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Clinical Trial Paper

Comorbidity between chronic obstructive pulmonary disease and type 2 diabetes: A nation-wide cohort twin study

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

[a] Respiratory Research Unit, Bispebjerg University 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

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality and is associated with several systemic diseases, such as type 2 diabetes. It has been suggested that comorbidity between COPD and type 2 diabetes is due to shared genetic factors.
Aim: To examine the relationship between type 2 diabetes and chronic bronchitis and COPD in adult twins, and to examine to what extent comorbidity between these diseases is explained by shared genetic or environmental factors.
Methods: Questionnaire data on chronic bronchitis and hospital discharge data on diagnosed COPD in 13,649 twins, aged 50–71 years, from the Danish Twin Registry were cross-linked with hospital discharge diagnosis data on type 2 diabetes from the Danish National Patient Registry.
Results: The risk of type 2 diabetes was higher in persons with symptoms of chronic bronchitis than in those without symptoms (3.5 vs. 2.3%), OR = 1.57 (1.10–2.26), p = 0.014, and in individuals with diagnosed COPD than in those without the diagnosis (6.6 vs. 2.3%), OR = 2.62 (1.63–4.2), p < 0.001. The results were significant after adjusting for age, sex, smoking, and BMI. Correlations between genetic effects on chronic bronchitis and type 2 diabetes, and between genetic effects on diagnosed COPD and type 2 diabetes, respectively, were 0.33 (0.00–0.79), p = 0.103, and 0.43 (0.00–0.98), p = 0.154. Non-shared environmental correlations between chronic bronchitis and type 2 diabetes were −0.13 (−0.43 to 0), p = 0.498 and diagnosed COPD and type 2 diabetes −0.12 (−0.48 to 0), p = 0.665.
Conclusions: Patients with chronic bronchitis or COPD have an increased risk of type 2 diabetes independent of sex, age, smoking and BMI. The genetic correlation between type 2 diabetes and chronic bronchitis was 33% and type 2 diabetes and COPD was 43%, however neither were statistically significant. The increased risk of type 2 diabetes should be accommodated in the management of patients with chronic bronchitis or COPD.

1. Introduction

Chronic bronchitis is defined by chronic cough and sputum from the airways for at least three months in each of two successive years, provided there are no other causes of chronic cough [1]. When associated with irreversible airflow limitation, chronic bronchitis and emphysema have been grouped and named chronic obstructive pulmonary disease (COPD).

The prevalence and mortality associated with COPD is increasing worldwide [2], and COPD is predicted to be the third leading cause of death by 2030 [3]. COPD presents a substantial burden on both the individual and society in terms of health consequences inasmuch as high consultation rates and exacerbations constitute a large part of hospital admissions [4]. Furthermore, health outcomes are worsened even more when COPD-related comorbidities are taken into account.

COPD has been associated with systemic and comorbid conditions, such as ischaemic heart disease, type 2 diabetes, osteoporosis, skeletal muscle dysfunction and lung cancer [5,6]. The association between COPD and these comorbidities can possibly be

* Corresponding author. Respiratory Research Unit, Entrance 66, Bispebjerg Hospital, DK-2400 Copenhagen NV, Denmark.
E-mail address: hmeteran@gmail.com (H. Meteran).

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explained by common risk factors, such as ageing, smoking and physical inactivity [7–9]. Furthermore, systemic inflammation has been suggested as a common factor underlying these comorbidities [10,11]. The inflammatory cytokines tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-8, and C-reactive protein (CRP) have been associated with both COPD and type 2 diabetes [12,13]. The role of smoking in the inflammatory response in the lungs is well known and it has been hypothesised that the association between COPD and its comorbidities can be explained by an "overspill" effect from the lungs causing systemic inflammation. However, since only a proportion of smokers develop COPD [14] a genetic predisposition to the disease has also been suggested as well. Furthermore, it has earlier been shown that CRP levels in COPD have a genetic background [15].

Previous studies of the association between lung function impairment, type 2 diabetes, and metabolic syndrome are conflicting. In particular, an increased risk of type 2 diabetes in patients with COPD was found in some studies [16,17], whereas other studies did not find any association between COPD and type 2 diabetes, or between metabolic syndrome and obstructive airway limitation [18–21].

