Asthma, other atopic conditions and risk of infections in 105 519 general population never and ever smokers

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Background. Individuals with atopic conditions may have increased susceptibility to infections outside the organs directly affected by their atopic condition.

Objective. We tested the hypothesis that atopic conditions overall, and stratified by smoking history, are associated with increased risk of hospitalization for infections.

Methods. We collected information on smoking history and self-reported atopic conditions from 105 519 individuals from the general population and followed them for up to 23 years for infectious disease hospitalizations and deaths. For asthma, we focused on never smokers with asthma diagnosed before age 50 (early asthma) to minimize confounding by chronic obstructive pulmonary disease.

Results. During follow-up, 11 160 individuals had infections. Never smokers with early asthma versus no atopic conditions had significantly increased risks of any infection (hazard ratio 1.65; 95% confidence interval 1.40–1.94), pneumonia (2.44; 1.92–3.11) and any non-respiratory tract infection (1.36; 1.11–1.67); results were similar in ever smokers. Never smokers with any asthma had significantly increased risks of any infection (1.44; 1.24–1.66) and pneumonia (1.99; 1.62–2.44). Neither atopic dermatitis (1.00; 0.91–1.10) nor hay fever (1.00; 0.93–1.07) was associated with risk of any infection. In never smokers, risk estimates for any infection were comparable between asthma and diabetes, as were the population attributable fractions of 2.2% for any asthma and 2.9% for diabetes.

Conclusion. Early asthma was associated with significantly increased risks of any infection, pneumonia and any non-respiratory tract infection in never and ever smokers. In never smokers, risk estimates as well as population attributable fractions for any infection were comparable between asthma and diabetes, suggesting that asthma may be a substantial risk factor for infections in the general population.

Keywords: allergy, asthma, epidemiology, infectious disease.

Introduction

Atopic conditions are common in developed countries where around 30% of the adult general population suffers from asthma, atopic dermatitis or hay fever [1, 2]. Individuals with atopic conditions are at increased risk of infections in the organ directly affected, for example, asthma is associated with increased risk of pneumonia [3, 4], whilst atopic dermatitis is associated with increased risk of skin infections [5]. Asthma might also be associated with increased risk of Escherichia coli bloodstream infections [6, 7] and asthma, as well as other atopic conditions, is associated with a increased risk of severe pneumococcal disease [8–10]. These findings suggest that individuals with atopic conditions may suffer from impaired innate and adaptive immune functions, leading to increased susceptibility to non-respiratory tract infections in individuals with asthma or hay fever and increased susceptibility to non-skin infections in individuals with atopic dermatitis [11].
hypothesis has not yet been tested amongst individuals from the general population, but the question is important as atopic conditions are highly prevalent and could therefore represent an important infectious disease risk factor for the individual with an atopic condition and for society as a whole. The hypothesis is difficult to test for asthma – in contrast to atopic dermatitis and hay fever – as overlapping chronic obstructive pulmonary disease (COPD) could complicate the analysis. COPD is common, associated with increased risk of infections [12, 13], and is difficult to distinguish from asthma in epidemiological studies [14]. Misclassification between asthma, COPD, heart failure and other age-related conditions may especially occur when diagnosing older adults with respiratory symptoms [15–17], possibly due to a high burden of comorbidities, underuse of spirometry and a high prevalence of asthma-COPD overlap syndrome in these individuals [15, 18, 19].

In a prospective study of 105 519 individuals from the general population followed for up to 23 years, we tested the hypothesis that asthma and other atopic conditions, overall and stratified by smoking history, are associated with increased risk of hospitalization due to infectious diseases and with increased risk of infection-related death. We examined asthma, atopic dermatitis and hay fever, and for asthma we focused on never smokers with early asthma diagnosed at age 50 years or earlier to minimize confounding due to COPD and other smoking- and age-related conditions.

Methods

Participants

Study participants were 105 519 individuals from two prospective studies of the general population. We included 9976 individuals from the Copenhagen City Heart Study [20, 21] enrolled between 1991 and 1994, and 95 543 individuals from the Copenhagen General Population Study [21, 22] enrolled between 2003 and 2013. Recruitment was based upon the Danish Civil Registration System and similar for the two studies. Of those invited, 61% participated in the Copenhagen City Heart Study and 46% participated in the Copenhagen General Population Study. All participants completed a questionnaire regarding health and lifestyle, reviewed by a trained examiner to correct possible errors. At the date of enrolment, a physical examination and spirometry were performed as described in detail previously [4, 23]. No individuals participated in both studies. More than 99% of study participants were white and of Danish descent. The studies were approved by the Research Ethics Committee of the Capital Region of Denmark (H-KF 01-144/01) and the Research Ethics Committee of Copenhagen and Frederiksberg (KF-100.2039/91). All participants provided written informed consent.

