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Association between alcohol consumption and aeroallergen sensitization in Danish adults

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Summary

Background It has been proposed that alcohol consumption may be one of the lifestyle factors associated with a westernized, urban, and affluent lifestyle contributing to the rise in atopic disease.

Objective The aim was to investigate the association between alcohol consumption and atopy (aeroallergen sensitization).

Methods In 1982, a population-based cross-sectional study of 3608 Danes (79% of the invited), aged 30, 40, 50, and 60 years, was carried out. Information on alcohol consumption was obtained by a questionnaire. Aeroallergen sensitization was defined as a positive test for the detection of specific IgE against a panel of 19 common inhalant allergens in stored serum samples. A total of 3317 subjects with complete information on all variables were included in the analyses.

Results We found a statistically significant association between alcohol consumption and aeroallergen sensitization (independent of the type of alcoholic drink consumed). This association appeared to relate only to those who consumed more than 8 drinks/week. After adjustment for confounders this association was only statistically significant for those who consumed 15–21 drinks/week (adjusted odds ratio 1.8, 95% confidence interval 1.2–2.8).

Conclusion In this adult general population, self-reported alcohol consumption was positively associated with aeroallergen sensitization.

Keywords aeroallergen sensitization, alcoholic beverages, alcohol drinking, IgE, respiratory hypersensitivity

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Introduction

It is becoming increasingly clear that aeroallergen sensitization has increased in adults over recent decades [1–4]. The specific factors responsible for these trends are not known. However, changes towards a westernized [5, 6], urban [7], and affluent [8] lifestyle appears to be followed by an increasing prevalence of aeroallergen sensitization and atopic diseases such as allergic rhinitis, asthma, and atopic dermatitis. Recent decades of research into the causes of this epidemic have to a large extent, been focusing on environmental factors such as exposure to allergens, microorganisms, and outdoor or indoor air pollution. However, the rapid change in the prevalence of atopic disease, as documented in some countries [1–4], may indicate that lifestyle factors play an important role

in the allergy epidemic. Indeed, significant changes in lifestyle have occurred in parallel to the rise in the prevalence of atopic disease. These include dietary factors, physical activity, obesity, and other components of the metabolic syndrome. One other factor that has increased dramatically in many countries, e.g. the United Kingdom [9] and Denmark [10], is the consumption of alcoholic drinks. Alcoholic drinks are well-known triggers of hypersensitivity reactions [11] and there is strong evidence that alcohol influences the immune system in several ways, e.g. alcohol increases total serum IgE [12, 13], 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 [14]. Less is known about the influence of alcohol on the atopic immune response, although

a few studies have linked alcohol consumption to IgE sensitization. Interestingly, alcohol during pregnancy has been linked to increased levels of total IgE in the cord-blood and the risk of early-onset atopic dermatitis in the off-spring [15, 16]. In spite of this, little attention has been paid to the effect of alcohol on the allergic immune response. We propose that alcohol consumption might be one of the lifestyle factors associated with a westernized, urban, and affluent lifestyle contributing to an increase in atopic disease [17, 18].

We aimed to investigate the association between alcohol consumption and the prevalence of aeroallergen sensitization in a Danish general population.

Methods

Participants

The WHO MONICA project was initiated in order to measure the trends and determinants in cardiovascular mortality and disease [19]. The project comprised 38 populations in 21 countries [20]. At each centre, three repeated cross-sectional studies (MONICA I, II, and III) were carried out in defined populations between 1982 and 1995. The present study was based on the Danish MONICA I study of the WHO MONICA project [21, 22]. In October 1982, an age- and sex-stratified random sample of 4807 men and women, born in 1922, 1932, 1942, and 1952 (age 30, 40, 50 and 60 years), residing in 11 municipalities in the western part of Copenhagen County, was drawn from the National Danish Civil Registration System, in which all people living in Denmark are registered by a unique 10-digit number. All sample members received a standard letter containing information about the project and were invited to a general health examination. Enclosed was a questionnaire concerning medical history and health and lifestyle to be completed in advance. Repeated requests were made in cases of non-response. From the total sample of 4807 subjects, 226, who were not of Danish origin were excluded. Between November 1982 and February 1984, 3608 persons (78.8% of the invited) were examined. Blood samples were drawn, serum separated, and stored at -20°C pending analysis. There was a slight overrepresentation of tobacco smokers and people with a short duration of schooling and a low social status in the non-responder group as compared with the responder group. Subjects with complete information on all variables including measurement of specific IgE in the serum were included in subsequent analyses ($n = 3317$). No available serum sample was the most common reason for exclusion ($n = 289$).

