



Asthma Associates With Human Abdominal Aortic Aneurysm and Rupture Significance

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Asthma associates with human abdominal aortic aneurysm and rupture

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Running Title: Asthma and abdominal aortic aneurysms

Key words: abdominal aortic aneurysm, aortic rupture, asthma, risk factor

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ABSTRACT

Objective: Asthma and abdominal aortic aneurysms (AAA) both involve inflammation. It remains unknown whether these diseases interact.

Approach and Results: Databases analyzed included DNRP: a population-based nationwide case-control study included all patients with ruptured AAA (rAAA) and age- and sex-matched AAA controls without rupture in Denmark from 1996-2012. VIVA: Subgroup study of participants from the population-based randomized Viborg vascular screening trial. Asthmatic patients were categorized by hospital diagnosis, bronchodilator use, and the recorded use of other anti-asthma prescription medications. Logistic regression models were fitted to determine whether asthma associated with the risk of rAAA in DNRP, and an independent risk of having an AAA at screening in the VIVA trial. From the DNRP study, asthma diagnosed less than one year or six months before the index date increased the risk of AAA rupture before (odds ratio OR=1.60, 2.12) and after (OR=1.51, 2.06) adjusting for AAA comorbidities. Use of bronchodilators elevated the risk of AAA rupture from ever use to within 90 days from the index date, before (OR=1.10~1.37) and after (OR=1.10~1.31) adjustment. Patients prescribed anti-asthma drugs also showed an increased risk of rupture before (OR=1.12~1.79) and after (OR=1.09~1.48) the same adjustment. In VIVA, anti-asthmatic medication use associated with increased risk of AAA before (OR=1.45) or after adjustment for smoking (OR=1.45) or other risk factors (OR=1.46).

Conclusions: Recent active asthma increased risk of AAA and AAA-rupture. These findings document and furnish novel links between airway disease and AAA, two common diseases that share inflammatory aspects.

ABBREVIATIONS

AAA: abdominal aortic aneurysms; rAAA: ruptured AAA; IgE: immunoglobulin E; FLAP: 5-lipoxygenase activating protein; LTA₄: leukotriene A₄; SMC: smooth muscle cell; DNRP: Danish National Registry of Patients; VIVA: Viborg Vascular; CPR: civil personal register; C.I.: confidence interval; ATC: Anatomical Therapeutic Chemical; BMI: body mass index; OR: odds ratio; COPD: chronic obstructive pulmonary disease; ROPD: reversible obstructive pulmonary disease; CVD: cardiovascular disease

INTRODUCTION

Asthma and abdominal aortic aneurysms (AAA) both involve inflammation. Asthmatic patients exhibit increased plasma IgE and accumulation of eosinophils, lymphocytes, macrophages, and mast cells in the bronchi and alveoli, while AAA patients harbor macrophages, lymphocytes, and neutrophils in the arterial wall.¹⁻³ We recently reported that human AAA lesions have increased mast cells and immunoglobulin E (IgE), and presented evidence that these effectors of reagenic immunity contribute directly to experimental aneurysmogenesis.^{4,5} These unexpected observations suggested the hypothesis that common elements of pathogenesis link allergy or asthma to AAA. Indeed, mediators that participate in airway disease, including 5-lipoxygenase, 5-lipoxygenase-activating protein (FLAP), and leukotriene A₄ (LTA₄) hydrolase and leukotriene C₄ (LTC₄) synthase, enzymes responsible for LTA₄, LTB₄, LTC₄, LTD₄, and

LTE₄ production,⁶ also localize in macrophages, neutrophils, T cells, and mast cells in human AAA.⁷ LTB₄ contributes to inflammatory cell chemotaxis to the bronchi and alveoli, whereas the cysteinyl leukotrienes LTC₄, LTD₄, and LTE₄ increase vascular permeability and smooth muscle cell (SMC) contraction, leading to bronchoconstriction and vasoconstriction in asthmatic patients.^{6,8} Increased levels of LTB₄ and cysteinyl leukotrienes in asthmatic patients may promote AAA development by increasing aortic wall inflammatory cell accumulation and expansion.

This study probed this possible link between asthma or reversible obstructive airway disease (ROPD) and AAA in 15,942 individuals with AAA from the Danish National Registry of Patients (DNRP), and 18,749 men with both AAA and non-AAA controls from the Viborg Vascular (VIVA) screening trial.

MATERIALS AND METHODS

Materials and Methods are available in the online-only Data Supplement.

