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The relationship of alcohol consumption to total immunoglobulin E and the development of immunoglobulin E sensitization: the Copenhagen Allergy Study

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Summary

Background Several studies in patient populations have reported a positive association between alcohol consumption and serum total IgE. Furthermore, we have previously reported a positive association between alcohol consumption and the prevalence of skin prick test (SPT positivity) to inhalant allergens in a population-based cross-sectional study.

Objective To investigate the relationship of alcohol consumption to levels of serum total IgE and the development of IgE sensitization to inhalant allergens.

Methods In 1990, self-reported consumption of alcohol, serum total IgE, SPT positivity and specific IgE positivity to inhalant allergens were assessed in 1112 subjects, aged 15–69 years, participating in a population-based cross-sectional study in Copenhagen, Denmark. In 1998, they were invited to a follow-up and 734 were re-examined (participation rate 69.0%). Adjustment for potential confounders was performed by using multivariable regression analyses.

Results In non-atopic (specific IgE negative) subjects there was a positive association between alcohol consumption and the concentration of total IgE ($P = 0.001$). During the follow-up period, 45 and 33 subjects developed SPT positivity and specific IgE positivity, respectively. There was no significant association between alcohol consumption and the development of SPT positivity or specific IgE positivity. However, the risk of developing SPT positivity tended to increase with increasing consumption of alcohol ($P = 0.055$).

Conclusions This epidemiological study confirms that alcohol consumption has an influence on levels of serum total IgE. A significant association between alcohol consumption and the development of IgE sensitization was not established. However, there seems to be a lack epidemiological data on this issue.

Keywords alcohol, epidemiology, respiratory hypersensitivity, skin prick test, specific IgE, total IgE

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Introduction

The prevalence of IgE-mediated allergic respiratory disease is increasing in many countries [1] as well as in Denmark [2]. This increase is likely to be caused by recent changes in lifestyle or environmental factors associated with western lifestyle. However, these factors have not yet been fully elucidated. Alcohol consumption could be a factor of potential interest, as an increasing consumption of alcohol and changing drinking patterns among adolescents has been reported in many countries [3], including Denmark [4].

In a previously reported analysis of a cross-sectional study in 1990 we found a somewhat unexpected positive association between alcohol consumption and the prevalence of skin prick test (SPT) positivity to inhalant allergens [5]. However, it is difficult to assess from cross-sectional data the temporal relationship between potential risk factors and the development of disease. A follow-up of the above population was undertaken in 1998. We therefore had the opportunity to investigate the association between alcohol consumption and the development (incidence) of IgE sensitization over an 8-year period.

IgE antibodies play a central role in allergic respiratory disease, which is strongly associated with increased levels of serum total IgE. Nevertheless, other factors such as sex and smoking may have an influence on levels of serum total IgE [6–11]. Alcohol consumption may be an additional factor, which may have an influence on serum total IgE. Thus, studies in alcoholics [12–17] and other patient populations [6, 18] have reported a positive association between alcohol consumption and serum total IgE. To our knowledge, there is no previous report on this relationship in a population-based study.

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The aim of this study was to investigate the relationship of alcohol consumption to levels of serum total IgE and the development of IgE sensitization to inhalant allergens.

Methods

Baseline study

The baseline study was conducted according to a two-stage protocol. In the first stage a screening questionnaire on respiratory symptoms was mailed in November 1989 to a sample of 15–69-year-olds ($n = 8000$), living in the western part of Copenhagen, the capital of Denmark. The total population living in this area consisted of 324 931 subjects, which was 54% of Copenhagen County. The representiveness of the sampling area has been assessed by comparing inhabitants in the sampling area, in Copenhagen County and in all of Denmark using data from the National Statistics [19]. The sampling area was representative of the total Danish population as regards the age and sex distribution and marital status. Regarding industrial categories and employment status, farming and fishing were under-represented in the sampling area, and there were fewer self-employed individuals. The sample was drawn randomly from the civil registration system. A total of 6998 or 87.5% responded to the screening questionnaire. In the second stage, a random group and a symptom group selected among the respondents were invited to a health examination. The symptom group comprised all respondents ($n = 788$) who had reported rhinitis symptoms (itchy or stuffy nose or sneezing) or shortness of breath on exposure to either pollen or furry animals in the screening questionnaire. The random group comprised 647 subjects who were randomly selected from the remaining respondents.

