

The association between alcohol consumption and contact sensitization in Danish adults: the Glostrup Allergy Study

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Summary

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Key words

alcohol consumption, contact dermatitis, contact sensitization, delayed-type hypersensitivity, general population, risk factor

Conflicts of interest

None declared.

Background Population-based epidemiological studies have indicated that alcohol consumption is associated with IgE-mediated immune diseases (i.e. allergic rhinitis, asthma and urticaria). These studies have been strongly supported by several immunological studies. Furthermore, an inhibitory effect of alcohol consumption on the development of delayed-type hypersensitivity has been shown in healthy controls. However, a possible association between contact sensitization and alcohol consumption in a general population has never been reported.

Objectives To investigate whether alcohol consumption is associated with contact sensitization in a general population.

Methods In 1990, self-reported consumption of alcohol and patch testing results were assessed in 1112 subjects, aged 15–69 years, participating in a population-based cross-sectional study in Glostrup, 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 logistic regression analyses.

Results Women who reported no consumption of alcoholic drinks per week were more likely to develop contact sensitization (adjusted odds ratio 2.12, 95% confidence interval 0.98–4.61) during a 8-year follow-up period. A positive trend among women was detected ($P = 0.045$).

Conclusions These data support the hypothesis that alcohol consumption leads to IgE-mediated immune responses rather than delayed-type hypersensitivity reactions. It is probable that alcohol consumption prevents the development of contact sensitization. Further epidemiological studies are warranted.

In Denmark, a general increase in the consumption of alcohol has been observed during the second half of the 20th century.^{1,2} Excess alcohol intake may lead to liver cirrhosis, acute and chronic pancreatitis, hypertension, cardiomyopathy, some types of cancers and death.³ There is substantial evidence that alcohol consumption has an effect on the immune system: alcohol leads to impaired T-helper 1 (Th1) lymphocyte-regulated cell-mediated immune responses favouring a Th2 lymphocyte deviation of the immune system.^{4–8} Furthermore, in alcohol abstinence syndrome, an increased level of Th2 lymphocyte-related cytokines has been demonstrated in comparison with healthy controls.⁹ Thus, alcohol consumption is associated with changes in the cytokine profile consistent with a relative Th2 lymphocyte deviation of the immune system.

The Th1/Th2 dichotomy has for some years been the cornerstone of immunological thinking.^{10,11} The basic idea is that naïve precursor CD4+ T cells differentiate to either Th1 or

Th2 cells under the influence of cytokines.¹² Th1 cells are crucial for the host to control the replication of intracellular pathogens but also contribute to the pathogenesis of autoimmune diseases and contact sensitization. Th2 cells support the development of humoral immunity but are, furthermore, associated with IgE-mediated allergic diseases (i.e. allergic rhinitis, asthma and urticaria). The reciprocal downregulation of Th1 cells by Th2 cytokines and Th2 cells by Th1 cytokines is a key element in this hypothesis and accordingly IgE-mediated immune diseases result from a predominance of Th2 cells and are, furthermore, negatively regulated by Th1 cells. Contact sensitization, asthma and allergic rhinitis are all common conditions of which increasing prevalences have been reported.^{13–15} Recently, population-based epidemiological studies have indicated that alcohol consumption is associated with IgE-mediated immune diseases, probably due to an imbalance in favour of Th2 cell predominance.^{16–19} From

these findings, it is likely that alcohol consumption may also have an influence on the development of contact sensitization where a Th1-dominated immune response plays a major role in the pathogenesis. Hence, we decided to investigate whether alcohol consumption is associated with contact sensitization in a general population.

Materials and methods

Baseline study

The study was conducted according to a two-stage protocol. In the first stage a screening questionnaire on respiratory symptoms was mailed to a sample of 15- to 69-year-olds ($n = 8000$) living in the Western part of Copenhagen, the capital of Denmark. 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 in the screening questionnaire upper ('itchy or stuffy nose or sneezing') or lower ('shortness of breath or trouble breathing') respiratory symptoms on exposure to either pollen or furry animals.²⁰ The random group comprised 647 subjects who were randomly selected from among the remaining respondents. Subsequently, 635 (participation rate 80.6%) and 477 (participation rate 75.5%) subjects were examined in the symptom and random group, respectively. Thus, in total 1112 subjects (overall participation rate 77.5%) were examined, and of these 1056 were patch tested. On the test day, all participants filled out another questionnaire with a variety of health questions including questions on eczema, atopic dermatitis and exposure to allergens. The invitational procedure and characteristics of both participants and nonparticipants have previously been described in more detail.²⁰ Examinations took place between February 1990 and January 1991. The Ethical Committee of Copenhagen County approved the study. A written, informed consent form was obtained from all participants prior to the beginning of the study.