The MONICA I study was approved by the Ethical Committee for Copenhagen County. In 2002, the present study, including measurement of specific IgE in serum samples that had been kept in our biobank was approved

by the Ethical Committee for Copenhagen County (KA 02136).

Measurement of aeroallergen sensitization

Serum samples were analysed consecutively in 2004. Measurement of aeroallergen sensitization was performed by using the ADVIA Centaur[®] Allergy Screen (AS) assay (Bayer HealthCare Diagnostics division, Tarrytown, NY, USA) [23, 24]. The AS assay is a multi-allergen assay for the qualitative detection of specific IgE antibodies specific to common inhalant allergens in the serum. The test encompasses the 19 most commonly encountered inhalant allergens: Two house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*), three animal danders (horse, cat, and dog), two grasses (*Phleum pratense* and *Cynodon dactylon*), three moulds (*Cladosporium herbarium*, *Aspergillus fumigatus*, and *Alternaria alternata*), four trees (*Betula verucosa*, *Quercus alba*, *Olea europae*, and *Cryptomeria japonica*), four weeds (*Amrosia artemisifolia*, *Artemisia vulgaris*, *Plantago lanceolata*, and *Parietaria officinalis*), and finally one insect (*Blattella germanica*). Aeroallergen sensitization was defined as a positive result of the dichotomized AS assay test output. The diagnostic efficacy of the AS assay has been evaluated in another population-based study in our background population [24]. The AS assay proved to be a valid objective measure of allergic respiratory disease as reflected by skin prick test (SPT) reactivity and a clinical diagnosis of allergic respiratory disease.

Assessment of alcohol consumption

The participants were asked about their average weekly consumption of beer (bottles), wine (glasses), and spirits (standard drinks), respectively, during the last 12 months ('During the last 12 months, how many of the following have you been drinking on average per week? Number of beers per week? Number of glasses of wine per week? Number of glasses/units of spirits per week?'). It was assumed that one bottle of beer, one glass of wine, and one serving of spirits contain approximately 12 g/1.5 cL ethanol. The total weekly alcohol consumption was calculated by adding the intake of beer, wine, and spirits. In the statistical analyses, total alcohol consumption was categorized by using cut-offs adopted from another population-based study in Copenhagen, Denmark [25].

Validation of questionnaire on alcohol consumption

The questions used for assessment of alcohol consumption were validated against increased levels (≥ 80 IU/L) of serum γ -glutamyl transferase (GGT), a marker of alcohol exposure [26], in another study in our background population. A cohort of 579 men born in 1936 and living in

four municipalities in the western part of Copenhagen, Denmark, were followed since 1976 [27]. In 1987, this population was re-examined at the age of 51 years ($n = 439$) [28]. Questions on alcohol consumption were identical to the ones used in the MONICA I study as described above. GGT was measured by a routine method at the Glostrup University Hospital. The results showed that self-reported total alcohol intake (total number of drinks/week) was significantly and positively associated with increased levels of GGT (Table 1).

Statistical analyses

The association between alcohol consumption and aeroallergen sensitization was analysed by logistic regression models and expressed as odd ratios with 95% confidence intervals (CIs). Odds ratios were adjusted for the following potential confounders: sex, age (30, 40, 50, or 60 years), body mass index in quartiles, smoking status (never smoker, ex-smoker, 1–14, 15–24, ≥ 25 g daily) (1 g of tobacco assumed to be equivalent of one cigarette), and vocational training (yes/no).

