

## Concordance and interrelationship of atopic diseases and markers of allergic sensitization among adult female twins

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**Background:** Previous twin studies of asthma and allergy implicate both genetic and environmental factors in disease risk, but few have related the occurrence of clinical disease to objective markers of allergic sensitization in twins.

**Objective:** We sought to investigate the concordance and interrelationships of self-reported allergic disease and total and aeroallergen-specific IgE levels within pairs of British adult female twins.

**Methods:** Three hundred forty monozygotic and 533 dizygotic pairs, aged 18 to 72 years, completed questionnaires about allergic disease. Of these, 282 monozygotic and 270 dizygotic pairs were tested for total IgE and specific IgE to Der p 1, mixed grass pollen, and cat dander by means of fluoroimmunoassay.

**Results:** Concordance rates for all variables were higher for monozygotic than for dizygotic twins, significantly ( $P < .05$ ) so for hay fever, eczema, and specific IgE positivity but not ( $P > .05$ ) for self-reported asthma or allergies. Within-pair correlations of log-transformed IgE were 0.59 for monozygotic twins and 0.29 for dizygotic twins, implying heritability of 60%. Within both monozygotic and dizygotic pairs discordant for hay fever or reported allergies, the affected twin had significantly higher total and specific IgE levels. Within pairs who were doubly discordant for 3 allergic diseases, associations between diseases were of similar strength for monozygotic and dizygotic pairs.

**Conclusions:** These results confirm that genetic factors influence susceptibility to aeroallergen sensitization and clinical allergic disease. However, genetically identical twins are often discordant in their expression of atopy, suggesting a substantial modifying role for environmental factors. (*J Allergy Clin Immunol* 2001;108:901-7.)

**Key words:** Asthma, hay fever, eczema, atopy, twins

Twin studies may offer unusual insights into the relative contributions of genetic and nongenetic (environmental and lifestyle) factors in the causation of allergic diseases.<sup>1</sup> Several studies have compared concordance rates for asthma among monozygotic and dizygotic twins,<sup>2</sup> but similar comparisons of other allergic diseases have been less commonly reported. Few twin studies have included objective markers of allergic sensitization.<sup>3-7</sup>

In this article we analyze the concordance of a range of self-reported allergic diseases and levels of circulating total and aeroallergen-specific IgE among a sample of adult female twins examined in London, England. We also compare how different allergic diseases and markers of allergic sensitization aggregate within monozygotic and dizygotic twin pairs.

### METHODS

The St Thomas's UK Adult Twin Registry was used as the source of twins.<sup>8</sup> Briefly, this comprises mainly female twins from throughout the United Kingdom who were recruited by means of media campaigns<sup>9,10</sup> without specifying the diseases for study or the hypotheses to be tested. Pairs were invited to attend the Twin Research Unit, St Thomas's Hospital, London, for a full day of clinical tests, including a self-completed questionnaire relating to allergic diseases. The questions on asthma and related symptoms were those used in the European Community Respiratory Health Survey.<sup>11</sup> Questions on hay fever, allergic rhinitis, and eczema were derived from the International Study of Asthma and Allergies in Childhood.<sup>12</sup> Respondents were asked, "Would you say you were allergic to anything?" They were also asked to specify whether they were allergic to pets, pollen, dust, insect bites, nuts, metals, or other things.<sup>13</sup> Blood was drawn, and cell pellets and serum samples were frozen at  $-40^{\circ}\text{C}$  before analysis. Both members of each pair were examined on the same day, during the period from July 1996 to August 1997. The study was approved by the Local Research Ethics Committee of St Thomas's Hospital, and subjects gave full informed consent.

Zygosity was determined with a standard questionnaire,<sup>14</sup> and multiplex DNA fingerprinting was determined with variable tandem repeats. Levels of total IgE and specific IgE to Der p 1, mixed grass pollen (timothy, rye, sweet vernal, velvet, and cultivated rye grasses), and cat fur were measured by means of fluoroimmunoassay with the Pharmacia Unicap system. Tests were performed in duplicate, and specimens from both members of each twin pair were analyzed on the same batch in each assay. Because of restrictions in available funding, these tests were performed on half of the dizygotic pairs and an equiv-

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**Abbreviations used**

DZ: Dizygotic  
 DZF: Dizygotic female  
 Der p 1: *Dermatophagoides pteronyssinus* 1 allergen  
 MZ: Monozygotic  
 MZF: Monozygotic female  
 O:E: Observed to expected [ratio]  
 PBC: Probandwise concordance

alent number of monozygotic pairs. In both groups the restriction was determined by the date of attendance for examination.