Atopic conditions and diabetes

Information on atopic conditions was derived from the questionnaire, with asthma assessed using the question ‘Do you have asthma?’ (yes/no), hay fever assessed using the question ‘Do food items, medications, grass, flowers, animal hair or anything else give you hayfever?’ (yes/no), and atopic dermatitis assessed using the question ‘Do food items, medications, grass, flowers, animal hair or anything else give you dermatitis?’ (yes/no). Individuals with asthma were asked to answer the question ‘How many years have you had asthma?’ and age at asthma diagnosis was calculated by subtracting the duration of asthma in years from the individual’s age at examination. Use of asthma medication was assessed by the question ‘Do you take medication for asthma/bronchitis (including spray/powder) on a daily or almost daily basis?’ (yes/no). Information on diabetes was derived from the questionnaire using the question ‘Do you have diabetes?’ (yes/no).

Smoking history and other covariates

Based on the questionnaire and physical examination, the following covariates were derived: smoking history (current/former/never), cumulative smoking in pack-years (with one pack year defined as 20 cigarettes or equivalent per day for 1 year), alcohol consumption (none/moderate/heavy, with heavy defined as >168 g per week for men and >84 g per week for women as recommended by the Danish National Board of Health) and body mass index (measured weight in kilograms divided by measured height in metres squared). From the spirometry, we derived forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) in litres and as per cent of predicted [23], as well as FEV₁/FVC ratio in per cent.

Ascertainment of endpoints and COPD

The Danish Civil Registration System is 100% complete and contains a unique identification
number for all individuals with permanent residence in Denmark [24]. Using this number, we retrieved information on infectious disease hospitalizations until November 5, 2014 from the national Danish Patient Registry [25], which covers all Danish hospitals. Only inpatient hospitalizations and emergency room visits with a primary discharge diagnosis of an infectious disease were included in the analyses. Vital status and date of death were obtained from the Danish Civil Registration System until November 5, 2014. We also retrieved information on infection-related deaths from study enrolment until December 31, 2012 from the national Danish Register of Causes of Death [26], which covers all deaths in Denmark and contains death certificates with ranked diagnoses contributing to the cause of death as certified by a physician.

Infectious diseases were classified based on the World Health Organization International Classification of Diseases revision 8 (ICD-8) until December 31, 1993 and revision 10 (ICD-10) for events happening after this date. For the main analyses, infectious diseases were categorized as either pneumonia or any non-respiratory tract infection according to the ICD-8 and ICD-10 codes shown in Table S1. As validation of diagnoses, 141 hospital admissions coded as infectious diseases in the national Danish Patient Registry were compared with detailed clinical information obtained from hospital charts reviewed by a medical doctor [20]; in 139 of the 141 admissions (99%), the registry data captured relevant signs and symptoms of infectious disease, a positive culture from a sterile site or relevant specimen and/or treatment with antibiotics.

Information on asthma hospitalizations and hospital diagnosed COPD were obtained from the national Danish Patient Registry (asthma codes for ICD-8: 493, ICD-10: J45-J46; COPD codes for ICD-8: 491-492, ICD-10: J41-J44).

Statistical analysis

Statistical analyses were performed using Stata version 13.1. All statistical tests were two-sided. For comparisons of baseline characteristics, Pearson’s chi-square test was used for categorical variables and Mann-Whitney U test was used for continuous variables. Hazard ratios for risk of infectious disease hospitalizations and infection-related deaths were modelled separately using Cox proportional hazards regression with left-truncated age as the timescale. Follow-up began at the date of enrolment in the study. For risk of infectious disease hospitalization, follow-up ended on date of event, death, emigration (n = 484) or November 5, 2014, whichever came first. For risk of infection-related death, follow-up ended on date of death, emigration or December 31, 2012, whichever came first. No participants were lost to follow-up. We observed no major violations of the proportional hazards assumption when assessed using Schoenfeld residuals and by plotting –ln (–ln(survival)) against ln(analysis time). When examining whether risk estimates from two groups were different, the Z-test described by Altman and Bland was used [27]. To account for the competing risk of death from other causes than infections, the analyses on risk of infection-related death were repeated using Fine-Gray regression [28], which produced results similar to those from the Cox model (data not shown).