Follow-up study

At the time of follow-up, 28 subjects had died, eight had emigrated and 12 could not be located. Thus, 1064 of the participants in the baseline study were invited to the follow-up study; 734 subjects were examined (participation rate 69%). We invited eligible subjects in the same months as they had been examined in the baseline study to avoid potential seasonal differences. Hence, 469 of 734 (63.9%) 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 and 10 months (range 6 years and 10 months–8 years and 8 months). The participants were examined between October 1997 and November 1998. The study was approved by the Ethics Com-

mittee of Copenhagen County. A comparison of characteristics among participants and nonparticipants has previously been presented²¹ and revealed that male sex and high educational level at baseline were significantly associated with participation in the follow-up study.

Patch tests

The patch tests used were the ready to apply TRUE-Test (ALK-Abelló A/S, Hørsholm, Denmark).^{22,23} The haptens differed from the European Standard Series (Hermal-Chemi, Reinbek, Germany) by including thiomersal and excluding primine and formaldehyde. Directions to apply the patch tests to the upper back 2 days before the examination were mailed with the patch test. The patch tests were read 30–90 min after removal. Reactions were classified according to the International Contact Dermatitis Research Group.²⁴ A positive reaction (+) was defined as at least homogeneous redness and palpable infiltration in the test area. Reactions not fulfilling these criteria, whether these were follicular reactions, faint erythema or typical irritant reactions, were classified as nonallergic reactions. Contact sensitization was defined as a positive patch test to at least one of 23 allergens. In 1990/1991, N.H.N. read all reactions. In 1997/1998, A.L. read all reactions. In both studies, all photographs of the test sites were reviewed by the same professor in dermatology, and in case of disagreement consensus was reached by discussion. If the tests were not applied 2 days before attending, or if the contact with the skin was poor, a new appointment was made when possible.

Questionnaire

A questionnaire about health, lifestyle and socioeconomic factors was sent with the standard invitation letter to the participants. 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 12 g/15 mL ethanol. The total weekly consumption was calculated by adding the intake of beer, wine and spirits. The total alcohol consumption was categorized as 0, 1–7, 8–14 and ≥ 15 drinks per week for the prevalence calculations and as 0, 1–7 and ≥ 8 drinks per week for the incidence calculations. The questions used for assessment of alcohol consumption have previously been validated against increased levels ($\geq 80 \text{ IU L}^{-1}$) of serum γ -glutamyltransferase (GGT), a marker of alcohol exposure.²⁵ The results revealed that self-reported total alcohol intake (total number of drinks per week) was significantly and positively associated with increased levels of GGT.²⁶ Information about tobacco exposure was obtained in the questionnaire in as much detail as possible and has been described previously.^{24,27} Ear piercing was

defined as an affirmative answer to the question 'Have you ever had your ears pierced?' Questions about eczema and hand eczema included: 'Have you ever had eczema from exposure to earpins or earrings, under the tightener of your watch strap or under the button of your jeans?' and 'have you ever had hand eczema?' The following socioeconomic variables were defined: vocational training (yes, no), educational level (≤ 9 , 10–11, 12–13, ≥ 14 years), type of residence (house, apartment, other), ownership of residence (yes, no) and social group (self-employed, white-collar workers, skilled blue-collar workers, unskilled blue-collar workers, others).