Statistical analyses were performed with Statistical Analysis System software.<sup>15</sup> Probandwise concordance rates were derived for each questionnaire item among monozygotic and dizygotic pairs separately as  $2a/(2a+b)$ , where  $a$  is the number of pairs in which both twins are affected and  $b$  is the number of pairs in which only one twin is affected. The observed/expected concordance ratio was calculated after stratification for age (in 2 groups,  $<50$  and  $\geq 50$  years).<sup>16</sup> The age stratification was necessary for calculating expected concordance rates because the dizygotic pairs were on average younger than the monozygotic pairs, and the prevalence of many of the outcomes varied with age.

Levels of total IgE were log-transformed for analysis. Within-pair correlation coefficients were derived for monozygotic and dizygotic pairs before and after adjustment for age by means of regression modeling. The proportion of variance attributable to additive genetic factors (heritability) was estimated as follows:

$$h^2 = 2(r_{\text{monozygotic}} - r_{\text{dizygotic}}).$$

The proportion of variance attributable to common environmental factors was estimated as follows:

$$c^2 = 2r_{\text{dizygotic}} - r_{\text{monozygotic}}.$$

The proportion of variance attributable to unshared environmental factors was estimated as follows:

$$e^2 = 1 - r_{\text{monozygotic}}.^{17}$$

The relationship between different allergic diseases within twin pairs was investigated by means of matched-pair analyses of disease-discordant pairs in the fashion of an individually matched case-control study.<sup>18</sup> The informative pairs in these analyses are those that are doubly discordant (eg, one twin has asthma, and the other does not; one twin has hay fever, and the other does not). Relative risks were derived from the ratio of discordant pairs (eg, number of pairs in which the asthmatic twin has hay fever divided by the number of pairs in which the nonasthmatic twin has hay fever). CIs were derived indirectly from the  $\chi^2$  test with the McNemar approximation.<sup>18</sup>

## RESULTS

Questionnaires were completed by both members of 873 female twin pairs (340 monozygotic and 533 dizygotic pairs), of whom 552 pairs (282 monozygotic and 270 dizygotic) were tested for total and specific IgE. Their ages at examination ranged from 18 to 72 years (mean, 47 years). Some results are presented separately for the pairs aged less than 50 years (140 monozygotic and 325 dizygotic pairs) and those aged greater than 50 years (200 monozygotic and 208 dizygotic pairs).

### Self-reported symptoms

Table I summarizes the paired responses to symptom questions for each age group. Probandwise concordance rates for reported outcomes ranged widely among both

monozygotic and dizygotic twins. Zero concordances were found for rare outcomes, such as nut allergy, but these are not reliably estimated. The highest concordance rates for both monozygotic and dizygotic twins relate to "any reported allergy." However, even for this highly prevalent outcome, approximately one half of all affected monozygotic twin pairs were discordant for reported allergy.

The concordance rates varied somewhat by age group, partly as a reflection of differences in disease prevalence. The effect of age was particularly marked for asthma: There were too few older asthmatic subjects to make reliable comparisons between monozygotic and dizygotic concordance rates, but the concordance for wheezing did not vary greatly by zygosity (Table I).

Table II shows the observed/expected concordance ratios for each symptom among monozygotic and dizygotic pairs and the ratio comparing monozygotic and dizygotic pairs. These ratios allow for the prevalence of each outcome and therefore permit a more standardized comparison of different allergic diseases.

### Specific IgE

Table I also shows the paired results of specific IgE tests by using a cutoff point of 0.35 kU/L to define a positive outcome. With the exception of specific IgE to cat, where the estimates are imprecise because of low prevalence, concordance rates for monozygotic twins were higher in the younger group than among older twins, whereas among dizygotic twins, concordance rates were similar between the 2 age groups. The highest concordance rates observed (70% and 71%) were for IgE positivity to house dust mite and mixed grass pollen among monozygotic twins aged 18 to 49 years. Thus the combination of genetic susceptibility and an ubiquitous aeroallergen exposure, such as grass pollen, did not inevitably lead to allergic sensitization.

Table II shows the corresponding observed/expected concordance ratios, which were significantly higher in monozygotic pairs than in dizygotic pairs for grass, dust, and any specific IgE positivity. The monozygotic/dizygotic ratio was of similar magnitude for specific IgE to cat, although it was not significant because of the smaller numbers of positive test results.