Multivariable models were adjusted for baseline values of age, sex, smoking history, cumulative smoking in pack-years, alcohol consumption, body mass index, self-reported diabetes, hospital diagnosed COPD and study cohort. These covariates were chosen based on previous studies which have found them to be associated with risk of atopic conditions and/or infections [2, 3, 12, 20, 29].

Smoking can possibly confound associations between asthma and risk of infectious disease as some individuals with self-reported asthma may in reality suffer from smoking-related asthma may in reality suffer from smoking-related airway disease [14], for example COPD, and previous studies have found that COPD is associated with increased risk of infectious disease hospitalization [12, 13]. As COPD is relatively uncommon in never smokers and in individuals younger than 50 years of age [30], confounding by COPD as well as other smoking- and age-related conditions may be reduced by focusing the analyses on never smokers with asthma diagnosed before 50 years of age. Therefore, we performed analyses stratified on smoking history and on age at asthma diagnosis, with early asthma defined as asthma diagnosed at age 50 years or earlier, and late asthma as asthma diagnosed after age 50 years, similarly to the methods used in studies on asthma and risk of invasive pneumococcal infections [10, 31]. To further reduce confounding due to COPD, we also adjusted the multivariable model for hospital diagnosed COPD at study enrolment.
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The population attributable fractions (PAF) for infectious disease risk factors were calculated on the basis of the multivariable adjusted Cox-model using the method described by Greenland and Drescher [32].

Information on age, sex, smoking history and study cohort was 100% complete, whilst information on each of the remaining covariates was more than 95% complete. Missing values were coded as missing for categorical variables, whilst missing values for the continuous variables cumulative smoking (n = 2045) and duration of asthma (n = 269) were imputed based on a linear regression on sex, age, study cohort and smoking history. However, when excluding individuals with missing values, all analyses produced results similar to those presented.

Results

Baseline characteristics of participants from the general population according to presence versus absence of atopic conditions are shown in Table 1. Individuals with asthma are further divided into early asthma (diagnosed at age 50 years or earlier) and late asthma (diagnosed after age 50). Importantly, early asthma was associated with decreased prevalence of ever smoking and decreased cumulative smoking, whilst late asthma was associated with increased prevalence of ever smoking and increased cumulative smoking. The prevalence of hospital diagnosed COPD was lower in the early asthma (8.0%) than in the late asthma group (24.7%). When stratifying baseline characteristics according to smoking history, the prevalence of hospital diagnosed COPD was lower in never smokers with early asthma (2.9%) than in never smokers with late asthma (10.4%) (Table S2).

Risk of any infection

During a median follow-up of 6 years (range: 0–23 years), 11 160 individuals were hospitalized at least once due to an infectious disease cause. Individuals with any asthma versus no atopic conditions had significantly increased risk of any infection (hazard ratio [HR] 1.10; 95% confidence interval [CI] 1.07–1.10), or individuals with any asthma versus no atopic conditions had significantly increased risk of any infection (HR 1.29; 95% CI 0.94–1.77). Risk estimates for infections were unchanged for individuals with atopic dermatitis alone, individuals with hay fever alone, and individuals with both atopic dermatitis and hay fever (Figure S1).

Asthma and risk of specific infections

To reduce possible confounding due to COPD and other smoking- and age-related conditions, the analyses on asthma and risk of specific infections were stratified on smoking history and on age at asthma diagnosis. In never smokers, individuals with any asthma versus no atopic conditions had significantly increased risk of any infection (HR 1.44; 95% CI 1.24–1.66) and pneumonia (1.99; 1.62–2.44); never-smokers with early asthma versus no atopic conditions had significantly increased risk of any infection (1.65; 1.40–1.94), pneumonia (2.44; 1.92–3.11) and any non-respiratory tract infection (1.36; 1.11–1.67) (Fig. 2). When examining subtypes of non-respiratory tract infections (Figures S2 and S3), the increased risk of non-respiratory tract infections in never smokers with early asthma was pronounced for skin infection (HR 1.29; 95% CI 0.94–1.77), urinary tract infection (1.47; 1.02–2.12), sepsis (1.37; 0.82–2.29), diarrhoeal disease (1.42; 0.89–2.27) and other infections (1.42; 0.59–3.43) (Figure S3). We found no interaction between any asthma and smoking history or between early asthma and smoking history on any type of infection (Figures S2 and S3).

