

Comorbidity and Multimorbidity of Asthma and Allergy and Intolerance to Chemicals and Certain Buildings

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Objectives: We tested the hypothesis of high comorbidity between asthma/allergy and chemical intolerance (CI) and between asthma/allergy and building intolerance (BI), and high multimorbidity between asthma/allergy, CI, and BI. **Methods:** Population-based questionnaire data were used from 530 participants with asthma/allergy (allergic asthma, non-allergic asthma, allergic rhinitis, and/or atopic dermatitis), 414 with self-reported and 112 with physician-diagnosed CI, and 165 with self-reported and 47 with physician-diagnosed BI. Separate reference groups were formed for each of the five case groups. **Results:** Adjusted odds ratios varied from 4.6 to 13.1 for comorbidity, and from 6.6 to 46.4 for multimorbidity. **Conclusion:** The large comorbidity and multimorbidity between asthma/allergy, CI, and BI evokes the question as to whether there are similarities in underlying mechanisms between these conditions.

A large and increasing proportion of the general population suffer from various types of asthma and allergy,^{1,2} resulting in distress³ and impaired quality of life for the afflicted individual⁴ as well as high costs for society.⁵ The asthmatic reaction with bronchoconstriction is commonly categorized as either allergic (caused by allergens, ie, pollen and pet dander) or nonallergic (ie, exercise and cold air). In Sweden, 8.3% to 11.5% of the general population have been shown to suffer from asthma,^{6,7} and as many as 300 million persons worldwide may be affected.⁵ Allergic rhinitis is an allergen-induced nasal-airway inflammation with symptoms such as nasal congestion, nasal itching, excessive mucus production, and sneezing.⁸ It has been estimated that 10% to 17% of the Swedish population are afflicted,⁹ and as many as 500 million people worldwide.¹⁰ Atopic dermatitis (eczema) is characterized by intense itching and skin lesion, from which 11.5% of the Swedish population suffer.¹¹ It is considerably more common in children than in adults, with worldwide prevalence rates of 15% to 20% for children and 1% to 3% for adults.¹²

A certain proportion of the population falling ill from low-level environmental exposure is believed to be harmless. In many ways, these environmental intolerances (EIs) share defining characteristic features with asthma and allergy. For example, the afflicted person reports symptoms, often from barrier tissue such as the airways and skin, when exposed to environmental factors previously or commonly tolerated.

Chemical intolerance (CI) is an EI with symptom attributed to low levels of, typically, odorous chemicals, such as perfume and

cleaning products. Thus, CI is a general term used here to refer in a broad sense to adverse reactions to nontoxic chemicals. CI is often assessed as self-reported (eg, based on questions such as “Do you get symptoms from odorous exposure”) or clinically-related (eg, a physician-based diagnosis). Multiple chemical sensitivity (MCS),¹³ idiopathic EI,¹⁴ and sensory hyperreactivity (SHR)¹⁵ are common clinical definitions of CI. The prevalence of self-reported CI is rather high, 9% to 33%,^{16–20} whereas it drops to 0.5% to 6.3% when fulfilling criteria for clinical CI.^{16,19–21} Another form of EI is symptom-attribution to certain buildings, referred here to as building intolerance (BI). Its clinical condition is often referred to as nonspecific building-related symptoms (NBRS; “sick building syndrome”).²² Similar to CI, BI is a general term used here to refer in a broad sense to adverse reactions to certain indoor environments and is often assessed as either self-reported or clinical (eg, physician-diagnosed), with prevalence rates of 4.3% to 5.0% and 2.5%, respectively.^{23,24}

Asthma and allergy appear to be associated with CI and BI. Regarding CI, population-based studies in the United States have estimated that 17% report both allergy and self-reported CI,²⁵ that 19% of asthmatic individuals have a physician-diagnosed CI or other environmental illness,²⁰ and that 30% of those with self-reported CI also have asthma.¹⁶ Data from two samples that were telephone interviewed in 2002 to 2003/2005 to 2006 showed that among asthmatic individuals, 27/31% also had a self-reported CI, and 7.4/11.7% also had a physician-diagnosed CI. Asthma was reported in 34/35% of those with self-reported CI, and in 42/39% with physician-diagnosed CI.²⁶ A Japanese study showed that 84% of those with physician-diagnosed CI also had allergy to pollen, house dust, or drugs.²⁷