Concordance for the presence of specific IgE to any of the 3 allergens did not always imply that both members of the twin pair were sensitized to the same allergens. In the 2 age groups combined, there were 35 monozygotic pairs in which both twins had one or more positive test results (pairs concordant for "any specific IgE"). Twenty-one (60%) of these pairs showed the same pattern of positive results on the 3 specific IgE tests. Among the 29 dizygotic pairs who were concordant for "any specific IgE," 14 (48%) had the same pattern of positivity.

Conversely, discordance for IgE to each specific allergen did not always imply absence of IgE responsiveness in the unaffected twin. Table III summarizes the results of all specific IgE tests for monozygotic and dizygotic pairs identified by a proband with specific IgE positivity to each of the 3 allergens in turn. Among the co-twins who expressed atopy (ie, had positive results to at least

**TABLE I.** Probandwise concordance\* of allergic outcomes by age and zygosity

|                              | Monozygotic pairs, age <50 y (max n = 140) <sup>†</sup> |    |     |     | Dizygotic pairs, age <50 y (max n = 325) <sup>†</sup> |     |     |     | Monozygotic pairs, age ≥50 y (max n = 200) <sup>†</sup> |    |     |     | Dizygotic pairs, age ≥50 y (max n = 208) <sup>†</sup> |    |     |     |
|------------------------------|---------------------------------------------------------|----|-----|-----|-------------------------------------------------------|-----|-----|-----|---------------------------------------------------------|----|-----|-----|-------------------------------------------------------|----|-----|-----|
|                              | ++                                                      | +- | --  | PBC | ++                                                    | +-  | --  | PBC | ++                                                      | +- | --  | PBC | ++                                                    | +- | --  | PBC |
| Wheeze ever                  | 22                                                      | 43 | 75  | 50% | 46                                                    | 119 | 159 | 44% | 19                                                      | 57 | 120 | 40% | 19                                                    | 69 | 117 | 35% |
| Wheeze past year             | 12                                                      | 32 | 93  | 43% | 27                                                    | 94  | 197 | 36% | 8                                                       | 40 | 142 | 29% | 9                                                     | 52 | 141 | 26% |
| Asthma ever                  | 14                                                      | 28 | 93  | 50% | 10                                                    | 77  | 225 | 21% | 2                                                       | 34 | 155 | 11% | 2                                                     | 40 | 155 | 9%  |
| Asthma past year             | 5                                                       | 12 | 117 | 45% | 7                                                     | 35  | 267 | 29% | 0                                                       | 13 | 175 | 0%  | 1                                                     | 20 | 176 | 9%  |
| Hay fever ever               | 22                                                      | 34 | 76  | 56% | 43                                                    | 131 | 125 | 40% | 23                                                      | 53 | 109 | 46% | 20                                                    | 54 | 114 | 43% |
| Seasonal rhinoconjunctivitis | 10                                                      | 22 | 105 | 48% | 12                                                    | 78  | 227 | 24% | 6                                                       | 27 | 152 | 31% | 3                                                     | 23 | 160 | 21% |
| Eczema ever                  | 16                                                      | 31 | 86  | 51% | 25                                                    | 99  | 179 | 34% | 14                                                      | 32 | 137 | 47% | 2                                                     | 42 | 152 | 9%  |
| Flexural rash                | 4                                                       | 19 | 114 | 30% | 1                                                     | 53  | 255 | 3%  | 4                                                       | 19 | 164 | 30% | 0                                                     | 21 | 178 | 0%  |
| Dry skin now                 | 27                                                      | 38 | 68  | 59% | 36                                                    | 138 | 130 | 34% | 30                                                      | 47 | 106 | 56% | 28                                                    | 62 | 110 | 47% |
| Urticaria ever               | 3                                                       | 18 | 109 | 25% | 8                                                     | 59  | 230 | 21% | 4                                                       | 28 | 149 | 22% | 6                                                     | 31 | 156 | 28% |
| Allergies                    |                                                         |    |     |     |                                                       |     |     |     |                                                         |    |     |     |                                                       |    |     |     |
| Any                          | 51                                                      | 48 | 39  | 68% | 112                                                   | 130 | 76  | 63% | 53                                                      | 75 | 65  | 59% | 57                                                    | 79 | 65  | 59% |
| Pets                         | 9                                                       | 14 | 98  | 56% | 12                                                    | 56  | 223 | 30% | 1                                                       | 13 | 160 | 13% | 3                                                     | 14 | 162 | 30% |
| Pollen                       | 12                                                      | 25 | 79  | 49% | 22                                                    | 102 | 169 | 30% | 7                                                       | 35 | 131 | 29% | 10                                                    | 41 | 130 | 33% |
| Dust                         | 16                                                      | 21 | 82  | 60% | 10                                                    | 73  | 207 | 22% | 3                                                       | 36 | 137 | 14% | 8                                                     | 32 | 145 | 33% |
| Insect bites                 | 4                                                       | 16 | 96  | 33% | 3                                                     | 58  | 221 | 9%  | 4                                                       | 32 | 138 | 20% | 8                                                     | 35 | 135 | 32% |
| Nuts                         | 0                                                       | 2  | 111 | 0%  | 0                                                     | 11  | 274 | 0%  | 0                                                       | 1  | 169 | 0%  | 0                                                     | 6  | 170 | 0%  |
| Metals                       | 3                                                       | 17 | 98  | 26% | 11                                                    | 57  | 220 | 28% | 8                                                       | 26 | 137 | 38% | 5                                                     | 28 | 144 | 26% |
| Other                        | 20                                                      | 38 | 58  | 51% | 47                                                    | 105 | 131 | 47% | 23                                                      | 57 | 92  | 45% | 24                                                    | 69 | 89  | 41% |
| Specific IgE <sup>‡</sup>    |                                                         |    |     |     |                                                       |     |     |     |                                                         |    |     |     |                                                       |    |     |     |
| Any                          | 20                                                      | 23 | 56  | 32% | 18                                                    | 45  | 67  | 44% | 15                                                      | 28 | 140 | 52% | 11                                                    | 33 | 96  | 40% |
| Cat                          | 5                                                       | 13 | 81  | 43% | 6                                                     | 18  | 106 | 40% | 4                                                       | 5  | 174 | 62% | 0                                                     | 8  | 132 | 0%  |
| Grass                        | 15                                                      | 12 | 72  | 71% | 8                                                     | 34  | 88  | 32% | 9                                                       | 17 | 157 | 51% | 5                                                     | 23 | 112 | 30% |
| Der p 1                      | 15                                                      | 13 | 71  | 70% | 10                                                    | 35  | 85  | 36% | 4                                                       | 24 | 155 | 25% | 6                                                     | 20 | 114 | 38% |