Statistics

Potential differences in alcohol consumption between groups with different baseline characteristics were examined by a 2×2 frequency table using the χ^2 test. The association between alcohol consumption (independent variable) and contact sensitization (dependent variable) was analysed by logistic regression models and expressed as odds ratios (ORs) with 95% confidence intervals (CIs). In this model, the following potential confounders (independent variables) were considered: sex, age (15–34, 35–49, 50–69 years), smoking (ex-smoker, never-smoker, ≤ 15 g daily, > 15 g daily) and ear piercing (yes, no). In further analyses possible confounding by socioeconomic variables were investigated but revealed essentially similar results and were excluded from the final analysis. *A priori* it was decided to analyse the results separately for each gender as both contact sensitization and alcohol consumption are known to be strongly related to gender. All data were analysed with the Statistical Products and Service Solutions package (SPSS Inc., Chicago, IL, U.S.A.) for Windows (release 15.0).

Results

Tables 1, 2 show the baseline characteristics among 1112 participants in the 1990 study. The prevalence of contact allergy and nickel contact allergy was substantially higher among women than among men (Table 1). Alcohol abstinence as compared with drinking at least one drink per week was associated with female sex ($P < 0.001$), a history of ear piercing ($P < 0.001$) and never-smoking status ($P < 0.02$), whereas no significant age differences were detected (Table 2). Similarly, consumption of one to seven alcoholic drinks per week was associated with female sex ($P < 0.001$), age 15–34 years ($P < 0.001$), a history of ear piercing ($P < 0.01$) and never-smoking status ($P < 0.01$). Finally, heavy drinking (≥ 15 drinks per week) as compared with drinking < 15 drinks per week was associated with male sex ($P < 0.001$), age 50–69 years ($P < 0.001$), no history of ear piercing ($P < 0.001$) and heavy smoking (> 15 g daily) ($P < 0.001$).

Table 3 shows the association between alcohol consumption and the prevalence of contact sensitization to at least one of 23 allergens in 1990. Among men, no statistical significant association was found and the adjusted ORs were almost similar for drinkers and nondrinkers. Among women, the prevalence of contact sensitization was significantly lower among nondrinkers (adjusted OR 0.53, 95% CI: 0.31–0.94) in comparison with women who consumed one to seven drinks per week (reference group). However, the prevalence of contact sensitization was not increased among women drinking 8–14 or ≥ 15 drinks per week. No relation between the type of alcoholic drink and contact sensitization was found.

Table 4 shows the association of alcohol consumption with the incidence of contact sensitization between 1990 and 1998. In total, 573 (292 men and 281 women) persons with

Table 1 The prevalence of contact sensitization (to at least one of 23 allergens), nickel contact allergy, allergic nickel contact dermatitis, a history of ear piercing, skin prick test reactivity and smoking among women and men

	Women	Men	
	n/total (%)	n/total (%)	P-value ^a
Contact sensitization	133/574 (23.2)	50/482 (10.4)	< 0.001
Nickel contact sensitization	87/574 (15.2)	7/482 (1.5)	< 0.001
Allergic nickel contact dermatitis ^b	79/573 (13.8)	4/482 (0.8)	< 0.001
Ear piercing	419/595 (70.4)	73/517 (14.1)	< 0.001
Skin prick test reactivity	226/593 (38.1)	248/517 (48.0)	< 0.001
Smoking status			
Never	210/595 (35.3)	158/517 (30.6)	< 0.001 (3 d.f.)
Previously	99/595 (16.6)	122/517 (23.6)	
≤ 15 g daily	199/595 (33.4)	106/517 (20.5)	
> 15 g daily	87/595 (14.6)	131/517 (25.3)	
Lifetime smoking			
0 pack-years	227/589 (38.5)	171/513 (33.3)	< 0.001 (2 d.f.)
≤ 15 pack-years	238/589 (40.4)	158/513 (30.8)	
> 15 pack-years	124/589 (21.1)	184/513 (35.9)	

^aP-value of χ^2 test for the comparison of women and men. ^bPersons with a history of eczema from wearing earpins or earrings, under the tightener of one's watch strap or under the button of one's jeans and a positive patch test to nickel were defined as cases of allergic nickel contact dermatitis.