Twin studies offer a powerful approach to examine the effects of genes and environment on human diseases. The aim of this study was, in a large nationwide twin cohort to i) investigate the association between chronic bronchitis, hospital diagnosed COPD and type 2 diabetes in Danish adults, and ii) estimate whether comorbidity between these diseases is due to shared genetic and/or environmental factors.

2. Methods

2.1. Design

The Danish Twin Registry is one of the largest twin registries in the world and currently contains more than 85,000 twin pairs. In the present study, we used data on twins born during 1931–1952 [22]. These correspond to 69% of all twin pairs born in Denmark during these years. In 2002, these twins participated in a multidisciplinary questionnaire study concerning health and lifestyle in which a history of smoking and chronic bronchitis was recorded. We identified 13,649 twin individuals (6529 intact pairs with complete data on chronic bronchitis and smoking). The response rate to the questionnaire was 75%. Among the respondents we identified 1160 individuals with chronic bronchitis, 380 were identified as COPD patients and 332 as type 2 diabetes patients. Since the establishment of the Danish Civil Register in 1968, all individuals in Denmark have received a unique identification number allowing cross-linking between national registries. In this study, questionnaire data on chronic bronchitis from the Danish Twin Registry were cross-linked with hospital discharge diagnosis data on COPD and type 2 diabetes (based on the 8th (1977–1993) and the 10th (1994–2003) revision of the International Classification of Diseases and Related Health Problems, ICD-8 and ICD-10) from the Danish National Patient Registry [23]. We have previously reported separate heritability estimates for chronic bronchitis [24], COPD [25], and type 2 diabetes [26], for this population.

2.2. Identification of cases and determination of zygosity

Persons who answered 'yes' to the question, 'Have you experienced at least three months per year of coughing with production of phlegm during the past two years?' were classified as having chronic bronchitis. COPD cases were identified based on one of the following ICD-8 codes: 490.09 through 492.09 and ICD-10 codes: J40-J44.9, whereas individuals with type 2 diabetes were identified by the following ICD-8 codes: 250.00 through 250.09, and ICD-10 codes: E11.0 through E11.9 [36]. Patients with insulin-dependent diabetes plus a type 2 diabetes diagnosis were categorized as having type 2 diabetes. Twin zygosity was determined using four questions of similarity and mistaken identity, which have been shown to assign zygosity correctly in more than 95% of the cases compared with results from genetic marker analysis [28].

2.3. Statistical analysis

Chi-square, t-tests and multiple logistic regression analysis were used to compare the distribution of risk factors for chronic bronchitis, hospital diagnosed COPD and type 2 diabetes. Sex, age, smoking status and body mass index (BMI) were included as covariates in the multiple regression. The risk of type 2 diabetes in patients with chronic bronchitis or COPD was estimated in multiple logistic regression analyses with sex, age, smoking and BMI as covariates. The probandwise concordance rate denotes the probability of one twin being affected given the co-twin is affected and is calculated as [29]:

$$\textit{Probandwise concordance rate} = \frac{2{*}\textit{number of concordant pairs}}{2{*}\textit{number of concordant pairs} + \textit{number of discordant}}.$$

Twin studies can be used to examine whether different traits share genetic or environmental factors. Classical twin modelling assumes that a given phenotypic trait is influenced by genetic and environmental factors, which can be further decomposed into additive genetic influences (A), representing the sum of the effects of all alleles influencing the trait, non-genetic influences (D), representing interactions between the alleles on the same or different loci, shared environmental factors (C), and unique environmental factors (E), the latter also includes variance due to measurement error.

The total phenotypic variance, P, is the sum of all components: $P = A + C + D + E$; however, since the components C and D are confounded in the classical twin study, in which MZ and DZ twins are reared together, these cannot be estimated simultaneously. As the concordance between DZ twins was more than half the concordance in MZ twins, the C component was included in the model. Thus we applied an ACE model for the analysis.

The expected covariance for MZ twins is $A + C$, whereas it is $0.5A + C$ for DZ twins. The relative genetic and environmental influence on the traits was estimated by using a likelihood ratio test between the saturated model and nested models (for example the AE model). If the fit of the nested model is not significantly worse than the saturated model, the nested model is preferred as the most parsimonious explanation of the data [30]. The preferred model for all traits was the AE model; subsequently, bivariate analyses were applied to estimate genetic and environmental correlation between chronic bronchitis, COPD and type 2 diabetes.

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