

Time Trends in Allergic Sensitisation and *Helicobacter pylori* Prevalence in Finnish Pregnant Women

Tapio Seiskari^{a, b} Hanna Viskari^a Minna Kaila^{c, d} Anna-Maija Haapala^b
Pentti Koskela^e Heikki Hyöty^{a, b}

^aDepartment of Virology, University of Tampere, ^bDepartment of Clinical Microbiology, Centre for Laboratory Medicine, Pirkanmaa Hospital District, ^cFinohta, STAKES, Satellite Office Tampere, and ^dDepartment of Paediatrics, Tampere University Hospital, Tampere, and ^eNational Public Health Institute, Oulu, Finland

Key Words

Birth cohort • Environmental factors • *Helicobacter pylori* • Hygiene hypothesis • IgE antibodies • Pregnancy • Sensitisation

Abstract

Background: An increase in the prevalence of allergic conditions has been documented in Finland, correlating with the diminishing prevalence of *Helicobacter pylori* infections. We investigated whether the increase of allergic sensitisation still continues and correlates with the prevalence of *H. pylori* infections. **Methods:** The sera from 958 pregnant women in 1983, 1989, 1995 and 2001 were analysed for the presence of antibodies against *H. pylori*. In addition, allergen-specific IgE antibodies and total levels of IgE antibodies were measured. **Results:** A clear birth cohort effect was found in the prevalence of allergic sensitization: allergen-specific IgE was more frequent among recent birth cohorts than earlier ones ($p = 0.001$). The frequency of *H. pylori* antibodies followed the opposite trend ($p < 0.001$) and the increase in allergic sensitisation was only seen among *H. pylori*-negative women. A modest increase was also seen in allergic sensitisation between the 4 time series among the *H. pylori*-negative subjects ($p = 0.04$). Total IgE levels did not differ between birth cohorts or

time series. **Conclusion:** The results suggest that hygiene-related environmental factors have played a role in the increase of allergic sensitisation during the last decades.

Copyright © 2009 S. Karger AG, Basel

Introduction

An increase in the prevalence of immunoglobulin E-mediated atopy and allergic diseases has been documented in industrialised countries [1–4]. There is also evidence that in some countries this increase might have reached a plateau [5, 6]. Western lifestyle and urban environment have been related to atopy [4, 7–10], and environmental factors such as childhood exposure to microbes have been proposed to influence allergic sensitisation [7, 9, 11, 12]. Kosunen et al. [1] demonstrated an increase in the levels of allergen-specific IgE antibody from 1973 to 1994 in Finnish subjects, particularly in males. Moreover, they found an inverse relation between allergic sensitisation and antibodies against *Helicobacter pylori* [1].

We investigated this further in a different set of subjects. Our aim was to find out whether the increase in allergen-specific IgE levels has continued beyond the pe-

Table 1. The prevalence (%) of specific IgE antibodies against at least 1 of the tested allergens (cat, birch, egg albumin) in the years 1983, 1989, 1995 and 2001 among Finnish pregnant women with and without IgG antibodies against *H. pylori*

Subjects	Year				p value for trend	Adjusted odds ratio (95% CI) ¹
	1983	1989	1995	2001		
All	30/209 (14)	30/210 (14)	37/235 (16)	47/243 (19)	0.05	1.03 (1.0–1.06)
<i>H. pylori</i> +	6/59 (10)	7/42 (17)	8/56 (14)	4/47 (9) ²	NS	
<i>H. pylori</i> –	24/149 (16)	22/163 (13)	28/172 (16)	43/196 (22) ²	0.04	1.03 (1.0–1.07)

NS = Non-significant.

¹ Odds ratio for increase in 1 year. Analyses were carried out using a logistic regression model that excluded the effects of age and year of birth.

² The proportion of women having allergen-specific IgE differs between *H. pylori*-positive and -negative women in the year 2001 (8.5 vs. 21.9%, $p = 0.036$).

riod previously studied, and if this still correlates with the prevalence of *H. pylori* infections. In addition, we wanted to investigate whether this increase has also happened among Finnish women, resembling that previously reported in males.

Material and Methods

Subjects

For this study, coded (anonymous) serum samples were obtained from the FMC-serum bank of the Finnish National Public Health Institute (KTL). Since 1983, in Finland practically all (>98%) pregnant women have participated in screening for congenital infections (such as HIV, syphilis and hepatitis B) organised by KTL. The purpose of this is to find and prevent possible infectious diseases that would cause a threat to the health and life of the unborn child. Serum samples for screening are drawn from women at the maternity clinics during the first trimester of pregnancy (10–12 weeks of gestation). These sera are stored (–25°C) at the FMC-serum bank. By the end of 2001, the FMC-serum bank contained about 1,350,000 samples from 683,000 women.

