

Incidence and Remission of Specific IgE Aeroallergen Sensitization from Age of 40 to 60 Years, and Association with Alcohol Consumption

A. Linneberg^a N. Friedrich^{a, d} L.L.N. Husemoen^a B. Thuesen^a
A. Gonzalez-Quintela^e C. Vidal^f U. Bodtger^a N. Johansen^b T. Drivsholm^{a, c}

^aResearch Centre for Prevention and Health, Glostrup Hospital, Glostrup, ^bALK-Abelló A/S, Hørsholm, and

^cResearch Unit and Department of General Practice, University of Copenhagen, Copenhagen, Denmark;

^dInstitute for Community Medicine, Ernst Moritz Arndt University, Greifswald, Germany; Departments of

^eMedicine and ^fAllergy, Complejo Hospitalario Universitario, Santiago de Compostela, Spain

Key Words

Alcoholic beverages • Alcoholic drinking • Atopy • IgE • Incidence

Abstract

Background: Data on incidence and long-term persistence of IgE aeroallergen sensitization in older adults are limited. Alcohol consumption is a strong immune-modulator with a significant impact on the IgE response. **Objectives:** We aimed to assess the incidence and remission of aeroallergen sensitization from the age of 40 to 60 years. Furthermore, we examined the relationship of alcohol consumption to the prevalence and incidence of aeroallergen sensitization. **Methods:** In 1976–1977, a total of 1,200 people born in 1936 and randomly selected from the general population were invited for a health examination (1,052 were examined). At 60 years, they were invited for a re-examination (695 were examined). Stored serum samples from both examinations were analyzed consecutively for serum-specific IgE to aeroallergens by using a qualitative multi-allergen immunoassay. **Results:** We observed a total of 32 (7.1% of those not sensitized at 40 years) incident cases and 35 (41.1% of those sensitized at 40 years) remittent cases of aeroallergen sensi-

tization over this 20 year period. Persistent as well as incident sensitization was significantly associated with self-reported atopic disease at 60 years. Alcohol consumption (>14 drinks per week) at 40 years was significantly associated with a higher prevalence of sensitization at 40 years, but not with the incidence of sensitization. **Conclusions:** In older adults, aeroallergen sensitization as reflected by serum-specific IgE positivity to aeroallergens is a dynamic process. Both persistent and incident sensitization was associated with atopic disease. Further studies are needed to clarify the influence of alcohol on the allergen-specific IgE response.

Copyright © 2009 S. Karger AG, Basel

Introduction

Data on the incidence and long-term persistence of IgE aeroallergen sensitization in older adults are limited [1, 2]. It is generally accepted that the development of IgE aeroallergen sensitization reaches a peak incidence during childhood and adolescence. Accordingly, the development of aeroallergen sensitization in middle-aged and older persons has previously been considered relatively rare, although data on aeroallergen sensitization devel-

opment at this age is sparse. Nevertheless, there is reason to assume that development of IgE aeroallergen sensitization also occurs at this age [1, 3].

Persistent aeroallergen sensitization is an independent risk factor for hay fever and allergy in children and young adults [2, 4–7]. It is not known whether aeroallergen sensitization confers a similar risk in middle-aged and older adults, as birth before the 1960s is believed to be associated with a lower prevalence of sensitization [8]. Furthermore, it may be speculated that the adult immune system undergoes age-related alterations that may decrease the susceptibility to the development of allergy.

Allergy has consistently been linked to an affluent Westernized urban lifestyle, but it is not clear which factors underlie these patterns [9]. Alcohol consumption has been identified as a strong immune modulating factor with a possible link to atopy [10]. Thus, there is strong evidence that alcohol consumption increases total serum IgE [as reviewed in 11]. Less is known about the influence of alcohol on the allergen-specific immune response, for example as reflected by allergen-specific IgE sensitization. Several epidemiological studies have linked alcohol consumption to IgE sensitization against inhalant allergens, but only 1 of these was prospective [12–16]. Furthermore, maternal alcohol consumption during pregnancy has been linked to early atopic phenotypes (cord blood IgE and early-onset atopic dermatitis) in the offspring, indicating that alcohol may influence the immune system in utero [17, 18]. One recently published experimental study confirmed the ability of alcohol to induce a marked increase in total serum IgE and suppression of the allergen-specific Th1-dependent IgG response (IgG2a), but in this mouse model with intraperitoneally administered ovalbumin alcohol did not influence the allergen-specific IgE response [19]. Although it is documented that alcoholic drinks are common triggers of hypersensitivity reactions, such as symptoms from upper and lower airways and skin [20], it is not known whether alcohol increases the risk of development of allergic diseases. One study in Danish women found that increased consumption of alcohol was associated with increased risk of self-reported perennial, but not seasonal, allergic rhinitis [21].