Asthma characteristics and risk of infections

When examining risk of any infection, pneumonia and any non-respiratory tract infection according to age at asthma diagnosis, risk estimates were similar for never smokers with asthma diagnosed before age 18, 30, 40 and 50 years (early asthma) (Fig. 3). Likewise, risk estimates for infections were similar in all subgroups when stratifying never smokers with early asthma according to each of the following characteristics: asthma hospitalization before study enrolment (yes/no), use of asthma medication (yes/no), FEV1/FVC ratio (<70% vs. ≥70%), FEV1 per cent of predicted (<80% vs. ≥80%), duration of asthma (≤20 years vs. >20 years) and presence of atopic dermatitis and/or hay fever concurrent with asthma (yes/no) (Figures S4–S6). Amongst the 167 never smokers with early asthma who were hospitalized for infections, only five had
Table 1 Baseline characteristics of individuals from the general population according to presence versus absence of atopic conditions. Individuals with asthma are further divided into early asthma (diagnosed at age 50 years or earlier) and late asthma (diagnosed after age 50). Individuals with asthma are classified as having ‘any asthma’ regardless of whether they also have hayfever and/or atopic dermatitis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No atopic conditions</th>
<th>Any asthma</th>
<th>Early (&lt;50 years)</th>
<th>Late (&gt;50 years)</th>
<th>Atopic dermatitis alone</th>
<th>Hayfever alone</th>
<th>Atopic dermatitis and hayfever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, no. (%)</td>
<td>77 015 (73)</td>
<td>47 85 (5)</td>
<td>1765 (2)</td>
<td>5042 (5)</td>
<td>13 515 (13)</td>
<td>3 977 (3)</td>
<td></td>
</tr>
<tr>
<td>Age, years (IQR)</td>
<td>59 (49–68)</td>
<td>52 (44–60)</td>
<td>69 (64-75)</td>
<td>P = 7 × 10⁻¹³</td>
<td>55 (45-65)</td>
<td>P = 8 × 10⁻⁶⁶</td>
<td>54 (45-64)</td>
</tr>
<tr>
<td>Male sex (no. %)</td>
<td>36 161 (47)</td>
<td>1933 (40)</td>
<td>668 (38)</td>
<td>P = 3 × 10⁻¹⁴</td>
<td>1 323 (26)</td>
<td>P = 6 × 10⁻¹³</td>
<td>6 398 (47)</td>
</tr>
<tr>
<td>Ever smokers, no. (%)</td>
<td>47 488 (62)</td>
<td>2760 (58)</td>
<td>1 304 (74)</td>
<td>P = 1 × 10⁻⁵⁵</td>
<td>3 111 (62)</td>
<td>P = 0.95</td>
<td>7 001 (52)</td>
</tr>
<tr>
<td>Cumulative smoking, pack-years (IQR)</td>
<td>5 (0–23)</td>
<td>3 (0–19)</td>
<td>17 (0–35)</td>
<td>P = 3 × 10⁻¹⁷</td>
<td>5 (0–21)</td>
<td>P = 0.017</td>
<td>1 (0–13)</td>
</tr>
<tr>
<td>Alcohol consumption &gt;168 g per week</td>
<td>30 148 (39)</td>
<td>1 572 (33)</td>
<td>710 (49)</td>
<td>P = 0.021</td>
<td>1 833 (36)</td>
<td>P = 0.0002</td>
<td>5 068 (37)</td>
</tr>
<tr>
<td>Body mass index, kg/m² (IQR)</td>
<td>25.6 (23.2–28.4)</td>
<td>25.9 (23.4–29.1)</td>
<td>26.4 (23.8–29.5)</td>
<td>P = 8 × 10⁻¹¹</td>
<td>25.3 (22.9–28.4)</td>
<td>P = 7 × 10⁻⁵</td>
<td>25.3 (23.1–28.1)</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>2968 (1.9)</td>
<td>1 886 (1.9)</td>
<td>1 118 (6.7)</td>
<td>P = 1 × 10⁻⁷</td>
<td>1 722 (3.4)</td>
<td>P = 0.11</td>
<td>3 732 (2.8)</td>
</tr>
<tr>
<td>Hospital diagnosed COPD, no. (%)</td>
<td>1 182 (1.5)</td>
<td>3 85 (8.0)</td>
<td>436 (24.7)</td>
<td>P = 5 × 10⁻²³</td>
<td>63 (1.2)</td>
<td>P = 0.11</td>
<td>1 26 (0.9)</td>
</tr>
<tr>
<td>Hospitalization due to asthma, no. (%)</td>
<td>113 (0.1)</td>
<td>628 (13.1)</td>
<td>197 (11.2)</td>
<td>P &lt; 1 × 10⁻³⁰</td>
<td>11 (0.2)</td>
<td>P = 0.21</td>
<td>60 (0.4)</td>
</tr>
<tr>
<td>Medication for asthma or bronchitis, no. (%)</td>
<td>1084 (1)</td>
<td>3109 (65)</td>
<td>1432 (81)</td>
<td>P &lt; 1 × 10⁻³⁰</td>
<td>67 (1)</td>
<td>P = 0.65</td>
<td>487 (4)</td>
</tr>
<tr>
<td>FEV₁/FVC ratio &lt;70%, no. (%)</td>
<td>11 178 (15)</td>
<td>1 428 (30)</td>
<td>840 (48)</td>
<td>P &lt; 1 × 10⁻¹⁷⁹</td>
<td>588 (12)</td>
<td>P = 2 × 10⁻⁶⁸</td>
<td>1 450 (11)</td>
</tr>
<tr>
<td>Characteristics</td>
<td>No atopic conditions</td>
<td>Any asthma</td>
<td></td>
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<tr>
<td></td>
<td>Early (≤ 50 years)</td>
<td>Late (&gt; 50 years)</td>
<td>Atopic dermatitis alone</td>
<td>Hayfever alone</td>
<td>Atopic dermatitis and hayfever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 80% of predicted, no. (%)</td>
<td>12 205 (16)</td>
<td>1527 (32)</td>
<td>&lt;sup&gt;P = 4 × 10&lt;sup&gt;-18&lt;/sup&gt;&lt;/sup&gt;</td>
<td>923 (52)</td>
<td>&lt;sup&gt;P &lt; 1 × 10&lt;sup&gt;-300&lt;/sup&gt;&lt;/sup&gt;</td>
<td>745 (15)</td>
<td>&lt;sup&gt;P = 0.04&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age at asthma diagnosis, years (IQR)</td>
<td>30 (14–40)</td>
<td>59 (55–65)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Duration of asthma, years (IQR)</td>
<td>20 (12–35)</td>
<td>8 (4–12)</td>
<td></td>
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</tr>
<tr>
<td>Atopic dermatitis and/or hayfever concurrent with asthma, no. (%)</td>
<td>2956 (62)</td>
<td>597 (34)</td>
<td></td>
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</tr>
</tbody>
</table>

