

ORIGINAL PAPER

Prevalence of self-reported hypersensitivity symptoms following intake of alcoholic drinks

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Summary

Background Although hypersensitivity symptoms following alcoholic drink consumption are common in asthmatics, the prevalence of such symptoms in the general population is not known.

Objective To assess the prevalence of hypersensitivity symptoms following alcoholic drink consumption in an adult Northern European general population and the association of these symptoms with the prevalence of allergic rhinitis (AR) and asthma.

Methods In 2006, a postal questionnaire was sent to a random sample of 18–69-year-olds living in Copenhagen, the capital of Denmark. The response rate was 70.7% (4242/6000).

Results The prevalence of alcohol-induced symptoms from the upper airways, lower airways, and skin was 7.6% [95% confidence interval (CI): 6.8–8.4%], 3.2% (95% CI: 2.7–3.8%), and 7.2% (95% CI: 6.4–8.9%), respectively. A total of 13.9% (95% CI: 12.9–15.0%) had ever experienced alcohol-induced symptoms from at least one of the three regions (upper airways, lower airways, or skin), and 9.9% (95% CI: 9.0–10.8%) had experienced symptoms in the last 12 months. All types of beverages were commonly reported as triggers of hypersensitivity symptoms, red wine being the most common. Alcohol-induced hypersensitivity symptoms from the upper and lower airways were significantly more prevalent in persons with AR and asthma (odds ratios between 3.0 and 8.1, *P*-value <0.001 for all associations).

Conclusions In this Northern European general population, self-reported hypersensitivity symptoms following the intake of alcoholic drinks are common. These symptoms were markedly more prevalent in persons with AR and asthma. The underlying mechanisms and the clinical significance of these symptoms remain to be elucidated.

Keywords alcohol drinking, alcoholic beverages, atopy, respiratory hypersensitivity

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Introduction

There is evidence that alcohol influences the immune system in several ways, e.g. alcohol increases total serum IgE, induces changes in the cytokine profile, and impairs the T-helper type 1 lymphocyte-regulated cell-mediated immune response leading to increased susceptibility to bacterial infections [1–3]. Less is known about the influence of alcohol on the atopic immune response, although a few studies have linked alcohol consumption to IgE sensitization against inhalant allergens [4–8]. Furthermore, alcohol during pregnancy has been linked to atopic markers (cord blood IgE and early-onset atopic dermatitis) in the offspring [9, 10].

In Asian populations, alcoholic drink consumption is known to be a contributing factor to the so-called alcohol-induced asthma (ALA). ALA has mainly been attributed to impaired enzymatic activity of acetaldehyde dehydrogenase 2 (ALDH2), genetically reduced in approximately half of the Asian populations, resulting in high blood levels of acetaldehyde following intake of alcoholic drinks [11, 12]. This genetic defect in ethanol metabolism is also responsible for the Oriental flushing [13].

In Caucasian populations, where this enzymatic defect is extremely rare [14], alcoholic beverages also appear to be able to trigger hypersensitivity symptoms [15–17]. This knowledge mainly stems from clinical experience and studies of patient populations. More than one third of

Australian asthmatics report that alcoholic drinks trigger asthma symptoms [18]. A similar figure has been obtained in English asthmatics [19]. However, little is known about the prevalence of such symptoms in general populations.

We aimed to investigate the prevalence of self-reported hypersensitivity symptoms following intake of alcoholic drinks and the prevalence of these symptoms in persons with allergic rhinitis (AR) and asthma in a general Danish population. Furthermore, the possible mechanisms underlying these symptoms are reviewed.

Methods

Study population

This population-based cross-sectional study was conducted in Copenhagen, the capital of Denmark, between February and August 2006. A random sample of 18–69-year-old persons ($n = 6000$) was drawn from the Danish Civil Registration System. All participants were Danish citizens born in Denmark, and living in one of 11 municipalities of Copenhagen County (Ballerup, Brøndby, Glostrup, Herlev, Albertslund, Hvidovre, Høje Taastrup, Ledøje-Smørum, Rødovre, Ishøj, and Vallensbæk). The study was approved by the Danish Data Protection Agency. According to Danish legislation, questionnaire surveys do not need approval by an ethical committee.