RESULTS

DNRP population

Table 1 shows the baseline characteristics of the participants (patients admitted with rAAA) and controls (patients admitted with non-ruptured AAA) from the DNRP population. A total of 15,942 AAA patients were selected, 4,497 of whom had rAAA (81.2% males and 18.8% females). The 11,445 AAA controls were age- and sex-matched with the 4,497 rAAA cases. Of the 15,942 AAA patients, 514 had hospital-diagnosed asthma including outpatients, from which 146 had rAAA and 368 did not. At time of AAA admission, anti-asthma drug users comprised 13.9% of the cases. Of these, 83.9% used selective beta-2-adrenergic receptor agonists, 28.1% used anti-cholinergic agents, 35.0% used inhaled glucocorticoids, and 11.0% used theophylline. Individuals in this study included 81.2% men, and the median age was 74.0 (i.q.r. 68.1-79.6) years. Table 1 shows patient information with preadmission medications within 90 days of the index date, including bronchodilator (with selective beta-2-adrenergic receptor agonists, anti-cholinergic agents) or inhaled glucocorticoids. Table 1 also includes patient to general practitioner interaction information, household income, and marital status.

Risk of AAA rupture in asthmatic patients

In 15,942 AAA patients aged 50 and older, we defined asthma in those who were hospital-diagnosed including outpatient contacts, used bronchodilators containing either beta-2-adrenergic receptor agonists or anti-cholinergic agents or both, or were non-bronchodilator users but prescribed other asthma-based medications in Denmark, including inhaled glucocorticoids and theophylline. Asthmatic patients may have also received other treatments, such as oral glucocorticoids. Patients with non-asthmatic diseases may have also used these drugs, and therefore were not included in the rAAA risk assessment.

A total of 146 rAAA patients had a history of hospital-diagnosed asthma, among which 26 rAAA patients were diagnosed with asthma less than 360 days and 22 patients less than 180 days before the index date. When all 146 ever rAAA patients were compared with 654 age- and

sex-matched AAA controls, asthma did not associate with AAA rupture before (OR=1.08, [95% C.I. 0.90-1.30], $P=0.413$) or after (OR=1.02, [95% C.I.: 0.84-1.24], $P=0.840$) adjustment for seven AAA-relevant comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, diabetes with or without complications, and moderate to severe renal disease), five different anti-hypertension drugs, (ACE-inhibitors, Ang-II antagonists, aldosterone antagonists, beta-2-adrenergic blocking agents and calcium antagonists), statins, anti-platelet therapy, or anti-diabetic therapy. Yet recently diagnosed asthma (less than 360 days and 180 days from the index date) associated with a risk of rAAA (crude OR=1.60 [95% C.I.: 1.03-2.50], $P=0.038$ and OR=2.12 [95% C.I.: 1.28-3.51], $P=0.003$ respectively). Among patients with asthma diagnosed within 180 days from the index date, asthma remained a significant risk factor for AAA rupture (OR=2.06 [95% C.I.: 1.21-3.53], $P=0.008$) after adjustment (Figure 1 and Table 2).

The patient group that consisted of users of bronchodilators (beta-2-adrenergic receptor agonists or anti-cholinergic agents or both), was also analyzed based on the time from the index date, including those who ever used, and used within 360 days, 180 days, and 90 days of the index date. Recent use of bronchodilators correlated with a higher risk of AAA rupture, increasing with the proximity of use to the index date. OR values ranged from 1.10 [95% C.I.: 1.02-1.19], $P=0.014$ to 1.37 [95% C.I.: 1.24-1.52], $P<0.001$ before adjustment and from 1.10 [95% C.I.: 1.01-1.19], $P=0.035$ to 1.31 [95% C.I.: 1.18-1.46], $P<0.001$ after adjustment (Figure 1 and Table 2).