We have recently reported that specific building-related environmental factors, in addition to odorous/pungent factors, trigger symptoms among persons with asthma and allergy in the general population.²⁸ Although not population-based, additional studies favor the notion of associations between asthma/allergy and both self-reported and physician-diagnosed BI.^{22,29,30} However, the scientific literature lacks documentation of multimorbidity between asthma/allergy, CI, and BI.

On the basis of the given review, the objective of the current study was to test the hypotheses of comorbidity and multimorbidity between asthma/allergy, CI, and BI in the general population. This included (i) CI separately, BI separately, and CI and BI combined in participants with asthma/allergy, (ii) asthma/allergy separately, and asthma/allergy and BI combined in participants with CI, and (iii) asthma/allergy separately, and asthma/allergy and CI combined in participants with BI. Comorbidity between CI and BI that does not involve asthma/allergy has previously been reported from this sample³¹ and was therefore not included in the present study. For a broad approach, CI and BI were studied regarding both self-reported and physician-diagnosed, and comorbidity and multimorbidity were studied in both absolute (prevalence) and relative (increased risk in relation to a reference group) terms. Asthma/allergy was classified in a general sense to ensure good statistical power, by defining it as being based on a diagnosis of allergic asthma, nonallergic asthma, allergic rhinitis, and/or atopic dermatitis given by a physician.

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METHODS

Population and Samples

The study was conducted within the Västerbotten Environmental Health Study (VEHS),³¹ which investigates diagnoses, symptomatology, annoyance, intolerance, risk factors, coping and social support in EI, asthma, and allergy. Västerbotten, a county in northern Sweden, has approximately 260,000 inhabitants and an age and sex distribution similar to the general Swedish population.^{31,32} A random sample of 8600 persons, aged 18 to 79 years, and stratified for age and sex was drawn from the municipal register and invited to participate. Of the 8600 individuals, accurate addresses were obtained for 8520, who could be reached with the questionnaire, among whom 3406 (40.0%) participated. The lowest response rate (17.3%) was among men aged 18 to 29 years, and the highest rate (63.9%) among men aged 70 to 79 years.

Self-reported CI was assessed with the question “Are you getting symptoms from odorous/pungent chemicals (not limited to certain buildings), such as perfumes and cleaning agents, in doses that you were not getting symptoms from before or that you believe most other people are not getting symptoms from?”³¹ Self-reported BI was assessed with the question “Are you getting symptoms from residing in certain buildings (nonspecific building-related symptoms) that you were not getting symptoms from before or that you believe most other people are not getting symptoms from?”³¹

Assessment of lifetime physician diagnoses of asthma/allergy, CI, and BI was conducted with the question “Have you been diagnosed with this condition by a physician?”, separately referring to allergic asthma, nonallergic asthma, allergic rhinitis and atopic dermatitis, MCS, and NBRS. It should be noted that self-reported and physician-diagnosed EIs are not exclusive conditions. Instead, physician-diagnosed intolerance is likely to be a more strict criterion than self-reported intolerance. Reference groups (i) without a diagnosis of asthma/allergy, (ii) without self-reported CI, (iii) without self-reported BI, (iv) without a diagnosis of CI, and (v) without a diagnosis of BI were compared with the groups with a diagnosis of asthma/allergy, self-reported CI and BI, and a diagnosis of CI and BI, respectively.

Procedure

The participants were mailed the questionnaire and prepaid postage, and when needed, up to two reminders, and responded to it during March to April, 2010 (before the onset of the pollen season in Västerbotten, Sweden). A database was created by scanning the questionnaires. A data-entry verification test was performed to check the accuracy of the scanning procedure. Each item of 35 (~1%) randomly selected filled-in paper questionnaires was compared with the entries in the database, revealing an error rate of 0.11%, which was considered negligible. Quality control checks (eg, range checks and logical checks) were conducted to test the accuracy of the data before analysis.³¹ All participants gave their informed consent to participate, and the study was conducted according to the Helsinki Declaration and approved by the Umeå Regional Ethics Board (Dnr 09-171M).