The aim of this study was to assess the incidence and remission of aeroallergen sensitization in a general population-based cohort of 40-year-olds that were re-examined at 60 years of age. Furthermore, we examined the relationship of alcohol consumption to the prevalence and incidence of aeroallergen sensitization.

Methods

Study Population: The 1936 Cohort

A random sample of subjects living in 4 municipalities (Broendby, Glostrup, Herlev, and Ledøje-Smørum) of Copenhagen County was drawn from the Danish Civil Registration System, in which all people living in Denmark are registered by a unique 10-digit number. In 1976, a total of 1,200 randomly selected persons born in 1936 (aged 40 years at the time of the study) were invited by a standard letter for a health examination focusing on risk factors for cardiovascular disease. Enclosed was a questionnaire concerning medical history and health and lifestyle to be completed in advance. Between August 1976 and July 1977, a total of 1,052 persons were examined (87.7% of those invited) [22]. In 1995–1996 all participants were invited for a re-examination and 695 were examined (66%) [23]. The 1936 cohort study and the methods employed, including analyses of non-participation, have previously been described [23]. The present study was approved by the Ethics Committee of Copenhagen County (KA 02136).

The questionnaire used in 1995–1996 (at 60 years of age) included the following questions on atopic diseases:

- (1) ‘Has a doctor ever told you that you have hay fever?’ (self-reported hay fever)
- (2) ‘Has a doctor ever told you that you have asthma?’ (self-reported asthma)
- (3) ‘Has a doctor ever told you that you have atopic eczema?’ (self-reported atopic eczema)

These questions were not included in the baseline study at 40 years of age.

Measurement of Aeroallergen Sensitization

At each examination blood was drawn, left to coagulate, serum separated and kept at –20°C until the analysis in 2004. Participants had no knowledge that their participation would later involve serological allergy testing as part of the present study. Measurement of aeroallergen sensitization was performed by using the ADVIA Centaur® Allergy Screen assay (Bayer HealthCare Diagnostics division, Tarrytown, N.Y., USA) [24, 25]. The assay is a multi-allergen assay for the qualitative detection of specific serum IgE antibodies specific to common inhalant allergens in serum. The test includes 19 common inhalant allergens. Aeroallergen sensitization was defined as a positive result of the dichotomized assay output. Serum samples from examinations at both 40 and 60 years of age were analyzed consecutively in 2004.

Assessment of Alcohol Consumption

Both at baseline (40 years) and follow-up (60 years), the participants were asked about their average weekly consumption of beer (bottles), wine (glasses) and spirits (standard drinks) 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 1 bottle of beer, 1 glass of wine and 1 serving of spirits each contain approximately 12 g/15 ml ethanol. The total weekly alcohol consumption was calculated by adding the intake of beer, wine and spirits. Thus, 1 beer, 1 glass of wine or 1 glass of spirit was approximated to 1 standard drink. Total weekly alcohol intake as assessed by this method has previously been found to be strongly

Table 1. Characteristics of study participants with information on aeroallergen sensitization at 40 years (both those with and without follow-up data at 60 years) and at 60 years of age

Characteristics	40 years old		60 years old (n = 612)
	all subjects (n = 989)	subjects without data at 60 years (n = 352)	
Women, % (n)	53.3 (527)	50.0 (176)	52.9 (324)
Smoking, % (n)			
Never smoker	32.8 (324)	22.4 (79)	36.0 (216)
Former smoker	13.3 (131)	12.5 (44)	28.8 (173)
Current smoker	54.0 (534)	65.1 (229)	35.2 (244)
Alcohol intake in drinks/week, % (n)			
0	20.3 (201)	18.5 (65)	15.7 (96)
1–7	43.1 (426)	37.5 (132)	37.4 (228)
8–14	17.2 (170)	18.8 (66)	20.8 (127)
15–21	8.4 (83)	8.8 (31)	11.8 (72)
≥22	11.2 (109)	16.5 (58)	14.3 (87)
Vocational training, % (n)	71.5 (706)	64.1 (225)	80.2 (490)
Aeroallergen sensitization, % (n) ¹	14.9 (147)	15.6 (55)	14.4 (88)
Self-reported hay fever, % (n)	–	–	9.4 (58)
Self-reported eczema, % (n)	–	–	2.3 (14)
Self-reported asthma, % (n)	–	–	7.2 (44)

