

# There is no evidence of an inverse relationship between T<sub>H</sub>2-mediated atopy and T<sub>H</sub>1-mediated autoimmune disorders: Lack of support for the hygiene hypothesis

Aziz Sheikh, MD, MSc, MRCP, MRCGP,<sup>a</sup> Liam Smeeth, MD, MSc, MRCGP,<sup>b</sup> and Richard Hubbard, MD, MSc, MRCP<sup>c</sup> *London and Nottingham, United Kingdom*

**Background:** The findings of an inverse relationship between T<sub>H</sub>1- and T<sub>H</sub>2-mediated disorders would provide strong empiric support to the hygiene hypothesis.

**Objective:** We sought to investigate the relationship between T<sub>H</sub>2-mediated atopic allergy and T<sub>H</sub>1-mediated autoimmune conditions in a nationally representative population.

**Methods:** We used logistic regression to analyze adult data from the Third National Health and Nutrition Examination Survey. Data on allergic and autoimmune disease history were available for 20,050 subjects, and data on atopy were available for a subsample of 7304 subjects. Atopy was defined by one or more positive skin prick test responses (wheal of  $\geq 3$  mm) to 10 common aeroallergens. Allergic disease was defined by patient reports of physician-diagnosed asthma, hay fever, or both. T<sub>H</sub>1-mediated autoimmune disease was defined by patient reports of physician-diagnosed type 1 diabetes mellitus, thyroid disorders, and/or rheumatoid arthritis.

**Results:** Adjusted for age and sex and taking into account the complex survey design, there was no relationship between atopy and a history of autoimmune disorders (adjusted odds ratio, 1.01; 95% CI, 0.61-1.67;  $P = .97$ ). In contrast, physician diagnosis of allergic disorders was associated with a significant increased risk of physician-diagnosed autoimmune disorders (adjusted odds ratio, 1.67; 95% CI, 1.35-2.07;  $P < .001$ ).

**Conclusion:** We found no evidence of an inverse relationship between atopy and patient reports of physician-diagnosed common autoimmune disorders in the adult American population. Contrary to our initial hypothesis, reports of physician-diagnosed common allergic disorders are positively associated with reports of physician-diagnosed autoimmune disorders, with this possibly being caused by ascertainment bias. These findings suggest that the T<sub>H</sub>1/T<sub>H</sub>2 paradigm might be an oversimplification. (*J Allergy Clin Immunol* 2003;111:131-5.)

**Key words:** Adult, allergic rhinitis, allergy, asthma, atopy, autoimmune, T cell

The T<sub>H</sub>1/T<sub>H</sub>2 paradigm has been proposed as an explanation for the hygiene hypothesis; that is, that risk of allergic diseases is reduced by infection in early childhood.<sup>1</sup> Immune responses are critically regulated by 2 subtypes of T<sub>H</sub> cells.<sup>2</sup> T<sub>H</sub>1 cells produce IFN- $\gamma$  and IL-2, which are now known to be important mediators for the development of organ-specific autoimmune disorders.<sup>3</sup> In contrast, T<sub>H</sub>2 cells produce the cytokines IL-4, IL-5, IL-9, and IL-13, which are responsible for promoting the development of IgE-mediated atopic allergy.<sup>4</sup> Childhood infections might have a key role in stimulating the maturation of the immune system away from the T<sub>H</sub>2 profile that predominates at birth toward a predominantly T<sub>H</sub>1-type phenotype.<sup>5</sup> Although biologically plausible, there is a dearth of epidemiologic evidence to support the T<sub>H</sub>1/T<sub>H</sub>2 model of disease risk.<sup>6,7</sup>

The aim of this study was to investigate the relationship between atopic status and allergic diseases and the risk of autoimmune disorders in the American adult population. A secondary aim was to investigate the relationship between a history of atopic allergic disorders and T<sub>H</sub>1-mediated autoimmune disease.

