 8 years old, 372 after age 8 years but before the offspring's birth year, and 710 had TB diagnosed after the offspring's birth year. Pulmonary TB was present in 820 and extra-pulmonary in 970; finally, 1110 were listed as migrants, while 602 were Norwegians.

Asthma was more common in offspring if the parent had had TB in childhood (OR 1.73, 95%CI 1.20-2.50) or after age 8 years but before conception (1.38, 1.00-1.91), as compared to offspring of a parent with TB diagnosed after that child was born (Table 2). Regarding offspring rhinitis, no significant association with parental TB in childhood or before conception was identified (Table 2).

When analysing the male and female lines separately, associations of parental childhood/ later preconception TB was only statistically significant in the female line

(Table 3). Further sensitivity analyses with stratification according to offspring's sex and both parent and offspring sex (Table 3), suggested that the association of offspring asthma with parental TB in childhood was relatively consistent in several strata, but not even indicated in the father-son group in which the effect estimate was around 1.0. Regarding parental TB in preconception, a strong association was present in the mother-daughter stratum, but not suggested in the other strata – the interaction term showed borderline significance with p=0.089.

Stratification by parental migrant status suggested stronger associations of offspring asthma with parental TB in foreigners. Stratification by site of TB showed no clear differences regarding parental childhood TB, while an association of preconception TB after age 8 was significantly associated with offspring asthma in those with parental extra-pulmonary TB only (Table 3). Interactions by parental migrant status or site of parental TB were not statistically significant.

DISCUSSION

We have established a two-generation cohort using data from Norwegian registries with excellent, nationwide coverage, including a tuberculosis registry, a population registry and a prescription registry. Analyses from this unselected cohort, reveals that asthma, but not rhinitis, was substantially more common if the parent had had TB disease in childhood, or at a later preconception time window. Analyses addressing sex-specific patterns suggested a more pronounced risk in the maternal line and in daughters, while no associations were detected in the father-son group. Further sensitivity analyses indicated more consistent associations in persons with a migrant parent. In all subgroups, except the mother-daughter group, the associations were stronger and more consistent for parental TB in childhood than for parental TB that occurred at a later preconception age.

To our knowledge, no previous literature, of humans or animals, analyse the associations of parental TB at different ages with offspring asthma. Jögi et al. explored seropositivity towards *Toxocara canis* in humans and found substantially increased risk

of asthma and allergies in offspring of seropositive parents, following a pronounced sex-specific pattern[18]. The serological status of the parent was measured after the offspring was born and could not specify potential preconception exposure; however, the sex-specific pattern could possibly indicate mechanisms including transfer of epigenetic material from parents to offspring.

Regarding multi-generation studies of chemical or metabolic exposures in humans, emerging literature shows stronger evidence that parental exposures before conception may influence the phenotype of future offspring[25,26]. In particular, there are studies uncovering that exposures in pre-puberty/puberty, such as early onset smoking[27-29] or overweight[30], could influence offspring asthma and lung function. Pre-puberty is suggested to be a susceptible time window due to extensive epigenetic reprogramming in germ cell precursors before becoming mature cells with reproductive potential[31]. An intervention study of nutritional supplement in school children in Guatemala, found that, in the female line, the nutritious supplement also improved the outcome of future pregnancies[32].

Based on our results, we propose that immunological changes induced by TB in humans can be transferred to influence the immune phenotype in offspring. Although the study does not reveal any mechanisms, maternal offspring influence could involve epigenetic, immunological or environmental cues such as transfer of exosomes or T cells through breast milk[33,34] or microbiome transfer[35]. There are murine studies supporting the notion that infections may impact immunity in subsequent generations. Darby et al., found that maternal helminth infection in mice, cleared before mating and conception, enhanced immunity towards that same infection in the pups[19]. This effect was mostly, but not only, transferred through breast milk. We did find more pronounced associations in the maternal line, but it might seem unlikely, although not impossible given the results referred to above, that maternal TB, particularly in childhood, should lead to altered properties in breast milk and thereby influence future offspring. Another murine study showed that a preconception systemic infection influenced male offspring immune characteristics through alterations to sperm[20]. Our analyses did identify an

association of father's childhood TB with asthma in daughters, and potential impact through alterations of sperm precursor cells from the profound immunological impact of TB, would be in line with the results of Bomans et al., referred to above.