Statistical Analysis

The five case groups and corresponding referent groups were compared on background variables with independent *t* test (age) and Chi-square analysis (remaining variables; Table 1). Odds ratios (ORs), both crude (unadjusted) and adjusted for age, sex, marital/cohabitant status, university education and smoking, were calculated with binary logistic regression analysis for each possible comorbidity and multimorbidity, with corresponding reference group as referents. The α -level was set at 0.05. The Statistical

TABLE 1. Characteristics of Case Groups and Corresponding Referent Groups, and Results of Tests of Group Differences With *t* test (Age) and Chi-Square Analysis (Remaining Variables)

	Asthma/Allergy*		Self-Reported Chemical Intolerance		Physician-Diagnosed Chemical Intolerance		Self-Reported Building Intolerance		Physician-Diagnosed Building Intolerance	
	Cases	Referents	Cases	Referents	Cases	Referents	Cases	Referents	Cases	Referents
Age (years, $\pm$ SD)	48.8 $\pm$ 17.0 ^a	51.7 $\pm$ 16.8	53.6 $\pm$ 15.7 ^a	50.9 $\pm$ 17.0	62.8 $\pm$ 12.3 ^a	50.8 $\pm$ 16.8	53.5 $\pm$ 15.5 ^b	51.1 $\pm$ 16.9	60.2 $\pm$ 13.1 ^a	51.1 $\pm$ 16.9
Women (%)	57.7 ^{ns}	55.4	67.6 ^a	54.1	69.6 ^c	55.3	69.7 ^a	55.0	72.3 ^b	55.5
Married/cohabitant (%)	71.1 ^{ns}	74.6	72.9 ^{ns}	74.3	66.4 ^{ns}	74.4	66.9 ^b	74.5	73.9 ^{ns}	74.1
University education (%)	44.7 ^{ns}	41.2	42.4 ^{ns}	41.7	23.9 ^a	42.4	46.6 ^{ns}	41.5	32.6 ^{ns}	41.9
Presently smoking (%)	7.6 ^{ns}	9.0	10.2 ^{ns}	8.6	10.0 ^{ns}	8.8	9.1 ^{ns}	8.8	17.4 [*]	8.7
Physical exercise > twice/week (%)	66.2 ^{ns}	67.3	66.2 ^{ns}	67.2	70.0 ^{ns}	67.0	71.2 ^{ns}	66.9	69.6 ^{ns}	67.1
Alcohol consumption > twice/week (%)	13.7 ^{ns}	12.4	12.2 ^{ns}	12.7	10.0 ^{ns}	12.7	12.3 ^{ns}	12.6	10.9 ^{ns}	12.7
Perceived general health (%)										
Very good or excellent	35.6 ^c	40.9	23.2 ^a	42.4	12.7 ^a	41.0	29.1 ^a	40.6	17.0 ^a	41.3
Good	32.9	34.4	34.9	34.1	22.7	34.6	29.7	34.4	29.8	34.3
Poor or fairly good	31.5	24.7	41.9	23.5	64.6	24.4	41.2	24.9	53.1	25.4

*Combined group with allergic asthma, nonallergic asthma, allergic rhinitis, and atopic dermatitis.

^a*p* < 0.001.

^b*p* < 0.05.

^c*p* < 0.01.

Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0; IBM, Armonk, NY) was used for all data analyses.

RESULTS

In total, 530 responders reported that they had been given a physician-based diagnosis of allergic asthma, nonallergic asthma, allergic rhinitis, and/or atopic dermatitis. These 530 participants are referred to as the asthma/allergy group, comprising all four conditions. Among them, 398 (75.1%) had one of the four asthma/allergy diagnoses, 115 (21.7%) had two of the diagnoses, 17 (3.2%) had three of the diagnoses, and none had all four diagnoses.