## METHODS

### Study sample

The Third National Health and Nutrition Examination Survey (NHANES III) was conducted from 1988 to 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention.<sup>8</sup> This study reports on the 20,050 adults sampled in the adult phase (age  $\geq 17$  years) of the survey, of whom all those aged between 17 and 19 years and a random half sample of those aged between 20 and 59 years ( $n = 7304$ ) were included in the allergy subset. The original cross-sectional survey used a complex, multi-stage, stratified probability cluster method to arrive at a sample that represents the total civilian noninstitutionalized population in the 50 states of the United States.<sup>9</sup>

### Assessments and procedures

Subjects with a history of thyroid disorder, rheumatoid arthritis, and/or type 1 diabetes mellitus were classified as having a history of T<sub>H</sub>1-mediated autoimmune disorders (Appendix). Subjects were defined as having type 1 diabetes mellitus if they reported (1) physician-diagnosed diabetes mellitus, (2) current use of insulin, and (3)

From <sup>a</sup>the Department of Public Health Sciences, St George's Hospital Medical School, London; <sup>b</sup>the Department of Epidemiology, London School of Hygiene and Tropical Medicine; and <sup>c</sup>the Department of Epidemiology, University of Nottingham.

Dr Sheikh is supported by an NHS R&D National Primary Care Fellowship. Liam Smeeth is supported by a research fellowship from Thames NHS Executive Research and Development.

Received for publication May 29, 2002; revised September 23, 2002, and October 4, 2002; accepted for publication October 4, 2002.

Reprint requests: Aziz Sheikh, MD, Primary Care Epidemiology Unit, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, United Kingdom.

© 2003 Mosby, Inc. All rights reserved.

0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.8

**Abbreviation used**

NHANES III: Third National Health and Nutrition Examination Survey

no use of oral medications for diabetes.<sup>10</sup> Subjects were categorized as having a history of allergic disease if they provided a history of physician-diagnosed hay fever, asthma, or both.

Skin prick tests were performed on those in the allergy subset by using standardized procedures and allergen extracts for a maximum of 10 common allergens: cat, grass, thistle, oak, peanut, rye, *Alternaria* species, cockroach, house dust mite, and ragweed. Tests with positive (histamine) and negative (glycerinated diluent) controls were also performed. Persons with a wheal length or width of at least 3 mm to one or more allergen skin prick tests were categorized as atopic; all remaining subjects were categorized as nonatopic.<sup>11</sup>

**Statistical analysis**

In keeping with published guidance on analytic methods for NHANES III, sample weights were assigned to adjust for differential selection probabilities, noncoverage, and nonresponse.<sup>12</sup> Analyses were performed to ensure statistically reliable estimates, adjusting for the complex survey design with STATA version 6.0 software.<sup>13</sup> The survey commands used were specifically designed for the analysis of complex survey data. The distinct advantage of using these commands is that the clustered nature of the data, stratification, and weighting are taken into account in the calculation of SEs.<sup>13</sup> Separate, hierarchical, backward, stepwise logistic regression analyses were performed with atopy and history of allergic disorders as the independent variables and history of autoimmune disorders as the dependent variable; the Wald test was used to assess the importance of a variable to models of the relationships under question.

Unless biologically plausible, evidence of interaction between variables was not sought.

Data were extracted on important demographic and socioeconomic factors that could be regarded, on the basis of published evidence, as possible confounders or effect modifiers in the relationship between  $T_H2$ -mediated atopic allergy and  $T_H1$ -mediated autoimmune disorders. The following variables were considered: age, sex, race-ethnicity, and socioeconomic status.<sup>14</sup> Socioeconomic status was measured by using the poverty income ratio, the ratio between a composite measure of the midpoint of the observed family income category and poverty threshold (numerator) and a composite measure of the age of the family reference person and calendar year (denominator). A distinct advantage of this measure over other techniques of measuring socioeconomic status is that it allows income data to be analyzed in a comparable manner across the 6-year period during which NHANES III was conducted.<sup>12</sup>

**Sample size calculations**

Calculations were based on an estimated prevalence of atopy in the study population of 20%.<sup>14</sup> Assuming that 4% of the unexposed (nonatopic) population had a history of  $T_H1$ -mediated autoimmune disorders,<sup>2</sup> a total of 6312 subjects were needed to provide 90% power of detecting an odds ratio of 0.5 at the 5% level of significance.