Table 2 Baseline characteristics of the participants. Weekly alcohol consumption (drinks per week) stratified by gender, age, ear piercing and smoking

Alcohol consumption (drinks per week)	Gender		Age (years)		Ear piercing		Smoking		Ex-smoker, n (%)	≤ 15 g daily, n (%)	> 15 g daily, n (%)
	Male, n (%)	Female, n (%)	15–34, n (%)	35–49, n (%)	50–69, n (%)	No, n (%)	Yes, n (%)	Never smoker, n (%)			
0	33 (6.4)	126 (21.2)	73 (16.9)	34 (8.9)	52 (17.4)	64 (10.3)	95 (19.3)	66 (17.9)	19 (8.6)	44 (14.5)	30 (13.8)
1–7	246 (47.6)	359 (60.4)	276 (63.7)	192 (50.5)	137 (46.0)	311 (50.2)	294 (59.9)	226 (61.4)	120 (54.3)	176 (57.9)	83 (38.1)
8–14	108 (20.9)	85 (14.3)	55 (12.7)	92 (24.2)	46 (15.4)	121 (19.5)	72 (14.7)	48 (13.0)	41 (18.6)	62 (20.4)	42 (19.3)
≥ 15	130 (25.1)	24 (4.0)	29 (6.7)	62 (16.3)	63 (21.1)	124 (20.0)	30 (6.1)	28 (7.6)	41 (18.6)	22 (7.2)	63 (28.9)
Total	517 (100)	594 (100)	433 (100)	380 (100)	298 (100)	620 (100)	491 (100)	368 (100)	221 (100)	304 (100)	218 (100)
χ^2	146.5		68.9			62.2		88.4			
P-value	< 0.001		< 0.001			< 0.001		< 0.001			

negative patch test results in 1990 were patch tested again in 1998. Of these, 69 (12%) developed a positive patch test reaction. No men tested positive among nondrinkers and it was therefore impossible to calculate ORs for this category. Among women, individuals who reported no consumption of alcohol were more likely to develop contact sensitization (adjusted OR 2.12, 95% CI: 0.98–4.61) during the 8-year follow-up period. A positive trend test among women was detected ($P = 0.045$). No relation between the type of alcoholic drink and contact sensitization was found.

Discussion

This investigation revealed an inverse dose–response relationship between alcohol consumption and incident contact sensitization among women (i.e. women who consume alcohol are less likely to develop contact sensitization than nondrinkers) (Table 4). A possible association could not be evaluated among men as the number of incident positive patch test reactions was too low. Furthermore, it appeared that alcohol abstinence was associated with a lower prevalence of contact sensitization among women (Table 3). The findings of the cross-sectional and prospective analyses appear to be contradictory as a nondrinking status (among women) was associated with a lower prevalence of contact sensitization (Table 3) but a higher incidence of contact sensitization (Table 4). The reason for this discrepancy is not clear. In general, the results of prospective analyses are considered as more reliable when determining cause–effect relationships and as less prone to bias and confounding. Confounding seems unlikely as independent well-known determinants of contact sensitization were included in the analyses (i.e. female sex, history of ear piercing and cigarette smoking).^{27–29} A possible source of bias in the study could be that persons with excess alcohol consumption were less likely to participate. Similarly, it is possible that persons with a history of eczema were more likely to participate in the study as its focus was on allergy. Random error cannot be ruled out as this is the first epidemiological study on this topic. Previous population-based epidemiological studies have indicated that contact sensitization and IgE-mediated immune diseases are independent³⁰ and that alcohol consumption is associated with IgE-mediated allergic diseases.^{16,18} Furthermore, the Th1/Th2 dichotomy would suggest an inverse relation between alcohol consumption and contact sensitization. Our prospective analyses indicated that the well-documented alcohol-induced impairment of Th1 immune response found in immunological studies also can be demonstrated in population-based epidemiological studies. Finally, it has been hypothesized that the effect of alcohol consumption on Th2-mediated immune responses is due to ethanol itself and not to the nonethanol content of alcoholic drinks.^{26,31} In line with this, the present results did not reveal any significant effects of the type of alcoholic drink. However, the study size may not have been sufficient to examine for this issue properly.