Subsequently, 635 (participation rate 80.6%) and 477 (participation rate 73.7%) subjects were examined in the symptom and the random groups, respectively. Thus, a total of 1112 subjects (overall participation rate 77.5%) were examined. Examinations took place between February 1990 and January 1991. The invitational procedure and characteristics of both participants and non-participants have previously been described in more detail [20].

Follow-up study

At the time of follow-up, 28 subjects had died, eight had emigrated and 12 could not be located. Thus, a total of 1064 of the participants in the baseline study were invited to the follow-up study; 734 subjects were examined (participation rate 69.0%). We invited eligible subjects in the same month as they had been examined in the baseline study to avoid potential seasonal differences. Hence, a total of 63.9% (469/734) of the participants in the follow-up study were examined on a date within 2 months (62 days) of the date of examination in the baseline study. The median follow-up time was 7 years 10 months (range: 6 years and 10 months to 8 years and 8 months). The participants were examined between October 1997 and November 1998. The study was approved by the ethics committee of Copenhagen County.

Specific IgE measurements

In both the baseline and the follow-up study, venous blood was taken on the day of examination, and the blood samples were left to coagulate for 2 h. The serum was then separated by centrifugation at 3000 ***g*** for 10 min and frozen immediately afterward. The serum samples used for specific IgE analysis were kept at $-20\,^{\circ}C$ without thawing until the analysis in 1999. Serum samples were available for analysis from 98.7% (1098/1112) and 99.5% (730/734) of the subjects examined at baseline and follow-up, respectively. The serum samples were analysed for specific IgE to birch, grass (timothy), mugwort, dog, cat and house-dust mite (*Dermatophagoides pteronyssinus*) with the ADVIA® Centaur™ specific IgE assay system (Bayer Corporation) [2]. The stability of specific IgE in serum samples stored at $-20\,^{\circ}C$ has previously been confirmed [2]. The analysis for specific IgE was judged to be positive if the measurement was in excess of 0.35 kU/L. Specific IgE positivity was defined as a positive test for specific IgE to one or more of six allergens.

Total IgE measurements

Serum total IgE was measured at baseline. Serum samples obtained in the baseline study were analysed for total IgE in 1991 by using the Pharmacia CAP System (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). Analyses were performed in samples from 99.2% (1103/1112) of the participants.

Skin prick testing

All subjects participating in the follow-up study had skin prick tests performed both at the baseline and the follow-up study. The Phazet® system (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) was used for the SPTs in the baseline study. The Phazet system was not available in 1997, and the Soluprick SQ® system (ALK Abelló, Hørsholm, Denmark) was used in the follow-up study. Both methods used lancets and standardized allergen extracts (100 000 BU for Phazet and 10 HEP for Soluprick). The allergen extracts and the positive control were in a dried form on the tip of the Phazet lancets, and in a liquid form for the Soluprick SQ system. The Phazet and the Soluprick SPT systems previously have been compared, and the Phazet system tended to induce a slightly higher overall number of positive reactions [21]. The panel of allergens comprised birch, grass (timothy), mugwort, horse, cat, dog, two species of house-dust mites (*D. pteronyssinus* and *D. farinae*) and two moulds (*Cladosporium* and *Alternaria*). A negative control and a positive control (10 mg/mL histamine in both studies) were included.

The test sites were placed at intervals of 20 mm on the volar side of the forearm in a straight line from approximately 5 cm below the elbow flexure to about 10 cm above the wrist. The skin reactions were read after 15 min by drawing the perimeter of the weal with a fine-point, felt-tip pen, and transferred to the data collection sheet. The largest and the smallest diameters (at the widest point and at the perpendicular bisector) of the weals were measured with a transparent ruler. The participants were asked to abstain from antihistamines for 72 h (astemizole 8 weeks) before the examination. The same technician performed all SPTs in both the baseline and the follow-up study. The reproducibility of the SPT in the hands of the technician was established by performing two histamine SPTs on 20 volunteers. The coefficient of variation was 0.14 and 0.10 in 1990 and 1998, respectively. SPT positivity was defined as a positive SPT (allergen mean weal diameter ≥ 3 mm) to one or more of 10 allergens.