No. (%) is shown for categorical variables. Median (interquartile range, IQR) is shown for continuous variables. \( P \)-values are for comparisons with the group of individuals with no atopic conditions. Pearson’s chi-square test was used for comparisons of categorical variables and Mann–Whitney U test was used for comparisons of continuous variables.

COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity.

\( > 168 \text{ g per week for men and } > 84 \text{ g per week for women.} \)
been hospitalized due to asthma within 6 months prior to the infectious disease hospitalization. When excluding these five individuals, all analyses produced results similar to those presented (data not shown).

**Asthma and risk of infection-related death**

In never smokers, individuals with any asthma versus no atopic conditions had significantly increased risk of death related to pneumonia (HR 1.99; 95% CI 1.17–3.38), whilst risks of death related to any infection (1.36; 0.84–2.20) and any non-respiratory tract infection (0.67; 0.25–1.77) were largely unchanged (Fig. 4). Amongst never smokers with early asthma there were only six infection-related deaths, all of which were pneumonia-related death in never smokers with early asthma versus no atopic conditions. For ever smokers, individuals with any asthma versus no atopic conditions had significantly increased risk of death related to any infection (HR 1.77; 95% CI 1.47–2.13), pneumonia (1.87; 1.51–2.31) and any non-respiratory tract infection (1.62; 1.18–2.23); ever smokers with early asthma versus no atopic conditions had significantly increased risk of death related to any infection (1.94; 1.46–2.57) and pneumonia (2.12; 1.53–2.93).