¹ Aeroallergen sensitization was defined as a positive multi-allergen test for the qualitative determination of serum-specific IgE to a panel of aeroallergens.

and positively associated with increased blood levels of liver enzymes (GGT) [16]. In the statistical analyses, total alcohol consumption was categorized by using cutoffs adopted from another population-based study in Copenhagen, Denmark [16]. As these cutoffs had been arbitrarily chosen, sensitivity analyses using other cutoffs were explored.

Results

Table 1 shows the characteristics of participants at 40 years among those who participated at 60 years and those who did not. Of note is that the prevalence of aeroallergen sensitization at 40 years was similar among participants and non-participants in the follow-up (table 1).

The associations between characteristics of participants at 40 years of age with the prevalence of aeroallergen sensitization at 40 and 60 years are shown in table 2. The 2 highest categories of alcohol consumption were both significantly associated with the prevalence of aeroallergen sensitization at 40 years of age, also after adjusting for other variables (table 2). The results were essentially similar when total alcohol consumption was categorized as 0, 1–10 and >10 drinks per week (data not shown). Of note is that the risk estimate for gender

changed its direction after adjustment for confounders. Further analyses revealed that the greatest change in the risk estimate for gender was seen when alcohol was added to the logistic regression model. Thus, the odds ratio estimate (95% confidence intervals) for gender changed from 1.27 (0.89–1.80) to 1.22 (0.85–1.75) when adding smoking to the unadjusted model, and to 0.93 (0.62–1.41) when further adding alcohol consumption to this model. Alcohol consumption at 40 years was not significantly associated with the prevalence of aeroallergen sensitization at 60 years.

We observed a total of 32 (7.1%) incident and 35 (41.1%) remittent cases of aeroallergen sensitization over the 20-year period from 40 to 60 years of age (table 3). Alcohol consumption at 40 years of age was not significantly associated with either the incidence or remission of aeroallergen sensitization (table 3).

The clinical significance of aeroallergen sensitization was examined by comparing aeroallergen sensitization status at 40 and 60 years of age to the prevalence of self-reported doctor-diagnosed atopic disease at 60 years (table 4). Persistent aeroallergen sensitization (positive at both 40 and 60 years of age) was strongly and statistically significantly associated with self-reported atopic

Table 2. The cross-sectional relationship of smoking and alcohol consumption to the prevalence of aeroallergen sensitization at 40 and 60 years of age

Characteristics	Prevalence and risk of aeroallergen sensitization					
	40 years old			60 years old		
	% (n/total)	crude OR (95% CI)	adjusted OR ¹ (95% CI)	% (n/total)	crude OR (95% CI)	adjusted OR ¹ (95%-CI)
Gender						
Women	13.5 (71/527)	reference	reference	12.4 (40/324)	reference	reference
Men	16.5 (76/462)	1.27 (0.89; 1.80)	0.86 (0.57; 1.31)	16.7 (48/288)	1.42 (0.90; 2.24)	1.20 (0.71; 2.01)
Smoking						
Never smoker	12.4 (40/324)	reference	reference	13.0 (28/188)	reference	reference
Former smoker	13.0 (17/131)	1.06 (0.58; 1.94)	1.03 (0.55; 1.93)	17.9 (31/173)	1.47 (0.84; 2.56)	1.27 (0.71; 2.27)
Current smoker	16.9 (90/534)	1.43 (0.96; 2.14)	1.36 (0.89; 2.07)	12.3 (26/211)	0.94 (0.53; 1.67)	0.86 (0.48; 1.56)
Alcohol intake in drinks/week ²						
0	11.0 (22/201)	reference	reference	11.5 (11/96)	reference	reference
1–7	13.6 (58/426)	1.28 (0.76; 2.16)	1.17 (0.69; 2.01)	14.0 (32/228)	1.26 (0.61; 2.62)	1.09 (0.52; 2.32)
8–14	12.4 (21/170)	1.15 (0.61; 2.17)	1.05 (0.54; 2.06)	11.8 (15/127)	1.04 (0.45; 2.37)	0.85 (0.36; 2.04)
15–21	24.1 (20/83)	2.58 (1.32; 5.05)*	2.36 (1.15; 4.84)*	18.1 (13/72)	1.70 (0.71; 4.06)	1.55 (0.63; 3.79)
≥22	23.9 (26/109)	2.55 (1.37; 4.76)*	2.34 (1.16; 4.72)*	18.4 (16/87)	1.74 (0.76; 3.99)	1.49 (0.61; 3.66)