A total of 958 randomly selected blood samples from pregnant Finnish women were included in the analysis. The breakdown of the numbers of samples and age of subjects by the year in which the sample was taken was as follows. 1983: $n = 232$, age 17–42 years (median 26); 1989: $n = 240$, age 16–42 years (median 28); 1995: $n = 243$, age 16–43 years (median 29), and 2001: $n = 243$, age 16–49 (median 29). Age distributions between these series were not equal, owing to an observed increase in median ages from 1983 to 2001. This is probably due to the increasing mean age of Finnish pregnant women [13]. Because of these observed differences, the series were further separated into the following age groups: less than 25 years, 25–30 and over 30. The median ages within these groups were 22, 27 and 33 years, respectively. In addition, we analysed subjects by their birth cohort, grouping the following years of birth: 1941–1949 ($n = 34$), 1950–1954 ($n = 81$), 1955–1959 ($n =$

163), 1960–1964 ($n = 254$), 1965–1969 ($n = 198$), 1970–1974 ($n = 122$), 1975–1979 ($n = 71$) and 1980–1985 ($n = 35$).

The study protocol was approved by the KTL ethical committee.

IgE and *H. pylori* Antibodies

Total IgE levels were measured by a microparticle enzyme immunoassay (IMx® Total IgE, Abbott Laboratories) according to the manufacturer's instructions.

The levels of allergen-specific IgE were measured using the ImmunoCap® fluoroenzyme immunoassay (Phadia Diagnostics, Uppsala, Sweden). Specific IgE for 2 common inhalant allergens (birch and cat) and for egg albumin was analysed according to the manufacturer's instructions. These allergens were selected because we wanted to include important representatives of animal and pollen allergens as well as food allergens in this study.

For each allergen-specific IgE, 0.35 kU/l was considered as the cut-off level for positive. In line with earlier studies, total IgE values exceeding 100 kU/l were considered high and possible markers of atopic predisposition [7, 14].

IgG antibodies against *H. pylori* were measured by an enzyme immunoassay (Pyloriset EIA-G III, Orion Diagnostica, Espoo, Finland) according to the manufacturer's instructions. Values 20 U/ml or more were considered to be positive.

Statistical Methods

Statistical analyses were performed with the SPSS program version 14.0 (SPSS Inc., Chicago, Ill., USA). Cross-tabulation and χ^2 tests were applied for the analyses of associations between classified variables. For these purposes, the presence of allergen-specific IgE in the sera was classified as having specific IgE against at least 1 of the tested allergens that exceeded the cut-off levels mentioned above. Kruskal-Wallis and Mann-Whitney tests were applied for the comparisons of continuous variables with skewed distributions against classified variables. As a multivariate technique, logistic regression was applied to identify the independent effect of each parameter when appropriate. In this, the model selection was based on a forward stepwise procedure, where the limit to enter and to remove the term was equal to 0.10.

Fig. 1. Prevalence (%) of IgE antibodies against at least 1 of tested allergens (cat, birch and egg albumin) and IgG antibodies against *H. pylori* among pregnant Finnish women. Subjects were classified according to their year of birth. Blood samples were collected in years 1983, 1989, 1995 and 2001. White bars = allergen-specific IgE >0.35 kU/l ($p = 0.001$ for trend); black bars = *H. pylori* IgG >20 U/ml ($p < 0.001$ for trend).

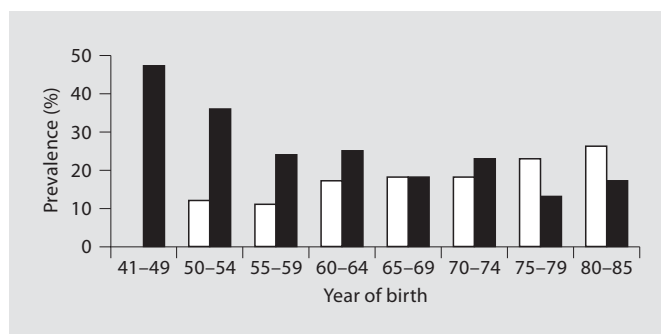


Table 2. Prevalence (%) of IgG class *H. pylori* antibodies among different age groups of Finnish pregnant women

Age groups (years)	Year				All	p value for trend	Adjusted OR (95% CI) ¹
	1983	1989	1995	2001			
<25	20/86 (23) ²	8/61 (13)	14/53 (26)	9/65 (14)	51/265 (19)	NS	
25-30	21/78 (27)	21/98 (21)	14/83 (17)	14/72 (19)	70/331 (21)	NS	
>30	29/65 (45)	21/75 (28)	28/100 (28)	24/106 (23)	102/346 (29)	0.003	0.95 (0.91-0.98)
All	70/229 (31)	50/234 (21)	56/236 (24)	47/243 (19)	223/942 (24)	0.002	0.96 (0.94-0.99)

NS = Non-significant.