Questionnaire and definitions

Questions on asthma were adopted from the stage I questionnaire of the European Community Respiratory Health Study (ECRHS) [20]. Asthma was defined according to criteria used previously by the ECRHS [21] as a positive answer to at least one of the following three questions:

- Have you been woken by an attack of shortness of breath at any time in the last 12 months?
- Have you had an attack of asthma in the last 12 months?
- Are you currently taking any medicine (including inhalers, aerosols, or tablets) for asthma?

AR was defined as a positive answer to at least one of two questions:

- Have you had an itchy or stuffy nose or have you been sneezing when near grass, trees, or flowers?
- Have you had an itchy or stuffy nose or have you been sneezing following exposure to furry animals, e.g. horse, dog, cat, rabbit, guinea-pig, or hamster?

These questions on AR symptoms have been validated previously in population-based studies in our background

population and were found to be strongly related to IgE sensitization to relevant inhalant allergens [22, 23].

We used three main questions on alcohol-related symptoms from the nose, lower airways, and the skin, following intake of alcoholic drinks (shown in Table 1). The questions had been pre-tested in another population-based study, where participants easily understood and answered the questions (unpublished data).

Statistical analyses

Questionnaires with missing answers to at least one of the three main questions on hypersensitivity symptoms following alcohol intake were excluded ($n = 151$), leaving 4091 for the analyses.

Ninety-five percent confidence intervals (CIs) for the estimated prevalence of hypersensitivity symptoms were calculated by using the normal approximation to the binomial distribution [24]. Sex- and age (categorized as <30, 30–40, 40–50, 50–60, and >60 years)-standardized prevalence estimates of hypersensitivity symptoms were calculated using the direct standardization method and the entire population ($n = 6000$) as the standard [25]. The χ^2 test was used for comparisons. Associations between hypersensitivity symptoms and asthma (or AR) were evaluated by logistic regression analysis adjusted for age and sex with asthma (or AR) as the dependent variable. The trend test was performed by including the categorical variable as a trend (continuous) variable in the model (the P -value reflects the Wald test for this variable). Statistical analyses were performed with SPSS version 13.0 for Windows.

Results

The response rate after one reminder was 70.7% (4242/6000). A total of 151 persons had missing information on at least one of the three main questions and were excluded from subsequent analyses. Young age and male sex were significantly associated with non-response (data not shown). Among the 4091 respondents included in the analyses, symptoms from the nose, lower airways, and the skin, following alcoholic drink consumption, were reported by 7.6% (95% CI: 6.8–8.4%), 3.2% (95% CI: 2.7–3.8%), and 7.2% (95% CI: 6.4–8.9%), respectively (Table 1). Sex and age standardization of these prevalence estimates did not result in major changes. Thus, the sex- and age-standardized prevalence estimates of symptoms from the nose, lower airways, and skin, following alcoholic drink consumption were 7.4 (95% CI: 6.6–8.2%), 3.1% (95% CI: 2.6–3.8%), and 7.1% (95% CI: 6.3–7.9%), respectively. The prevalence of at least one of the symptoms from the nose, lower airways, or the skin was 13.9% (95% CI: 12.9–15.0%). The majority (between 63% and 77%) of persons reporting symptoms following alcohol intake had experienced symptoms in the last 12 months.

Table 1. Prevalence of self-reported hypersensitivity symptoms following intake of alcoholic drinks

	Prevalence % (n/total n)	
(1) Have you ever experienced itchy nose, sneezing, runny nose, or stuffy nose following intake of alcoholic drinks?		7.6 (311/4091)
If yes, which types of alcoholic drinks?		
Beer	38.6 (120/311)	
Red wine	69.1 (215/311)	
White wine	23.8 (74/311)	
Dessert wine	21.9 (68/311)	
Spirits	29.9 (93/311)	
Have you experienced these reactions in the last 12 months?	77.3 (235/311)	
(2) Have you ever experienced wheezing or whistling in your chest, breathlessness, or coughing, following intake of alcoholic drinks?		3.2 (130/4091)
If yes, which types of alcoholic drinks?		
Beer	32.3 (42/130)	
Red wine	52.3 (68/130)	
White wine	18.5 (24/130)	
Dessert wine	20.6 (27/130)	
Spirits	51.5 (67/130)	
Have you experienced these reactions in the last 12 months?	63.1 (82/130)	
(3) Have you ever experienced symptoms from the skin such as a rash, itching, or swelling of the skin following intake of alcoholic drinks?		7.2 (294/4091)
If yes, which types of alcoholic drinks?		
Beer	36.4 (107/294)	
Red wine	71.1 (209/294)	
White wine	25.5 (75/294)	
Dessert wine	21.1 (62/294)	
Spirits	37.4 (110/294)	
Have you experienced these reactions within the last 12 months?	68.0 (200/294)	
At least one of symptoms 1, 2, or 3		13.9 (569/4091)
At least one of symptoms 1, 2, or 3 in the last 12 months		9.9 (404/4091)