\*Probandwise concordance (PBC) is defined as affected twins in concordant pairs divided by all affected twins.

<sup>†</sup>Numbers with paired responses vary for each outcome. IgE tests are restricted as noted in the text.

**TABLE II.** Observed/expected concordance ratios of allergic outcomes by zygosity

|                              | Monozygotic pairs, all ages;<br>O/E ratio (95% CI) | Dizygotic pairs, all ages;<br>O/E ratio (95% CI) | Monozygotic vs dizygotic pairs,<br>monozygotic/dizygotic ratio (95% CI) |
|------------------------------|----------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------|
| Wheeze ever                  | 1.56 (1.26-1.94) <sup>‡</sup>                      | 1.34 (1.13-1.59) <sup>‡</sup>                    | 1.17 (0.89-1.54) <sup>§</sup>                                           |
| Wheeze past year             | 1.90 (1.39-2.59) <sup>‡</sup>                      | 1.53 (1.22-1.93) <sup>‡</sup>                    | 1.24 (0.84-1.82) <sup>§</sup>                                           |
| Asthma ever                  | 1.86 (1.32-2.63) <sup>‡</sup>                      | 1.16 (0.78-1.74) <sup>§</sup>                    | 1.60 (0.94-2.71) <sup>§</sup>                                           |
| Asthma past year             | 3.52 (1.90-6.55) <sup>‡</sup>                      | 3.05 (1.87-4.98) <sup>‡</sup>                    | 1.15 (0.52-2.54) <sup>§</sup>                                           |
| Hay fever ever               | 1.70 (1.38-2.09) <sup>‡</sup>                      | 1.23 (1.03-1.46) <sup>*</sup>                    | 1.39 (1.06-1.82) <sup>*</sup>                                           |
| Seasonal rhinoconjunctivitis | 2.65 (1.87-3.74) <sup>‡</sup>                      | 1.60 (1.12-2.28) <sup>†</sup>                    | 1.66 (1.01-2.73) <sup>*</sup>                                           |
| Eczema ever                  | 2.31 (1.79-2.97) <sup>‡</sup>                      | 1.28 (0.98-1.67) <sup>§</sup>                    | 1.81 (1.25-2.61) <sup>†</sup>                                           |
| Flexural rash                | 2.91 (1.78-4.74) <sup>‡</sup>                      | 0.33 (0.08-1.32) <sup>§</sup>                    | 8.84 (2.03-38.4) <sup>†</sup>                                           |
| Dry skin now                 | 1.80 (1.50-2.16) <sup>‡</sup>                      | 1.19 (1.00-1.42) <sup>§</sup>                    | 1.51 (1.18-1.95) <sup>‡</sup>                                           |
| Urticaria ever               | 2.13 (1.26-3.60) <sup>†</sup>                      | 1.78 (1.23-2.58) <sup>‡</sup>                    | 1.20 (0.63-2.27) <sup>§</sup>                                           |
| Allergies                    |                                                    |                                                  |                                                                         |
| Any                          | 1.22 (1.07-1.40) <sup>†</sup>                      | 1.16 (1.04-1.29) <sup>†</sup>                    | 1.06 (0.89-1.26) <sup>§</sup>                                           |
| Pets                         | 3.45 (2.23-5.35) <sup>‡</sup>                      | 2.19 (1.53-3.13) <sup>‡</sup>                    | 1.58 (0.90-2.78) <sup>§</sup>                                           |
| Pollen                       | 1.97 (1.44-2.71) <sup>‡</sup>                      | 1.33 (1.04-1.70) <sup>*</sup>                    | 1.48 (0.99-2.21) <sup>§</sup>                                           |
| Dust                         | 2.09 (1.52-2.88) <sup>‡</sup>                      | 1.67 (1.20-2.31) <sup>†</sup>                    | 1.25 (0.79-1.98) <sup>§</sup>                                           |
