

# Relation Between Common Allergic Symptoms and Coronary Heart Disease Among NHANES III Participants

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We investigated whether there is an increased risk of coronary heart diseases (CHD) in those with common allergic symptoms using the NHANES III, which is a representative sample of the United States population in 1988 to 1994. CHD was defined by Rose questionnaire and history of heart attack. Allergic symptoms were categorized into no symptoms (NO), rhinoconjunctivitis without wheezing (RC), and wheezing (WZ) based on symptoms. Multivariate logistic regression was used to obtain odds ratios (ORs) of CHD. Eight thousand six hundred fifty-three nonpregnant subjects  $\geq 20$  years old with overnight fasting  $\geq 8$  hours were included. CHD was present in 5.9% of the population; 36.5% did not have allergic symptoms (NO), 45.9% had RC, and 17.6% had WZ. The prevalence of CHD was 3.9% in NO, 4.8% in RC, and 12.8% in WZ ( $p < 0.001$ ). Compared to NO, unadjusted ORs of CHD were 1.24 (95% confidence interval 0.94 to 1.62) in RC and 3.58 (2.68 to 4.78) in WZ and ORs adjusted for sociodemographic factors and co-morbidities were 1.40 (1.02 to 1.92) in RC and 2.64 (1.79 to 3.90) in WZ. Only the group of women  $< 50$  years of age had significantly increased ORs in RC and WZ. In conclusion, common allergic symptoms were significantly associated with an increased risk of CHD. © 2010 Elsevier Inc. All rights reserved. (Am J Cardiol 2010;106:984–987)

We examined the relation of common allergic symptoms and coronary heart disease (CHD) based on a representative survey of the United States population. Because asthma can be complicated by accelerated decrease in pulmonary function,<sup>1</sup> increased airway infection,<sup>2</sup> and use of a  $\beta$  agonist, which are risk factors for cardiovascular disease,<sup>3–5</sup> we focused on symptoms of allergic rhinoconjunctivitis and wheezing, which stands for nonspecific bronchial hyper-reactivity with adjustment of several co-morbidities including asthma, chronic obstructive pulmonary disease (COPD), and congestive heart failure.

## Methods

The National Health and Nutrition Examination Survey (NHANES) III was a sampled survey of the noninstitutionalized civilian population in the United States from 1988 through 1994. In this survey 39,695 subjects were sampled and 30,818 participated in the interview and examination at a mobile examination center. We included subjects  $\geq 20$  years of age (16,573) who fasted overnight  $\geq 8$  hours (10,308). After excluding those who had missing values or who were pregnant, a final sample of 8,653 was obtained.

Self-reported allergic symptoms were categorized into no symptoms (NO), symptoms of allergic rhinoconjunctivitis without wheezing (RC), and wheezing (WZ). The RC group was defined by those who answered “yes” to “During

the past 12 months, have you had any episodes of stuffy, itch or runny nose, or watery or itchy eyes?,” excluding those who had wheezing to examine the effect of allergic rhinoconjunctivitis without bronchial hyper-reactivity because allergic rhinoconjunctivitis often coexists with asthma or nonspecific bronchial hyper-reactivity.<sup>6,7</sup> The WZ group was defined by those who answered yes to “Have you had any wheezing or whistling in your chest at any time in the past 12 months?” to see the effect of nonspecific bronchial hypersensitivity irrespective of asthma. Because these symptoms can be manifestations of underlying cardiopulmonary disease, we controlled for asthma, COPD, and congestive heart failure.

CHD was defined by history of heart attack or a positive response to the angina pectoris section of the Rose questionnaire.<sup>8</sup> Participants were considered to have CHD when they answered “yes” to “Have you ever had any pain or discomfort in your chest,” answered “yes” to “Do you get it when you walk uphill or hurry?” or “Do you get it when you walk at an ordinary pace on level ground?,” answered “stop or slow down” to “What do you do if you get it while you are walking?,” answered “relieved” to “If you stand still, what happens to it?,” and located chest pain/discomfort at midsternum or left chest and arm.

All analysis was done with consideration of sampling methods and weights using R 2.6.1 with the survey package (<http://www.r-project.org>). Pearson chi-square with Rao-Scott second-order correction was performed for categorical variables. Linear regression and subsequent Wald test was used for continuous variables. Multivariate logistic regression was used to obtain odds ratios (ORs) of CHD according to allergic symptoms with serial adjustments. A  $p$  value  $< 0.05$  was considered statistically significant.

