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

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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.

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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 hyper-responsiveness 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.
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.

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>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
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<th>Age range, years</th>
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<th>Asthma definition</th>
</tr>
</thead>
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<tr>
<td>Mennie [15]</td>
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<td>Genotyping</td>
<td>Quest asthma</td>
</tr>
<tr>
<td>Dahl [3]</td>
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<td>20–100</td>
<td>Genotyping</td>
<td>Quest asthma</td>
</tr>
<tr>
<td>Lowenfels [8]</td>
<td>1998</td>
<td>Multinational</td>
<td>1801</td>
<td>54 (mean)</td>
<td>Obligate</td>
<td>Quest asthma</td>
</tr>
<tr>
<td>Lázaro [16]</td>
<td>1999</td>
<td>Spain</td>
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<td>27–81</td>
<td>Genotyping</td>
<td>MD asthma</td>
</tr>
<tr>
<td>de Cid [9]</td>
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</tr>
<tr>
<td>Castellani [10]</td>
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<tr>
<td>Ngiam [5]</td>
<td>2006</td>
<td>Singapore</td>
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<td>21–76</td>
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<td>MD asthma, symptoms</td>
</tr>
<tr>
<td>Douros [12]</td>
<td>2008</td>
<td>Greece</td>
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<td>19–63</td>
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<td>MD asthma, hospitalization</td>
</tr>
<tr>
<td>Kim [13]</td>
<td>2010</td>
<td>Korea</td>
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<td>10 (mean)</td>
<td>Genotyping</td>
<td>MD asthma</td>
</tr>
<tr>
<td>Wang [17]</td>
<td>2012</td>
<td>China</td>
<td>189</td>
<td>18–72</td>
<td>Genotyping</td>
<td>MD asthma</td>
</tr>
<tr>
<td>Muthuswamy [7]</td>
<td>2014</td>
<td>India</td>
<td>650</td>
<td>?</td>
<td>Genotyping</td>
<td>MD asthma</td>
</tr>
<tr>
<td>Dixit [14]</td>
<td>2015</td>
<td>India</td>
<td>500</td>
<td>Children</td>
<td>Genotyping</td>
<td>?</td>
</tr>
</tbody>
</table>

| 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. |
Asthma (GINA) guidelines or in accordance with the American Thoracic Society (ATS) guidelines [5,7,11–13,16,17]. In 5 studies asthma diagnosis was based on questionnaire or self-reported [3,8–10,15] and in 1 study asthma diagnosis was based on current wheeze and use of medications [6]. In 2 studies it was not specifically reported how asthma was diagnosed [4,14]. In 8 studies the age of the populations was above 18 years [3,5,8,10,12,15–17]. In 2 studies both children and adults were studied [4,9] and in 4 studies only children were studied [6,11,13,14]. In 1 study the age of the participants was not mentioned [7]. In 6 studies the population size (N) was ≥500 [3,7,8,11,14,15].

All of the studies in this meta-analysis were case–control studies except from 1 [3] that was cross-sectional. 8 studies were conducted in Europe [3,4,9–12,15,16], 6 in Asia [5–7,13,14,17] and 1 study was multinational [8].

None of the studies in this meta-analysis fulfilled all our pre-specified quality criteria defined as physician-diagnosed asthma, patients aged 18 years or older and population size N ≥ 500.

3.2. Risk of asthma

The pooled analysis for the 15 studies is summarized in Fig. 1. The risk of asthma was significantly higher in people heterozygous for CF than in non-carriers (summary OR 1.61, 95% CI: 1.18–2.21).

The test for heterogeneity showed a p-value < 0.05 and thus a trim-and-fill analysis was performed. This analysis did not alter the data-set. No studies were added or deleted from the original data-set. The funnel plot of OR versus standard error was symmetric, and Egger’s test was negative for publication bias (p = 0.44). To ensure that no single study skewed the overall results, each study was removed one at a time and the summary OR recalculated. Removal of each individual study did not significantly alter the summary OR (range of recalculated summary ORs: 1.45–1.73).

### Subgroup-analyses

Subgroup analyses were performed based on the pre-specified quality criteria. When analyzing only those studies which were based on physician-diagnosed asthma [5,7,11–13,16,17], the OR was similar but elevated at 1.96 (1.02–3.80) compared to the overall OR of 1.61. When analyzing those studies in which patients were 18 years or older [3,5,8,10,12,15–17], a similar but attenuated summary OR was seen at 1.39 (1.11–1.74). When analyzing the studies where the sample size was ≥500 [3,7,8,11,14,15], similar results were seen with an OR at 1.60 (1.11–2.30). Heterogeneity was possible in the subgroup analyses of physician-diagnosed asthma (p = 0.004) and study size ≥500 (p = 0.04).

As a secondary aim we also performed subgroup analysis based on ethnicity. When analyzing only those papers in which patients were Caucasians [3,4,9–12,15,16], the summary OR was attenuated at 1.23 (0.81–1.87). When analyzing the papers in which patients were of Asian origin [5–7,13,14,17] the summary OR was elevated at 2.78 (1.99–3.89). Heterogeneity was possible in the Caucasian subgroup analysis as p = 0.03.

Six (67%) European studies met two of the pre-specified quality criteria [3,8,11,12,15,16], and three (50%) Asian studies met two pre-specified quality criteria [5,7,17]. None of the studies fulfilled all of the pre-specified criteria.