| Insect bites                 | 2.08 (1.27-3.39) <sup>†</sup>                      | 1.49 (0.98-2.27) <sup>§</sup>                    | 1.39 (0.73-2.65) <sup>§</sup>                                           |
| Nuts                         | 0.00                                               | 0.00                                             | Indeterminate                                                           |
| Metals                       | 2.48 (1.63-3.77) <sup>‡</sup>                      | 2.08 (1.47-2.94) <sup>‡</sup>                    | 1.19 (0.69-2.05) <sup>§</sup>                                           |
| Other                        | 1.45 (1.17-1.79) <sup>‡</sup>                      | 1.29 (1.10-1.52) <sup>‡</sup>                    | 1.12 (0.86-1.47) <sup>§</sup>                                           |
| Positive specific IgE        |                                                    |                                                  |                                                                         |
| Any                          | 2.31 (1.83-2.92) <sup>‡</sup>                      | 1.57 (1.21-2.03) <sup>‡</sup>                    | 1.47 (1.04-2.08) <sup>*</sup>                                           |
| Cat                          | 4.63 (2.92-7.35) <sup>‡</sup>                      | 3.14 (1.78-5.53) <sup>‡</sup>                    | 1.48 (0.71-3.06) <sup>§</sup>                                           |
| Grass                        | 3.71 (2.80-4.92) <sup>‡</sup>                      | 1.92 (1.31-2.83) <sup>‡</sup>                    | 1.93 (1.20-3.11) <sup>†</sup>                                           |
| Dust                         | 3.07 (2.23-4.22) <sup>‡</sup>                      | 1.91 (1.35-2.70) <sup>‡</sup>                    | 1.61 (1.01-2.58) <sup>*</sup>                                           |

O/E, Observed/expected.

<sup>\*</sup>P < .05.

<sup>†</sup>P < .01.

<sup>‡</sup>P < .001.

<sup>§</sup>P > .05, not significant.

**TABLE III.** Concordance of allergen-specific sensitization in monozygotic and dizygotic twin pairs

| Co-twin has specific IgE to:                                                                                   | Monozygotic pairs—<br>Proband has specific IgE to: |      |     | Dizygotic pairs—<br>Proband has specific IgE to: |      |     |
|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------|-----|--------------------------------------------------|------|-----|
|                                                                                                                | Grass                                              | Dust | Cat | Grass                                            | Dust | Cat |
| Same allergen ( $\pm$ others)                                                                                  | 24                                                 | 19   | 9   | 13                                               | 16   | 6   |
| Different allergen only                                                                                        | 6                                                  | 8    | 8   | 12                                               | 8    | 8   |
| None of the 3 allergens                                                                                        | 23                                                 | 29   | 10  | 45                                               | 47   | 18  |
| Co-twins sensitized to the same allergen as a percentage of co-twins sensitized to any of the 3 aeroallergens* | 89%                                                | 83%  | 69% | 68%                                              | 80%  | 60% |

\*Concordant pairs contribute 2 co-twins to both numerator and denominator.