**RESULTS**

Of the 20,050 adult subjects agreeing to complete the interviewer-administered questionnaire, valid responses to all of the relevant diabetes, thyroid, arthritis, hay fever,

and asthma questions were available for 20,009 (99.8%) subjects; data were available on history of autoimmune conditions for 20,016 subjects and on allergic disease history for 20,043 subjects. Of the 7304 subjects in the allergy subset, valid responses to the relevant components of the interview questionnaire (diabetes, thyroid, arthritis, hay fever, and asthma questions) were available for 7293 (99.9%) subjects. Atopic status could be assigned for 6532 (89.4%) subjects. All relevant information (ie, valid interview and skin prick test results) was available for a total of 6523 (89.3%) subjects. Subjects with missing skin prick test data did not differ significantly in terms of age and sex from those for whom all relevant data items were available.

Of those interviewed, 1938 (8.5%) of 20,016 subjects reported having a physician diagnosis of one or more  $T_H1$ -mediated autoimmune disorders (type 1 diabetes mellitus,  $n = 527$ ; rheumatoid arthritis,  $n = 840$ ; thyroid disease,  $n = 704$ ). A total of 2708 (16.7%) of 20,043 subjects reported having had a physician diagnosis of one or more allergic disorders (asthma,  $n = 1376$ ; hay fever,  $n = 1773$ ).

A total of 1177 (18.4%) subjects in the allergy subset were defined as atopic by using a wheal cut-off point of at least 3 mm on one or more allergy skin prick tests. There was a total of 424 (6.1%) of 7293 subjects within the allergy subsample who reported a history of physician-diagnosed  $T_H1$ -mediated autoimmune disorders (type 1 diabetes mellitus,  $n = 124$ ; thyroid disorders,  $n = 149$ ; rheumatoid arthritis,  $n = 158$ ).

Table I compares characteristics of subjects in the interview sample with and without a history of  $T_H1$ -mediated autoimmune disorders. Table II compares characteristics of subjects in the allergy subsample with and without a history of  $T_H1$ -mediated autoimmune disorders. We report  $P$  values that have been adjusted for the complex study design (Tables I and II).

The crude odds ratio for the relationship between history of allergic disorders and  $T_H1$ -mediated autoimmune disease was 1.58 (95% CI, 1.41-1.79;  $P < .001$ ). The final weighted age and sex adjusted odds ratio for the relationship between history of allergic disorders and  $T_H1$ -mediated autoimmune disorders was 1.67 (95% CI, 1.35-2.07;  $P < .001$ ), suggesting that a history of physician-diagnosed allergic disorders (hay fever, asthma, or both) is associated with an approximately 70% increase in the odds of having a physician-diagnosed  $T_H1$ -mediated autoimmune condition. No other variables considered were confounding factors or effect modifiers in this relationship, as assessed using the Wald test.

The crude odds ratio for the relationship between a history of atopy and  $T_H1$ -mediated autoimmune disease was 1.09 (95% CI, 0.84-1.42;  $P = .52$ ). Age and sex were the only confounding factors. The final weighted age- and sex-adjusted odds ratio for the relationship between atopy and  $T_H1$ -mediated autoimmune disorders was 1.01 (95% CI, 0.61-1.67;  $P = .97$ ; Table III). Again, no other variables considered were confounding factors or effect modifiers in this relationship, as assessed by using the Wald test.