Self-reported CI was reported by 414 (12.2%), self-reported BI by 165 (4.8%), physician-diagnosed CI (MCS) by 112 (3.3%), and physician-diagnosed BI (NBRS) by 47 (1.4%) of the respondents. The reference groups included 2876 respondents without a diagnosis of asthma/allergy, 2992 without self-reported CI, 3241 without self-reported BI, 3294 without a diagnosis of CI, and 3359 without a diagnosis of BI. The five case groups and their corresponding referent group are described with respect to demographics, lifestyle, and perceived general health in Table 1. At least one of the five pair-wise group comparisons showed significant group differences for age, sex, marital/cohabitant status, university education, and smoking (Table 1). One-hundred twenty-two (29.5%) of those with self-reported CI and 45 (40.2%) of those with a lifetime physician-diagnosed CI fulfilled the 1999 consensus criteria for MCS¹³ at the time of the questionnaire. Eighty-four (50.1%) of those with self-reported BI and 19 (40.4%) of those with a lifetime physician-diagnosed BI fulfilled the WHO's symptom criteria for NBRS (at least one general, one mucosal, and one skin symptom).³³

Prevalence of comorbidity and multimorbidity is presented in Fig. 1. In asthma/allergy, the prevalence of comorbidity with CI is higher than with BI, and the prevalence of multimorbidity with two other conditions is highest in BI, followed by CI and asthma/allergy, in that order. The overlap between conditions is illustrated in Venn diagrams in Fig. 2. Among the participants with self-reported and physician-diagnosed CI, 38.2% and 63.4%, respectively, also had asthma/allergy. Corresponding proportions of participants with BI who also had asthma/allergy were 43.0% and 66.0%.

Figure 1 also shows ORs for the comorbidities and multimorbidities, both crude and adjusted for age, sex, marital/cohabitant status, university education, and smoking. The ORs were in all cases significantly larger than unity for both crude and adjusted models

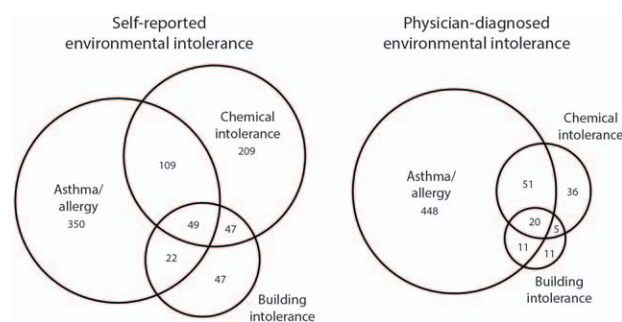


FIGURE 2. Venn-diagrams of comorbidity and multimorbidity between asthma/allergy and chemical and building intolerance. The numbers refer to participants with the condition. The circle areas for the asthma/allergy groups are set equal to enhance direct comparison of proportions.

($P < 0.001$), and can be considered as large or very large in size (4.3 to 64.9 for crude and 4.6 to 46.4 for adjusted). Although the confidence intervals overlap in many cases, the ORs were systematically larger in physician-diagnosed than in the self-reported CI and BI. Furthermore, the ORs for multimorbidity were in general larger than for comorbidity. Note that the OR for comorbidity in CI with asthma/allergy is the same as for comorbidity in asthma/allergy with CI, and that the OR for comorbidity in BI with asthma/allergy is the same as for comorbidity in asthma/allergy with BI (cf. Fig. 1).

DISCUSSION

The results show clear support for the hypotheses of comorbidity and multimorbidity between asthma/allergy, CI, and BI. This was the case irrespective of whether the EIs were self-reported or physician-diagnosed, and irrespective of whether the comorbidity and multimorbidity were expressed in absolute (prevalence) or relative (increased risk in relation to a reference group) terms.