Aeroallergen sensitization was defined as a positive multi-allergen test for the qualitative determination of serum-specific IgE to a panel of aeroallergens. OR = Odds ratio. * $p < 0.05$.

¹ Model adjusted for gender, smoking, alcohol intake and vocational training.

² Analyses at 40 and 60 years use alcohol consumption recorded at 40 and 60 years, respectively.

Table 3. The relationship of smoking and alcohol consumption at 40 years of age to the development (incidence) and remission of aeroallergen sensitization

Baseline characteristics	Incidence of aeroallergen sensitization			Remission of aeroallergen sensitization		
	% (n/total)	crude OR (95% CI)	adjusted OR ¹ (95% CI)	% (n/total)	crude OR (95% CI)	adjusted OR ¹ (95%-CI)
Gender						
Women	5.5 (15/271)	reference	reference	45.5 (20/44)	reference	reference
Men	7.7 (17/220)	1.43 (0.70; 2.93)	1.86 (0.81; 4.31)	36.6 (15/41)	0.69 (0.29; 1.65)	0.62 (0.22; 1.74)
Smoking						
Never smoker	6.2 (12/193)	reference	reference	41.4 (12/29)	reference	reference
Former smoker	5.9 (4/68)	0.94 (0.29; 3.03)	0.89 (0.26; 3.04)	20.0 (2/10)	0.35 (0.06; 1.97)	0.36 (0.06; 2.10)
Current smoker	7.0 (16/230)	1.13 (0.52; 2.45)	1.05 (0.47; 2.34)	45.7 (21/46)	1.19 (0.47; 3.05)	1.39 (0.45; 4.30)
Alcohol intake, drinks/week						
0	6.2 (7/113)	reference	reference	50.0 (5/10)	reference	reference
1–7	7.7 (17/220)	1.27 (0.51; 3.15)	1.17 (0.46; 3.00)	36.7 (15/41)	0.58 (0.14; 2.32)	0.53 (0.11; 2.60)
8–14	4.6 (4/87)	0.73 (0.21; 2.58)	0.61 (0.16; 2.32)	58.3 (7/12)	1.40 (0.26; 7.58)	1.26 (0.16; 10.08)
15–21	2.9 (1/35)	0.45 (0.05; 3.75)	0.33 (0.04; 2.94)	58.3 (7/12)	1.40 (0.26; 7.58)	1.14 (0.16; 8.19)
≥22	8.3 (3/36)	1.38 (0.34; 5.63)	0.92 (0.20; 4.24)	10.1 (1/10)	0.11 (0.01; 1.24)	0.09 (0.01; 1.21)

Aeroallergen sensitization was defined as a positive multi-allergen test for the qualitative determination of serum-specific IgE to a panel of aeroallergens. OR = Odds ratio.

¹ Model adjusted for gender, smoking, alcohol intake and vocational training.

Table 4. The relationship of aeroallergen sensitization at 40 and 60 years of age to self-reported atopic disease at 60 years

Aeroallergen sensitization status at 40 and 60 years	Self-reported hay fever		Self-reported eczema		Self-reported asthma	
	% (n/total)	OR (95% CI)	% (n/total)	OR (95% CI)	% (n/total)	OR (95% CI)
Negative at 40 and negative at 60	5.2 (24/458)	reference	2.0 (9/458)	reference	5.0 (23/458)	reference
Positive at 40 and negative at 60	2.9 (1/35)	0.53 (0.07; 4.05)	0 (0/35)	–	5.7 (2/35)	1.15 (0.26; 5.07)
Negative at 40 and positive at 60	18.8 (6/32)	4.17 (1.57; 11.10)*	3.1 (1/32)	1.61 (0.20; 13.11)	9.4 (3/32)	1.96 (0.56; 6.90)
Positive at 40 and positive at 60	52.0 (26/50)	19.60 (9.82; 39.08)*	8.0 (4/50)	4.34 (1.29; 14.64)*	26.0 (13/50)	6.65 (3.11; 14.19)*