Definition of variables

Three age groups were defined (15–34 years, 35–49 years and 50–69 years) based on the age of the participants at the time of the baseline study. Information on health, lifestyle and socioeconomic variables was obtained at baseline in a detailed questionnaire, which was completed at home. Thus, consumption of alcohol was recorded at baseline. The participants were asked about their consumption of beer (bottles), wine (glasses) and spirits (units), respectively, per week on average 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?'). One bottle of Danish beer contains 12 g of alcohol, which was considered the average for the other types of drinks. A test of the reliability of self-reported alcohol intake using these questions previously conducted in our background population showed consistency with self-reported alcohol intake and the alcohol intake information obtained by a diet interview, just as reporting bias between types of alcoholic beverages seemed to cause only minor problems [22].

Alcohol consumption was defined as the total number of drinks per week (beer, wine and spirits) on average during the last 12 months (0, 1–2, 3–4, 5–10, ≥ 11, coded as 0, 1.5, 3.5, 7.5, 14.0 when used as trend variable). Furthermore, the following variables were defined: atopic status (specific IgE positivity, 'yes'/'no'), group (random group/symptom group), and smoking status ('never smoker'/'past smoker'/'current smoker').

Statistical analysis

The relationship between alcohol consumption and concentrations of total IgE was analysed by using multivariable linear regression analysis. Total IgE was logaritmized to obtain normal distribution. Sex, age, smoking status, atopic status and group were included in the model. Potential first order interactions between these variables and alcohol consumption were investigated.

The chi-square test or the Mann–Whitney *U*-test evaluated differences in baseline characteristics between participants and non-participants in the follow-up study. Odds ratios and 95% confidence intervals expressed the association between alcohol consumption and the development of SPT positivity (SPT negative at baseline and SPT positive at follow-up). Thus, subjects who were SPT positive at baseline were excluded from this analysis. The odds ratios were adjusted for sex, age, smoking status and group, by using multivariable logistic regression analysis. Potential first order interactions between alcohol consumption and sex, age, smoking status and group were investigated. The association between alcohol consumption and the development of specific IgE positivity was analysed accordingly.

Data were analysed with the SPSS for windows (Release 10.0) and SAS (Release 8.01).

Results

Alcohol and total IgE

The effect of alcohol consumption on levels of total IgE was significantly dependent on atopic status (test for interaction: $P < 0.01$). Therefore, the estimated effect of alcohol consumption is presented separately for non-atopic (specific IgE negative) and atopic (specific IgE positive) subjects (Table 1). It appears that in non-atopic subjects alcohol consumption was positively associated with total IgE, while in atopic subjects alcohol consumption was negatively associated with total IgE. It was noted that among non-atopic subjects there was no significant association between sex and total IgE ($P = 0.295$). However, when excluding alcohol consumption from the model, the association between sex and total IgE gained statistical significance ($P = 0.014$), indicating that alcohol consumption explained some of the effect of sex. The reported alcohol intake was significantly (Mann–Whitney *U*-test: $P < 0.001$) higher among men (median 6, range 0–196 drinks per week) as compared with women (median 3, range 0–56 drinks per week).

The effect of alcohol consumption on levels of total IgE did not appear to be dependent on the type of beverage (beer, wine or spirits) (data not shown).

A regression model with sex, age, group, smoking status, alcohol consumption, atopic status and an interaction term between alcohol consumption and atopic status explained 27% of the variation in log total IgE. In this model, males had higher levels of log total IgE than females (coefficient 0.25, 95% CI 0.08–0.43), and current smokers had higher levels of log total IgE than never-smokers (coefficient 0.33, 95% CI 0.14–0.52). Male sex and smoking have also been reported to be associated with increased levels of total IgE in other studies [6–11].

The estimated adjusted mean levels of log total IgE by consumption of alcohol in non-atopic and atopic subjects are shown in Figs 1 and 2, respectively.

Table 1. Multivariate linear regression analysis of the influence of alcohol consumption on logaritmized serum total IgE concentrations (the dependent variable) among non-atopic (specific IgE negative) and atopic (specific IgE positive) subjects

Alcohol consumption (per week)	Non-atopic subjects (n = 700)				Atopic subjects (n = 398)			
	Coefficient*	Lower CL	Upper CL	Overall *P*-value	Coefficient*	Lower CL	Upper CL	Overall *P*-value
0 drinks	0 (reference)			0.001	0 (reference)			0.035
1–2	−0.29	−0.64	0.06		−0.38	−0.87	0.10	
3–4	−0.03	−0.38	0.31		−0.71	−1.19	−0.23	
5–10	0.00	−0.33	0.34		−0.68	−1.17	−0.20	
≥ 11	0.46	0.10	0.83		−0.56	−1.08	−0.05	

*Estimates are adjusted for sex, age, smoking status and group. CL = confidence limit.