¹ OR for increase in 1 year. Analyses were done by a logistic regression model that excluded the effect of age.

² Increase in *H. pylori* antibody prevalence with age: $p = 0.002$ for trend in all, $p = 0.006$ for trend in 1983 time series, $p = 0.036$ for trend in 1989 time series, non-significant for other time series.

If there were missing or indifferent values, cases were not included in the analyses involving those particular parameters. The number of subjects in different analyses may therefore differ. As an illustration, table 1 shows 210 subjects of the 1989 time series with valid allergen-specific IgE results, whereas 205 subjects of the same cohort have valid *H. pylori* test result. All testing was 2-sided. $p < 0.05$ was considered statistically significant.

Results

The proportion of the women positive for serum allergen-specific IgE increased during the study period ($p = 0.05$). Nevertheless, this increase was quite modest and happened only among women who lacked antibodies against *H. pylori* (table 1). Altogether, 12.3% of *H. pylori*-positive women had allergen specific IgE, compared to 17.2% of *H. pylori*-negative women (non-significant). However, in the last time series (2001) *H. pylori*-negative women had significantly higher prevalence of specific IgE than *H. pylori*-positive women (table 1).

Women in the earlier birth cohorts had a clearly lower prevalence of specific IgE compared to women who were born more recently (fig. 1). Furthermore, birth year had an effect on specific IgE prevalence. This effect was confirmed in a logistic regression model excluding the effects of age, *H. pylori* antibodies and year at the time of blood sampling ($p = 0.001$, OR for the effect of 1 year to the increase = 1.037, 95% CI 1.014-1.060). The effect of birth year on prevalence of specific IgE was evident among *H. pylori*-negative women ($p = 0.001$, OR for the effect of 1 year to the increase = 1.041, 95% CI 1.016-1.068). In contrast, it was not seen among *H. pylori*-positive women.

Older age groups had lower prevalence of specific IgE (>0.35 kU/l): 11.4% of women aged over 30 years had specific IgE, compared to 15.8% of women aged 25-30 years and 21.7% of women aged less than 25 years ($p = 0.001$ for trend). This age-dependent effect was strongest in the first time series collected in the year 1983: 7.4% of women aged over 30 had specific IgE, compared to 10.4% of those aged 25-30 years and 23.1% of those younger than 25

years ($p = 0.008$ for trend). Other time series also showed similar kinds of age trends (not statistically significant). The highest prevalence (26.2%) of allergen-specific IgE was observed among the youngest age group within the year 2001 cohort.

A clear decrease occurred in the prevalence of IgG antibodies against *H. pylori* between the years 1983 and 2001 (table 2). Analogously women who were born more recently had fewer *H. pylori* antibodies (fig. 1). The effect of birth year on prevalence of *H. pylori* antibodies was confirmed in a logistic regression model excluding the effects of the age and year at the time of blood sampling ($p < 0.001$, OR for the effect of 1 year to the increase = 0.957, 95% CI 0.939–0.976). *H. pylori* prevalence among women born between 1941 and 1955 was 39.1% (45/115), whereas among women born between 1975 and 1985 it was 14.6% (15/103, $p < 0.001$; fig. 1).

Total IgE levels did not correlate with *H. pylori* IgG. Altogether, 44.8% of women who had a total IgE value exceeding 100 kU/l had specific IgE against at least 1 of the tested allergens, compared to 8.7% among those with lower levels of total IgE ($p < 0.001$). High (at least 100 kU/l) total IgE levels were most frequent in the youngest age groups: 26.2% of women aged less than 25 years had a high value of total IgE, compared to 20.0% of those aged 25–30 years and 16.3% of those aged over 30 years ($p = 0.003$ for trend). When different time series were analysed separately, only the second time series showed a significant trend between the age groups: 32.8% of women aged less than 25 years had high total IgE, compared to 18.4% of those aged 25–30 years and 16.0% of those aged over 30 ($p = 0.021$ for trend). Other time series showed similar kinds of trends (not statistically significant). Total IgE levels showed no differences between different time series or birth cohorts.