Aeroallergen sensitization was defined as a positive multi-allergen test for the qualitative determination of serum-specific IgE to a panel of aeroallergens. OR = Odds ratio. * $p < 0.05$.

disease (both hay fever, asthma and atopic eczema) at 60 years (table 4). Also incident aeroallergen sensitization (negative at 40 years and positive at 60 years) was strongly and statistically significantly associated with self-reported hay fever at 60 years. Remittent aeroallergen sensitization (positive at 40 years and negative at 60 years) was not associated with self-reported atopic disease at 60 years.

Discussion

We found that development of aeroallergen sensitization from the age of 40 to 60 years was relatively frequent, and was seen in 7% of persons not sensitized at 40 years. Transient sensitization may have occurred more frequently, as the use of a screening assay of 19 allergens with a dichotomous outcome may conceal cases of remission of one sensitization and onset of another. The proportion of persons sensitized at 40 years who were still sensitized at 60 years was 60%. The prevalence of IgE aeroallergen sensitization in the total population did not change from 40 to 60 years of age. Furthermore, both incidence and persistence of aeroallergen sensitization was a strong predictor of self-reported allergic respiratory disease at 60 years, emphasizing the clinical relevance of aeroallergen sensitization also in older adults.

To the best of our knowledge, these are the first published data on a long-term follow-up of middle-aged persons born before the 1960s. Settupane et al. [7] published a study in young adults born ca. 1940. They were initially scratch-tested with 15 allergens (tree, grass and ragweed pollen, *Alternaria*, cat, dog, and also kapok, feather mix, cow milk and wheat [26]). No data on development of sensitization were presented, but data on symptoms showed that sensitization implied a 3-fold risk of asthma and hay fever.

The immunoassay used in the present study has been shown to be a valid diagnostic test and measure of allergic respiratory disease in the general population [24]. All serum samples were analyzed consecutively by using the same immunoassay and at the same laboratory thereby minimizing bias due to inter-observer and inter-laboratory variability. Moreover, we have previously confirmed the stability of specific IgE in serum samples stored at -20°C for 8 years in our biobank [27]. There was no evidence of degradation of specific IgE during this period. On the contrary, concentrations of specific IgE tended to be higher when samples were re-analyzed after 8 years' storage as compared to the initial analysis, indicating that evaporation during storage or thawing might have occurred. Assuming that evaporation increases with increasing storage time, this would tend to overestimate the concentrations of specific IgE in serum samples kept for the longest time in the biobank, thereby possibly underestimating the incidence of aeroallergen sensitization and overestimating the rate of remission.

We found that alcohol consumption was significantly associated with the prevalence of aeroallergen sensitization but not with its incidence. There are several possible explanations for the lack of association with the incidence of aeroallergen sensitization in spite of a significant association with its prevalence. On the one hand, the limited size of the population and consequently low number of incident cases of aeroallergen sensitization may have increased the likelihood of a false-negative result (a type 2 error). On the other hand, the observed positive cross-sectional association could be due to confounding (e.g. by socioeconomic factors), the influence of which may not be so strong on the incidence of aeroallergen sensitization.

The clinical importance of potential alcohol-induced aeroallergen sensitization is not clear. Few studies have investigated this issue. Bendtsen et al. [21] found in a co-

hort of Danish women that increasing consumption of alcohol was associated with an increased risk of the development of self-reported perennial allergic rhinitis, but not seasonal allergic rhinitis. Due to the lack of information on allergic disease at baseline (in 1976–1978), we cannot investigate the role of alcohol in the development of new (incident) allergic disease. We have recently shown that persons who drink moderate to large amounts of alcohol have a significantly increased prevalence of IgE sensitization to cross-reactive carbohydrate determinants (CCDs) [28, 29]. In these studies, serum-specific IgE sensitization to CCDs was associated with false-positive serum-specific IgE sensitization to CCD-bearing allergens, such as pollens and latex. Inhibition assays supported that IgE sensitization to CCDs can cause false-positive in vitro serum-specific IgE tests to pollen and latex allergens due to cross-reactivity with CCDs. Hence, the cross-sectional positive association between alcohol consumption and aeroallergen sensitization observed in the present study might also be explained by alcohol-induced IgE sensitization to CCDs. CCDs are abundantly present on plant proteins and thus present in different