The Th1/Th2 hypothesis was introduced in the mid 1980s and has been applied as an immunological model since then.¹⁰

Table 3 The association between alcohol consumption and the prevalence of contact sensitization (a positive patch test to at least one of 23 allergens) in 1990

Alcohol consumption (drinks per week)	Men			Women		
	Contact sensitization, n (%)	Odds ratio (95% CI)	Adjusted odds ratio ^a (95% CI)	Contact sensitization, n (%)	Odds ratio (95% CI)	Adjusted odds ratio ^a (95% CI)
0	2 (6.7)	0.52 (0.12–2.23)	0.62 (0.13–2.83)	19 (15.3)	0.54 (0.31–0.95)	0.53 (0.31–0.94)
1–7	28 (12.2)	1.00	1.00	85 (24.9)	1.00	1.00
8–14	9 (9.1)	0.72 (0.33–1.59)	0.67 (0.30–1.51)	23 (27.7)	1.16 (0.67–1.99)	1.20 (0.68–2.20)
≥ 15	11 (8.9)	0.71 (0.34–1.47)	0.67 (0.30–1.44)	6 (25.0)	1.00 (0.38–2.62)	0.90 (0.33–2.48)
Total	50/482 (10.4)			133/573 (23.2)		

^aAdjusted for age, ear piercing and smoking. CI, confidence interval.

Table 4 The effect of alcohol consumption on the incidence of contact sensitization between 1990 and 1998

Alcohol consumption (drinks per week)	Men			Women		
	Contact sensitization, n (%)	Odds ratio (95% CI)	Adjusted odds ratio ^a (95% CI)	Contact sensitization, n (%)	Odds ratio (95% CI)	Adjusted odds ratio ^a (95% CI)
0	0 (0)	–	–	14 (23.0)	1.69 (0.82–3.48)	2.12 (0.98–4.61)
1–7	13 (9.4)	1.00	1.00	27 (15.0)	1.00, <i>P</i> = 0.071 ^b	1.00, <i>P</i> = 0.045 ^b
≥ 8	11 (8.1)	0.94 (0.38–2.23)	0.84 (0.37–1.96)	4 (12.5)	0.72 (0.23–2.26)	0.91 (0.28–2.89)
Total	24/292 (8.2)			45/281 (16.0)		

^aAdjusted for age, ear piercing and smoking. ^b*P*-value for test for trend. CI, confidence interval.

It is becoming evident that allergic immune responses are not always as strongly polarized as dictated by the Th1/Th2 dichotomy,^{11,32} as allergen-specific Th1 and Th2 cells have been isolated from skin biopsies³³ and coexpression of Th1 and Th2 cytokines following sensitization has been observed.³⁴ Furthermore, it appears that the secreted Th2 cytokines are independent of the type of sensitizer.³⁵ Recently it was demonstrated that a subgroup of T cells, 'T-regulatory' (Treg) cells, suppresses both Th1- and Th2-mediated immune responses^{36,37} and, furthermore, that Th17 cells secrete interleukin (IL)-17 that provides defence against extracellular bacteria and is involved in the inflammatory process of cancer and autoimmune diseases.^{38–40} The differentiation of Th17 cells is inhibited by cytokines from both Th1 and Th2 cells [interferon (IFN)- γ and IL-4] and is stimulated by transforming growth factor- β 1 and IL-23.⁴⁰ Similar to the reciprocal interaction of Th1 and Th2 cells, Th17 cells are involved in reciprocal interaction with Th1 cells (i.e. Th1 cells inhibit the inflammatory damage caused by Th17 cells via the secretion of IFN- γ).¹¹ Finally, Th17 cells and Treg cells show reciprocal interactions through the action of IL-6.¹¹

The exact mechanism played by alcohol consumption in allergic skin diseases has only partly been elucidated, whereas the effect of alcohol on pulmonary host defence has been investigated to a greater extent.⁴¹ Alcohol mainly displays its effect on antigen-presenting cells (APCs) (both

