Respiratory Medicine (2014) 108, 1321–1326

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Heredity of chronic bronchitis: A registry-based twin study

Howraman Meteran [a,*], Vibeke Backer [a], Kirsten Ohm Kyvik [b,c], Axel Skytthe [c], Simon Francis Thomsen [a]

[a] Respiratory and Allergy Research Unit, Bispebjerg Hospital, Copenhagen, Denmark
[b] Odense Patient Data Exploratory Network, Institute of Regional Health Services Research, University of Southern Denmark, Odense, Denmark
[c] The Danish Twin Registry, University of Southern Denmark, Odense, Denmark

Received 10 April 2014; accepted 28 June 2014
Available online 4 July 2014

KEYWORDS
Chronic bronchitis;
COPD;
Heritability;
Twin studies

Summary
Background: Smoking is a major risk factor for lung diseases and lower respiratory symptoms, but since not all smokers develop chronic bronchitis and since chronic bronchitis is also diagnosed in never-smokers, it has been suggested that some individuals are more susceptible to develop chronic bronchitis due to genetics.
Objective: To study the relative influence of genetic and environmental factors on the variation in the susceptibility to chronic bronchitis.
Methods: In a population-based questionnaire study of 13,649 twins, 50–71 years of age, from the Danish Twin Registry, we calculated sex-specific concordance rates and heritability of chronic bronchitis. The response rate was 75%.
Results: The prevalence of chronic bronchitis was 9.3% among men and 8.5% among women. The concordance rate for chronic bronchitis was higher in monozygotic twins than in dizygotic twins among women; 0.30 vs. 0.17, but not among men; 0.15 vs. 0.18. The heritability of chronic bronchitis adjusted for smoking and age was 55% (36–71%) in women, whereas the susceptibility to chronic bronchitis in men for 25% (8–41%) was ascribable to familial environment but not to genetic factors.
Conclusions: Chronic bronchitis shows a moderate familial aggregation, particularly in women. Increased susceptibility to respiratory disease among female smokers relative to male smokers may have a genetic origin.

* Corresponding author. Respiratory and Allergy Research Unit, Bispebjerg Hospital, Bispebjerg Bakke 23, DK-2400 Copenhagen NV, Denmark. Tel.: +45 6067 7296; fax: +45 35312179.
E-mail address: hmeteran@gmail.com (H. Meteran).

http://dx.doi.org/10.1016/j.rmed.2014.06.010
0954-6111/

Introduction

Chronic bronchitis is a disease characterized by chronic cough and sputum from the airways for at least three months in each of two successive years, as long as there are no other causes of chronic cough [1]. The prevalence and mortality associated with chronic obstructive pulmonary disease (COPD) is increasing throughout the world and COPD is estimated to be one of the most common causes of death in 2020 [2,3]. COPD poses an important challenge for society as consultation rates in primary care are high and COPD exacerbations account for a substantial part of hospital admissions [4].

Smoking is a well-known risk factor for chronic bronchitis and COPD [5] and the risk of chronic bronchitis increases with the amount of tobacco consumed and with age [5–8]. Pelkonen and colleagues found that by the age of 75 years the cumulative incidence of chronic bronchitis was 42% in continuous smokers, 26% in ex-smokers and 22% in never-smokers in the finnish population [9]. Other risk factors such as farming, industrial work and asthma have also been suggested [10–12]. Furthermore, some studies have shown an association between passive smoking during childhood and accelerated decline in lung function and lower respiratory symptoms in adulthood [13,14].

Smoking remains the major risk factor for chronic bronchitis and COPD, but since not all smokers develop obstructive respiratory disease, and more interestingly, since chronic bronchitis and COPD have been diagnosed in never-smokers, it has been suggested that the susceptibility could be due to genetics. The most important genetic risk factor for COPD is α1-antitrypsin deficiency, which has been known for several decades. However, α1-antitrypsin deficiency only accounts for 1–2% of the susceptibility to COPD in the population [15,16].

Previous studies have shown a familial aggregation of obstructive pulmonary disease [17–21]. Furthermore, it has been shown that women have a greater degree of airway obstruction for a given amount of tobacco consumption compared with men [22,23]. This low degree of airflow obstruction was also found among non-smokers and individuals with less than five pack-years' smoking history [24] and it has been suggested that women are more susceptible to smoking induced diseases compared with men [25,26].

Hallberg and colleagues have assessed to what extent genetic factors contribute to the development of chronic bronchitis [27]. The study, which examined Swedish twins, found a moderate heritability of chronic bronchitis of 40% [27]. Their criterion used to define chronic bronchitis was wider than the classical criterion, which we have used in our study. Furthermore, the Swedish authors dichotomized smoking, using 10 pack – years as cutoff and thereby light smokers were classified as nonsmokers.

Twin studies offer a powerful approach to examine the impact of genes and environment on human diseases. The aim of this study was, in a large Danish twin sample, to study the relative influence of genetic and environmental factors on the variation in susceptibility to chronic bronchitis.

Methods

Design

Data was collected from the Danish Twin Registry and the present study sample comprised twins born between 1931 and 1952 [28]. These corresponded to 69% of all twin pairs born in Denmark during these years. In 2002, these twins (and twins born between 1953 and 1982) were sent a multidisciplinary questionnaire concerning health and lifestyle in which a history of smoking and chronic bronchitis was recorded. The response rate to the questionnaire was 75%.

The study was approved by The Danish National Committee on Biomedical Research Ethics.

Study population

In total, 13,649 twin individuals (4030 intact pairs with complete data on chronic bronchitis and smoking) were from the cohort born 1931–1952. Chronic bronchitis was defined as an affirmative response to the question 'Have you experienced at least three months per year of coughing with production of phlegm during the past two years? Twin zygosity was determined using four questions of similarity and mistaken identity, which assign zygosity correctly in more than 95% of the cases [29].

Statistical analysis

The prevalence and concordance rate for chronic bronchitis were calculated for the different sex-by-zygosity groups. The concordance rate denotes the probability that one twin is affected given that the co-twin is affected. Since we have complete ascertainment of twins the concordance rate was estimated as two times the number of concordant pairs (both twins are affected) divided by two times the number of concordant affected pairs plus the number of discordant pairs (one twin is affected) [30].

Latent factor models of genetic and environmental factors were fitted to the raw data following the methods described by Neale & Cardon [31]. These are customary twin analyses assuming that the variation in the susceptibility to chronic bronchitis can be partitioned into genetic and environmental sources of variance. Genetic variance can be further partitioned into *additive genetic* (loci contributing additively to disease risk, A) and *non-additive genetic variance* (interacting alleles, either from the same locus – genetic dominance – or from separate loci – epistasis, D). Environmental variance can be further partitioned into *shared environmental* (environmental factors that increase the resemblance between members of the same family, C) and *non-shared – random – environmental variance* (influences unique to individuals that result in differences between family members, E) [32]. For most human traits it is reasonable to assume that all four sources of variance (A, D, C, and E) act simultaneously. However, components C and D are not identified under the same model in studies that include only twins reared together [33]. Therefore, the likelihood of the data was determined