**TABLE I.** Comparison of subjects with a history of T<sub>H</sub>1-mediated autoimmune disorders with those with no such history in the interview sample (n = 20,009 unless indicated)

| Variable                                 | Subjects with history (n = 1938) | Subjects without history (n = 18,071) | P value |
|------------------------------------------|----------------------------------|---------------------------------------|---------|
| Atopic (n = 6523), n (%)                 | 74 (19.3)                        | 1103 (18.0)                           | .99     |
| Allergic disease history, n (%)          | 370 (19.1)                       | 2338 (12.9)                           | <.001   |
| Age, mean (SD)                           | 59.6 (17.4)                      | 46.3 (20.7)                           | <.001   |
| Age category (y), n (%)                  |                                  |                                       | <.001   |
| <20                                      | 17 (0.9)                         | 1572 (8.7)                            |         |
| 21-30                                    | 115 (5.9)                        | 3685 (20.4)                           |         |
| 31-40                                    | 219 (11.3)                       | 3365 (18.6)                           |         |
| 41-50                                    | 236 (12.2)                       | 2389 (13.2)                           |         |
| 51-60                                    | 286 (14.8)                       | 1817 (10.1)                           |         |
| 61-70                                    | 459 (23.7)                       | 2143 (11.9)                           |         |
| 71-80                                    | 401 (20.7)                       | 1780 (9.9)                            |         |
| ≥81                                      | 205 (10.6)                       | 1327 (7.3)                            |         |
| Female sex, n (%)                        | 1393 (71.9)                      | 9233 (51.1)                           | <.001   |
| Poverty income ratio (n = 17,872), n (%) |                                  |                                       | .50     |
| 0-1.99                                   | 944 (54.5)                       | 8372 (51.9)                           |         |
| 2-3.99                                   | 627 (36.2)                       | 6223 (38.6)                           |         |
| 4-5.99                                   | 143 (8.3)                        | 1322 (8.2)                            |         |
| 6-7.99                                   | 15 (0.9)                         | 182 (1.1)                             |         |
| >8                                       | 4 (0.2)                          | 40 (0.3)                              |         |
| Race-ethnicity, n (%)                    |                                  |                                       | .01     |
| Non-Hispanic white                       | 963 (49.7)                       | 7502 (41.5)                           |         |
| Non-Hispanic black                       | 503 (26.0)                       | 4978 (27.5)                           |         |
| Mexican American                         | 409 (21.1)                       | 4886 (27.0)                           |         |
| Other                                    | 63 (3.3)                         | 712 (3.9)                             |         |

**TABLE II.** Comparison of subjects with a history of T<sub>H</sub>1-mediated autoimmune disorders with those with no such history in the allergy subsample (n = 7293 unless indicated)

| Variable                               | Subjects with history (n = 424) | Subjects without history (n = 6869) | P value |
|----------------------------------------|---------------------------------|-------------------------------------|---------|
| Atopic (n = 6523), n (%)               | 74 (19.3)                       | 1103 (18.0)                         | .91     |
| Allergic disease history, n (%)        | 89 (21.0)                       | 917 (13.3)                          | .11     |
| Age (y), mean (SD)                     | 42.9 (11.2)                     | 32.9 (12.0)                         | <.001   |
| Age category (y), n (%)                |                                 |                                     | <.001   |
| <20                                    | 16 (3.8)                        | 1390 (20.2)                         |         |
| 21-30                                  | 51 (12.0)                       | 1803 (26.2)                         |         |
| 31-40                                  | 103 (24.3)                      | 1732 (25.2)                         |         |
| 41-50                                  | 121 (28.5)                      | 1152 (16.8)                         |         |
| 51-60                                  | 133 (31.4)                      | 792 (11.5)                          |         |
| Female sex, n (%)                      | 330 (77.8)                      | 3523 (51.2)                         | <.001   |
| Poverty income ratio (n = 6546), n (%) |                                 |                                     | .38     |
| 0-1.99                                 | 204 (52.4)                      | 3202 (52.0)                         |         |
| 2-3.99                                 | 147 (37.8)                      | 2382 (38.7)                         |         |
| 4-5.99                                 | 36 (9.3)                        | 510 (8.3)                           |         |
| 6-7.99                                 | 2 (0)                           | 60 (0.1)                            |         |
| >8                                     | 0 (0)                           | 3 (0)                               |         |
| Race-ethnicity, n(%)                   |                                 |                                     | .08     |
| Non-Hispanic white                     | 159 (37.5)                      | 2193 (31.9)                         |         |
| Non-Hispanic black                     | 503 (32.3)                      | 2190 (31.9)                         |         |
| Mexican American                       | 111 (26.2)                      | 2164 (31.5)                         |         |
| Other                                  | 17 (4.0)                        | 322 (4.7)                           |         |