foods. Of interest, Bakos et al. [30] found a positive association between alcohol consumption and sensitization to food allergens, as determined by skin prick test reactivity to food allergens. The possible mechanisms that may underlie this association include alcohol-induced abnormal protein glycosylation [31], increased permeability of the gastro-intestinal tract, and changes in gastric acid levels [32]. Unfortunately, the present study does not have data on sensitization to food allergens, but this should be considered in future studies on this topic.

In conclusion, aeroallergen sensitization as reflected by serum-specific IgE positivity to aeroallergens is also a dynamic process from 40 to 60 years of age, and novel as well as persistent sensitization were strongly associated with self-reported doctor-diagnosed atopic disease at 60 years of age. Alcohol consumption was found to be significantly associated with the prevalence, but not incidence, of aeroallergen sensitization. Hence, the role of alcohol in the development of aeroallergen sensitization and the possible clinical implications remain to be elucidated.

References

- Jarvis D, Luczynska C, Chinn S, Potts J, Sunyer J, Janson C, Svanes C, Kunzli N, Leynaert B, Heinrich J, Kerkhof M, Ackermann-Lieblich U, Anto JM, Cerveri I, De Marco R, Gislason T, Neukirch F, Vermeire P, Wjst M, Burney P: Change in prevalence of IgE sensitization and mean total IgE with age and cohort. *J Allergy Clin Immunol* 2005;116:675–682.
- Bodtger U, Linneberg A: Remission of allergic rhinitis: an 8-year observational study. *J Allergy Clin Immunol* 2004;114:1384–1388.
- Linneberg A: Changes in atopy over 25 years: allergy epidemic has spread to old age. *BMJ* 2005;331:352.
- Asaranoj A, Ostblom E, Kull I, Lilja G, Pershagen G, Hedlin G, van HM, Wickman M: Sensitization to inhalant allergens between 4 and 8 years of age is a dynamic process: results from the BAMSE birth cohort. *Clin Exp Allergy* 2008;38:1507–1513.
- Bodtger U, Poulsen LK, Malling HJ: Asymptomatic skin sensitization to birch predicts later development of birch pollen allergy in adults: a 3-year follow-up study. *J Allergy Clin Immunol* 2003;111:149–154.
- Bodtger U: Prognostic value of asymptomatic skin sensitization to aeroallergens. *Curr Opin Allergy Clin Immunol* 2004;4:5–10.
- Settipane RJ, Hagy GW, Settipane GA: Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc* 1994;15:21–25.
- Linneberg A, Nielsen NH, Madsen F, Frølund L, Dirksen A, Jørgensen T: Is the increase in allergic respiratory disease caused by a cohort effect? *Clin Exp Allergy* 2002;32:1702–1705.
- Linneberg A: Are we getting enough allergens? *Int Arch Allergy Immunol* 2008;147:93–100.
- Scadding G: Alcohol consumption and allergic rhinitis. *Clin Exp Allergy* 2008;38:1071–1073.
- Gonzalez-Quintela A, Vidal C, Gude F: Alcohol, IgE and allergy. *Addict Biol* 2004;9:195–204.
- Linneberg A, Nielsen NH, Madsen F, Frølund L, Dirksen A, Jørgensen T: Factors related to allergic sensitization to aeroallergens in a cross-sectional study in adults: the Copenhagen Allergy Study. *Clin Exp Allergy* 2001;31:1409–1417.
- Linneberg A, Petersen J, Nielsen NH, Madsen F, Frølund L, Dirksen A, Jørgensen T: The relationship of alcohol consumption to total immunoglobulin E and the development of immunoglobulin E sensitization: the Copenhagen Allergy Study. *Clin Exp Allergy* 2003;33:192–198.
- Gonzalez-Quintela A, Gude F, Boquete O, Rey J, Meijide LM, Suarez F, Fernandez-Merino MC, Perez LF, Vidal C: 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.
- Vidal C, Armisen M, Dominguez-Santalla MJ, Gude F, Lojo S, Gonzalez-Quintela A: Influence of alcohol consumption on serum immunoglobulin E levels in atopic and non-atopic adults. *Alcohol Clin Exp Res* 2002;26:59–64.
- Linneberg A, Hertzum I, Husemoen LL, Johansen N, Jørgensen T: Association between alcohol consumption and aeroallergen sensitization in Danish adults. *Clin Exp Allergy* 2006;36:714–721.
- Bjerke T, Hedegaard M, Henriksen TB, Nielsen BW, Schiotz PO: Several genetic and environmental factors influence cord blood IgE concentration. *Pediatr Allergy Immunol* 1994;5:88–94.
- Linneberg A, Petersen J, Gronbaek M, Benn CS: Alcohol during pregnancy and atopic dermatitis in the offspring. *Clin Exp Allergy* 2004;34:1678–1683.
- Linneberg A, Roursgaard M, Hersoug LG, Larsen ST: Effects of alcohol consumption on the allergen-specific immune response in mice. *Alcohol Clin Exp Res* 2008;32:553–556.