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Table 1  
Characteristics of subjects by allergic symptoms

Variable	NO	RC	WZ	p Value
Age (years), mean $\pm$ SE	45.1 $\pm$ 0.6	43.2 $\pm$ 0.5	43.0 $\pm$ 0.7	<0.001
Women	47.9%	52.5%	50.3%	0.112
White	70.6%	80.0%	81.3%	<0.001
African-American	13.5%	9.1%	7.8%	
Mexican-American	7.2%	4.3%	3.5%	
Education (years)				<0.001
<9	13.2%	8.9%	11.7%	
9–11	15.9%	10.0%	16.6%	
$\geq$ 12	70.9%	81.1%	71.7%	
Current smoker	27.8%	20.9%	48.8%	<0.001
Alcohol (drinks)				0.001
0	14.6%	12.1%	8.5%	
$\leq$ 10/month	56.8%	55.1%	56.6%	
>10/month	28.6%	32.7%	34.9%	
Inactivity within 1 month	15.5%	11.7%	17.0%	0.002
Coronary heart disease	3.9%	4.8%	12.8%	<0.001
Asthma	3.6%	4.1%	29.2%	<0.001
Congestive heart failure	1.4%	1.2%	5.1%	<0.001
Chronic obstructive pulmonary disease	3.1%	4.9%	22.0%	<0.001
Hypertension	26.0%	27.2%	33.3%	0.004
Type 2 diabetes	6.0%	5.4%	7.1%	0.141
Body mass index (kg/m <sup>2</sup> )				
<25	43.4%	47.1%	41.7%	0.004
25–30	34.3%	33.0%	30.6%	
$\geq$ 30	22.3%	19.8%	27.7%	
Waist circumference (men >102 cm, women >88 cm)	37.3%	32.9%	43.1%	0.002
Cholesterol $\geq$ 240 mg/dl	18.5%	17.4%	17.6%	0.698
Low high-density lipoprotein cholesterol (men <40 mg/dl, women <50 mg/dl)	37.0%	35.8%	42.1%	0.062
C-reactive protein (mg/dl), mean $\pm$ SE	0.393 $\pm$ 0.013	0.372 $\pm$ 0.012	0.470 $\pm$ 0.024	0.008

## Results

CHD was present in 5.9% of the population. Characteristics of the population by allergic symptoms are listed in Table 1. Across the spectrum of allergic symptoms from NO to WZ, subjects became younger and more frequently white. Alcohol intake, asthma, COPD, and hypertension were also more prevalent as subjects had more severe allergic symptoms from NO to WZ. Prevalence of smoking, physical inactivity, congestive heart failure, obesity, abdominal obesity, and levels of C-reactive protein were highest in the WZ group followed by the NO and RC groups.

ORs of CHD according to allergic symptoms with sequential adjustments are listed in Table 2. Without adjustment, RC showed a weak but insignificant association, whereas WZ showed a strong association with CHD compared to NO. Interestingly, the association according to RC and WZ became stronger and significant with adjustment of age, gender, race, education, current smoking, alcohol intake, and physical inactivity (model 2). Even after adjustment with cardiopulmonary diseases such as asthma, congestive heart failure, and COPD (model 3), allergic symptoms remained significantly associated with CHD. After further adjustment for hypertension, type 2 diabetes, abdominal obesity, high-density lipoprotein cholesterol, cholesterol, and C-reactive protein (model 4), RC and WZ were significantly associated with CHD. ORs according to

traditional risk factors are also listed in Table 2 for comparison.

To better characterize the relation between allergic symptoms and CHD, we divided the study population by gender and age (<50 and  $\geq$ 50 years; Figure 1). This association was significant in women but not in men and stronger in subjects <50 years old than in subjects  $\geq$ 50 years old. Only the group of women <50 years old had significantly increased ORs in RC and WZ.

## Discussion

In the present study, we showed that common allergic symptoms of allergic rhinoconjunctivitis or wheezing were associated with CHD. This association was mainly driven by women <50 years of age. In addition, symptoms of allergic rhinoconjunctivitis increased the risk of CHD in women <50 years of age.

