The Impact of Cigarette Smoking on Asthma: A Population-Based International Cohort Study

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Key Words
Asthma · Cigarette smoking · Epidemiology

Abstract
Background: The prevalence rates of smoking in subjects with asthma have frequently been reported as similar to those in the general population; however, available data are not up-to-date. There is only limited and somewhat conflicting information on the long-term effects of smoking on health outcomes among population-based cohorts of subjects with asthma. We aimed to investigate changes in smoking habits and their effects on forced expiratory volume in 1 s (FEV1) in subjects with asthma in comparison with the rest of the population, focusing on the healthy smoker effect. Methods: We studied 9,092 subjects without asthma and 1,045 with asthma at baseline who participated in both the European Community Respiratory Health Survey I (20–44 years old in 1991–1993) and II (1999–2002). Results: At follow-up, smoking was significantly less frequent among subjects with asthma than in the rest of the population (26 vs. 31%; p < 0.001). Subjects with asthma who were already ex-smokers at the beginning of the follow-up in the 1990s had the highest mean asthma score (number of reported asthma-like symptoms, range 0–5), probably as a result of the healthy smoker effect (2.80 vs. 2.44 in never smokers, 2.19 in quitters and 2.24 in smokers; p < 0.001). The influence of smoking on FEV1 decline did not depend on asthma status. Smokers had the highest proportion of subjects with chronic cough/phlegm (p < 0.01).

Conclusion: One out of 4 subjects with asthma continues smoking and reports significantly more chronic cough and phlegm than never smokers and ex-smokers. This stresses the importance of smoking cessation in all patients with asthma, even in those with less severe asthma.

Introduction

Many recent papers have reported that cigarette smoking is surprisingly frequent in asthma patients, with a prevalence that is relatively close to that found in the general population [1–4]. However, smoking has been great-
ly reduced in the last 20 years in the developed countries [5], and available data on the prevalence of cigarette smoking in subjects with and without asthma are not up-to-date.

Cigarette smoking and asthma can be a dangerous mix, but there are only limited published data on the long-term effects of smoking on symptoms, lung function, response to asthma treatment and health care utilization among population-based cohorts of subjects with asthma. The most important longitudinal surveys specifically addressing this topic showed additive or even multiplicative effects of smoking and asthma on the decline in forced expiratory volume in 1 s (FEV₁) [6–8]. These surveys were conducted between the 1970s and 1990s, when smoking was more common than it is nowadays, and it is expected that the association between asthma and smoking has been modified these past decades because of clinical recommendations [9].

In the more recent, large, international, population-based cohort of subjects with asthma followed up for 9 years in the European Community Respiratory Health Survey (ECRHS), a somewhat surprising lack of association between smoking and lung function decline was found. This aroused the speculation that this finding could reflect, at least in part, the healthy smoker effect, i.e. only subjects with asthma with fewer symptoms and/ or preserved lung function smoke or continue smoking [10, 11], whereas subjects with more severe asthma refrain from smoking. The healthy smoker effect could also explain the lack of association between cigarette smoke and the risk of developing asthma found in some recent papers [12–14].

Thus, we specifically reanalysed the 9-year follow-up data from the ECRHS to evaluate changes in smoking habits and their effects on lung function decline in subjects with asthma in comparison with the rest of the population, focusing on the healthy smoker effect.

Methods

Study Design
The ECRHS is an international multicentre study of respiratory health. The first survey (ECRHS I) [15] was carried out from 1991 to 1993 on random community-based samples of adults aged 20–44 years. Each participant was sent a brief questionnaire (stage 1), and from those who responded, a random sample of 20% was invited to undergo a more detailed clinical examination (stage 2). In addition, a sample consisting of subjects from stage 1 not already included in the random sample who reported asthma-like symptoms in the last 12 months or who were using asthma medication was also studied. The ECRHS II was a follow-up study of all the participants in stage 2 of the ECRHS I, performed between 1998 and 2002 (the full protocol can be found at http://www.ecrhs.org) [16]. In both studies, subjects answered a standardized questionnaire administered by trained interviewers, and they underwent lung function and blood tests. Ethical approval was obtained for each centre from the appropriate institutional or regional ethics committee, and written consent was obtained from each participant.