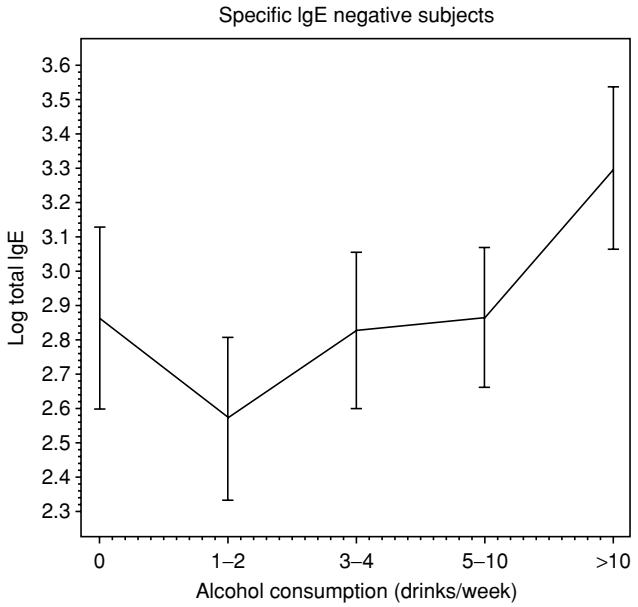

Fig. 1. Estimated mean levels of log serum total IgE with 95% confidence intervals by alcohol consumption among specific IgE negative subjects. Estimated mean levels are obtained in a multivariate linear regression model including the following variables: sex, age, group and smoking status.

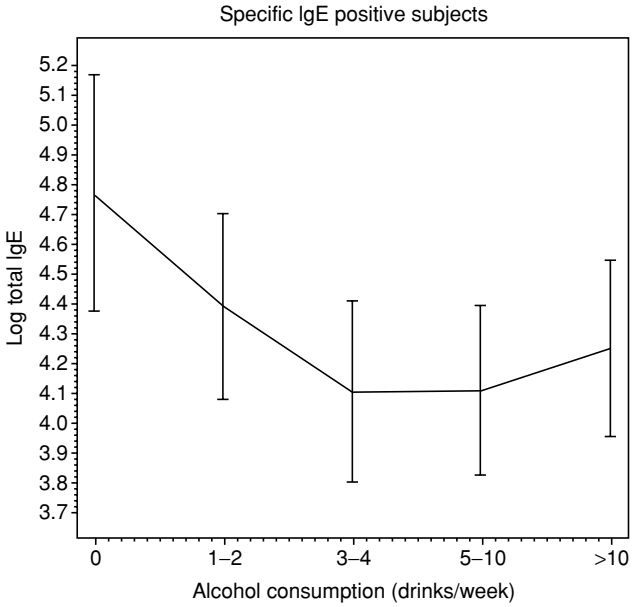

Fig. 2. Estimated mean levels of log serum total IgE with 95% confidence intervals by alcohol consumption among specific IgE positive subjects. Estimated mean levels are obtained in a multivariate linear regression model including the following variables: sex, age, group and smoking status.

Alcohol and incidence of IgE sensitization

Table 2 shows the distribution of baseline characteristics among participants and non-participants in the follow-up. Male sex and a high educational level at baseline were significantly associated with participation in the follow-up study. No other significant differences in baseline characteristics between participants and non-participants were observed.

During the follow-up period, 45 and 33 subjects developed SPT positivity and specific IgE positivity, respectively. A total of 15 subjects were both among those who developed incident SPT positivity and those who developed incident-specific IgE positivity. The relationship between alcohol consumption and the incidence of SPT positivity is shown in Table 3. The risk of developing SPT positivity tended to increase with increasing consumption of alcohol, but this trend was not statistically significant (test for trend: $P = 0.055$). A similar trend was not seen for the association between alcohol consumption and the incidence of specific IgE positivity, which was considerably lower than the incidence of SPT positivity (Table 4). This lack of trend for specific IgE positivity might be linked to the finding that the association between alcohol consumption and total IgE was not seen in atopic individuals.

Discussion

We found a significant positive association between alcohol consumption and levels of total IgE in non-atopic subjects. There was no statistically significant association between alcohol consumption and the development of IgE sensitization, although the risk of developing SPT posivity tended to increase with increasing consumption of alcohol.