**TABLE IV.** Relationship between allergic diseases, reported allergy, and specific IgE among monozygotic and dizygotic twin pairs discordant for 2 outcomes

| Case definition           | Doubly discordant monozygotic pairs |     |                                     | Doubly discordant dizygotic pairs |     |                                     |
|---------------------------|-------------------------------------|-----|-------------------------------------|-----------------------------------|-----|-------------------------------------|
|                           | Case: Yes                           | No  | Matched-pair relative risk (95% CI) | Case: Yes                         | No  | Matched-pair relative risk (95% CI) |
|                           | Co-twin: No                         | Yes |                                     | Co-twin: No                       | Yes |                                     |
| Asthma ever               |                                     |     |                                     |                                   |     |                                     |
| Hay fever ever            | 18                                  | 7   | 2.6 (1.0-6.5)*                      | 29                                | 13  | 2.2 (1.2-4.2)*                      |
| Eczema ever               | 12                                  | 6   | 2.0 (0.6-6.3)                       | 25                                | 12  | 2.1 (1.1-4.1)*                      |
| Reported allergy          | 17                                  | 6   | 2.8 (1.1-7.5)*                      | 41                                | 8   | 5.1 (2.6-10.1)‡                     |
| Hay fever ever            |                                     |     |                                     |                                   |     |                                     |
| Asthma ever               | 18                                  | 7   | 2.6 (1.0-6.5)*                      | 29                                | 13  | 2.2 (1.1-4.2)*                      |
| Eczema ever               | 11                                  | 7   | 1.6 (0.4-5.5)                       | 35                                | 24  | 1.5 (1.0-4.3)                       |
| Reported allergy          | 41                                  | 2   | 20.5 (7.4-56.9)‡                    | 99                                | 6   | 16.5 (2.5-10.3)‡                    |
| Eczema ever               |                                     |     |                                     |                                   |     |                                     |
| Asthma ever               | 12                                  | 6   | 2.0 (0.6-6.3)                       | 25                                | 12  | 2.1 (1.1-4.1)*                      |
| Hay fever ever            | 11                                  | 7   | 1.6 (0.4-5.5)                       | 35                                | 24  | 1.5 (0.8-2.6)                       |
| Reported allergy          | 14                                  | 3   | 4.7 (1.3-16.2)†                     | 32                                | 17  | 1.8 (0.9-30.4)‡                     |
| Any positive specific IgE |                                     |     |                                     |                                   |     |                                     |
| Asthma ever               | 8                                   | 3   | 2.7 (0.5-13.1)                      | 15                                | 4   | 3.8 (1.2-11.6)*                     |
| Hay fever ever            | 15                                  | 4   | 3.8 (1.2-11.6)*                     | 33                                | 4   | 8.3 (3.4-20.3)*                     |
| Eczema ever               | 4                                   | 6   | 0.7 (0.05-8.2)                      | 9                                 | 8   | 1.1 (0.4-2.9)                       |
| Reported allergy          | 16                                  | 2   | 8.0 (2.1-30.3)‡                     | 25                                | 2   | 12.5 (3.9-40.2)‡                    |

\* $P < .05$ .

† $P < .01$ .

‡ $P < .001$ .

one allergen), the proportion who were sensitized to the same allergen as the proband was significantly ( $P < .05$ ) greater among monozygotic twins than among dizygotic twins for grass pollen (89% vs 68%) but not for dust mite or cat (Table III). These data, based on small numbers, offer only weak support for allergen-specific genetic influences on atopic sensitization.

### Total IgE

Total IgE measurements followed an approximately log-normal distribution, ranging from 2 to 3433 kU/L, with a geometric mean of 29 kU/L. The within-pair correlations of log-transformed total IgE levels were 0.60 for monozygotic pairs and 0.28 for dizygotic pairs. These were virtually unchanged by adjustment for age (0.59 and 0.29, respectively). These within-pair correlations imply a heritability of about 60% for total IgE in this population, with the remaining 40% of the variance in log IgE being attributable to unshared environmental influences and a negligible contribution from shared environmental factors.

### Relationship between allergic markers with-in discordant pairs

The association between allergic diseases, reported allergy, and specific IgE positivity was explored further by focusing on doubly discordant twin pairs (Table IV). Despite the small numbers of doubly discordant pairs, many of the associations were statistically significant. The weakest relationships were with a lifetime history of eczema, whereas there were strong associations within discordant pairs of self-reported allergy with both hay fever and the presence of specific IgE to one or more allergens. The strength of the associations were generally similar for monozygotic and dizygotic pairs and did not differ significantly by zygosity.