Subjects and Definitions
In the analysis of the longitudinal data, we considered all the subjects identified in stage 2 of ECRHS I who participated in ECRHS II (n = 17,480). Four hundred and eighty-six subjects with past (but not current) diagnosed asthma at the ECRHS I or with missing information on self-reported asthma, asthma-like symptoms or medication utilization in the last 12 months were excluded from this analysis. In the end, 15,293 subjects without asthma and 1,701 subjects with diagnosed current asthma were considered. Out of the subjects with asthma, 1,045 (61.4%) participated in ECRHS II (1998–2002), and out of the subjects without asthma, 9,092 (59.4%) participated (p value for the difference = 0.114).

Diagnosis of Asthma
Asthma was defined by the report of asthma confirmed by a doctor and respiratory symptoms (wheeze, nocturnal chest tightness, attack of breathlessness following activity, at rest or at nighttime, at least one asthma attack) or utilization of asthma medications in the previous 12 months [11]. The change in asthma status over the 2 surveys was also classified as follows: no asthma (subjects who did not report current asthma, either at ECRHS I or ECRHS II), remittent asthma (subjects who reported current asthma at ECRHS I but not at ECRHS II), incident asthma (subjects who did not report current asthma at ECRHS I but reported current asthma at ECRHS II) and persistent asthma (subjects who reported current asthma both at ECRHS I and ECRHS II).

Smoking Habits at ECRHS I and II and Pattern of Change in Smoking Habits
In both surveys, subjects were classified according to their smoking habits as never smokers, ex-smokers or current smokers (at least one cigarette per day in the past month). To describe the change in smoking habits, subjects were classified as follows: (1) never smokers, (2) ex-smokers (ex-smoker both at ECRHS I and ECRHS II), (3) never-smoker at ECRHS I but ex-smoker at ECRHS II, (4) quitters (current smoker at ECRHS I and ex-smoker at ECRHS II) and (4) smokers [17].

Smoking Intensity and Equivalences
The mean daily number of cigarettes in smokers and the mean number of lifetime pack-years in smokers and ex-smokers were calculated.

Cigarillos were considered equivalent to 3 cigarettes, and cigars to 5; pipe tobacco was converted to equivalence by weight [18].

Lung Function
The maximum FEV₁ and forced vital capacity of at least 2 and as many as 5 technically acceptable maneuvers were recorded, according to the American Thoracic Society (ATS) criteria for reproducibility [19].
At ECRHS I, lung function was missing for 2,110 subjects without diagnosed current asthma (13.8%), and it was not measured in compliance with the ATS criteria for 516 subjects without asthma (3.4%). The same figures in subjects with asthma were 181 (10.6%) and 59 (3.5%), respectively.

At the ECRHS II, lung function was missing for 1,513 subjects without diagnosed current asthma (17.5%) and was not measured in compliance with the ATS criteria or was considered unreliable due to the utilization of inhaled long-acting β₂-agonists in the 12 h before the test for 244 subjects without asthma (2.8%). The same figures in subjects with asthma were 216 (15.9%) and 84 (6.2%), respectively.

Airflow obstruction was defined as FEV₁/forced vital capacity less than the lower limit of normal at the first (ECRHS I) and second visit (ECRHS II) [20].

Bronchial Responsiveness
Subjects were considered to have hyperresponsiveness on the methacholine bronchial provocation test if the provocative dose of methacholine causing a 20% fall in FEV₁ was <1 mg [21]. At ECRHS I, among subjects without asthma, the methacholine challenge test was not performed in 90 subjects (0.6%) due to exclusion criteria and in 4,366 subjects (28.6%) due to other reasons. The same figures in subjects with asthma were 108 (6.4%) and 540 (31.8%), respectively.

Chronic Cough/Phlegm
Subjects with asthma were considered to have chronic cough/phlegm if they reported to have had cough or phlegm on most days for a minimum of 3 months a year and for at least 2 successive years.