The prevalence of at least one of the symptoms in the last 12 months was 9.9% (95% CI: 9.0–10.8%). All types of alcoholic beverages were commonly reported as triggers of hypersensitivity symptoms (Table 1). Red wine was most frequently reported to induce hypersensitivity symptoms, although spirits were reported to cause symptoms from the lower airways just as frequently as red wine.

Symptoms from the nose and skin were significantly more common among women than men (Table 2). Symptoms, in particular rhinitis symptoms, following alcohol intake were significantly associated with age, with a peak prevalence among 40–60-year-olds (Table 2).

Reporting of alcohol-related hypersensitivity symptoms from any organ was significantly associated with AR and asthma (Table 3), and the prevalence of AR and asthma increased with the number of regions affected by alcohol-related hypersensitivity symptoms (Table 4) (test for trend <0.001 for both AR and asthma).

Discussion

We found that self-reported hypersensitivity symptoms following alcoholic drink consumption were common in this Northern European population.

All types of alcoholic beverages were commonly reported as triggers of alcohol-induced symptoms, with red wine as the most common. This finding might reflect that substances specific to red wine are important to the development of these hypersensitivity symptoms. Alternatively, this may merely reflect the alcoholic drink preferences in the population. In Denmark, wine represents a major contributor to the total consumption of ethanol [26]. The finding that all types of beverages were commonly reported to elicit hypersensitivity symptoms suggests that substances common to all alcoholic beverages contribute to alcohol sensitivity.

One limitation of the present study was that we did not collect data on self-reported alcohol consumption or avoidance behaviour, i.e. persons previously experiencing alcohol-induced hypersensitivity avoid or reduce alcoholic beverages. Furthermore, it should be considered to what extent non-response may have influenced the results. Although sex and age were significantly associated with non-response, sex and age standardization did not result in major changes in the prevalence estimates. Nevertheless, it cannot be excluded that the true prevalence of symptoms might be lower or higher than those observed.

Table 2. Prevalence of self-reported hypersensitivity symptoms following intake of alcoholic drinks in relation to age and sex

	Prevalence % (n/total n)		
	Have you ever experienced itchy nose, sneezing, runny nose, or stuffy nose following intake of alcoholic drinks?	Have you ever experienced wheezing or whistling in your chest, breathlessness, or coughing, following intake of alcoholic drinks?	Have you ever experienced symptoms from the skin such as a rash, itching, or swelling of the skin following intake of alcoholic drinks?
Age in years			
< 30	3.7 (18/486)	2.7 (13/486)	7.4 (36/486)
30–40	5.9 (44/745)	2.3 (17/745)	7.0 (52/745)
40–50	8.5 (86/1007)	3.2 (32/1007)	9.0 (91/1007)
50–60	10.4 (101/974)	4.6 (45/974)	7.2 (70/974)
> 60	7.1 (62/879)	2.6 (23/879)	5.1 (45/879)
	<0.001 [†]	0.043 [†]	0.028 [†]
Sex			
Male	6.6 (124/1871)	3.1 (58/1871)	5.5 (103/1871)
Female	8.4 (187/2220)	3.2 (72/2220)	8.6 (191/2220)
	0.031 [†]	0.795 [†]	0.010 [†]

[†]P-value for the χ^2 test.**Table 3.** Prevalence of self-reported hypersensitivity symptoms following intake of alcoholic drinks in relation to asthma and AR (for definitions of asthma and AR, see text)

	Have you ever experienced itchy nose, sneezing, runny nose, or stuffy nose following intake of alcoholic drinks?		Have you ever experienced wheezing or whistling in your chest, breathlessness, or coughing, following intake of alcoholic drinks?		Have you ever experienced symptoms from the skin such as a rash, itching, or swelling of the skin following intake of alcoholic drinks?	
	Prevalence % (n/n)	OR*	Prevalence % (n/n)	OR*	Prevalence % (n/n)	OR*
Asthma						
Yes	17.5 (83/473)	3.21 (2.44–4.22)	12.9 (61/473)	8.07 (5.60–11.63)	11.2 (53/473)	1.79 (1.30–2.45)
No	6.2 (224/3593)	1 (reference)	1.8 (66/3593)	1 (reference)	6.6 (237/3593)	1 (reference)
AR						
Yes	13.8 (160/1157)	3.01 (2.43–3.91)	6.4 (74/1,157)	3.59 (2.51–5.13)	10.6 (123/1157)	1.85 (1.45–2.36)
No	5.1 (148/2906)	1 (reference)	1.9 (56/2906)	1 (reference)	5.8 (170/2906)	1 (reference)

*OR (95% confidence intervals) adjusted for sex and age by logistic regression analyses.