Among the participants with asthma/allergy, about 13% reported a physician-diagnosed CI, 6% reported a physician-diagnosed BI, and 4% reported both physician-diagnosed intolerances. Corresponding prevalence rates for self-reported EIs among those with asthma/allergy were about 30%, 13%, and 9%, respectively. The results for CI agree well with those reported by Caress and Steinemann^{16,26} from two population-based surveys in the U.S. They found that among those diagnosed with asthma, 27% and 31% also reported self-reported CI (30% in the present study), and 7% and 12% had also been diagnosed with MCS (13% in the present study). A large proportion (about 12% to 18%, depending on criterion) of those with CI reported both asthma/allergy and BI, and an even larger proportion (about 30% to 43%) of those with BI reported both asthma/allergy and CI. The prevalence of asthma/allergy was high among participants with self-reported CI (38%) and BI (43%), and strikingly high among participants with physician-diagnosed CI (63%) and BI (66%).

The comorbidities and multimorbidities in asthma/allergy were also high in relative terms. Having asthma/allergy was associated with an approximately 5- to 13-fold increased risk (depending on EI criterion) for also having either CI or BI, when adjusting for age, sex, marital/cohabitant status, education, and smoking, and a 7- to 25-fold increased risk for also having both CI and BI. The size of these comorbidities is the same in CI or BI for also having asthma/allergy. The multimorbidity in asthma/allergy with the two EIs, expressed as an increased risk, was found to be generally larger than the comorbidity with either one of the two EIs. From the perspective of having either CI or BI, there was an approximately 12- to 46-fold increased risk (depending on EI criterion) for also having both

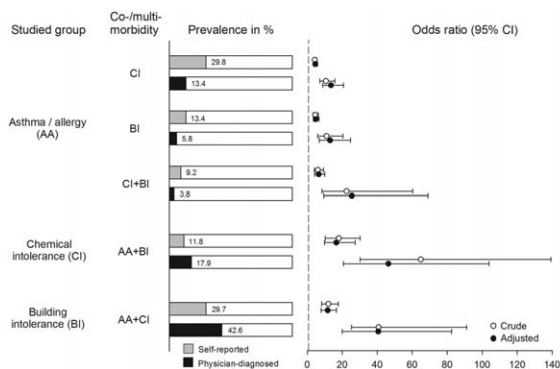


FIGURE 1. Comorbidity and multimorbidity between asthma/allergy and chemical and building intolerance expressed as prevalence and odds ratios (ORs) and confidence intervals (CIs) when unadjusted (crude) and adjusted for age, sex, marital/cohabitant status, university education, and smoking. Referents are used as a reference group. The vertical dashed line represents an OR of unity, from which all ORs differ significantly ($P < 0.001$).

asthma/allergy and the other EI. To our knowledge, this is the first study to report multimorbidity between asthma/allergy, CI, and BI. Although clearly very large ORs, the estimates of multimorbidity for physician-diagnosed EI should be interpreted cautiously due to large confidence intervals, presumably referable to the small sample size of participants with physician-diagnosed BI ($n = 47$).

Among the participants with asthma/allergy, the prevalence of comorbidity was higher for CI than for BI, whereas the increased risk of comorbidity was similar between the two EIs. This may be explained by CI being more common than BI also among the referents for the asthma/allergy group (cf. Fig. 1).

The choice to study both physician-diagnosed and self-reported intolerance was based on the fact that the field lacks definitions for chemical- and building-related intolerance that are generally agreed on. However, commonly used diagnoses and concepts for these EIs are MCS/SHR, NBRS, and self-reported chemical and building-related intolerance, which were included in the current study. It is important to point out that these two conditions, physician-diagnosed and self-reported, are not mutually exclusive, but rather conditions with a different criterion. Thus, it is reasonable to assume that persons with more severe cases more likely will seek medical care, and thus more likely have been given a diagnosis. Notably, both conditions are in a strict sense self-reported, as the participant reports whether a diagnosis has been given. When comparing the two criteria, it is of interest to note that the comorbidity and multimorbidity in asthma and allergy with EI was highest in self-reported EI in terms of prevalence, but highest in physician-diagnosed EI in terms of increased risk. This is what would be expected, as having a self-reported EI is more common than a physician-diagnosed intolerance (cf. Fig. 1), supposedly due to the criterion for a self-report being less strict.