Allergen Sensitization
At baseline (ECRHS I), specific IgE antibodies against house dust mite, cat dander, timothy grass, Cladosporium species and a local allergen were measured. A subject was considered sensitized to any allergen if the assay result for at least 1 allergen was higher than 0.35 kU/l.

Asthma Score
The asthma score used in the analyses was derived from Sunyer et al. [22] and consisted of a simple count of the positive answers to 5 questions on the ECRHS I and ECRHS II questionnaires; i.e. the score ranges from 0 to 5. The items were as follows: (1) breathless when wheezing and wheezing apart from cold at any time in the last 12 months; (2) woken up with a feeling of chest tightness in the last 12 months; (3) attack of shortness of breath at rest in the last 12 months; (4) attack of shortness of breath after exercise in the last 12 months, and (5) woken by attack of shortness of breath in the last 12 months [22].

Statistics
Data are summarized as percentages, or means with standard deviation. Percentages and means were adjusted for sex, age, height and body mass index (BMI) by means of 2-level (with level-1 units, subjects, nested into level-2 units, centres) random-intercept multiple linear, Poisson or logistic regression models. The χ² test and the Wilcoxon test were used to test differences, as appropriate (α = 0.05).

The association between the pattern of change in smoking habits and FEV₁ decline was assessed by a 2-level random-intercept multiple linear regression model fitted on subjects participating in both surveys. Age and BMI at ECRHS I, sex, height and change in asthma status between the 2 surveys were included in the model as covariates. The interactions between the pattern of change in smoking habits and change in asthma status between the 2 surveys and between the pattern of change in smoking habits and sex were also assessed using the Wald test.

The statistical analysis was performed using Stata software, release 10.1 (Stata Corp., College Station, Tex., USA).

Results
Comparison of Participants and Non-Participants in the Follow-Up
Of the 17,480 subjects participating in the ECRHS I from 28 centres, 10,296 participated in ECRHS II (response rate 59%), and the average follow-up time was 8.9 years (range 5.8–11.7 years). The median number of participants across centres was 586.5 (range 310–1,252). The participation rate in the ECRHS II was lower among those who were smokers at ECRHS I (54.4%) than among ex-smokers (60.9%) or never smokers (62.2%; p < 0.001).

Change in Smoking Habits from ECRHS I to ECRHS II
Smoking habits were significantly different between subjects with and without asthma at ECRHS I (p < 0.05). Among subjects without asthma, 43% were never smokers, 18% ex-smokers, 10% quitters and 30% smokers. The corresponding figures for subjects with asthma were 48, 18, 8 and 26%, respectively. At the ECRHS I, the mean daily number of cigarettes smoked was significantly lower in subjects with asthma than in subjects without asthma (14.7 ± 9.7 vs. 15.9 ± 10.4; p = 0.007). The change in smoking habits between the 2 surveys was fairly similar in subjects with and without asthma; the proportion of never smokers was stable, the proportion of smokers decreased and the proportion of ex-smokers increased (fig. 1). The mean variation in the mean daily number of cigarettes in smokers was not significantly different in the 2 groups. Smoking habits were also significantly different between subjects with and without allergen sensitization at ECRHS I (p < 0.0001), with the proportion of never smokers being greater in subjects with allergen sensitization than in subjects without, and the percentage of smokers being greater in subjects without allergen sensitization than in subjects with. When considering gender differences, among men at the ECRHS I, 41% were never smokers, 22% ex-smokers and 37% smokers; the corre-
sponding figures for females were 48, 20 and 32%, respectively. The change in smoking habits during the follow-up was more evident among males than females and was even more evident when considering ex-smokers and quitters together (29% in males vs. 25% in females); this resulted in a similar percentage of smokers at the end of follow-up (table 1).