The uniqueness of our study is based on the high time resolution that allowed studying parental TB in different time windows in relation to asthma in offspring, in a large number of offspring-parent pairs. The strengths of the analysis include the unselected study population obtained from registry data, and that misclassification could not possibly be differential with regard to the association of age of parental TB with offspring outcomes. The diagnosis of TB is assumed to be practically complete in this population. However, misclassification in our definition of asthma may exist, as not all persons with asthma are using appropriate medication. Information on potential confounders in the registries was limited. Lower socioeconomic class is relevant for the occurrence of TB in children, parents' socioeconomic conditions at the time of childbearing could be associated with asthma in their children and tracking of socioeconomic conditions over the lifespan and across generations is likely. Considering generalisability, one may assume that the observation that parental TB in particular susceptible time windows was related with offspring asthma, would be relevant for a general Western population. However, the reference group was parental TB after birth of the offspring and not a group with no parental TB, thus, we cannot draw conclusions as to whether ancestors' TB could influence the overall prevalence of asthma in a population.

In conclusion, we find that parental TB before conception, in the parent's childhood, is associated with higher asthma risk in the offspring, as compared to offspring of persons who had TB after their child was born. Our registry-based study allowed us to disentangle preconception time windows, and we raise the hypothesis that a parental infection, such as TB, with its profound immunological impact, may influence the phenotype in future offspring. Further research on this is warranted to possibly shed light on the pathophysiology of asthma as well as potential inheritable impacts of TB.

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402

Table 1. Characteristics of the study sample.

	n=2965
Birth year, median	1993
Gender, n (%)	
Male	1499 (50.5)
Female	1466 (49.5)
Diagnosis, n (%)	
Asthma[1]	582 (19.6)
Rhinitis[1]	929 (31.3)
Asthma and rhinitis[1]	256 (8.6)
Tuberculosis	55 (1.5)

n: number

[1]Defined by diagnosis, relevant medication, and use of such medication for ≥1 year.

Table 1. General characteristics of the study participants, including 2965 offspring-parent pairs born 1985-2004, alive in 2020, with one or two parents born after 1960 with a history of tuberculosis.

Table 2. Association of asthma and rhinitis in offspring, with parental tuberculosis in different age windows.

Age at diagnosis of parental tuberculosis	Asthma OR (95% CI)[2]	Rhinitis OR (95% CI)
After offspring's year of birth[1]	1	1
Before parental age 8 years	1.73 (1.20-2.50)	1.04 (0.77-1.40)
After age 8 years and before offspring's year of birth	1.38 (1.00-1.91)	1.11 (0.86-1.43)

[1]Reference category

[2]Odds ratio (95% Confidence Intervals)

Table 2. Multilevel logistic regressions that estimate the association of asthma and rhinitis in offspring, with parental tuberculosis in different age windows.

Table 3. Associations of parental tuberculosis at different age windows with offspring asthma stratified in different subgroups.