AR, allergic rhinitis; OR, odds ratio.

Our results suggest that hypersensitivity symptoms are particularly common in asthmatics. The reasons for this are not known. A possible explanation could be that asthmatics have a generally increased bronchial hyper-reactivity that decreases the threshold of the bronchial response to non-specific exposures contained in alcoholic drinks. In line with this, we found that asthma was more strongly associated with alcohol-related symptoms of the lower airways as compared with alcohol-related symptoms from the skin.

Alcoholic drinks as triggers of lower airways' symptoms

To our knowledge, no previous study has assessed the prevalence of lower airway symptoms following intake of alcoholic drinks in a general population. In our Caucasian

population, alcohol-induced hypersensitivity was significantly more prevalent in persons with asthma. Further, persons reporting alcohol-induced hypersensitivity symptoms from more than one of the three localizations (from the upper airways, lower airways, and the skin) had an even higher prevalence of asthma and AR (Table 4). This finding indicates a dose-response relationship, i.e. the higher the level of alcohol-induced hypersensitivity, the greater the risk of asthma. It should, however, be acknowledged that this association could partly be due to increased awareness of respiratory symptoms among asthmatics.

The role of alcoholic drinks as triggers of asthma has been extensively studied among Asians where ALA is characteristic and quite common, affecting more than 50–60% of patients [11, 12]. In Asians, symptoms appear

Table 4. Prevalence of asthma and AR according to the number of hypersensitivity symptoms following intake of alcohol

Number of alcohol symptoms	Prevalence of AR % (n/n)	OR*	Prevalence of asthma % (n/n)	OR*
No symptoms	25.7 (900/3498)	1 (reference)	9.8 (344/3504)	1 (reference)
One symptom	40.5 (170/420)	1.95 (1.58–2.40)	17.8 (75/421)	2.02 (1.53–2.66)
Two symptoms	59.7 (74/124)	4.29 (2.96–6.21)	33.3 (40/120)	4.64 (3.11–6.91)
Three symptoms	61.9 (13/21)	5.22 (2.14–12.72)	66.7 (14/21)	17.45 (6.97–43.66)

*OR (95% confidence intervals) adjusted for sex and age by logistic regression analyses.

AR, allergic rhinitis; OR, odds ratio.

shortly following alcohol ingestion [27], and can be prevented by histamine receptor blockers [28–30]. In this setting, severe cases of ALA are rare [31]. In the United Kingdom, alcohol abuse was noted in 20% of cases of asthma deaths [32], which might indicate that alcohol contributes to the deterioration of asthma in this particular population.

Acetaldehyde, a metabolite of alcohol (ethanol), has been proved to be a cause of broncho constriction in the Japanese population [11]. The enzymatic activity of ALDH2 is genetically reduced in half of the Japanese subjects because of the presence of the ALDH2²/ALDH2² polymorphism (mutant homozygote: a complete deficient type) [33]. As a consequence of this deficiency and after alcohol ingestion, a significant increase in serum acetaldehyde occurs [9], which is shortly followed by histamine release from mast cells and basophils [34] and results in broncho constriction (objectively demonstrated by a concomitant decrease in lung function, forced expiratory volume in 1 s) [11]. Accordingly, inhalation of acetaldehyde itself, but not ethanol, caused broncho constriction in guinea-pigs, and this effect was completely prevented by pre-treatment with a histamine receptor antagonist [34], and *in vitro* studies of rat mast cells showed increased release of histamine in response to acetaldehyde [35]. Thus, subjects with the ALDH2²/ALDH2² polymorphism experience the disulfiram–alcohol reaction (flushing, nausea, tachycardia, and broncho constriction) after alcohol intake, which influences alcohol drinking behaviour and has a strong protective effect against alcoholism [36–39]. Interestingly, in Western populations where this polymorphism is almost non-existent, asthmatic attacks can follow alcohol intake in chronic alcoholics taking disulfiram to enforce abstinence [40]. Despite this, alcohol-induced lower airways symptoms are less spectacular in Caucasians. To the best of our knowledge, the possible role of acetaldehyde as a histamine-releasing factor has never been investigated in Caucasians but the high frequency of alcohol-related asthma symptoms reported in Australian [18] and British [19] asthmatics may support this hypothesis.