Longitudinal Association between Smoking and Symptoms and Lung Function

After adjusting for age and BMI at ECRHS I, height and sex among subjects with asthma, the mean symptom score at ECRHS I was significantly different for never smokers, ex-smokers, quitters and smokers ($p = 0.0084$; table 2). In particular, those who were already ex-smokers at ECRHS I and remained ex-smokers at ECRHS II had the highest mean symptom score at ECRHS I. Smokers had the highest proportion of subjects with chronic cough/phlegm at ECRHS I ($p$ for the difference among groups $= 0.0497$). No significant difference in baseline lung function and bronchial hyperresponsiveness according to the pattern of change in smoking habits was found, even though the percentage of subjects with bronchial hyperresponsiveness among smokers with asthma was lower than that among the other groups (table 2). The only interaction between gender and smoking habit was found for FEV$_1$ ($p = 0.015$), which was 93% of predicted in males and 102% of predicted in females among ex-smokers; male ex-smokers in particular had the lowest FEV$_1$ at ECRHS I.

After adjusting for age and BMI at ECRHS I, height and sex, FEV$_1$ decline was similar in the 872 subjects with

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**Table 1.** Pattern of smoking habits at ECRHS II according to gender and asthma and allergen sensitization at ECRHS I

<table>
<thead>
<tr>
<th></th>
<th>Never smokers</th>
<th>Ex-smokers</th>
<th>Quitters</th>
<th>Smokers</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>men (n = 4,397)</td>
<td>39.4</td>
<td>18.7</td>
<td>10.5</td>
<td>31.4</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>women (n = 4,776)</td>
<td>46.8</td>
<td>16.8</td>
<td>8.3</td>
<td>28.1</td>
<td></td>
</tr>
<tr>
<td><strong>Asthma at ECRHS I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no (n = 8,224)</td>
<td>42.7</td>
<td>17.7</td>
<td>9.5</td>
<td>30.1</td>
<td>0.0175</td>
</tr>
<tr>
<td>yes (n = 949)</td>
<td>47.6</td>
<td>18.1</td>
<td>8.0</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td><strong>Allergen sensitization at ECRHS I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no (n = 5,497)</td>
<td>41.3</td>
<td>18.2</td>
<td>10.0</td>
<td>30.5</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>yes (n = 2,815)</td>
<td>47.5</td>
<td>17.2</td>
<td>8.5</td>
<td>26.9</td>
<td></td>
</tr>
</tbody>
</table>

All values adjusted for height and gender, as well as for age, asthma and BMI at ECRHS I. Numbers of subjects shown in parentheses only include those subjects who had no missing values for the considered variables (height and gender, as well as age, asthma, allergen sensitization and BMI at ECRHS I).
persistent asthma, in the 183 subjects with remittent asthma and in the 8,457 subjects who did not report current asthma either in the ECRHS I or ECRHS II. In contrast, the 534 subjects with incident asthma showed a greater decline in FEV1 than subjects who did not report current asthma either in the ECRHS I or ECRHS II. Considering together subjects with and without asthma, the FEV1 decline was significantly lower in ex-smokers and quitters and greater in smokers in comparison with never smokers (table 3). Allergen sensitization at ECRHS I was not significantly associated with FEV1 decline. No significant interaction between change in asthma status and change in smoking habits nor between sex and change in smoking habits was found.

### Table 2. Baseline clinical and functional status of the subjects with asthma at ECRHS I according to the pattern of change in smoking habits during the follow-up

<table>
<thead>
<tr>
<th>Symptom score</th>
<th>Never smokers (n = 508)</th>
<th>Ex-smokers (n = 178)</th>
<th>Quitters (n = 76)</th>
<th>Smokers (n = 264)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic cough/phlegm, %</td>
<td>42.1</td>
<td>42.5</td>
<td>48.4</td>
<td>51.7</td>
<td>0.0497</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>78.4 ± 0.8</td>
<td>78.9 ± 1.0</td>
<td>78.0 ± 1.3</td>
<td>77.9 ± 0.9</td>
<td>0.7412</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>97.3 ± 1.0</td>
<td>97.7 ± 1.5</td>
<td>97.6 ± 2.0</td>
<td>96.8 ± 1.2</td>
<td>0.9532</td>
</tr>
<tr>
<td>Airlflow obstruction, %</td>
<td>20.5</td>
<td>19.0</td>
<td>23.3</td>
<td>21.9</td>
<td>0.7713</td>
</tr>
<tr>
<td>Bronchial hyperresponsiveness, %</td>
<td>64.7</td>
<td>63.6</td>
<td>58.8</td>
<td>53.6</td>
<td>0.1555</td>
</tr>
</tbody>
</table>

Values represent means ± SD where appropriate. All values adjusted for sex, as well as for age, height and BMI at ECRHS I.