In a multiplicative model, the following interaction terms were tested by using the Wald test: alcohol $\times$ gender, alcohol $\times$ age, alcohol $\times$ smoking, and alcohol $\times$ vocational training. The statistical significance of interaction terms was tested in a model with all explanatory variables (only one interaction term in each model). The trend test was performed by including the categorical variable (alcohol consumption) as a trend (continuous) variable in the model. The P -value reflects the Wald test for this variable.

The question of differential influences of alcoholic beverage types on aeroallergen sensitization was examined in two ways: (1) estimating the effect of substituting the intake of one type of beverage by an equivalent intake of one of the other for constant total alcohol intake, by including the total alcohol intake and the intake of one

specific type of beverage [29], and (2) estimating the effect of intake of one type of beverage in an analysis where persons who reported to drink the two other types of beverages were excluded. These analyses were also performed with different (lower) cut-offs for the definition of alcohol categories due to the lower amounts of alcohol

Table 2. Characteristics of participants ($n = 3317$)

	% (n)	Median number of drinks/week (all types)
Aeroallergen sensitization		
Yes	16.8 (557)	6
No	83.2 (2760)	5
Alcohol consumption (drinks/week)		
0	13.2 (437)	0
1–7	48.4 (1606)	4
8–14	18.6 (617)	10
15–21	8.7 (287)	17
≥ 22	11.2 (370)	30
Beer consumption (drinks/week)		
0	30.0 (995)	1
1–3	34.7 (1152)	4
4–7	16.3 (542)	9
≥ 8	18.9 (628)	21
Wine consumption (drinks/week)		
0	32.0 (1061)	1
1–3	43.9 (1457)	5
4–7	16.3 (541)	11
≥ 8	7.8 (258)	20
Spirits consumption (drinks/week)		
0	54.5 (1809)	3
1–3	34.4 (1140)	7
4–7	8.4 (279)	15
≥ 8	2.7 (89)	26
Sex		
Male	50.5 (1674)	9
Female	49.5 (1643)	3
Age		
30 years	26.9 (892)	5
40 years	26.5 (880)	6
50 years	23.3 (774)	6
60 years	23.2 (771)	4
Body mass index in quartiles		
< 21.79	25.0 (828)	4
21.79–24.05	25.0 (829)	6
24.05–26.64	25.0 (830)	6
> 26.64	25.0 (830)	6
Smoking		
Never smoker	25.1 (831)	4
Ex-smoker	18.7 (620)	6
1–14 g/day	25.5 (847)	5
15–24 g/day	25.0 (830)	7
≥ 25 g/day	5.7 (189)	13
Vocational training		
Yes	71.0 (2356)	6
No	29.0 (961)	4

Table 1. Association between alcohol consumption reported by questionnaire and increased levels (≥ 80 IU/L) of serum γ -glutamyl transferase (GGT) in 51-year-old men ($n = 439$)

Alcohol consumption (drinks/week)	Prevalence of increased levels of GGT	Crude OR	Adjusted OR*
0	8.7% (2/23)	2.65 (0.48–14.53)	2.23 (0.39–12.64)
1–7	3.5% (5/144)	1.00, $P < 0.001^\dagger$	1.00, $P < 0.001^\dagger$
8–14	7.2% (8/111)	2.16 (0.69–6.79)	2.10 (0.66–6.69)
15–21	10.7% (6/56)	3.34 (0.98–11.41)	3.41 (0.99–11.81)
≥ 22	30.5% (32/105)	12.19 (4.56–32.61)	9.93 (3.65–27.03)

*Adjusted for smoking, serum cholesterol, and body mass index.

$^\dagger P$ -value for the Wald test.

OR, odds ratio (95% confidence intervals).

Table 3. Association between alcohol consumption and aeroallergen sensitization

	Prevalence of sensitization % (n)	Crude OR	Adjusted OR*	Adjusted OR†
Alcohol consumption (drinks/week)				
0	12.6 (55)	1.00, $P = 0.001^{\ddagger}$	1.00, $P = 0.048^{\ddagger}$	1.00, $P = 0.039^{\ddagger}$
1–7	16.0 (257)	1.32 (0.97–1.81)	1.13 (0.82–1.56)	1.11 (0.81–1.53)
8–14	17.5 (108)	1.47 (1.04–2.09)	1.22 (0.85–1.76)	1.20 (0.83–1.73)
15–21	23.7 (68)	2.16 (1.46–3.19)	1.83 (1.21–2.76)	1.83 (1.21–2.78)
≥ 22	18.6 (69)	1.59 (1.08–2.34)	1.24 (0.82–1.88)	1.25 (0.83–1.91)

*Odds ratio adjusted for sex and age.