In Caucasian populations, certain non-alcoholic components of alcoholic beverages, such as biogenic amines

and the sulphite additives, have been associated with asthma symptoms [41, 42], but allergic sensitivities to other specific components are possible. Wine, particularly red wine, considered the most common trigger of alcoholic-induced bronchial symptoms [43], was also the most frequently reported alcoholic drink to cause symptoms in our study. The natural histamine content in wine has been proposed as the substance responsible for red wine-induced asthmatic reactions [44] but results from double-blind challenge tests did not support the hypothesis [45]. Kanny et al. observed an increase in plasma histamine after intake of histamine-poor wine, but surprisingly no increase after intake of histamine-rich wine. The authors concluded that substances other than the histamine content in wine are responsible for intolerance reactions to wine [45].

The effects of oral ethanol in both healthy and asthmatic patients have been studied and different results have been obtained depending on the time spent in drinking [46], and even a bronchodilator effect has been reported [15]. Ehlers et al. [17] obtained positive responses in 50% of patients with a history of hypersensitivity reactions after consumption of different alcoholic beverages after a double-blind, placebo-controlled challenge with 30 mL pure ethanol, pointing to ethanol itself, or one of its metabolites, as the provoking substance.

Finally, sulphite additives have been implicated in wine-induced asthmatic reactions [41, 42, 47], but only a small number of wine-sensitive asthmatic patients respond to sulphite challenge under laboratory conditions [48, 49], suggesting that cofactors or other components may be needed for the reaction to occur.

Alcoholic drinks as triggers of symptoms from the upper airways

In a population-based study in Sweden, a total of 3.4% reported rhinitis symptoms following intake of alcoholic drinks [43]. The prevalence estimate obtained in the Swedish study is clearly lower than that observed in the present study and this may be due to the two-stage study design of the Swedish study, i.e. in the first stage subjects with food-induced hypersensitivity symptoms

were selected for a second stage. In the second stage, they were asked about symptoms following intake of specific food items including alcoholic drinks. Thus, people who did not consider alcoholic beverages as food might not have been selected for the second stage. The same group of researchers performed a placebo-controlled challenge with red wine in 20 patients with a history of red wine-induced rhinitis and could confirm 11 out of 20 cases. They found that pre-treatment with antihistamines reduced rhinitis symptoms and nasal secretion following red wine challenge, indicating that histamine plays a pivotal role in the induction of these symptoms [50].

Alcoholic drinks as triggers of skin symptoms

To our knowledge, no other study has reported the prevalence of alcohol-induced skin symptoms in a general population. Cases and case series of urticarial and anaphylactoid reactions following ethanol intake have been reported [17, 51–54]. An ethanol challenge performed in a patient with ethanol-induced urticaria resulted in urticaria and an increase in plasma histamine. Biopsy of the ethanol-induced urticarial lesions showed evidence of mast cell degranulation [55]. In this patient, pre-treatment with antihistamines inhibited both skin response and histamine release. Urticarial reactions (or flushing) may also be seen as an effect of an interaction between alcohol and certain drugs, e.g. disulfiram, a potent inhibitor of ALDH. Flushing in Asians correlates with increased levels of acetaldehyde following alcohol intake [56]. Pre-treatment with antihistamines reduces flushing in patients with alcohol-induced flushing undergoing an ethanol challenge, emphasizing a key role of histamine in these reactions [57].

Conclusion

Hypersensitivity symptoms following intake of alcoholic drinks are frequently reported and are markedly more prevalent in persons with AR and asthma. All types of beverages are commonly reported as triggers of symptoms, suggesting that substances common to all types of alcoholic beverages are important to the development of these symptoms. We hypothesize that a possible histamine-releasing effect of acetaldehyde contributes to the development of alcohol-induced hypersensitivity symptoms. *In vitro* studies are needed to establish the different components in alcoholic drinks that could trigger reactions. Furthermore, a population-based study, utilizing double-blind placebo-controlled food challenges, is needed to establish the true prevalence of hypersensitivity after the consumption of alcoholic drinks.

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