We separated AAA patients who received prescriptions for anti-asthmatic drugs, including beta-2-adrenergic receptor agonists, anti-cholinergic agents, inhaled glucocorticoids, or theophylline by the prescription date to the index date, as ever, less than 90, 180, and 360 days. AAA rupture risk increased from ever prescribed, within 360 days, within 180 days, to within 90 days from the index date, among all four asthmatic medications. For example, among rAAA patients with a prescription dated less than 90 days before the index date, the OR values before adjustment were 1.35 [95% C.I.: 1.22-1.50], $P<0.001$; 1.48 [95% C.I.: 1.24-1.76], $P<0.001$; 1.49 [95% C.I.: 1.28-1.75], $P<0.001$; and 1.79 [95% C.I.: 1.35-2.36], $P<0.001$ for beta-2-adrenergic receptor agonists, anti-cholinergic agents, inhaled glucocorticoids, and theophylline, respectively. After adjustment, the risks that remained with their corresponding OR values were at 1.28 [95% C.I.: 1.15-1.44], $P<0.001$; 1.42 [95% C.I.: 1.18-1.71], $P<0.001$; 1.35 [95% C.I.: 1.14-1.71], $P<0.001$; and 1.48 [95% C.I.: 1.11-1.97], $P=0.008$; respectively (Figure 1 and Table 2). When restricting the analyses to patients who never had a hospital discharge diagnosis of chronic obstructive pulmonary disease (COPD), the association between hospital-diagnosed asthma within 180 days and rAAA increased with adjusted OR from 2.06 [95% C.I.: 1.21-3.53], $P=0.008$ to 2.64 [95% C.I.: 1.25-5.58], $P<0.001$.

External adjustment helps to address the missing information on potential confounders.⁹⁻
¹¹ Information regarding cigarette smoking from the DNRP population remains incomplete, which may confound the risk assessment of asthma on AAA. Consequently, the respective observed proportion among AAA patients of smokers with or without use of bronchodilators permitted external adjustment for smoking in the DNRP. This adjustment increased the relative rAAA risk estimate to an adjusted OR of 1.46 [95% C.I.: 1.31-1.62], $P<0.001$ from 1.31 [95% C.I.: 1.18-1.46], $P<0.001$ associated with bronchodilator use within 90 days of index date (Table 2). This increase in the relative risk results from an observed lower proportion of smokers among users of bronchodilators compared to non-users in the VIVA trial.

VIVA screening trial

The VIVA screening trial contains both AAA (n=619) and non-AAA patients with complete cigarette smoking history. This group differs from the DNRP population, which contains only AAA patients. The VIVA population enabled testing for potential confounding by cigarette smoking of the association of AAA with asthma or ROPD. Logistic regression analysis demonstrated that use of bronchodilators, including anti-asthmatic medications with beta-2-adrenergic receptor agonists and/or use of glucocorticoids for inhalation or as tablets, associated with a 45% higher risk of an AAA (OR=1.45, [95% C.I.: 1.10-1.92], $P=0.009$) (Table 3, Model 1). Adjustment for current smoking did not attenuate the risk (OR=1.45, [95% C.I.: 1.10-1.93], $P=0.009$) (Table 3, Model 2). When current smoking was considered together with diabetes, hypertension, systolic blood pressure, diastolic blood pressure, body mass index, and age, the use of bronchodilators remained an independent and significant risk factor of AAA (OR=1.46, [95% C.I.: 1.10-1.94], $P=0.010$) (Table 3, Model 3). Consideration of current smoking together with former smoking reduced the risk of use of bronchodilators in AAA before (OR=1.14, [95% C.I.: 1.00-1.85], $P=0.049$) (Table 3, Model 4) and after considering other AAA risk factors (OR=1.34, [95% C.I.: 0.98-1.84], $P=0.069$), including diabetes, hypertension, systolic blood pressure, diastolic blood pressure, body mass index, and age, while the use of bronchodilators still remained an independent and significant risk factor of AAA (Table 3, Model 5). In this VIVA population, except for diabetes, all other potential confounders (smoking, hypertension, blood pressure, body mass index, and age) independently associated with the risk of AAA (Table 3).

Collection of plasma samples from 500 cases and 200 age- and gender-matched controls helped test whether the plasma YKL-40 associates with AAA development. YKL-40 acts as a biomarker of type-2 inflammation and its expression remains elevated in neutrophils from type-2 diabetic patients, in human cancer cells, and in the plasma samples from patients with cardiovascular events.¹²⁻¹⁴ Evidence suggests, however, that YKL-40 also correlates with acute exacerbation, total serum IgE, the percentage of peripheral blood eosinophils, and lung function among asthmatic patients,¹⁵⁻¹⁸ although a current asthma-specific biomarker does not exist. Therefore, YKL-40 provides strong, but not irrefutable evidence for asthma. Results showed significantly higher plasma YKL-40 levels from AAA patients (n=500) than from controls (n=200) (106.6 ± 102.8 $\mu\text{g/L}$ vs. 91.9 ± 147.6 $\mu\text{g/L}$, mean \pm standard deviation, $P<0.001$, Wilcoxon rank sum test). Patients who used bronchodilators also had significantly higher plasma YKL-40 levels than those who did not use bronchodilators (122.0 ± 129.8 $\mu\text{g/L}$ vs. 100.7 ± 116.9 $\mu\text{g/L}$, mean \pm standard deviation, $P=0.049$, Wilcoxon rank sum test).