Discussion

In the present study a clear birth cohort-effect was seen in the prevalence of allergen-specific IgE, indicating that allergic sensitization has kept increasing during the last decades. A similar increasing trend was also observed between different time series. Altogether, these findings do not herald a release from the growing burden of allergic diseases.

The prevalence of antibodies against *H. pylori* decreased between 1983 and 2001. The prevalence rate did not markedly decline by year of birth among women who were born after the 1960s. In contrast, this kind of de-

crease was seen in women born before the 1960s (fig. 1). In addition, we observed an inverse relation between the presence of *H. pylori* antibodies and allergic sensitisation in the most recent time series (year 2001).

H. pylori prevalence presumably reflects the standards of general hygiene [15]. Thus, the women without *H. pylori* antibodies are likely to represent a group that has lived in environment with high standards of hygiene. There may be some (yet unidentified) factors associated with poor hygiene that protect against allergic sensitisation. If so, the group of *H. pylori*-positive women might have been exposed to these protective factors. *H. pylori*-positive women would therefore be protected against allergy even in the current era when allergies are increasing due to the increasing proportion of population living in highly hygienic conditions. This may also be the explanation for our finding that allergic sensitisation has kept increasing among *H. pylori*-negative women but not among *H. pylori*-positive women. This finding is consistent with previous results by Kosunen et al. [1]. The small number of *H. pylori*-positive women in this study makes it difficult to find an increase in allergic sensitisation. However, as nothing suggested an increase in allergic sensitisation among *H. pylori*-positive women, it is unlikely that a larger sample size would have shown such trend.

The present study shows an increase in allergen-specific IgE among Finnish women in an era beyond the period previously studied. Kosunen et al. have reported an increase of allergen-specific IgE antibodies between 1973 and 1994 in Finland [1]. They measured IgE against 4 inhalant allergens (birch, timothy, cat and dog) in Finnish subjects aged 15–54 years, further distributed to age groups representing ages 15–24, 25–34, 35–44 and 45–54. Of these groups, only the youngest showed a statistically significant increase in the prevalence of allergen-specific IgE. This increase was most remarkable in the subgroup without antibodies against *H. pylori*. The increase was apparent among male subjects, whereas it was not statistically significant among females. Our results indicate that marked increase in allergic sensitisation has also occurred in females, resembling that previously reported in males.

Several studies have focused on the possible role of infections as factors providing protection against allergic sensitisation [7, 9, 11, 12, 16]. *H. pylori*, representing a chronic infection in gastric mucosa, might have microbe-specific potency in diminishing immune responses that lead to allergic sensitisation. *H. pylori* can induce production of IL-10. This suppresses T cell proliferation and cy-

tokine production and can therefore play a role in *H. pylori* persistence by damping the host's immune response [17]. IL-10 is also secreted by allergen-specific T regulatory cells and can suppress IgE production [18]. Moreover, *H. pylori* can suppress the production of IL-6 [17] and thereby promote differentiation of CD4 T cells into Foxp3+ regulatory T cells [19, 20]. On the other hand, in the whole study population allergic sensitisation among *H. pylori*-positive women was not significantly lower than among *H. pylori*-negative women. This suggests that possibly not *H. pylori* itself but some other associated factors may be protecting *H. pylori*-positive women from increasing allergic sensitisation. It is also possible that atopic children have a defective immune response against *H. pylori*, which could lead to false seronegativity in microbe antibodies. This kind of defective immune response has previously been described [21].

We observed higher total IgE levels among youngest age groups. This is in line with previous observations showing an inverse connection with allergic sensitisation and age [1, 3]. However, Jarvis et al. [22] demonstrated that there are only low net changes in sensitisation as the subjects grow older. Hence, the observed age-related differences in this study are probably due to subjects having been born in a different era. In fact, we observed that birth cohort had a stronger effect on the prevalence of allergen-specific IgE than did age.

The present study included only women. Nonetheless, no major differences have been reported between genders in allergic sensitisation, even though some studies have suggested higher prevalence of allergen-specific IgE among male subjects [1, 10]. As previously reported, the increase in the prevalence of allergic sensitisation in Finland during years 1973 to 1994 [1] was largely explained by an increase among male subjects. Atopic eczema is more common among females, while hay fever seems to affect more boys, with a change to a female predominance in adolescence [2, 23]. Furthermore, sex differences have been documented in total IgE levels, males having higher levels irrespectively of age or atopic status [24]. These sex differences can at least partly be explained by differences involving the secretion and function of sex hormones [23].