### Table 3. Mean FEV1 at baseline and mean FEV1 decline according to the change in asthma status and change in smoking habits between ECRHS I and II, and multiple regression coefficients for the association between FEV1 decline, change in asthma status and change in smoking habits between ECRHS I and II

<table>
<thead>
<tr>
<th>Change in asthma status</th>
<th>FEV1 at baseline ml</th>
<th>Mean FEV1 decline ml/year</th>
<th>Regression coefficient for FEV1 decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>No asthma</td>
<td>3.76 (3.72, 3.79)</td>
<td>29.0 (25.9, 32.0)</td>
<td>0</td>
</tr>
<tr>
<td>Remittent asthma</td>
<td>3.65 (3.57, 3.73)</td>
<td>32.1 (26.3, 37.8)</td>
<td>3.1 (–1.9, 8.1)</td>
</tr>
<tr>
<td>Incident asthma</td>
<td>3.56 (3.50, 3.61)</td>
<td>32.2 (28.0, 36.4)</td>
<td>–3.2 (0.2, 6.3)*</td>
</tr>
<tr>
<td>Persistent asthma</td>
<td>3.38 (3.33, 3.42)</td>
<td>27.1 (23.3, 30.9)</td>
<td>–1.9 (–4.4, 0.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in smoking habits</th>
<th>FEV1 at baseline ml</th>
<th>Mean FEV1 decline ml/year</th>
<th>Regression coefficient for FEV1 decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>3.73 (3.70, 3.77)</td>
<td>28.3 (25.2, 31.5)</td>
<td>0</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>3.74 (3.70, 3.78)</td>
<td>25.9 (22.5, 29.3)</td>
<td>–2.4 (–4.4, –0.4)*</td>
</tr>
<tr>
<td>Quitters</td>
<td>3.70 (3.65, 3.74)</td>
<td>25.8 (22.0, 29.5)</td>
<td>–2.6 (–5.1, –0.1)*</td>
</tr>
<tr>
<td>Smokers</td>
<td>3.67 (3.63, 3.70)</td>
<td>33.1 (29.9, 36.3)</td>
<td>–4.8 (3.1, 6.5)*</td>
</tr>
</tbody>
</table>

All values adjusted for age and BMI at ECRHS I, as well as for sex and height. Values in parentheses represent 95% CIs. * Statistically significant at the 5% level.

### Discussion

The most important findings of our study are as follows: (1) smoking is significantly less frequent among subjects with asthma than in the rest of the population; however, 1 out of 4 subjects with asthma continues smoking; (2) subjects with asthma with the highest mean symptom score and, among males, those with the lowest lung function were already ex-smokers at the beginning of the follow-up in the 1990s, and the percentage of subjects with bronchial hyperresponsiveness among smokers with asthma was lower than among the other groups at ECRHS I, which is probably a result of the healthy smoker effect; (3) the influence of smoking on FEV1 de-
cline is similar for subjects with and without asthma, and
(4) smokers with asthma report significantly more chronic cough/phlegm than never smokers and ex-smokers.

The prevalence rates of smoking in subjects with asthma have frequently been reported in the literature as similar to those of the general population [2, 23]. However, more recent cross-sectional results from the large database of the Epidemiological Study on the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness and Atopy study have already documented that subjects with asthma smoke significantly less than subjects without [24]. A prospective epidemiological cardiopulmonary study conducted in a sample of the Copenhagen population from 1976 to 2004 showed that the prevalence of smokers among subjects with asthma declined significantly over the study period from approximately 60% to approximately 30% [25]. Our European data collected at the beginning of 2000 confirm this trend, setting the percentage of smokers among subjects with and without asthma at 26 and 51%, respectively.