Total IgE levels were compared within pairs discordant for allergic diseases by using pairwise  $t$  tests on the log-transformed IgE concentrations. Significant ( $P < .05$ ) differences when comparing the affected twin with the unaffected twin were found only for hay fever and reported allergy and not for asthma or eczema. The within-pair

ratios ranged from 1.0 (no difference) to 1.8 and were generally similar for monozygotic and dizygotic pairs. The greatest difference between affected and unaffected twins was among 68 monozygotic pairs discordant for hay fever (IgE ratio, 1.8; 95% CI, 1.3-2.5), although this did not differ significantly from the corresponding ratio for 80 dizygotic pairs (IgE ratio, 1.2; 95% CI, 0.8-1.8). For reported allergy, the within-pair ratios were similar for 65 disease-discordant monozygotic pairs (IgE ratio, 1.4; 95% CI, 1.0-2.1) and 71 dizygotic pairs (IgE ratio, 1.6; 95% CI, 1.1-2.3).

## DISCUSSION

This is the largest twin study yet published that has included objective markers of allergic sensitization. Our sample of twins was recruited mainly by means of advertisement and therefore in theory may be less representative of all twins than series derived from comprehensive national registers. The most likely type of volunteer bias is toward a higher degree of concordance, particularly among monozygotic pairs.<sup>19</sup> It is unlikely that this would seriously affect comparisons of affected and unaffected twins within discordant pairs, although it may have reduced the number of discordant pairs available for analysis. Major volunteer bias is unlikely because the twins were not recruited specifically for an allergy-related project and were unaware of the hypotheses being tested. Comparisons of the St Thomas twin cohort with general population studies in the United Kingdom suggest that there are no large differences in lifestyle variables or measures of musculoskeletal disease.<sup>9,10,20</sup>

The prevalence of positive specific IgE test results in our twin sample aged 18 to 49 years (Table I) was less than half that reported among young adults of both sexes in Eastern England by using the same cutoff point for a positive test result.<sup>21</sup> In that study 25% had specific IgE to house dust mite, 25% to timothy grass, and 11% to cat fur. A reduced prevalence of allergic rhinitis has been reported among Swedish military recruits who were twins compared with those who were singletons,<sup>22</sup> and rates of hospital admission for childhood asthma in Scotland were lower among twins.<sup>23</sup> Our findings are consistent with a reduced prevalence of allergic sensitization among twins, a phenomenon that deserves further exploration.

Early studies of concordance of allergic disease among monozygotic and dizygotic twins were based on small clinical case series and considered asthma, allergic rhinitis, and eczema in combination. Pairwise concordances, summarized by Wüthrich et al.,<sup>5</sup> were 58% for monozygotic twins and 38% for dizygotic twins, which are equivalent to probandwise concordance rates of 73% and 55%, respectively. In contrast, Edfors-Lubs,<sup>24</sup> in a population-based sample of 6736 Swedish twins, found pairwise concordances for self-reported history of asthma, hay fever, or eczema of 25% for monozygotic twins and 16% for dizygotic twins (equivalent to probandwise concordances of 40% and 28%, respectively). This difference probably reflects the recognized tendency of

clinical case series to overestimate concordance through selective identification of concordant pairs.<sup>25</sup>

Concordance rates for asthma on the basis of nationwide twin registers have recently been summarized by Koppelman et al.<sup>2</sup> For studies that have obtained a lifetime history of asthma by means of questionnaire, usually in children or younger adults,<sup>24,26-30</sup> probandwise concordance rates among monozygotic twins vary from 32% to 62% but are generally in the range 40% to 50%. The corresponding figures for dizygotic pairs vary from 9% to 26%. These are comparable with the concordance rates we obtained for asthma among female twins aged 18 to 49 years (Table I).

Lower concordance rates for adult asthma were reported from the Finnish national twin register (13% for monozygotic pairs and 7% for dizygotic pairs), but in that study asthma was ascertained by means of record linkage to hospital admissions and free medications, a more restrictive case definition.<sup>31</sup> We did not assess the severity of asthma in detail, but among children, monozygotic pairs who are concordant for asthma tend to have more similar indices of severity than dizygotic pairs.<sup>32</sup>

Fewer studies have reported twin concordance rates for other allergic diseases. Among 6736 Swedish twin pairs contacted in the late 1960s, probandwise concordance rates for hay fever were 35% for monozygotic twins and 24% for dizygotic twins.<sup>24</sup> Among 2003 female Australian twin pairs (mean age, 35 years; contacted in the early 1980s), probandwise concordances for "hay fever ever" were 60% for monozygotic twins and 45% for dizygotic twins. The corresponding figures among 919 male pairs were 60% and 33%.<sup>26</sup> Similar concordance rates of 60% for monozygotic pairs and 32% for dizygotic pairs were found among 2000 Finnish twins aged 16 years.<sup>33</sup> These recent figures are consistent with our results for females aged 18 to 49 years (Table I), although surprisingly, no difference in concordance of hay fever by means of zygosity was evident in our older age group.