in vitro and *in vivo*) where it leads to a decreased T-cell activation.⁴² It can inhibit the antigen-presenting capacity of these cells for nearly 7 days.⁴² Glutathione levels in APCs may influence whether a Th1 or Th2 response will develop.⁴³ Glutathione inhibition prevents IL-12 synthesis in APCs and leads to an increased production of IL-4 and thus a Th2-mediated immune response.^{44,45} As alcohol is an inhibitor of glutathione synthesis, consumption may lead to IgE-mediated allergic diseases and possibly prevent contact sensitization. Furthermore, ethanol leads to increased gut permeability which in turn leads to increased absorption of endotoxins (lipopolysaccharides).³¹ Monocyte CD14 receptors may then interact with absorbed lipopolysaccharides and indirectly favour IgE synthesis.³¹ In addition, it has been indicated that alcohol consumption inhibits Th1-mediated immune responses both *in vitro* and *in vivo* (and in acute and chronic alcohol intake).^{46–48} Smith *et al.*⁴⁸ showed that alcohol intake reduced the probability of developing a delayed-type hypersensitivity in 166 healthy individuals. Apparently, alcohol interferes with early cell surface-associated signal transduction phosphorylation events leading to impaired IFN- γ and IL-12 secretion, whereas IL-2 synthesis is almost unaffected.^{49–51} Administration of IL-12 can restore IFN- γ levels and delayed-type hypersensitivity reactions.⁵ A Th2-mediated immune response is caused by the synthesis of IL-4 that leads to elevated levels of serum IgE.⁴⁴ At present,

little is known about the effect of alcohol on Treg cells and Th17 cells but it has been demonstrated that alcohol can suppress IL-17 synthesis in the lungs.⁵²

Despite its shortcomings, the Th1/Th2 hypothesis remains illuminating. It is acknowledged that no single cytokine can regulate a vital process such as tissue damage and that a refinement of the model is necessary. However, it demonstrates that a reciprocal interaction between whole subsets of T cells (i.e. Th1 and Th2) is a key point in inflammatory responses. It therefore continues to guide our perspective on allergic immune responses to a great extent. There is evidence to support that alcohol leads to a Th2 deviation of the immune system and that a Th1-mediated response is impaired.^{16,18} For the first time ever, we are able to show that it is probable that alcohol consumption prevents the development of contact sensitization. This finding supports previous immunological studies but also raises important questions for future allergy testing (i.e. should patient medical histories contain information about alcohol consumption in order to interpret the outcome of patch testing or skin prick testing better?). Recently, we initiated the third consecutive Glostrup Allergy study. It will hopefully bring us another chance to investigate what role is played by alcohol in the development of contact sensitization and IgE-mediated allergic diseases.