Several studies have reported increased risks of cardiovascular disease in asthma.<sup>9–11</sup> However, the apparent association of asthma and CHD might have been confounded. Asthma is a long-term inflammatory status complicated by decreased pulmonary function,<sup>1</sup> increased airway infection,<sup>2</sup> and use of  $\beta$  agonists. These factors were not controlled in the cited studies and may increase risk of cardiovascular disease.<sup>3–5</sup> In addition, although allergic rhinitis alone increased the risk of atherosclerosis in a cohort from

Table 2

Odds ratios of coronary heart disease with serial adjustments according to allergic symptoms and other co-morbidities

	Model			
	1 OR (95% CI)	2 OR (95% CI)	3 OR (95% CI)	4 OR (95% CI)
Allergic symptoms				
None	1	1	1	1
Rhinoconjunctivitis	1.24 (0.94–1.62)	1.45 (1.08–1.94)*	1.42 (1.03–1.94)*	1.40 (1.02–1.92)*
Wheezing	3.58 (2.68–4.78) <sup>‡</sup>	4.20 (3.06–5.76) <sup>‡</sup>	2.85 (1.92–4.24) <sup>‡</sup>	2.64 (1.79–3.90) <sup>‡</sup>
Co-morbidities				
Asthma	2.06 (1.35–3.15) <sup>†</sup>	2.20 (1.41–3.43) <sup>†</sup>	0.96 (0.57–1.62)	0.95 (0.57–1.59)
Congestive heart failure	39.09 (23.64–64.65) <sup>‡</sup>	22.04 (12.91–37.61) <sup>‡</sup>	17.72 (10.32–30.42) <sup>‡</sup>	15.52 (9.17–26.26) <sup>‡</sup>
Chronic obstructive pulmonary disease	4.72 (3.38–6.60) <sup>‡</sup>	3.47 (2.44–4.95) <sup>‡</sup>	2.27 (1.49–3.47) <sup>‡</sup>	2.21 (1.42–3.43) <sup>†</sup>
Hypertension	3.53 (2.72–4.58) <sup>‡</sup>	2.00 (1.43–2.79) <sup>‡</sup>	—	1.44 (1.03–2.00)*
Type 2 diabetes	3.10 (2.32–4.13) <sup>‡</sup>	1.67 (1.29–2.16) <sup>‡</sup>	—	1.08 (0.74–1.56)
Waist circumference (men >102 cm, women >88 cm)	2.10 (1.68–2.61) <sup>‡</sup>	1.42 (1.12–1.81) <sup>†</sup>	—	1.04 (0.77–1.41)
High-density lipoprotein cholesterol (men <40 mg/dl, women <50 mg/dl)	1.89 (1.48–2.43) <sup>‡</sup>	1.86 (1.45–2.38) <sup>‡</sup>	—	1.62 (1.20–2.18) <sup>†</sup>
Cholesterol ≥240 mg/dl	1.30 (1.03–1.65)*	0.84 (0.65–1.08)	—	0.82 (0.63–1.07)
C-reactive protein (mg/dl)				
<0.22	1	1	—	1
0.22–1.00	2.01 (1.47–2.76) <sup>‡</sup>	1.54 (1.11–2.14)*	—	1.20 (0.83–1.72)
≥1.00	3.73 (2.62–5.32) <sup>‡</sup>	2.56 (1.73–3.80) <sup>‡</sup>	—	1.80 (1.14–2.83)*

\*  $p < 0.05$ ; <sup>†</sup>  $p < 0.01$ ; <sup>‡</sup>  $p < 0.001$ ; variables adjusted: model 1, none; model 2, age, gender, race, education, current smoking, alcohol intake, and physical inactivity; model 3, asthma, COPD, and congestive heart failure plus model 2; model 4, hypertension, type 2 diabetes, abdominal obesity, low high-density lipoprotein cholesterol, high cholesterol, and C-reactive protein plus model 3.

CI = confidence interval.