## DISCUSSION

Analysis of data from this national cross-sectional survey failed to show evidence of an inverse relationship between atopic status and a history of physician-diagnosed common T<sub>H</sub>1-mediated autoimmune disorders. Furthermore, the results show a strong positive association between a history of T<sub>H</sub>2-mediated allergic disorders and T<sub>H</sub>1-mediated

autoimmune disorders. By far the largest study undertaken to date, these results pose an important challenge to the T<sub>H</sub>1/T<sub>H</sub>2 paradigm as conventionally understood and need to be accommodated into any reformulation of this thesis.

## Study strengths

This study has several important strengths. NHANES III was a meticulously planned and carefully executed

**TABLE III.** Final logistic regression model for relationship between atopy and history of T<sub>H</sub>1-mediated autoimmune disorders (n = 6523)

| Variable                                      | OR    | 95% CI     | P value |
|-----------------------------------------------|-------|------------|---------|
| Atopic                                        | 1.01  | 0.61-1.67  | .97     |
| Age category, y (reference category, 17-20 y) |       |            |         |
| 21-30                                         | 2.48  | 1.10-5.92  | .04     |
| 31-40                                         | 16.44 | 3.69-73.28 | <.001   |
| 41-50                                         | 19.70 | 5.23-74.22 | <.001   |
| 51-60                                         | 25.58 | 7.84-83.45 | <.001   |
| Sex (female compared with male)               | 3.60  | 2.46-5.26  | <.001   |

OR, Odds ratio.

survey of a sample that was representative of the entire adult American population and that achieved an excellent overall response rate (89%). Atopic status was defined objectively by using methods that included standardized allergen solutions, standardized skin prick testing procedures, and technical staff who were trained in the reading of results. Another important strength is that T<sub>H</sub>1 status was defined broadly as a risk of one or more of the most common organ-specific autoimmune conditions<sup>2</sup>; all other studies conducted hitherto have focused on isolated autoimmune conditions, raising the possibility of misclassification of T<sub>H</sub>1 status. Finally, the range of data collected allowed exploration and control for the effects of many important potential confounding factors and effect modifiers in the relationship between atopic allergy and autoimmune conditions.

### Study limitations

Cross-sectional surveys have several important limitations, the most important of these in the context of the present study being the risk of misclassification error and concerns about residual confounding. We relied on patient reports of physician-diagnosed illness, resulting in the possibility of misclassification error as a result of physician misdiagnosis, patient recall error, or both. This is clearly more of a concern with respect to the secondary hypothesis under question (the relationship between allergic disease and T<sub>H</sub>1-type diseases) and might, if it occurred differentially for people with and without disease, provide an explanation for the rather unexpected finding of a positive relationship between allergic and autoimmune disease history. No data were available on maternal smoking during pregnancy, household size, birth order, infant dietary habits, vaccination status, history of childhood infections, antibiotic use, and migration history, raising concerns regarding possible residual confounding.<sup>14</sup>

### Findings in relation to previous work

Previous research investigating the T<sub>H</sub>1/T<sub>H</sub>2 paradigm has produced inconsistent results. Two case-control studies have found negative associations between atopy and multiple sclerosis and rheumatoid arthritis.<sup>15,16</sup> Furthermore, a recent case-control study found that children

with a history of atopic dermatitis (diagnosed on the basis of questionnaire answers) had a significantly reduced risk of subsequent type 1 diabetes.<sup>7</sup> In contrast, evidence in support of the T<sub>H</sub>1/T<sub>H</sub>2 paradigm comes from a large cross-sectional study of Japanese school-children showing an inverse relationship between tuberculin response (a T<sub>H</sub>1-mediated delayed hypersensitivity reaction) and both allergic disease and a T<sub>H</sub>2-type cytokine profile.<sup>17</sup>