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References

- 1 Fødevaredirektoratet (Danish Veterinary and Food Administration). The Supply of Food in 1955–1999. Development in Danish Diet – Consumption, Food, Purchases and Eating Habits. Fødevare Rapport. Soborg, Denmark: Fødevaredirektoratet, 2001 (in Danish).
- 2 Due EP, Broholm K, Holstein BE *et al.* [Alcohol consumption among young people]. *Ugeskr Laeger* 1999; **161**:3641–4.
- 3 Chou SP, Grant BF, Dawson DA. Medical consequences of alcohol consumption – United States, 1992. *Alcohol Clin Exp Res* 1996; **20**:1423–9.
- 4 Starkenburg S, Munroe ME, Waltenbaugh C. Early alteration in leukocyte populations and Th1/Th2 function in ethanol-consuming mice. *Alcohol Clin Exp Res* 2001; **25**:1221–30.
- 5 Waltenbaugh C, Vasquez K, Peterson JD. Alcohol consumption alters antigen-specific Th1 responses: mechanisms of deficit and repair. *Alcohol Clin Exp Res* 1998; **22**:S220–3.
- 6 Latif O, Peterson JD, Waltenbaugh C. Alcohol-mediated polarization of type 1 and type 2 immune responses. *Front Biosci* 2002; **7**:a135–47.
- 7 Schodde H, Hurst S, Munroe M *et al.* Ethanol ingestion inhibits cell-mediated immune responses of unprimed T-cell receptor transgenic mice. *Alcohol Clin Exp Res* 1996; **20**:890–9.
- 8 Cook RT. Alcohol abuse, alcoholism, and damage to the immune system – a review. *Alcohol Clin Exp Res* 1998; **22**:1927–42.
- 9 Gonzalez-Quintela A, Vidal C, Lojo S *et al.* Serum cytokines and increased total serum IgE in alcoholics. *Ann Allergy Asthma Immunol* 1999; **83**:61–7.
- 10 Mosmann TR, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol* 1989; **7**:145–73.
- 11 Steinman L. A brief history of T(H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage. *Nat Med* 2007; **13**:139–45.
- 12 O'Garra A, Arai N. The molecular basis of T helper 1 and T helper 2 cell differentiation. *Trends Cell Biol* 2000; **10**:542–50.
- 13 Linneberg A, Nielsen NH, Madsen F *et al.* Increasing prevalence of allergic rhinitis symptoms in an adult Danish population. *Allergy* 1999; **54**:1194–8.
- 14 Linneberg A, Nielsen NH, Madsen F *et al.* Increasing prevalence of specific IgE to aeroallergens in an adult population: two cross-sectional surveys 8 years apart: the Copenhagen Allergy Study. *J Allergy Clin Immunol* 2000; **106**:247–52.
- 15 Nielsen NH, Linneberg A, Menné T *et al.* Allergic contact sensitization in an adult Danish population: two cross-sectional surveys eight years apart (the Copenhagen Allergy Study). *Acta Derm Venereol (Stockh)* 2001; **81**:31–4.
- 16 Gonzalez-Quintela A, Gude F, Boquete O *et al.* Association of alcohol consumption with total serum immunoglobulin E levels and allergic sensitization in an adult population-based survey. *Clin Exp Allergy* 2003; **33**:199–205.
- 17 Linneberg A, Nielsen NH, Madsen F *et al.* Factors related to allergic sensitization to aeroallergens in a cross-sectional study in adults: the Copenhagen Allergy Study. *Clin Exp Allergy* 2001; **31**:1409–17.
- 18 Linneberg A, Petersen J, Nielsen NH *et al.* The relationship of alcohol consumption to total immunoglobulin E and the development of immunoglobulin E sensitization: the Copenhagen Allergy Study. *Clin Exp Allergy* 2003; **33**:192–8.
- 19 Vidal C, Armisen M, Dominguez-Santalla MJ *et al.* Influence of alcohol consumption on serum immunoglobulin E levels in atopic and nonatopic adults. *Alcohol Clin Exp Res* 2002; **26**:59–64.
- 20 Nielsen NH, Dirksen A, Madsen F. Can subjects with a positive allergen skin test be selected by a short questionnaire? The Glostrup Allergy Study, Denmark. *Allergy* 1993; **48**:319–26.
- 21 Linneberg A, Nielsen NH, Madsen F *et al.* Smoking and the development of allergic sensitization to aeroallergens in adults: a prospective population-based study. The Copenhagen Allergy Study. *Allergy* 2001; **56**:328–32.
- 22 Lachapelle JM, Bruynzeel DP, Ducombs G *et al.* European multicenter study of the TRUE Test. *Contact Dermatitis* 1988; **19**:91–7.
- 23 Wilkinson JD, Bruynzeel DP, Ducombs G *et al.* European multicenter study of TRUE Test, Panel 2. *Contact Dermatitis* 1990; **22**:218–25.
- 24 Wilkinson DS, Fregert S, Magnusson B *et al.* Terminology of contact dermatitis. *Acta Derm Venereol (Stockh)* 1970; **50**:287–92.
- 25 Whitfield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci* 2001; **38**:263–355.
- 26 Linneberg A, Hertzum I, Husemoen LL *et al.* Association between alcohol consumption and aeroallergen sensitization in Danish adults. *Clin Exp Allergy* 2006; **36**:714–21.
- 27 Linneberg A, Nielsen NH, Menné T *et al.* Smoking might be a risk factor for contact allergy. *J Allergy Clin Immunol* 2003; **111**:980–4.
- 28 Dotterud IK, Smith-Sivertsen T. Allergic contact sensitization in the general adult population: a population-based study from northern Norway. *Contact Dermatitis* 2007; **56**:10–15.
- 29 Schafer T, Bohler E, Ruhdorfer S *et al.* Epidemiology of contact allergy in adults. *Allergy* 2001; **56**:1192–6.
- 30 Nielsen NH, Menné T. The relationship between IgE-mediated and cell-mediated hypersensitivities in an unselected Danish population: the Glostrup Allergy Study, Denmark. *Br J Dermatol* 1996; **134**:669–72.