- 20 Linneberg A, Berg ND, Gonzalez-Quintela A, Vidal C, Elberling J: Prevalence of self-reported hypersensitivity symptoms following intake of alcoholic drinks. *Clin Exp Allergy* 2008;38:145–151.
- 21 Bendtsen P, Gronbaek M, Kjaer SK, Munk C, Linneberg A, Tolstrup JS: Alcohol consumption and the risk of self-reported perennial and seasonal allergic rhinitis in young adult women in a population-based cohort study. *Clin Exp Allergy* 2008;38:1179–1185.
- 22 Hollnagel H: The health structure of 40-year-old men and women in the Glostrup area, Denmark: an epidemiological survey. General design, sampling results and referrals for further medical care. *Dan Med Bull* 1980;27:121–130.
- 23 Drivsholm T, Eplov LF, Davidsen M, Jorgensen T, Ibsen H, Hollnagel H, Borch-Johnsen K: Representativeness in population-based studies: a detailed description of non-response in a Danish cohort study. *Scand J Public Health* 2006;34:623–631.
- 24 Linneberg A, Husemoen LL, Nielsen NH, Madsen F, Frolund L, Johansen N: Screening for allergic respiratory disease in the general population with the ADVIA Centaur Allergy Screen Assay. *Allergy* 2006;61:344–348.
- 25 Linneberg A, Gislum M, Johansen N, Husemoen LL, Jorgensen T: Temporal trends of aeroallergen sensitization over twenty-five years. *Clin Exp Allergy* 2007;37:1137–1142.
- 26 Hagy GW, Settipane GA: Bronchial asthma, allergic rhinitis, and allergy skin tests among college students. *J Allergy* 1969;44:323–332.
- 27 Linneberg A, Nielsen NH, Madsen F, Frølund L, Dirksen A, Jørgensen T: 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;106:247–252.
- 28 Coutinho V, Vidal C, Garrido M, Gude F, Lojo S, Linneberg A, Gonzalez-Quintela A: Interference of cross-reactive carbohydrates in the determination of specific IgE in alcohol drinkers and strategies to minimize it: the example of latex. *Ann Allergy Asthma Immunol* 2008;101:394–401.
- 29 Gonzalez-Quintela A, Garrido M, Gude F, Campos J, Linneberg A, Lojo S, Vidal C: Sensitization to cross-reactive carbohydrate determinants in relation to alcohol consumption. *Clin Exp Allergy* 2008;38:152–160.
- 30 Bakos N, Scholl I, Szalai K, Kundi M, Untersmayr E, Jensen-Jarolim E: Risk assessment in elderly for sensitization to food and respiratory allergens. *Immunol Lett* 2006;107:15–21.
- 31 Liinamaa MJ, Hannuksela ML, Ramet ME, Savolainen MJ: Defective glycosylation of cholesteryl ester transfer protein in plasma from alcohol abusers. *Alcohol Alcohol* 2006;41:18–23.
- 32 Untersmayr E, Jensen-Jarolim E: The role of protein digestibility and antacids on food allergy outcomes. *J Allergy Clin Immunol* 2008;121:1301–1308.