Many papers have speculated on the selection bias in asthma termed the healthy smoker effect but, at least to our knowledge, it has never been demonstrated [26]. The healthy smoker effect has been suggested as one of the possible explanations of the lack of a statistical relationship between current smoking and asthma risk [27, 28]. Our present analysis considers the changes in smoking habits during follow-up with respect to the previous studies in the ECRHS. Thus, we could specifically document that this important selection factor can explain the attenuation of the detrimental effect of smoking in subjects with asthma and in subjects with allergic sensitization. Subjects with asthma with the highest mean symptom score and, among males, those with the lowest lung function were already ex-smokers at the beginning of our follow-up in the early 1990s, probably as a result of the healthy smoker effect. This may also explain the low percentage of smokers with asthma with bronchial hyperresponsiveness even at ECRHS I and the lower FEV1 decline in ex-smokers and quitters compared to never smokers; only subjects with asthma with relatively good lung function at baseline smoke or start smoking, whereas subjects with more severe asthma traits refrain from smoking. Although it could be expected that women take better care of their health and therefore the healthy smoker effect could be stronger in women than in men, our findings do not support this hypothesis, in line with the findings of Norbäck et al. [29]. The relatively young age of our subjects and the relatively low exposure to active smoking could also play a role in explaining the absence of an interaction between asthma and smoking with regard to the decline in lung function. Interestingly, we found an effect of asthma on FEV1 decline only when considering subjects with incident asthma during the follow-up; probably, beside the relatively young age of our subjects, the possible explanation of this finding is that subjects with persistent asthma already had lower lung function at the beginning of the follow-up compared to those with remittent and incident asthma.

Our smokers with asthma had the highest proportion of subjects with chronic cough/phlegm. A strong association between mucus hypersecretion and smoking in young subjects with asthma was already found in the Copenhagen City Heart Study [25]. Chronic cough/phlegm is probably accepted as a natural consequence of smoking by subjects with asthma as well as by normal subjects and is thus not sufficient to induce subjects to give up smoking. Even if in epidemiology up to one third of smokers over the age of 50 years with an asthma diagnosis may in fact have chronic obstructive pulmonary disease, we believe that the problem of misclassification in our analysis would be limited by the young age of our sample (20–44 years) and by the use of the self-reported doctor diagnosis of asthma to identify our subjects.

A strength of our study is the large, international, population-based cohort of subjects with asthma followed up for 9 years and the detailed characterization of the changes in smoking habits during the entire follow-up. The somewhat conflicting results reported in the literature on the impact of smoking on asthma may be explained by the fact that patients recruited in clinics generally have a more severe form of asthma, and therefore they do not represent all the several phenotypes of the disease that can be found in the general population. The authors of one of the most recent studies state that, to generalize the findings, there is need of a larger population of subjects with asthma with different grades of severity [30].

A limitation of our study is the relatively low rate of response to the ECRHS II and the higher drop-out rate of smokers than never smokers or ex-smokers in the longitudinal analysis. However, the ECRHS response rate is similar to that obtained in many other long-term surveys. The overall response rate in the 20- to 35-year age group of the Copenhagen City Heart Study reported in a recent paper on the prevalence of self-reported asthma in young adults declined from 83.9% in the 1976–1978 survey to 55.1% in the 2001–2004 survey [25].

In conclusion, even if it is encouraging that a large proportion of subjects with asthma reporting more asthma-like symptoms had already quit smoking, 1 out of 4 sub-
jects with asthma continues smoking and reports significantly more chronic cough/phlegm than never smokers and ex-smokers. Besides the relatively young age of our sample and the relatively low exposure to active smoking, the healthy smoker effect could explain the absence of an interaction between asthma and smoking with regard to the decline in lung function. Further efforts should be devoted to encouraging smoking cessation in patients with asthma who continue smoking and to develop strategies for preventing tobacco use in young patients.

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