4. Discussion

To determine the risk of asthma in cystic fibrosis heterozygotes we performed a meta-analysis of 15 studies comprising 2,113 asthma cases and 13,457 controls. In our meta-analysis, the risk of asthma was significantly higher in people heterozygous for CF than in non-carriers (OR 1.61, 1.18–2.21). When analyzing the studies deemed of high quality in which asthma was diagnosed by a physician, patients were older than 18 years, or study size was ≥500, the summary ORs remained significantly elevated at 1.39 to 1.96, supporting the hypothesis that CF heterozygosity is a risk factor for asthma.

### Fig. 1. Case–control and cross-sectional studies of asthma in cystic fibrosis heterozygotes. Box sizes are proportional to inverse-variance weights. Lines represent 95% confidence intervals.
When CFTR function is absent in new-born animals, airway smooth muscle dysfunction and airway obstruction develops independently of airway inflammation and infection [2,20]. This supports a link between CFTR dysfunction and asthma. In support, case series have previously described asthma in CF heterozygotes, who had at least one normal CFTR sequence [20–22]. Following this, asthma has been suggested as a CFTR-related disorder, that may occur in CF heterozygotes when unknown additional factors further reduce CFTR function or interact with CFTR on asthma [22,23].

The study by Douros et al. [12] tended to show a non-significant protection from asthma in CF heterozygous (OR 0.54, 0.23–1.27), while the values of FEV1 and FEV1/FVC ratio were significantly lower in CF carriers (p = 0.001 and p < 0.001, respectively). This may imply that heterozygosity may be related with a silent obstructive pulmonary profile.

When analyzing the studies conducted in Asian countries the risk for developing asthma in individuals heterozygous for CF was remarkably higher than among studies conducted in European countries (ORs: 2.78 vs. 1.23). This finding is surprising, because it suggests that environmental and sociodemographic factors related to Asian areas may influence the association between CF heterozygosity and asthma. To conclusively determine whether this is the case future large population-based studies of Asian and European subjects are required.

If the results show the true magnitude of the effect on asthma, it can be estimated as an attributable fraction that heterozygous carriers of CF may account for up to 1.9% of asthma in Asians and 1.6% of asthma in Europeans. The results indicate that CF heterozygosity contributes to a significant number of asthma cases in Asian and European populations.

This meta-analysis has some drawbacks that warrant discussion. To date 2007 different CFTR mutations are known (http://www.genet.sickkids.on.ca/StatisticsPage.html, February 23rd 2016), but only a limited number of these are investigated in each of the studies used for the meta-analysis. Therefore, it cannot be ruled out that some of the persons included in the study groups carry other CFTR mutations. However, in all but one study [8], the cases and controls in each study are genotyped for the same mutations and a comparison between the two study groups is therefore possible. Only in Lowenfels et al. the cases and controls are not genotyped, and this study estimates that genetic testing of the controls would have identified 30–40 cystic fibrosis carriers. Correcting a priori for this slightly increases the OR for asthma in CF heterozygous from 1.30 to 1.36 (0.96–1.93), and results in a similar overall OR at 1.60 (1.35–1.90).

In total 34 different mutations were analyzed in the papers included in this meta-analysis (Supplementary Table 2). Nine of the 15 studies [3,6,7,9–12,15,16] were analyzed for the F508del-mutation. The individual ORs lie between 0.54 and 14.50, which indicates that the overall increased risk of developing asthma in heterozygotes cannot be explained by one single mutation. A study conducted in North America in 1995 found the F508del-mutation to be protective against asthma compared with other mutations in the CFTR gene [24]. This was though questioned by Mennie et al. who did not find any protection against asthma among carriers of the F508del-mutation compared with non-carriers [15]. Four studies [6,7,15,16] have analyzed for the G542X-mutation with ORs between 1.00 and 14.50. When analyzing only those studies which tested for F508del and G542X, a similar elevated OR was seen at 1.58 (1.28–1.95). When analyzing the remaining studies which tested for other CFTR mutations [4,5,8,13,14,17], similar results were seen with an OR at 1.59 (1.18–2.14). About 2007 mutations of the CFTR gene have been identified to date but it is still not certain whether all of these are related to CF. Therefore, some of the mutations investigated in the studies in this meta-analysis, might not be important for developing asthma, and consequently the results showing association between asthma and CF heterozygosity may have been skewed towards the null hypothesis. Therefore, in future studies the optimal study population for investigating whether CF heterozygosity increases the risk of asthma would be only to include clinically established CF mutations or obligate heterozygotes.

There are multiple known risk factors for asthma, which this meta-analysis did not control for (e.g. allergen exposure and smoking); however, these factors are most likely unrelated to CFTR genotype, and we do not think that they substantially influenced the results of the meta-analysis.

We cannot totally exclude that intragenic modifiers [25], extragenic modifiers [26], or unidentified gene variants in linkage disequilibrium with CFTR were responsible for the association between CF heterozygosity and asthma; however, studies also show that CFTR may play a direct role in underlying features associated with asthma [21–23].

We suggest that the CF asthma phenotype is examined in further details, e.g. with regard to mucus production, eosinophilia, and response to therapy.

In conclusion, the meta-analysis shows that heterozygous carriers for cystic fibrosis have a higher risk of asthma than non-carriers. The risk for asthma due to CF heterozygosity was found to be higher in individuals of Asian origin.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2016.06.001.

Conflict of interest

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Author contributions

AON, SQ and MD collected the data. All authors contributed to designing of the study and interpretation of the data. AON and MD analyzed the data and wrote the first draft.
of the paper, which was revised and accepted by the other authors.

References