†Odds ratio adjusted for sex, age, body mass index in quartiles, smoking, and vocational training (yes/no).

‡Test for trend.

OR, odds ratio (95% confidence intervals).

consumed of each type. Data were analysed with SPSS version 12.0.

Results

The characteristics of participants are shown in Table 2. There was a statistically significant association between alcohol consumption and aeroallergen sensitization (Table 3). Thus, the prevalence of aeroallergen sensitization was significantly higher among persons consuming 8–14, 15–21, and ≥ 22 drinks/week as compared with abstainers, although only the association with 15–21 drinks/week remained statistically significant after adjustment for all confounders considered. Further adjustment for social group and educational level did not alter the estimates for the effect of alcohol (data not shown). A significant test for trend was observed in all regression models, indicating a dose-response relationship. Of note is that the largest change in the estimates for the effect of alcohol consumption on the prevalence of aeroallergen sensitization was seen when age and gender were added to the regression model, indicating that age and gender were potential confounders (Table 3). In line with this, the consumption of alcohol was significantly higher among men than among women (Table 2). Interestingly, the effect of gender in the full model adjusted for all variables (odds ratio 1.19%, 95% CI: 0.96–1.48) increased when alcohol consumption was removed from this regression model (odds ratio 1.29%, 95% CI: 1.05–1.57), thereby reaching statistical significance.

None of the interactions examined were found to be statistically significant: alcohol × gender ($P = 0.171$), alcohol × age ($P = 0.232$), alcohol × smoking ($P = 0.390$), and alcohol × vocational training ($P = 0.621$).

There was no statistically significant effect of substituting the intake of one type of beverage by an equivalent intake of one of the other for constant total alcohol intake (data not shown). On examining the effect of type of beverage in models among persons who only drank one specific type of beverage, it showed that all three types of

beverages tended to be positively associated with aeroallergen sensitization, although this was only statistically significant for wine (Tables 4a–c).

Discussion

We found a statistically significant association between alcohol consumption and aeroallergen sensitization. This association appeared to relate only to those who consumed more than 8 drinks/week. However, after adjustment for confounders, this association was only statistically significant for those who consumed 15–21 drinks/week. Of note is that the effect of alcohol consumption on the prevalence of aeroallergen sensitization appeared to be independent of the type of beverage consumed, suggesting that ethanol itself may be the substance responsible for the observed association.

Several limitations should be considered in the interpretation of the results. First, misclassification of alcohol consumption is a potential problem. Self-reported intake of alcoholic drinks by questionnaire or interview remains the cornerstone of epidemiological studies of health effects caused by alcohol. At present, there is no generally accepted objective marker of alcohol exposure. However, in another study in our background population, the same questions as those used for assessment of alcohol consumption in the present study showed a statistically significant association with increased levels of GGT, a well-known marker of alcohol exposure [26]. At the time of the study, the hypothesis of the present article and the decision to analyse IgE antibodies in serum samples were not known to either study participants or the researchers responsible for the conduct of the study. Therefore, we have no reason to believe that any potential misclassification of alcohol exposure should be related to the outcome (IgE antibodies in serum), e.g. persons with aeroallergen sensitization would tend to overestimate their alcohol intake. Thus, assuming that any misclassification of alcohol consumption was non-differential, this would tend to underestimate an association, if present, between

Table 4a. Association between wine consumption and aeroallergen sensitization among persons who do not drink beer or spirits ($n = 784$)

Wine (drinks/week)	% (n)	Crude OR	Adjusted OR*
0	12.6 (55)	1.00	1.00
1–3	17.2 (41)	1.45 (0.93–2.24)	1.32 (0.83–2.07)
4–7	24.7 (18)	2.27 (1.24–4.15)	2.21 (1.17–4.15)
≥8	19.4 (7)	1.68 (0.70–4.01)	1.47 (0.58–3.69)

*Adjusted for sex, age, smoking, body mass index, and vocational training.