CI and BI as well as other EIs show large comorbidity and multimorbidity³¹ and may possibly share underlying mechanism.³⁴ Historically, EIs have been excluded from the asthma and allergy domains, and has been ascribed labels such as “false allergies” or “yuppie flu.”³⁵ Nevertheless, it appears to be common among patients with asthma and allergy to react stronger than normal to odorous/pungent substances and to environmental exposure associated with certain buildings.²⁸

Odorous exposure may worsen asthma³⁶ and cause a feeling of being ill among asthmatic individuals.³⁷ The odds for reporting symptoms from exposure to fragrance products was found to range between 1.6 and 4.0 for allergic and nonallergic asthma, bronchial hyperreactivity, and allergic rhinitis.³⁸ In addition to learned avoidance behavior, patients with respiratory symptoms show stronger than normal dose–response-related non-IgE-mediated histamine release from basophils when exposed to perfume, and are likely to show positive patch test to perfume.³⁹ A meta-analysis strongly suggests that indoor dampness or mold metabolites are associated with increased asthma development and exacerbation as well as current and lifetime diagnosis of asthma and various other allergy-related upper and lower respiratory symptoms and skin symptoms.⁴⁰ Hodgson and Addoriso²² argue that asthma exacerbations may be attributed to general indoor growth of microbial agents.

Important to notice in the present study is that a large proportion of those with asthma/allergy did not report a comorbid EI, suggesting that far from all patients with asthma/allergy suffer from other exposures in the environment, even though our data strongly suggest an increased risk. It is also quite possible that a large proportion of the participants reporting BI have an underlying CI that explains their reactions to certain buildings. It is, for example, very common among persons with building-related intolerance to attribute their symptoms to chemical emissions from mold odor.⁴¹ Another possible explanation is that the patients are actually suffering from various forms of asthma and allergy on its own that is not responding to traditional treatments.⁴² Given the high

comorbidity in asthma/allergy with either CI or BI, this reasoning may explain why a rather large proportion reports all three conditions, with very large ORs (6.6 to 46.4). Thus, an important common denominator in these two forms of EI appears to be CI.

A strong tendency of high perceived health-risk perception for environmental pollution has been reported in allergic asthma and atopic dermatitis.³ The belief of chemical exposure with odorous properties being hazardous may possibly result in symptoms among asthmatic/allergic persons. Chen and Miller⁴³ have proposed a biophysical model of stress-induced asthma exacerbation. According to this model, belief of chemical exposure with odorous properties being hazardous and, hence, a threat, can affect the autonomic nervous system and the hypothalamic–pituitary–adrenal axis.

The present study has certain limitations. Only 40% of the randomly selected individuals volunteered, which compromises the representativeness due to increased risk of selection bias. Young men had the largest proportion of nonresponders. Another limitation is that the participants with the four types of asthma and allergy were combined into one group, due to low statistical power, which does not enable conclusions about a specific type of asthma/allergy. However, it can be pointed out that those with a physician-diagnosed EI reported a high percentage of allergic asthma and allergic rhinitis, implying that these diagnoses may be most relevant to study in the future regarding comorbidities and multimorbidities with EI. Nevertheless, future studies should aim at investigating each of the four asthma/allergy diagnoses individually for a better understanding. Yet, another limitation is that only self-reported data of physician diagnosis are available. Future research on these questions should, if possible, use hospital records of diagnostic information for more reliable diagnoses.

CONCLUSION

The results from the current study suggest that CI only, BI only as well as the combination of both these intolerances are far more common in persons with asthma and allergy than among those without these conditions, although most persons with asthma and allergy do not experience these problems. Furthermore, from the perspective of having either CI or BI, the multimorbidity with asthma/allergy and the other type of EI is very high. These high comorbidities and multimorbidities, together with the compromised quality of life each of these may result in, calls for further research in these populations, and evoke the question as to whether there are similarities in underlying mechanisms between these conditions.

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