**Comparing asthma to diabetes**

Diabetes is a well-known risk factor for infectious disease, so to put the magnitude of infectious disease risk in individuals with asthma into perspective, we compared it with that for diabetes. When compared with a reference group of never smokers without diabetes or atopic conditions, risk estimates for any infection were similar for never smokers with any asthma (HR 1.48; 95% CI 1.28–1.71), never smokers with early asthma (1.70; 1.44–2.01) and never smokers with diabetes (1.79; 1.54–2.08) (Fig. 5).

When calculating the proportion of infectious disease hospitalizations that could theoretically be prevented on the population level if a single risk factor were completely eliminated, the population attributable fraction (PAF) for any infection amongst never smokers was similar for any asthma (PAF 2.2%;95% CI 1.2–3.2%), early asthma (2.1%;1.2–2.9%) and diabetes (2.9%;1.9–3.8%).

**Discussion**

In this prospective study of 105 519 general population individuals, we found that amongst never smokers, any asthma was associated with significantly increased risk of any infection and pneumonia, whilst early asthma diagnosed at age 50 years or
earlier was associated with significantly increased risk of any infection, pneumonia and any non-respiratory tract infection. Results were similar in ever smokers with early asthma. In never smokers, relative risk estimates as well as population attributable fractions for any infection were comparable between asthma and diabetes. Our finding that individuals with early asthma from the general population had increased overall risk of any non-respiratory tract infection is novel and corroborates earlier findings from case-control studies on asthma and risk of infections due to specific pathogens.

The association between early asthma and increased risk of non-respiratory tract infections could possibly be caused by an impaired immune response against bacterial infections, caused by the tendency towards a Th2-skewed immune response in individuals with allergy [11, 33]. Indeed, children with atopic conditions may produce fewer antibodies after pneumococcal vaccination than healthy children [34, 35], and in animal models, allergic mice exhibit impaired recruitment of neutrophils when faced with bacteria [36, 37]. These previous findings suggest that allergy may impair innate and humoral immunity [11]. However, although there are considerable similarities in the allergic immune response amongst individuals with asthma, atopic dermatitis and hay fever [38, 39], we found that neither

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### Table 1

<table>
<thead>
<tr>
<th>Any asthma vs. no atopic conditions</th>
<th>No. of individuals with/without asthma</th>
<th>No. of infections with/without asthma</th>
<th>Multivariable adjusted hazard ratio (95% CI) for infections</th>
<th>P for interaction with smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>2486 / 29527</td>
<td>231 / 2225</td>
<td>1.44 (1.24 to 1.66)</td>
<td>0.07</td>
</tr>
<tr>
<td>Ever smokers</td>
<td>4064 / 47488</td>
<td>850 / 6118</td>
<td>1.59 (1.47 to 1.72)</td>
<td></td>
</tr>
<tr>
<td>All individuals</td>
<td>6550 / 77015</td>
<td>1081 / 8343</td>
<td>1.54 (1.44 to 1.65)</td>
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</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>2486 / 29527</td>
<td>120 / 844</td>
<td>1.99 (1.62 to 2.44)</td>
<td>0.62</td>
</tr>
<tr>
<td>Ever smokers</td>
<td>4064 / 47488</td>
<td>554 / 2925</td>
<td>2.05 (1.86 to 2.27)</td>
<td></td>
</tr>
<tr>
<td>All individuals</td>
<td>6550 / 77015</td>
<td>674 / 5769</td>
<td>2.03 (1.86 to 2.22)</td>
<td></td>
</tr>
<tr>
<td>Any non-respiratory tract infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>2486 / 29527</td>
<td>130 / 1607</td>
<td>1.13 (0.94 to 1.36)</td>
<td>0.09</td>
</tr>
<tr>
<td>Ever smokers</td>
<td>4064 / 47488</td>
<td>436 / 4032</td>
<td>1.24 (1.12 to 1.38)</td>
<td></td>
</tr>
<tr>
<td>All individuals</td>
<td>6550 / 77015</td>
<td>566 / 5639</td>
<td>1.21 (1.10 to 1.32)</td>
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</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Early asthma vs. no atopic conditions</th>
<th>No. of individuals with/without asthma</th>
<th>No. of infections with/without asthma</th>
<th>Multivariable adjusted hazard ratio (95% CI) for infections</th>
<th>P for interaction with smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>2025 / 29527</td>
<td>167 / 2225</td>
<td>1.65 (1.40 to 1.94)</td>
<td>0.25</td>
</tr>
<tr>
<td>Ever smokers</td>
<td>2760 / 47488</td>
<td>455 / 6118</td>
<td>1.71 (1.55 to 1.90)</td>
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</tr>
<tr>
<td>All individuals</td>
<td>4785 / 77015</td>
<td>622 / 8343</td>
<td>1.68 (1.54 to 1.83)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never smokers</td>
<td>2025 / 29527</td>
<td>81 / 844</td>
<td>2.44 (1.92 to 3.11)</td>
<td>0.81</td>
</tr>
<tr>
<td>Ever smokers</td>
<td>2760 / 47488</td>
<td>275 / 2925</td>
<td>2.40 (2.10 to 2.74)</td>
<td></td>
</tr>
<tr>
<td>All individuals</td>
<td>4785 / 77015</td>
<td>356 / 3769</td>
<td>2.37 (2.11 to 2.66)</td>
<td></td>
</tr>
<tr>
<td>Any non-respiratory tract infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>2025 / 29527</td>
<td>103 / 1607</td>
<td>1.36 (1.11 to 1.67)</td>
<td>0.30</td>
</tr>
<tr>
<td>Ever smokers</td>
<td>2760 / 47488</td>
<td>254 / 4032</td>
<td>1.39 (1.21 to 1.58)</td>
<td></td>
</tr>
<tr>
<td>All individuals</td>
<td>4785 / 77015</td>
<td>357 / 5639</td>
<td>1.37 (1.22 to 1.53)</td>
<td></td>
</tr>
</tbody>
</table>