However, there are several challenges to the T<sub>H</sub>1/T<sub>H</sub>2 paradigm as currently proposed. Although allergic diseases have increased in prevalence during the last 2 to 3 decades, there has been no corresponding reduction in diseases believed to be driven by a T<sub>H</sub>1-type response.<sup>2</sup> Rather, data from the EURODIAB study show that the incidence of type 1 diabetes mellitus is increasing throughout Europe.<sup>18</sup> A recent ecological study in European and non-European countries showed strong positive correlations between type 1 diabetes mellitus and asthma symptoms.<sup>19</sup> In addition, factors indicative of greater risk of early infection are associated with a reduced risk of type 1 diabetes, which is in contrast to the increased risk predicted from the hygiene hypothesis and T<sub>H</sub>1/T<sub>H</sub>2 paradigms.<sup>20-22</sup> Further challenge to the T<sub>H</sub>1/T<sub>H</sub>2 hypothesis with regard to allergic disease comes from the fact that T<sub>H</sub>1- and T<sub>H</sub>2-mediated conditions might frequently coexist and that helminth infections (potent stimulators of a T<sub>H</sub>2-type response) are protective against allergic disease.<sup>23-25</sup>

A possible explanation is that although one effect of exposure to infections early in life is to stimulate a shift away from a predominantly T<sub>H</sub>2 response, early infection also plays an important role in maturation across the immune system, including downregulation of both T<sub>H</sub>1 and T<sub>H</sub>2 responses. The anti-inflammatory effect of IL-10 provides a possible mechanism for this broad effect.<sup>26</sup> It has recently been shown that higher levels of IL-10 in children with urinary schistosomiasis is associated with a reduced risk of atopy.<sup>24</sup> However, IL-10 is secreted by both T<sub>H</sub>1 and T<sub>H</sub>2 effector cells.<sup>27</sup> Lack of exposure to early infection could lead to a lack of IL-10 and possibly other downregulating factors, leading to a greater risk of both T<sub>H</sub>1-mediated and T<sub>H</sub>2-mediated diseases in later life.

When considered in light of previously published reports, our findings suggest that the T<sub>H</sub>1/T<sub>H</sub>2 model, as currently formulated, might be an oversimplification. More plausible, perhaps, is the recent suggestion that reduced exposure to infectious agents in early childhood might exert a profound adverse effect on the developing immune system, leading to the generation of inappropriate immunologic responses to autoantigens (manifesting as autoimmune disease), allergens (manifesting as atopic allergy), or both.<sup>28</sup>

### REFERENCES

- Strachan DP. Hay fever, hygiene and household size. *BMJ* 1989;299:1259-60.
- Rao A, Avni O. Molecular aspects of T-cell differentiation. *Br Med Bull* 2000;56:969-84.
- Marrack P, Kappler J, Kotzin BL. Autoimmune disease: why and where it occurs. *Nat Med* 2001;7:899-905.