Pregnancy might have influenced IgE responses detected in the current series. In fact, the prevalence of specific IgE for cat (7.7%) and birch (11.1%) in the 1995 cohort is much higher than observed previously, in 1994 (3.6% for cat and 5.4% for birch) [1]. This might reflect the fact that during pregnancy immune responses may shift from Th-1 responses towards Th-2 responses [25]. Amou-

dreuz et al. [26] showed that during pregnancy, there is a significantly higher spontaneous in vitro production of IL-1 β , IL-6 and IL-10 by peripheral blood mononuclear cells and that total IgE levels are elevated. Hence, pregnancy must be considered as a potential confounding factor, which may have increased the number of IgE positives in the present study.

It is unlikely that all sensitised study subjects were identified using the present panel of 3 allergens in IgE measurements. Nevertheless, cat and birch allergens are among the clinically most relevant allergens in Finland. Furthermore, they are among the allergens most frequently causing sensitisation in Finland [14, 27, 28]. This suggests that the current panel can be used to detect changes in allergic sensitization in this kind of large epidemiological survey.

Theoretically, the long storage time of the samples may have caused the observed change in IgE levels. However, this is unlikely because earlier studies have shown that allergen-specific IgE sustains its stability during long-term storage at -20°C [3, 29].

In conclusion, our results indicate an increase in prevalence of allergic sensitisation among Finnish women. Moreover, certain environmental factors may provide protection against the development of allergy, and *H. pylori* infection possibly reflects this kind of environment. Our results provide no evidence of allergy epidemic reaching a plateau. In fact, the highest prevalence of allergen-specific IgE was observed among the most recent birth cohorts.

Acknowledgments

This study has received support from the Päivikki and Sakari Sohlberg Foundation, the Academy of Finland, the Tuberculosis Foundation in Tampere, the University of Tampere and the Medical research fund of Tampere University Hospital.