### Fig. 2

Risk of infections in the general population for individuals with any asthma versus no atopic conditions and for early asthma versus no atopic conditions stratified by smoking history. Early asthma was defined as asthma diagnosed at age 50 years or earlier. The sum of specific infections exceeds the number of any infections as some individuals were hospitalized with more than one type of infection. CI, confidence interval.
dermatitis nor hay fever were associated with increased risk of any infection, pneumonia or any non-respiratory tract infection. This indicates that the increased risk of non-respiratory tract infections in individuals with early asthma may be caused by other mechanisms not directly related to the allergic immune response. The risk of non-respiratory tract infections is also increased in COPD [12], so alternatively, some common feature of lung diseases could increase susceptibility to non-respiratory tract infections. However, these mechanistic considerations are speculative and the exact mechanism explaining the observed associations is currently unknown.

Our finding amongst never smokers that early asthma was associated with increased risk of any non-respiratory tract infection has not previously been reported from studies of the general population. Although no previous studies have examined the overall risk of non-respiratory tract infections in individuals with asthma, these results are

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**Fig. 3** Risk of infections in the general population for never smokers with asthma versus never smokers without atopic conditions according to age at asthma diagnosis. The sum of specific infections exceeds the number of any infections as some individuals were hospitalized with more than one type of infection. CI, confidence interval.
supported by case–control studies on specific pathogens, reporting that asthma was associated with increased risk of Escherichia coli bloodstream infections [6], invasive pneumococcal disease [10, 31] and herpes zoster [40]. When comparing asthma to diabetes, which is a well-known infectious disease risk factor [3, 20, 41], the relative risk estimates for any infection in never smokers were similar for any asthma, early asthma and diabetes. Likewise, the population attributable fractions for any infection in never smokers were similar for any asthma, early asthma and diabetes. These findings imply that asthma may be a substantial risk factor for infections in the general population, and that health care professionals should be aware of the increased risk of respiratory as well as non-respiratory tract infections in individuals with early asthma.

Neither atopic dermatitis nor hay fever were associated with increased risk of any infection, pneumonia or any non-respiratory tract infection, so we cannot confirm the association between dermatitis and increased risk of lower respiratory tract infections reported in a cross-sectional study of 1008 individuals [42]. Another case–control study with 174 cases found that atopic dermatitis was associated with increased risk of serious pneumococcal disease, defined as pneumococcal pneumonia, pneumococcal sepsis or other invasive pneumococcal infections.

Fig. 4  Risk of infection-related death in the general population for individuals with any asthma versus no atopic conditions and for early asthma versus no atopic conditions stratified by smoking history. Early asthma was defined as asthma diagnosed at age 50 years or earlier. The sum of deaths related to specific infections exceeds the number of deaths related to any infection as some individuals had more than one type of infection listed on their death certificate. CI, confidence interval.
Theseresultsarenotdirectlycomparabletoours, aswe do not have information on the specific causative pathogens for most infectious disease cases, but our results suggest that dermatitis is not associated with an overall increased risk of serious non-skin infections. However, it is likely that individuals with hay fever and/or atopic dermatitis are more frequently prescribed antibiotics in the outpatient setting without requiring hospitalization, as previous studies have found increased risk of upper respiratory tract infections in individuals with hay fever and increased risk of skin infections in individuals with atopic dermatitis [5, 43]. Hypothetically, frequent exposure to antibiotics amongst individuals with hay fever and atopic dermatitis may decrease risk of more serious infections that would require hospitalization, and this may explain why hay fever and atopic dermatitis were not associated with increased risk of hospitalization for any infection.