Several studies have reported that total IgE is increased in alcoholics as compared with healthy controls [12–17]. One study by Vidal et al. in patients in an allergy clinic showed that total IgE is increased in patients with a low or moderate alcohol intake compared with patients who were abstainers [18]. This association appeared to be more pronounced in non-atopic patients compared with atopic patients. They speculated that this could be due to the fact that atopy *per se* is a much stronger determinant of IgE increases, and thus atopy may overshadow the influence of alcohol consumption. Our results appear to be in accordance with this interpretation, as total IgE increased with increasing consumption of alcohol in non-atopic persons only. Criqui et al. also found a positive association between alcohol consumption and serum total IgE in patients who were observed in a lipid research clinic protocol [6]. Interestingly, alcohol consumption appeared to explain some of the difference in levels of total IgE between males and females among non-atopic subjects in our study population.

It could be of interest, that alcohol consumption by mothers during pregnancy has been reported to be associated with increased levels of total IgE in cord blood of the offspring [23]. This raises the question of whether the effects of alcohol consumption on IgE levels can be transmitted to the foetus or the breast-fed child.

The previously reported significant association between alcohol consumption and the prevalence of SPT positivity at baseline in our study population [5] was not confirmed in this prospective analysis. One potential explanation could be that due to the relatively low number of incident cases of IgE sensitization, this study might not have had sufficient statistical power. To our knowledge there is no previous report on the association between alcohol consumption and the incidence of IgE sensitization. The previously mentioned cross-sectional

Table 2. Comparison of baseline characteristics between participants and non-participants in the follow-up study

	Participants in follow-up (n = 734) Prevalence in %	Non-participants in follow-up (n = 330) Prevalence in %	P-value*
Skin prick test positivity	43.9 (322/734)	41.5 (136/328)	0.465
Specific IgE positivity	38.2 (278/727)	33.7 (110/326)	0.162
Total IgE (geometric mean)	33.0	29.8	0.212
Alcohol consumption			
0 drinks per week	13.1 (96/734)	17.3 (57/329)	0.122
1–2	20.2 (148/734)	20.4 (67/329)	
3–4	21.4 (157/734)	17.6 (58/329)	
5–10	23.7 (174/734)	27.1 (89/329)	
≥ 11	21.7 (159/734)	17.6 (58/329)	
Smoking status			
Never-smoker	34.3 (252/734)	31.8 (105/330)	0.239
Past smoker	21.1 (155/734)	18.2 (60/330)	
Current smoker	44.6 (327/734)	50.0 (165/330)	
Female sex	52.0 (382/734)	58.8 (194/330)	0.041
Age (years) (at baseline)			
15–34	40.3 (296/734)	37.9 (125/330)	0.126
35–49	35.8 (263/734)	32.4 (107/330)	
50–69	23.8 (175/734)	29.7 (98/330)	
Group			
Random	41.0 (301/734)	47.0 (155/330)	0.069
Symptom	59.0 (433/734)	53.0 (175/330)	
Educational level in years (mean)	11.5	10.8	0.001

*Comparison of participants and non-participants (chi-square test or Mann–Whitney U-test).

Table 3. The relationship between alcohol consumption and the development (incidence) of skin prick test positivity to inhalant allergens

Alcohol consumption (per week)	Incidence (%)	Odds ratio* (95% CI) (included in analysis, n = 412)	Odds ratio† (95% CI) (included in analysis, n = 410)
0 drinks	7.4 (4/54)	1 (reference), $P = 0.055$‡	1 (reference), $P = 0.082$‡
1–2	9.6 (9/94)	1.06 (0.30–3.79)	1.02 (0.28–3.74)
3–4	11.7 (11/94)	1.81 (0.52–6.35)	1.56 (0.43–5.60)
5–10	10.3 (10/97)	1.65 (0.46–5.96)	1.41 (0.38–5.20)
≥ 11	15.1 (11/73)	3.31 (0.83–13.17)	2.94 (0.73–11.91)
Total	10.9 (45/412)		

*Adjusted for age, sex, group and smoking status.†Adjusted for age, sex, group, smoking status, dog in household, number of siblings and educational level. ‡P-value for test for trend.