References

- Kosunen TU, Hook-Nikanne J, Salomaa A, Sarna S, Aromaa A, Haahtela T: Increase of allergen-specific immunoglobulin E antibodies from 1973 to 1994 in a Finnish population and a possible relationship to *Helicobacter pylori* infections. *Clin Exp Allergy* 2002;32:373–378.
- Butland BK, Strachan DP, Lewis S, Bynner J, Butler N, Britton J: Investigation into the increase in hay fever and eczema at age 16 observed between the 1958 and 1970 British birth cohorts. *BMJ* 1997;315:717–721.
- Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen 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.
- von Hertzen L, Mäkelä M, Petäys T, Jousilahti P, Kosunen T, Laatikainen T, Vartiainen E, Haahtela T: Growing disparities in atopy between the Finns and the Russians: a comparison of 2 generations. *J Allergy Clin Immunol* 2006;117:151–157.
- Zöllner IK, Weiland SK, Piechotowski I, Gabrio T, von Mutius E, Link B, Pfaff G, Kourous B, Wuthe J: No increase in the prevalence of asthma, allergies, and atopic sensitisation among children in Germany: 1992–2001. *Thorax* 2005;60:545–548.
- Braun-Fahrlander C, Gassner M, Grize L, Takken-Sahli K, Neu U, Stricker T, Varonier HS, Wuthrich B, Sennhauser FH; Swiss Study on Childhood Allergy and respiratory symptoms, Air Pollution (SCARPOL) team: No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. *Eur Respir J* 2004;23:407–413.
- Seiskari T, Kondrashova A, Viskari H, Kaila M, Haapala AM, Aittoniemi J, Virta M, Hurme M, Uibo R, Knip M, Hyöty H; the EPIVIR study group: Allergic sensitization and microbial load – a comparison between Finland and Russian Karelia. *Clin Exp Immunol* 2007;148:47–52.
- Bjorksten B, Dumitrascu D, Foucard T, Khetsuriani N, Khaitov R, Leja M, Lis G, Pekkanen J, Priftanji A, Riikjarv MA: Prevalence of childhood asthma, rhinitis and eczema in Scandinavia and Eastern Europe. *Eur Respir J* 1998;12:432–437.
- von Hertzen L, Haahtela T: Asthma and atopy – the price of affluence? *Allergy* 2004;59:124–137.
- Nicolai T, Bellach B, Mutius EV, Thefeld W, Hoffmeister H: Increased prevalence of sensitization against aeroallergens in adults in West compared with East Germany. *Clin Exp Allergy* 1997;27:886–892.
- Matricardi PM, Rosmini F, Riondino S, Fortini M, Ferrigno L, Rapicetta M, Bonini S: Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000;320:412–417.
- Linneberg A, Ostergaard C, Tvede M, Andersen LP, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T: IgG antibodies against microorganisms and atopic disease in Danish adults: the Copenhagen allergy study. *J Allergy Clin Immunol* 2003;111:847–853.
- Kinnunen TI, Luoto R, Gissler M, Hemminki E: Pregnancy weight gain from 1960s to 2000 in Finland. *Int J Obes* 2003;27:1572–1577.
- Vartiainen E, Petäys T, Haahtela T, Jousilahti P, Pekkanen J: Allergic diseases, skin prick test responses, and IgE levels in North Karelia, Finland, and the Republic of Karelia, Russia. *J Allergy Clin Immunol* 2002;109:643–648.
- Malaty HM: Epidemiology of *Helicobacter pylori* infection. *Best Pract Res Clin Gastroenterol* 2007;21:205–214.
- Bach JF: The effect of infections on susceptibility to autoimmune and allergic disease. *N Engl J Med* 2002;347:911–920.
- Bergman MP, Engering A, Smits HH, van Vliet SJ, van Bodegraven AA, Wirth HP, Kapsenberg ML, Vandenbroucke-Grauls CM, van Kooyk Y, Appelmek BJ: *Helicobacter pylori* modulates the T helper cell 1/T helper cell 2 balance through phase-variable interaction between lipopolysaccharide and DC-SIGN. *J Exp Med* 2004;200:979–990.
- Taylor A, Verhagen J, Blaser K, Akdis M, Akdis CA: Mechanisms of immune suppression by interleukin-10 and transforming growth factor- β : the role of T regulatory cells. *Immunology* 2005;117:433–442.
- Weaver CT, Harrington LE, Mangan PR, Gavrieli M, Murphy M: Th17: an effector CD4 T cell lineage with regulatory T cell ties. *Immunity* 2006;24:677–688.
- Cua DJ, Kastelein RA: TGF- β , a ‘double agent’ in the immune pathology war. *Nat Immunol* 2006;7:557–559.
- Arkwright PD, Patel L, Moran A, Haeney MR, Ewing CI, David TJ: Atopic eczema is associated with delayed maturation of the antibody response to pneumococcal vaccine. *Clin Exp Immunol* 2000;122:16–19.
- Jarvis D, Luczynska C, Chinn S, Potts J, Sunyer J, Janson C, 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.
- Osman M: Therapeutic implications of sex differences in asthma and atopy. *Arch Dis Child* 2003;88:587–590.
- Barbee RA, Halonen M, Lebowitz M, Burrows B: Distribution of IgE in a community population sample: correlations with age, sex, and allergen skin test reactivity. *J Allergy Clin Immunol* 1981;68:106–111.
- Williams DJ: Immunological changes during pregnancy; in Warrell DA, Cox TM, Firth JD, Benz EJ (eds): *Oxford Textbook of Medicine*, ed 4. Oxford, Oxford University Press, 2003, vol 2, p 384.
- Amoudrez P, Minan TJ, Sundström Y, Nilsson C, Lilja G, Troye-Blomberg M, Sverremark-Ekstrom E: Pregnancy, but not allergic status, influences spontaneous and induced Interleukin-1 β (IL-1 β), IL-6, IL-10 and IL-12 responses. *Immunology* 2006;119:18–26.
- Pekkarinen PT, von Hertzen L, Laatikainen T, Mäkelä MJ, Jousilahti P, Kosunen TU, Pantelejev V, Vartiainen E, Haahtela T: A disparity in the association of asthma, rhinitis, and eczema with allergen-specific IgE between Finnish and Russian Karelia. *Allergy* 2007;62:281–287.
- von Hertzen LC, Laatikainen T, Pennanen S, Mäkelä MJ, Haahtela T; the Karelian Allergy Study Group: Is house dust mite monosensitization associated with clinical disease? *Allergy* 2008;63:379–381.
- Paganelli R, Ansotegui IJ, Sastre J, Lange CE, Roovers MH, de Groot H, Lindholm NB, Ewan PW: Specific IgE antibodies in the diagnosis of atopic disease. Clinical evaluation of a new in vitro test system, UniCAP, in six European allergy clinics. *Allergy* 1998;53:763–768.