- 31 Gonzalez-Quintela A, Vidal C, Gude F. Alcohol, IgE and allergy. *Addict Biol* 2004; **9**:195–204.
- 32 van Oosterhout AJ, Motta AC. Th1/Th2 paradigm: not seeing the forest for the trees? *Eur Respir J* 2005; **25**:591–3.
- 33 Probst P, Kuntzlin D, Fleischer B. TH2-type infiltrating T cells in nickel-induced contact dermatitis. *Cell Immunol* 1995; **165**:134–40.
- 34 Ulrich P, Grenet O, Bluemel J *et al.* Cytokine expression profiles during murine contact allergy: T helper 2 cytokines are expressed irrespective of the type of contact allergen. *Arch Toxicol* 2001; **75**:470–9.
- 35 Masjedi K, Ahlborg N, Gruvberger B *et al.* Methylisothiazolinones elicit increased production of both T helper (Th)1- and Th2-like cytokines by peripheral blood mononuclear cells from contact allergic individuals. *Br J Dermatol* 2003; **149**:1172–82.
- 36 Veldman C, Nagel A, Hertl M. Type I regulatory T cells in autoimmunity and inflammatory diseases. *Int Arch Allergy Immunol* 2006; **140**:174–83.
- 37 Girolomoni G, Gisondi P, Ottaviani C *et al.* Immunoregulation of allergic contact dermatitis. *J Dermatol* 2004; **31**:264–70.
- 38 Nakae S, Komiyama Y, Nambu A *et al.* Antigen-specific T cell sensitization is impaired in IL-17-deficient mice, causing suppression of allergic cellular and humoral responses. *Immunity* 2002; **17**:375–87.
- 39 He D, Wu L, Kim HK *et al.* CD8+ IL-17-producing T cells are important in effector functions for the elicitation of contact hypersensitivity responses. *J Immunol* 2006; **177**:6852–8.
- 40 Tato CM, O'Shea JJ. Immunology: what does it mean to be just 17? *Nature* 2006; **441**:166–8.
- 41 Happel KI, Nelson S. Alcohol, immunosuppression, and the lung. *Proc Am Thorac Soc* 2005; **2**:428–32.
- 42 Szabo G, Catalano D, White B *et al.* Acute alcohol consumption inhibits accessory cell function of monocytes and dendritic cells. *Alcohol Clin Exp Res* 2004; **28**:824–8.
- 43 Peterson JD, Herzenberg LA, Vasquez K *et al.* Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. *Proc Natl Acad Sci USA* 1998; **95**:3071–6.
- 44 Andrade MC, Menezes JS, Cassali GD *et al.* Alcohol-induced gastritis prevents oral tolerance induction in mice. *Clin Exp Immunol* 2006; **146**:312–22.
- 45 Sarnstrand B, Jansson AH, Matuseviciene G *et al.* N,N'-diacetyl-L-cystine – the disulfide dimer of N-acetylcysteine – is a potent modulator of contact sensitivity/delayed type hypersensitivity reactions in rodents. *J Pharmacol Exp Ther* 1999; **288**:1174–84.
- 46 Chen GJ, Huang DS, Watzl B *et al.* Ethanol modulation of tumor necrosis factor and gamma interferon production by murine splenocytes and macrophages. *Life Sci* 1993; **52**:1319–26.
- 47 Wagner F, Fink R, Hart R *et al.* Ethanol inhibits interferon-gamma secretion by human peripheral lymphocytes. *J Stud Alcohol* 1992; **53**:277–80.
- 48 Smith AJ, Vollmer-Conna U, Bennett B *et al.* Influences of distress and alcohol consumption on the development of a delayed-type hypersensitivity skin test response. *Psychosom Med* 2004; **66**:614–19.
- 49 Ostrovidov S, Howard LM, Ikeda M *et al.* Restoration of ethanol-compromised T(h)1 responses by sodium orthovanadate. *Int Immunol* 2002; **14**:1239–45.
- 50 Watson RR, Borgs P, Witte M *et al.* Alcohol, immunomodulation, and disease. *Alcohol Alcohol* 1994; **29**:131–9.
- 51 Watzl B, Lopez M, Shahbazian M *et al.* Diet and ethanol modulate immune responses in young C57BL/6 mice. *Alcohol Clin Exp Res* 1993; **17**:623–30.
- 52 Ye P, Rodriguez FH, Kanaly S *et al.* Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. *J Exp Med* 2001; **194**:519–27.