OR, odds ratio (95% confidence intervals).

Table 4b. Association between beer consumption and aeroallergen sensitization among persons who do not drink wine or spirits ($n = 830$)

Beer (drinks/week)	% (n)	Crude OR	Adjusted OR*
0	12.6 (55)	1.00	1.00
1–3	15.3 (27)	1.26 (0.77–2.07)	0.94 (0.54–1.61)
4–7	19.5 (16)	1.68 (0.91–3.11)	1.41 (0.71–2.77)
≥8	23.0 (31)	2.07 (1.273.38)	1.62 (0.88–2.99)

*Adjusted for sex, age, smoking, body mass index, and vocational training.

OR, odds ratio (95% confidence intervals).

Table 4c. Association between spirits consumption and aeroallergen sensitization among persons who do not drink wine or beer ($n = 495$)

Spirits (drinks/week)	% (n)	Crude OR	Adjusted OR*
0	12.6 (55)	1.00	1.00
≥1	13.8 (8)	1.11 (0.50–2.47)	1.36 (0.57–3.29)

*Adjusted for sex, age, smoking, body mass index, and vocational training.

OR, odds ratio (95% confidence intervals).

alcohol and aeroallergen sensitization. Second, it is difficult from cross-sectional data to determine whether alcohol consumption increases the risk of aeroallergen sensitization, or conversely, whether atopics tend to drink more alcohol. As alcohol is a well-known trigger of hypersensitivity reactions such as asthma [11], rhinitis [30], and urticarial reactions [31], in particular in atopic persons, it seems unlikely that atopic persons would tend to drink more alcohol on the basis of their atopic condition. As these alcohol-induced reactions are more common among atopics, it is conceivable that the positive association between alcohol consumption and aeroallergen sensitization as assessed from these cross-sectional data might have been underestimated rather than overestimated. However, it should be acknowledged that in some asthmatics ethanol might have a bronchodilating effect [32, 33].

Third, the positive association between aeroallergen sensitization and alcohol consumption may be due to some other underlying factors (confounders). The finding that some of the effects of alcohol consumption appeared

to be explained by gender lends some support to this interpretation. However, the effect of alcohol was apparent both among men and women, and in all age groups (data not shown). One interesting observation was that the effect of gender on the prevalence of aeroallergen sensitization attenuated when alcohol consumption was included in the regression model, indicating that gender differences in alcohol intake might contribute to gender differences in the prevalence of sensitization.

Fourth, the validity of the method used for the measurement of aeroallergen sensitization should be considered. As reported previously, a positive AS Assay test has been shown to be a valid measure of allergic respiratory disease and SPT reactivity against inhalant allergens [24]. In addition, the stability of specific IgE in serum samples stored at -20°C in our biobank has previously been confirmed [34].

To date, two other population-based studies, one from Denmark and one from Spain, have reported data on the association between alcohol consumption and sensitization. The Danish study found a positive cross-sectional association between alcohol consumption and the prevalence of sensitization as reflected by SPT reactivity and specific IgE positivity against inhalant allergens [35]. An 8-year follow-up of the same population confirmed a positive association (although only of borderline statistical significance) between alcohol consumption and the development (incidence) of SPT reactivity, but not specific IgE positivity [18]. The Spanish study found that alcohol consumption was positively associated with pollen sensitization, but not with mite or overall sensitization, as measured by SPT reactivity [36]. Another Spanish study in consecutive patients in an allergy clinic found that *D. pteronyssinus*-specific serum IgE levels were higher in habitual alcohol consumers than in abstainers, but again this was not the case for overall sensitization [37]. Thus, there are limited epidemiological data (and only data from one prospective study) on this issue.