Table 4. The relationship between alcohol consumption and the development (incidence) of specific IgE positivity to inhalant allergens

Alcohol consumption (per week)	Incidence (%)	Odds ratio* (95% CI) (included in analysis, n = 446)	Odds ratio† (95% CI) (included in analysis, n = 444)
0 drinks	9.4 (6/64)	1 (reference), $P = 0.535$‡	1 (reference), $P = 0.462$‡
1–2	8.9 (8/90)	0.86 (0.38–2.65)	0.99 (0.31–3.13)
3–4	8.2 (8/98)	0.85 (0.27–2.65)	0.83 (0.26–2.66)
5–10	4.6 (5/109)	0.45 (0.13–1.61)	0.44 (0.12–1.59)
≥ 11	7.1 (6/85)	0.77 (0.21–2.85)	0.76 (0.20–2.88)
Total	7.4 (33/446)		

*Adjusted for age, sex, group and smoking status. †Adjusted for age, sex, group, smoking status, dog in household, number of siblings and educational level. ‡P-value for test for trend.

study, reported by Vidal et al. in consecutive patients in an allergy clinic, found that among house dust mite sensitized patients, specific IgE values against *D. pteronyssinus* were higher in regular alcohol consumers than in abstainers [18].

It is well known that alcoholic beverages may trigger asthma symptoms in certain individuals [24]. In Orientals this alcohol-induced exacerbation has been related to a genetic defect in alcohol metabolism, which is common in Orientals. However, alcohol-triggered asthma symptoms are also commonly reported in Caucasians [24, 25]. Although this phenomenon has been attributed to allergic or intolerance reactions to preservatives in alcoholic beverages or the histamine content of wine, there seem to be an increasing evidence in support of the hypothesis that alcohol-induced asthma symptoms is caused by a histamine-releasing effect of acetaldehyde, a metabolite of ethanol [26–30]. Moreover, acetaldehyde has been shown to increase the release of histamine from rat peritoneal mast cells [31]. If acetaldehyde has a similar effect on human cutaneous mast cells, this could explain the previously reported cross-sectional association between alcohol consumption and SPT reactivity in our study population [5].

Histamine is also involved in the well-known alcohol-induced damage to the gastrointestinal mucosa [32]. The subsequent increased permeability of the gastrointestinal mucosa may increase the penetration of food allergens through the gastrointestinal mucosa and thereby exacerbate food intolerance or even increase the risk of developing food allergies.

It should be considered whether selection bias could have influenced the results. The prospective analysis of the relationship between alcohol and incidence of IgE sensitization may be less susceptible to selection bias, as prevalent cases at baseline have been excluded from the analysis. On the other hand, this design may be susceptible to bias induced by loss to follow-up. However, neither alcohol consumption nor IgE sensitization was associated with participation in follow-up (Table 2). The cross-sectional analysis of the relationship between alcohol consumption and total IgE would be susceptible to selection bias, if both were related to participation in the baseline study. We have no data on this, but indirectly the fact that total IgE was not related to participation in follow-up (Table 2) may indicate that selection bias was not a significant problem.

There is evidence that alcohol consumption has an effect on the immune system. However, the possible mechanisms are not clear. Besides the apparent ability to raise levels of serum IgE, alcohol may also have an influence on the cytokine profile. It has been reported that alcoholics admitted to hospital with alcohol abstinence syndrome had increased levels of some type 2 cytokines as compared with healthy controls [17]. Experimental studies in mice have shown that alcohol impairs the T helper 1 lymphocyte regulated cell-mediated immune response favouring a T helper 2 lymphocyte deviation of the immune response [33, 34]. In contrast, Domininquez-Santalla et al. reported a T helper 1 dominance in alcoholics, as estimated by the ratio of IL-4 to IFN-gamma production by stimulated blood mononuclear cells, as compared with healthy controls [16].

In conclusion, we found a significant positive association between alcohol consumption and total IgE in non-atopic persons. However, a significant epidemiological association between alcohol consumption and the development of IgE sensitization was not established in this study. Nevertheless, in our opinion this issue deserves further investigation in large-scale epidemiological studies and experimental studies. This is underlined by the fact that recent increases in weekly alcohol consumption and drunkenness among adolescents have been reported in many countries [3]. These increases may have coincided with increases in atopic diseases in these countries. In Denmark, the frequency of weekly drinking among 15-year-olds has increased from 18% to 42% between 1985 and 1998, and they furthermore tend to have experienced drunkenness at an earlier age in 1998 as compared with 1985 [4]. In the total population of Denmark, the consumption of alcohol per inhabitant (> 14 years old) more than doubled from 1955 to 1999 (4.5 and 12 L pure alcohol, respectively) [35]. In particular, the consumption of wine and beer increased substantially during that period.

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