4. Oettgen HC, Geha RS. IgE regulation and its role in asthma pathogenesis. *J Allergy Clin Immunol* 2001;107:429-40.
5. Warner JA, Warner JO. Early life events in allergic sensitisation. *Br Med Bull* 2000;56:883-93.
6. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis." *Thorax* 2000;55:S2-10.
7. Olesen AB, Juul S, Birkebaek N, Thestrup-Pedersen K. Association between atopic dermatitis and insulin-dependent diabetes mellitus: a case-control study. *Lancet* 2001;357:1749-52.
8. National Center for Health Statistics. Plan and operation of the Third Health and Nutrition Examination Survey 1988-94. *Vital Health Stat* 1994;Series 1:1-32.
9. National Center for Health Statistics. Third National Health and Nutrition Examination Survey. Available at: <http://www.cdc.gov/nchs/nhanes.htm>. Accessed July 2001.
10. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183-97.
11. Frew AJ. Skin tests. In: Kay AB, ed. *Allergy and allergic diseases*. Oxford, United Kingdom: Blackwell Science; 1997. p. 1007-11.
12. National Center for Health Statistics. Analytic and reporting guidelines: Third National Health and Nutrition Examination Survey. Hyattsville (MD): Centers for Disease Control and Prevention; 1996.
13. Stata Corporation. Intercooled STATA 6.0 for Windows 98. Available at: <http://www.stata.com/>. Accessed July 2001.
14. Jarvis D, Burney P. Epidemiology of atopic and atopic disease. In: Kay AB, ed. *Allergy and allergic diseases*. Oxford, United Kingdom: Blackwell Science; 1997. p. 1208-26.
15. Oro AS, Guarino TJ, Driver R, Steinman L, Umetsu DT. Regulation of disease susceptibility: decreased prevalence of IgE-mediated allergic disease in patients with multiple sclerosis. *J Allergy Clin Immunol* 1996;97:1402-8.
16. Allanora Y, Hilliquin P, Coste J, Renoux M, Menkes CJ. Decreased prevalence of atopy in rheumatoid arthritis. *Lancet* 1998;351:497.
17. Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse relationship between tuberculin responses and atopic disorder. *Science* 1997;275:77-9.
18. EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. *Lancet* 2000;355:873-6.
19. Stene LC, Nafstad P. Relation between occurrence of type 1 diabetes and asthma. *Lancet* 2001;357:607-8.
20. McKinney PA, Okasha M, Parslow RC, Law GR, Gurney KA, Williams R, et al. Early social mixing and childhood type 1 diabetes mellitus: a case control study in Yorkshire, UK. *Diabetes Med* 2000;17:236-42.
21. Illi S, von Mutius E, Lau S, Bergmann R, Niggemann B, Sommerfeld C, et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 2001;322:390-5.
22. Stene LC, Magnus P, Lie RT, Sovik O, Joner G. Maternal and paternal age at delivery, birth order, and risk of childhood onset type 1 diabetes: population based cohort study. *BMJ* 2001;323:369-71.
23. Kero J, Gissler M, Hemminki E, Isolauri E. Could TH1 and TH2 disease coexist? Evaluation of asthma incidence in children with celiac disease, type 1 diabetes, or rheumatoid arthritis: a register study. *J Allergy Clin Immunol* 2001;108:781-3.
24. van den Biggelaar AH, van Ree R, Rodrigues LC, Lell B, Deelder AM, Kremsner PG, et al. Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet* 2000;356:1723-7.
25. Scrivener S, Yemaneberham H, Tilahun D, Girma S, Ali S, McElroy P, et al. Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. *Lancet* 2001;358:1493-9.
26. Holt PG. Parasites, atopy, and the hygiene hypothesis: resolution of a paradox? *Lancet* 2000;356:1699-701.
27. Spellberg B, Edwards JE. Type 1/Type 2 immunity in infectious diseases. *Clin Infect Dis* 2001;32:76-102.
28. Tedeschi A, Airaghi L. Common risk factors in type 1 diabetes and asthma. *Lancet* 2001;357:1622.

## APPENDIX.

### Relevant questions from NHANES III

#### Diabetes questions

- Ever been told that you have sugar/diabetes?
- Other than during pregnancy, has a doctor ever told you that you have diabetes?
- Age when first told you had diabetes?
- Are you now taking insulin?
- Are you now taking diabetic pills?

#### Arthritis questions

- Doctor ever told you that you have arthritis?
- Type of arthritis: rheumatoid or osteoarthritis?

#### Thyroid question

- Doctor ever told you that you have thyroid disease?

#### Asthma question

- Doctor ever told you that you have asthma?

#### Hay fever question

- Doctor ever told you that you have hay fever?