DISCUSSION

This study established an association between AAA and asthma or ROPD in humans. Data collected from the large population of Danish AAA patients in DNRP showed that a hospital diagnosis of asthma or a recently filled prescription of an anti-asthmatic drug associated with an increased risk of admission with ruptured AAA compared to admission with intact AAA, both before and after adjusting for AAA comorbidities and relevant medications. Moreover, an asthma diagnosis or the use of bronchodilators or other anti-asthmatic drug prescriptions closer to the date of admission with AAA correlated directly with a higher risk of aortic rupture. The results remained robust after adjusting for a wide range of relevant possible confounders. The late onset of asthma and medication use associated with aortic rupture relates to findings from a

recent case-control study of 50 patients with childhood onset of asthma and 57 healthy children in which earlier onset of asthma during childhood did not affect abdominal aortic stiffness parameters, including aortic distensibility, aortic strain, pressure strain elastic modulus, and pressure strain normalized by diastolic pressure.¹⁹

The lack of information on cigarette smoking among the DNRP population could confound our conclusion, as smoking is a known independent risk factor for rAAA.²⁰ Indeed, external adjustment of the DNRP data of smoking habits among AAA patients using or not using bronchodilators only increased the independent relative risk of rupture by an asthma diagnosis or the use of bronchodilators or other anti-asthmatic drug prescriptions. In addition, supplemental analyses from the VIVA trial²¹ showed that adjustment for smoking did not change the independent estimates of risk of AAA among bronchodilator users, suggesting that bronchodilator use did not associate with smoking status. The risk of AAA among asthmatic patients remained 45% higher than that of non-asthmatic patients.

Prior studies established an association between AAA and COPD.²²⁻²⁵ While asthma and COPD can overlap in some patients, the majority of asthma patients do not have COPD. A diagnosis of asthma does not necessarily lead to hospitalization or outpatient contact. This potential limitation led us to define asthma as those patients who had ROPD and recorded the use of bronchodilators, as reported recently in an atherosclerosis risk-assessment study.²⁶ Higher odds ratios of aortic rupture from AAA patients with hospital-diagnosed asthma were identified than those from AAA patients who received anti-asthmatic medication (Figure 1 and Table 2), suggesting that we have underestimated the risk of asthma on AAA by defining asthma as the recorded use of bronchodilators and anti-asthmatic drugs (beta-2-adrenergic receptor agonists, anti-cholinergic medications, inhaled glucocorticoids, and xanthines). The strengths of this study include the use of two relatively large population-based cohorts, which both support the association of ROPD with the risk of having an AAA and rupture of an existing AAA. The interrogation of population-based cohorts minimizes the risk of selection bias, and the use of the drug registry minimizes the risk of misclassification as no relevant bronchodilator agent is given without a recorded prescription. Yet the inclusion in this group of users both patients with asthma and those with COPD with some reversible obstructive component presents a limitation. In Denmark, the number of prescriptions for inhaled bronchodilating agents for indications other than asthma or ROPD remains low, but the possibility exists that a small portion of patients using inhaled bronchodilating agents have COPD without a reversible component,^{25,27,28} which may confound our conclusion. Consequently, a subgroup analysis of patients with or without a diagnosis of asthma showed an increase in the relative risk of rupture to about twice as high a risk of rupture. This finding strongly supports the primary hypothesis of this study, as this analysis concentrates on a severe risk of misclassification since many asthmatic patients are solely managed by the general practitioners, introducing a bias towards the null hypothesis in this subgroup analysis.