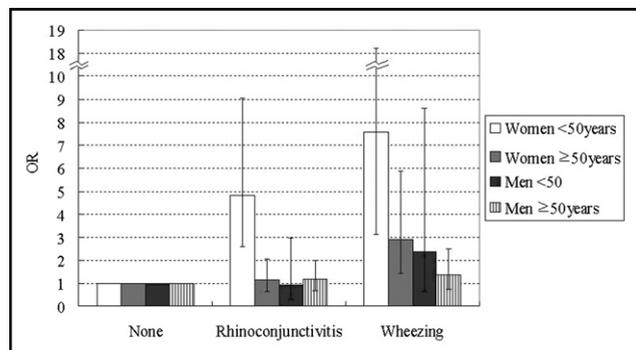


Figure 1. ORs of CHD according to allergic symptoms in women <50 years old (white bars) and ≥50 years old (gray bars) and men <50 years old (black bars) and ≥50 years old (striped bars); 95% confidence intervals are presented (whiskers).

Italy,<sup>12</sup> its effect on clinical cardiovascular disease has never been reported. Thus, the role of allergy itself in cardiovascular disease is still elusive. In this regard, we chose to focus on symptoms of allergic rhinoconjunctivitis and wheezing. The effect of wheezing is thought to represent the significance of nonspecific bronchial hyper-reactivity irrespective of having a diagnosis of asthma.

There are several possible mechanisms linking allergy to CHD. Type 1 hypersensitivity is mediated by cytokines, mast cells, histamines, leukotrienes, eosinophils, etc.<sup>13</sup> Several cytokines have been found to contribute to atherosclerosis. Interleukin-4-deficient mice have shown decreased atherosclerosis, suggesting that increased T-helper type 2 cytokines from allergy may contribute to CHD.<sup>14</sup> Higher histamine levels have been reported in CHD in animal

studies,<sup>15</sup> and histidine decarboxylase and histamine receptors have been associated with atherosclerosis.<sup>16</sup> Eosinophilia has been reported to increase the risk of cardiovascular disease.<sup>17</sup> However, whether these mediators derived from distant local allergic reactions can have significant effects on atherosclerosis is not certain.

A common mechanism may contribute to allergies and atherosclerosis. Targeted activation of perivascular mast cells has advanced atherosclerosis and its rupture, whereas cromolyn administration has decreased these events in mice.<sup>18</sup> Mast cells release several inflammatory mediators and contribute to fatty streak formation and generation of unstable plaques.<sup>19</sup> Likewise, leukotrienes are thought to play a role in the development of atherosclerosis.<sup>20</sup> A genetic variation of 5-lipoxygenase promoter has been associated with asthma<sup>21</sup> and atherosclerosis.<sup>22</sup>

Only women had a significantly increased risk of CHD from allergic symptoms. This finding is consistent with previous studies based on asthmatic patients.<sup>9–11</sup> In general, allergic disease is more common in women after adolescence and it is thought that sex hormones modulate immune response. Estrogen is considered to increase humoral immunity, whereas androgen and progesterone suppress it. In rodent studies, estrogen increased allergic sensitization and mast cell activation.<sup>23,24</sup> Therefore, women may have more consistent and severe inflammation during allergic response than men, but the exact mechanism of gender difference is not known. Age difference can also be explained by decreasing sex hormone synthesis, in particular, menopause in women.

The present study has several limitations. First, this study was cross sectional. Second, allergic symptoms were as-

sessed based on questionnaire. However, questionnaire and clinical examination have been shown to have a high correlation.<sup>25</sup> There might have been a recall bias because subjects were asked about allergic symptoms in the previous 12 months. In addition, allergic symptoms in shorter intervals and seasonal data were not available. Third, CHD was assessed on questionnaire using Rose criteria. The Rose questionnaire is reported to have high specificity (80% to 95%) but variable sensitivity (19% to 83%).<sup>26</sup> Thus, the prevalence of CHD might have been underestimated. Fourth, medications used for allergic symptoms may have confounded the results. However, potential harmful effects have mostly been suggested in regard to  $\beta$  agonists. Thus, in our analysis, we controlled for asthma and COPD for which  $\beta$  agonists are frequently used.

- Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of Ventilatory Function in Adults with asthma. *N Engl J Med* 1998;339:1194–1200.
- Martin RJ, Kraft M, Chu HW, Berns EA, Cassell GH. A link between chronic asthma and chronic infection. *J Allergy Clin Immunol* 2001; 107:595–601.
- Schroeder EB, Welch VL, Couper D, Nieto FJ, Liao D, Rosamond WD, Heiss G. Lung function and incident coronary heart disease: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2003; 158:1171–1181.
- Pesonen E, Andsberg E, Grubb A, Rautelin H, Meri S, Persson K, Puolakkainen M, Sarna S, Ohlin H. Elevated infection parameters and infection symptoms predict an acute coronary event. *Thorax* 2008;2:419–424.
- Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of  $\beta$ -agonists in patients with asthma and COPD. A meta-analysis. *Chest* 2004;125:2309–2321.
- Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(suppl):S147–S334.
- Nathan RA. The burden of allergic rhinitis. *Allergy Asthma Proc* 2007;28:3–9.
- Rose GA, Gillium RF, Prineas RJ. Cardiovascular Survey Methods. Geneva, Switzerland: World Health Organization, 1982.
- Tor K, Lindholm NB. Do patients with severe asthma run an increased risk from ischaemic heart disease? *Int J Epidemiol* 1996;25:617–620.
- Iribarren C, Tolstykh IV, Eisner MD. Are patients with asthma at increased risk of coronary heart disease? *Int J Epidemiol* 2004;33:743–748.
- Schanen JG, Iribarren C, Shahar E, Punjabi NM, Rich SS, Sorlie PD, Folsom AR. Asthma and incident cardiovascular disease: the Atherosclerosis Risk in Communities Study. *Thorax* 2005;60:633–638.
- Knoflach M, Kiechl S, Mayr A, Willeit J, Poewe W, Wick G. Allergic rhinitis, asthma, and atherosclerosis in the Bruneck and ARMY studies. *Arch Intern Med* 2005;165:2521–2526.
- Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr, Jansen-McWilliams L, D'Agostino RB, Kuller LH. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol* 1997;145:408–415.
- Davenport P, Tipping PG. The role of interleukin-4 and interleukin-12 in the progression of atherosclerosis in apolipoprotein E-deficient mice. *Am J Pathol* 2003;163:1117–1125.
- Sanda C, Shenkar J, Clemetson C, Sanjeev SH, Odile D, Talano JV. Blood histamine is associated with coronary artery disease, cardiac events and severity of inflammation and atherosclerosis. *J Cell Mol Med* 2002;6:583–592.
- Tanimoto A, Sasaguri Y, Ohtsu H. Histamine network in atherosclerosis. *Trends Cardiovasc Med* 2006;16:280–284.
- Hospers JJ, Rijcken B, Schouten JP, Postma DS, Weiss ST. Eosinophilia and positive skin tests predict cardiovascular mortality in a General Population sample followed for 30 years. *Am J Epidemiol* 1999;150:482–491.
- Bot I, de Jager SCA, Zerneck A, Lindstedt KA, van Berkel TJC, Weber C, Biessen EAL. Perivascular mast cells Promote atherogenesis and induce plaque destabilization in apolipoprotein E-deficient mice. *Circulation* 2007;115:2516–2525.
- Kovanen PT. Mast cells in atherogenesis: actions and reactions. *Curr Atheroscler Rep* 2009;11:214–219.
- Jala VR, Haribabu B. Leukotrienes and atherosclerosis: new roles for old mediators. *Trends Immunol* 2004;25:315–322.
- In KH, Asano K, Beier D, Grobholz J, Finn PW, Silverman EK, Silverman ES, Collins T, Fischer AR, Keith TP. Naturally occurring mutations in the human 5-lipoxygenase gene promoter that modify transcription factor binding and reporter gene transcription. *J Clin Invest* 1997;99:1130–1137.
- Dwyer JH, Allayee H, Dwyer KM, Fan J, Wu H, Mar R, Lusis AJ, Mehrabian M. Arachidonate 5-lipoxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. *N Engl J Med* 2004;350: 29–37.
- Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy* 2008;63:1418–1427.
- Jensen-Jarolim E, Untersmayr E. Gender-medicine aspects in allergology. *Allergy* 2008;63:610–615.
- Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. *BMJ* 1991;46:895–901.
- Fischbacher CM, Bhopal R, Unwin N, White M, Alberti K. The performance of the Rose angina questionnaire in South Asian and European origin populations: a comparative study in Newcastle, UK. *Int J Epidemiol* 2001;30:1009–1016.