As reviewed by Gonzalez-Qunitela et al. [12, 13], there is relatively strong evidence that alcohol intake increases total serum IgE. Firstly, alcohol consumption has consistently been associated with increased levels of total serum IgE in different populations such as alcoholics [38–43], other patient populations [37, 44], and general populations [18, 36]. This effect appears to be independent of other factors, e.g. gender and smoking, that may influence levels of total serum IgE [44–49]. Secondly, the effect appears to be dose–response dependent. Thirdly, the effect is transient, and the increase in total serum IgE observed in alcoholics decreases within weeks following alcohol abstinence. Fourthly, alcohol during pregnancy is associated with increased levels of total IgE in the cord blood of the offspring [15]. Interestingly, results from another birth cohort showed that alcohol during pregnancy was positively associated with early-onset atopic dermatitis in

the offspring [16]. Finally, an increase in total serum IgE can be demonstrated in ethanol-fed mice [50]. Several observations support that the effect of alcoholic drinks on levels of total serum IgE is due to ethanol itself, or one of its metabolites, and not due to other substances such as preservatives or the natural content of histamine in certain wines, as the effect appears to be independent of the type of beverage [12, 13], and an increase in total serum IgE can be induced by ethanol in experimental animal studies [50].

It is well known that alcohol impairs the T-helper type 1 lymphocyte-regulated cell-mediated immune response leading to increased susceptibility to viral and bacterial infections such as infections of the lower respiratory tract (e.g. pneumococcal pneumonia and tuberculosis) [14] and superficial infections of the skin [51]. It has been reported that alcoholics admitted to hospital with alcohol abstinence syndrome have increased levels of some T-helper type 2 lymphocyte-related cytokines as compared with healthy controls [43]. In contrast, Dominiguez-Santalla et al. [42] reported a T-helper type 1 lymphocyte dominance in alcoholics, as estimated by the ratio of IL-4 to IFN- γ production by stimulated blood mononuclear cells, as compared with healthy controls. Experimental studies in animals have shown that alcohol impairs the T-helper type 1 lymphocyte regulated cell-mediated immune response, thereby possibly favouring a T-helper type 2 lymphocyte deviation of the immune response [50, 52–55]. IL-12 administration has been shown to be able to restore the cell-mediated immune response in ethanol-fed mice [56]. In humans, it has been shown that alcohol consumption decreases the risk of developing a delayed-type hypersensitivity skin test response, supporting a negative effect of alcohol on the cellular immune response [57].

In vitro studies have shown that acetaldehyde (a metabolite of ethanol), but not ethanol, induces histamine release from mast cells of Japanese asthmatics [58]. To the best of our knowledge, this has not been studied in Caucasians. *In vitro* studies of rat mast cells support that acetaldehyde induces histamine release [59]. In contrast, *in vitro*, ethanol does not increase histamine release from rat mast cells [60, 61]. Further, *in vitro*, ethanol has been shown to decrease IgE-induced degranulation and cytokine production (IL-8 and TNF- α) of human mast cells, but the effect of acetaldehyde was not studied [62]. Thus, a possible acetaldehyde-induced release of histamine and other mast cell immune mediators would potentially explain the above-described alcohol-induced T-helper type 2 deviation of the immune system.

In conclusion, we found a positive association between self-reported alcohol intake and aeroallergen sensitization in this adult general population. Still, there are limited data on this issue. Longitudinal data are of particular interest, as it is possible that atopic conditions may have

an influence on alcohol-drinking behaviour, which may result in biased exposure–disease associations in cross-sectional studies. In the present study, we did not find a clear linear dose–response relationship. Many researchers have suggested that the observed non-linear (J- or U-shaped) relationship between alcohol consumption and cardiovascular disease reflects a protective effect of a moderate intake of alcoholic drinks, in particular wine, against cardiovascular disease. However, other interpretations are possible, e.g. reporting bias or confounding. We propose that it is possible that a gene–environment (lifestyle) interaction could also play a role. Thus, genetic variations in the genes encoding for enzymes involved in the metabolism of ethanol and acetaldehyde may influence both drinking behaviour and susceptibility to the effects of alcoholic drinks on the immune system and hypersensitivity reactions. In an epidemiological setting, such phenomena would potentially result in a non-linear dose–response relationship. Finally, the biological mechanisms and the clinical significance of the possible effects of alcohol on the atopic immune response are not known.

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