Journal of Cystic Fibrosis 15 (2016) 563 – 567

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Original Article

# Risk of asthma in heterozygous carriers for cystic fibrosis: A meta-analysis

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Received 4 January 2016; revised 30 May 2016; accepted 2 June 2016
Available online 17 June 2016

**Abstract**

*Background:* Patients with cystic fibrosis (CF) have a higher prevalence of asthma than the background population, however, it is unclear whether heterozygous CF carriers are susceptible to asthma. Given this, a meta-analysis is necessary to determine the veracity of the association of CF heterozygosity with asthma.
*Methods:* We screened the medical literature from 1966 to 2015 and performed a meta-analysis to determine the risk of asthma in CF heterozygotes vs. non-carriers.
*Results:* Aggregating data from 15 studies, the odds ratio for asthma in CF heterozygotes compared with non-carriers was significantly elevated at 1.61 (95% CI: 1.18–2.21). When analyzing the studies considered of high quality in which asthma was diagnosed by a physician, the patients were >18 years, or study size was ≥500, the trend remained the same, that heterozygous carriers of CF had elevated risk for asthma.
*Conclusions:* The results show that heterozygous carriers for CF have a higher risk of asthma than non-carriers.


*Keywords:* Airway obstruction; Asthma; Cystic fibrosis; Epidemiology; Review

## 1. Introduction

In patients with cystic fibrosis (CF), symptoms characteristic for asthma such as cough, wheezing, and airway hyperresponsiveness may be entirely due to CF airways disease, but a contribution of symptoms from coexisting asthma may occur in cases with comorbid asthma. A term known as CF asthma has been defined as a composite of clinical and laboratory features, including a personal or family history of atopy, a strong family history of asthma, seasonal benefit from bronchodilators, and eosinophilia [1,2]. Approximately 19% of CF patients have asthma according to this definition [1,2].

The high prevalence of asthma in patients with CF has been known for long. However, it is still unclear whether heterozygous carriers of CF are susceptible to asthma. Some studies have reported a positive association [3–7], while other studies have shown no association [8–17]. About 1 in 30 Caucasians, 1 in 65 Africans and 1 in 90 Asians carries a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene [18]. Therefore it is of interest to determine if CF heterozygosity is associated with an elevated risk of asthma.

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http://dx.doi.org/10.1016/j.jcf.2016.06.001

To determine the veracity and magnitude of the association between cystic fibrosis heterozygosity and asthma, we searched the medical literature and performed a meta-analysis. If heterozygous carriers of CF have an elevated risk for asthma, then this implies CF heterozygosity may account for a significant fraction of asthma cases in Caucasian, African and Asian populations.

## 2. Methods

### 2.1. Search strategy

Three researchers (AON, SQ, MD) independently searched PubMed and Embase from January 1966 to December 2015 for eligible studies on asthma risk in cystic fibrosis heterozygotes. The search terms used were "(cystic fibrosis OR CF OR CFTR) AND (asthma OR bronchial hyperreactivity)". The titles and abstracts of the articles were scanned, and papers with relevant information were identified and included in the meta-analysis (Supplementary Fig. 1 and online supplementary material). Reference lists of included articles and other relevant studies were screened to find additional studies. The meta-analysis was performed according to the PRISMA guidelines (Supplementary Table 1) [19].

### 2.2. Data collection

Inclusion criteria: We included studies that examined the association between asthma risk and cystic fibrosis heterozygosity and provided sufficient data for us to calculate an odds ratio with 95% confidence interval. Asthma was defined as a physician's diagnosis of asthma or as a result from a questionnaire about self-reported asthma, recurrent wheeze, and asthma symptoms. Only articles written in English were included. In cases where different studies used the same dataset, only the more current study was used.

### 2.3. Validity assessment

The study quality was assessed using the following questions: 1) Was asthma diagnosed by a physician?, 2) Were the patients in the study >18 years old?, 3) Was the population size (N) ≥ 500?

Studies using a physician's diagnosis as their definition for asthma were considered higher quality studies. Studies using other definitions (i.e. self-reported physician diagnosed asthma, self-reported asthma, self-reported recurrent/persistent wheeze, and self-reported recurrent asthma symptoms) were considered of lower quality. Studies examining adults were considered higher quality than studies examining children. Studies with N ≥ 500 were considered higher quality as compared to those with N < 500.

## 3. Results

The initial database search resulted in 1917 articles. Based on the titles and the abstracts 95 were found to be relevant for further detailed evaluation (Supplementary Fig. 1). Of these 80 studies were excluded because they did not meet the inclusion criteria, and thus 15 studies were included in the meta-analysis (Table 1).

### 3.1. Study quality

Table 1 lists the characteristics of the 15 papers. In 7 studies asthma was physician-diagnosed using the Global Initiative for

Table 1
Studies examining risk of asthma in individuals heterozygous for a mutation in the cystic fibrosis transmembrane conductance regulator gene *CFTR*.

| Author | Year | Country | N | Age range, years | CF heterozygosity[a] | Asthma definition |
|---|---|---|---|---|---|---|
| Mennie [15] | 1995 | UK | 523 | Adults | Genotyping | Quest asthma[b] |
| Dahl [3] | 1998 | Denmark | 9141 | 20–100 | Genotyping | Quest asthma |
| Lowenfels [8] | 1998 | Multinational | 1801 | 54 (mean) | Obligate | Quest asthma |
| Lázaro [16] | 1999 | Spain | 185 | 27–81 | Genotyping | MD asthma[c] |
| de Cid [9] | 2001 | France | 421 | 7–68 | Genotyping | Quest asthma |
| Castellani [10] | 2001 | Italy | 462 | 25–71 | Obligate (genotyping) | Quest asthma, medicines and PFTs[d] |
| Tzetis [4] | 2001 | Greece | 72 | 9 mos–63 | Genotyping | ? |
| Ngiam [5] | 2006 | Singapore | 100 | 21–76 | Genotyping | MD asthma |
| Munthe-Kaas [11] | 2006 | Norway | 697 | 10–11 | Genotyping | MD asthma, medicines, symptoms |
| Douros [12] | 2008 | Greece | 399 | 19–63 | Genotyping | MD asthma, medicines, hospitalization |
| Kim [13] | 2010 | Korea | 96 | 10 (mean) | Genotyping | MD asthma |
| Awasthi [6] | 2012 | India | 380 | 5 mos–15 | Genotyping | Current wheeze, medicines, hospitalization |
| Wang [17] | 2012 | China | 189 | 18–72 | Genotyping | MD asthma |
| Muthuswamy [7] | 2014 | India | 650 | ? | Genotyping | MD asthma |
| Dixit [14] | 2015 | India | 500 | Children | Genotyping | ? |

[a] Cystic fibrosis heterozygosity was determined by genotyping or by obligate heterozygosity in parents.
[b] Quest asthma = asthma on questionnaire or by self-report.
[c] Medical doctor (MD) asthma = physician-diagnosed asthma.
[d] PFTs = pulmonary function tests.