Amongst the strengths of this study are the prospective general population design, the large sample size of 105,519 individuals and the availability of detailed information on self-reported atopic conditions as well as smoking history and other possible infectious disease risk factors such as alcohol, body mass index, diabetes and COPD. This made it possible to minimize confounding due to COPD and other smoking- and age-related conditions by stratifying the analyses on smoking history and age at asthma diagnosis.

It was not possible for us to examine risk of infections in individuals using specific types of asthma medications such as inhaled corticosteroids, as we only have information on whether or not the participants took any type of daily or almost daily medication for asthma. However, we found no indication that the increased risk of any infection, pneumonia and any non-respiratory tract infection in never smokers with early asthma was caused by use of asthma medication as risk estimates were similar when comparing individuals with asthma taking asthma medication to those who did not.

Our study is limited by only having information on infections treated in hospitals, which makes us unable to assess whether asthma was also associated with increased risk of less severe cases of infections that are typically treated by general practitioners. Theoretically, our results may
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therefore be biased if general practitioners have a lower threshold for admitting patients with asthma to a hospital instead of treating them in an outpatient setting. However, as asthma was also associated with increased risk of infection-related death, it is less likely that our findings on increased risk of infections in individuals with asthma are caused solely by a lower threshold for hospital admission. Another potential limitation is that the study was conducted in a Danish population with a high prevalence of atopic conditions and a relative low burden of serious infections, as in most other developed countries [44, 45]. Thus, our results may not necessarily be applicable to other populations with different patterns of allergy and infectious diseases.

Taken together, in this prospective study of 105 519 general population individuals followed for up to 23 years, we found that amongst never smokers, any asthma was associated with significantly increased risks of any infection and pneumonia, whilst early asthma was associated with significantly increased risks of any infection, pneumonia and any non-respiratory tract infection. In never smokers, relative risk estimates as well as population attributable fractions for any infection were comparable between asthma and diabetes, suggesting that asthma may be a substantial risk factor for infections in the general population.

Conflict of interest statement
The authors have declared no conflicts of interest.

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Author contributions
J. Helby, B.G. Nordestgaard and S.E. Bojesen were involved in the conception and design. J. Helby, B.G. Nordestgaard, T. Benfield and S.E. Bojesen participated in collection of data and assembly of databases. J. Helby, B.G. Nordestgaard, T. Benfield and S.E. Bojesen analysed and interpreted data. J. Helby wrote the manuscript. J. Helby, B.G. Nordestgaard, T. Benfield and S.E. Bojesen were involved in revision and final approval of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Categorization of infectious diseases according to the World Health Organization International Classification of Diseases revision 8 (ICD-8) and revision 10 (ICD-10).

Table S2. Baseline characteristics stratified by smoking history for individuals with no atopic conditions, any asthma, early asthma and late asthma.

Figure S1. Risk of infections in the general population for individuals with atopic dermatitis alone versus no atopic conditions, hayfever alone versus no atopic conditions and atopic dermatitis and hayfever combined versus no atopic conditions.
**Figure S2.** Risk of any infection, pneumonia, any non-respiratory tract infection and subtypes of non-respiratory tract infections in the general population for individuals with any asthma versus no atopic conditions stratified by smoking history.

**Figure S3.** Risk of any infection, pneumonia, any non-respiratory tract infection and subtypes of non-respiratory tract infections in the general population for individuals with early asthma versus no atopic conditions stratified by smoking history.

**Figure S4.** Risk of any infection in the general population for never smokers with early asthma versus never smokers without atopic conditions stratified by asthma characteristics.

**Figure S5.** Risk of pneumonia in the general population for never smokers with early asthma versus never smokers without atopic conditions stratified by asthma characteristics.

**Figure S6.** Risk of any non-respiratory tract infection in the general population for never smokers with early asthma versus never smokers without atopic conditions stratified by asthma characteristics.