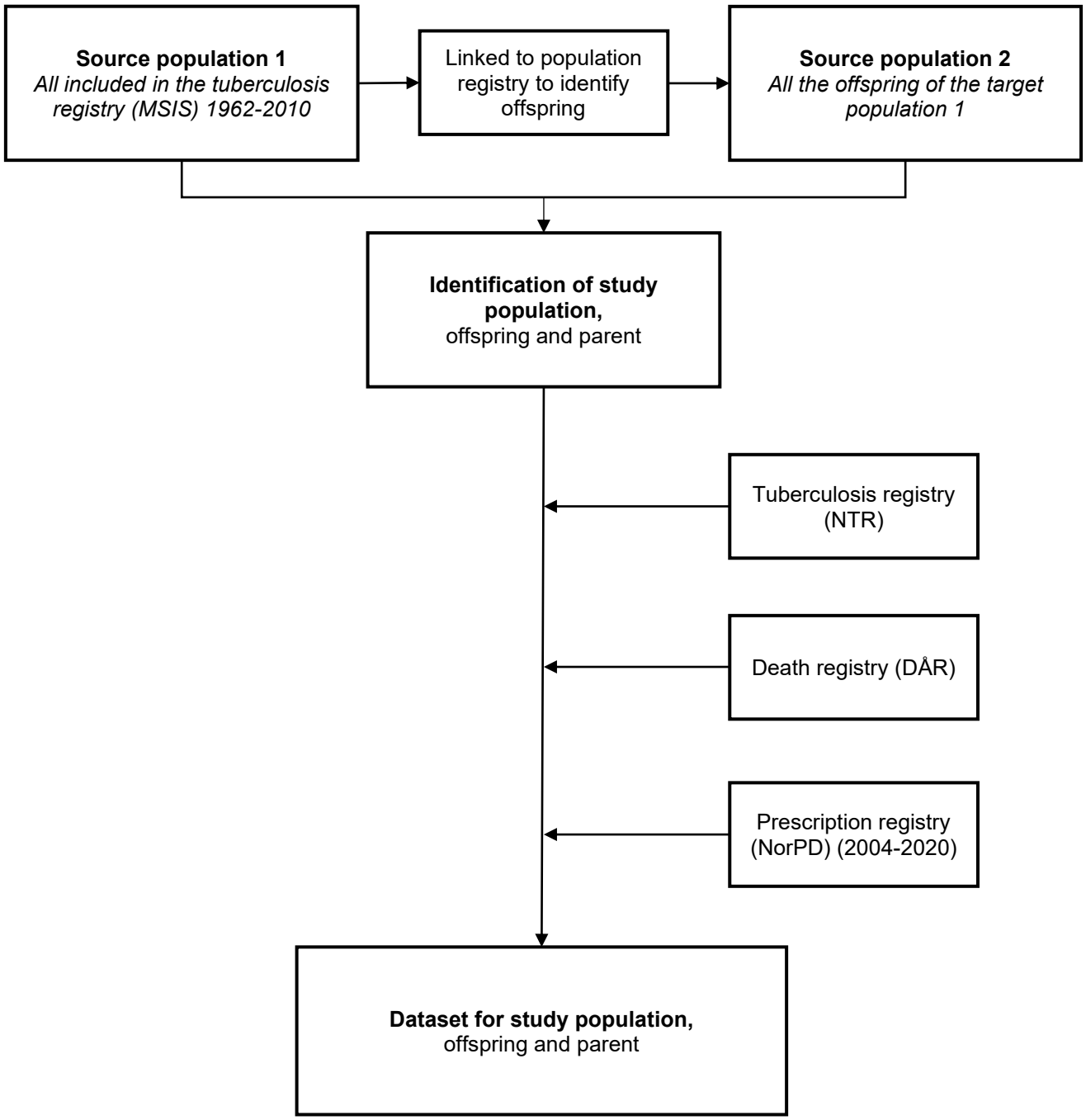
	After offspring's year of birth[1]	Before parental age 8 years	After age 8 years and before offspring's year of birth
	OR (95% CI)[2]	OR (95% CI)	OR (95% CI)
Parental lines			
Maternal	1	1.95 (1.13-3.37)	1.74 (1.08-2.80)
Paternal	1	1.39 (0.84-2.29)	1.02 (0.65-1.58)
Offspring's sex			
Female	1	2.03 (1.23-3.34)	1.66 (1.04-2.63)
Male	1	1.44 (0.89-2.34)	1.14 (0.76-1.72)
Parent-offspring sex			
Mother-daugther	1	1.94 (0.88-4.33)	2.59 (1.22-5.49)
Mother-son	1	1.99 (0.95-4.16)	1.23 (0.66-2.32)
Father-daugther	1	1.93 (0.99-3.73)	1.05 (0.56-1.98)
Father-son	1	1.01 (0.53-1.94)	0.99 (0.57-1.70)
Parent's migrant status			
Foreign-born	1	2.45 (0.97-6.17)	1.56 (1.08-2.28)
Norwegian-born	1	1.51 (0.57-4.24)	1.05 (0.37-2.94)
Tuberculosis location in parents			
Pulmonary	1	1.81 (1.06-3.12)	1.05 (0.68-1.66)
Extra-pulmonary	1	1.75 (1.05-2.92)	1.80 (1.13-2.88)

[1]Reference category

[2]Odds ratio (95% Confidence Intervals)

Table 3. Multilevel logistic regression. Estimates for associations of parental tuberculosis at age 8 years and age 8 years but before conception with offspring asthma (reference category: parental tuberculosis after offspring's birth year) in subgroups according to parent' sex, offspring' sex, both parental and offspring's sex, parental migrant status, and tuberculosis site in parents.

Figure 1. Matching process of the Norwegian registries.



MSIS: Norwegian Surveillance System for Communicable Diseases; NTR: Norwegian Tuberculosis Registry; DÅR: Death Registry; NorPD: Norwegian Prescription Database

Figure 1. Diagram showing the process of matching of the different registries to obtain the final database used for the study.