Several recent studies have provided direct and indirect evidence that link the risk of asthma on human AAA and rupture. In apolipoprotein E-deficient (*ApoE*^{-/-}) mice, development of allergic airway inflammation significantly enlarged atherosclerotic plaques and increased lesion inflammation.²⁹ Recent data from the Multi-Ethnic Study of Atherosclerosis show that asthmatic patients who use inhaled corticosteroids, leukotriene inhibitors, or oral corticosteroids have significantly higher plasma C-reactive protein and fibrinogen concentrations, lower unadjusted cardiovascular disease (CVD)-free survival rate and higher CVD risk than asthmatic patients who do not use these medications or those without asthma.²⁶ Although atherosclerosis may not underlie all AAA, atherosclerosis usually accompanies aneurysmal dilation,³⁰ and

constitutes a long-recognized risk factor of AAA.³¹ We recently demonstrated directly that the development of allergic airway inflammation in mice doubled the size of experimental AAA, regardless of whether allergic airway inflammation began before, after, or during AAA formation.³² The mechanisms by which humans and mice develop AAA and asthma or allergic lung inflammation can differ, but we found a comparable increase of plasma IgE in mice that developed AAA or allergic lung inflammation. A synergistic increase of plasma IgE in mice with both AAA and allergic lung inflammation³² and beneficial effects on both human asthma and mouse AAA development of targeting IgE^{5,33} supports the contribution of IgE to both diseases.

As discussed, inflammatory cell accumulation in the airway and aortic lesions accompanies both asthma and AAA. These leukocytes may participate in the pathogenesis of these two seemingly unrelated diseases. In the asthmatic lung, mast cells release cytokines, proteases, and histamine and thus stimulate airway tissue remodeling, mucus secretion, smooth muscle contraction and vasodilatation, and immune cell activation.^{34,35} Sputum from asthmatic patients contain significantly increased neutrophil and eosinophil numbers.³⁶ Eosinophils mediate airway inflammation in mild and moderate atopic asthma, whereas neutrophils predominate in non-atopic and severe asthma.³⁷⁻³⁹ The polymorphonuclear leukocytes release neutrophil elastase that may mediate airway goblet cell hyperplasia, degranulation, and mucous plugging.⁴⁰ Although a direct role of eosinophils in AAA remains untested, either mast cells or neutrophils promote AAA development. Mast cells contribute to AAA by releasing cytokines (e.g. interleukin 6 and interferon- γ) and proteases (e.g. chymase and tryptase) that can activate vascular cells and breakdown the arterial extracellular matrix.^{4,41,42} Neutrophils also release proteases that can contribute to arterial wall tissue remodeling.^{43,44} These shared mechanisms likely contribute to crosstalk between these diseases, a hypothesis that merits further investigation.

Finally, a risk of confounding exists – especially in the DNRP analyses, which lacks individual data regarding smoking status. Yet, the VIVA study indicates that users of bronchodilating drugs smoke less than although non-users. Although we adjusted for almost all known potential confounders, the risk of residual confounding always remains an issue in observational studies.

In conclusion, this observational study conducted in two independent cohorts established a new link between the allergic asthma and AAA. Because allergic inflammation with elevated plasma IgE may promote AAA pathogenesis,⁵ other allergic inflammatory diseases, such as atopic dermatitis, allergic rhinitis and several ocular allergic diseases may carry similar risks as asthma for AAA formation and rupture. The findings from this study highlight a commonality in the inflammatory pathways involved in AAA and other prevalent, and seemingly unrelated diseases. The results have implications for the development of much needed advances in the prevention, screening criteria, and treatment of AAA, common conditions for which we currently lack sufficiently effective approaches.

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Disclosure:

None

SIGNIFICANCE

Abdominal aortic aneurysms (AAA) and asthma are both inflammatory diseases that share many pathological events, including inflammatory cell accumulation and T-cell immunity. We have recently demonstrated that experimental allergic lung inflammation significantly promoted the progression of both angiotensin-II infusion-induced and peri-aortic CaCl₂ injury-induced AAA in mice. This study tests the hypothesis that asthma or reversible obstructive pulmonary disease associates with the risk of AAA in humans. From two populations of patients from Denmark:

one that enrolled all AAA patients including those with aortic rupture, and another contains both AAA and AAA-free control patients. This study demonstrates that patients with hospital-diagnosed asthma or those have records of asthma medication experience significantly higher risk of having AAA or aortic rupture than those without asthma or related medications.

FIGURE LEGEND

Figure 1. Odds ratio (95%C.I.) of human AAA rupture before and after adjusting for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, diabetes with or without complications, and moderate to severe renal disease), concomitant drug use (ACE-inhibitors, Ang-II antagonists, aldosterone antagonists, beta-2-adrenergic receptor blocking agents, calcium antagonists, statins, anti-platelet therapy, anti-diabetic therapy, corticosteroids, and non-steroidal anti-inflammatory drugs), the number of visits to a general practitioner in the year before admission, income, and marital status.