The only publication that has compared concordance rates for eczema in adults<sup>24</sup> generates probandwise concordance rates of 27% for monozygotic twins and 9% for dizygotic twins. These are substantially lower than our findings in both age groups (Table I). Much higher concordance rates (86% for monozygotic twins and 21% for dizygotic twins) have been reported for atopic dermatitis among Danish children.<sup>34</sup>

Our results for within-pair correlation of log-transformed total circulating IgE levels are consistent with those for American children and young adults reported by Hopp et al.<sup>3</sup> on the basis of 61 monozygotic pairs ( $r = 0.82$ ) and 46 dizygotic pairs ( $r = 0.52$ ). The heritability of total IgE in that study was 61%, which is very similar to our estimate of 60%. Another study, on the basis of a sample of 157 pairs from the Finnish twin registry,<sup>4</sup> analyzed IgE as a dichotomous characteristic rather than a continuous trait, making comparisons difficult.

Our estimates of the concordance of a range of allergic diseases, particularly among the younger age group, are consistent with data from the published literature. For

this reason, they are unlikely to be seriously biased by the method of sample recruitment. Although concordance rates are higher for monozygotic pairs than for dizygotic pairs, indicating a genetic contribution to disease risk, it is also notable that probandwise concordance rates for monozygotic pairs rarely exceed 60%, implying incomplete penetrance of the common genotypes associated with allergic diseases.

Discordance rates of 30% among monozygotic pairs for specific IgE positivity to grass pollen and house dust mite, aeroallergens that are almost ubiquitous in Britain, strongly suggest a modifying influence of nongenetic factors in the process of allergic sensitization. Further examination of pairs with identical genotypes but discordant phenotypes may be particularly informative regarding nongenetic (environmental and lifestyle) influences on atopy and allergic diseases and possible gene-environment interactions.

Small series of disease-discordant monozygotic twin pairs<sup>35-37</sup> have illustrated the potential for genetically identical individuals to differ in respect to patterns of skin prick positivity, specific IgE tests, and levels of total circulating IgE. We also found evidence of phenotypic variation in atopy within identical twin pairs. Among monozygotic pairs in which one twin had circulating IgE to a specific allergen, the other twin was sometimes sensitized only to a different allergen (Table III). This occurred among both monozygotic and dizygotic pairs, suggesting that unshared environmental factors influence the pattern of allergic sensitization in genetically susceptible individuals. One possibility is that infection during a critical period of early allergen exposure may determine whether sensitization develops to each specific allergen.<sup>38</sup>

Our study is one of few to have investigated the relationship between allergic markers within disease-discordant twin pairs. Hopper et al<sup>39</sup> reported a bivariate analysis of "asthma or wheezing ever" and "hay fever ever" in the Australian twin registry. If their data are restricted to the informative doubly discordant pairs, as we have done in Table IV, the matched-pair relative risks associating asthma with hay fever are similar for monozygotic and dizygotic pairs (54/16 = 3.4 for monozygotic female pairs; 51/13 = 3.9 for dizygotic female pairs). In the Finnish adult twin cohort,<sup>40</sup> the corresponding matched-pair relative risks for twins of both sexes were 3.5 (ie, 21/6) for dizygotic pairs and 2.3 (ie, 7/3) for monozygotic pairs. This is consistent with our findings for "asthma ever" and "hay fever ever" and for other interrelationships (Table IV), in which the strength of association among dizygotic twins rarely exceeded that among monozygotic twins and never to a statistically significant degree.

In a more detailed clinical study of Australian twin pairs who were discordant for a history of wheezing, Duffy et al<sup>41</sup> found a significantly larger difference in skin prick test positivity to outdoor allergens (including pollen) between asthma-discordant dizygotic pairs than among asthma-discordant monozygotic pairs, suggesting a genetic association between pollen allergy and asthma. However, the difference between affected and unaffected co-twins in

respect to skin prick positivity to indoor allergens was of similar magnitude for monozygotic and dizygotic pairs, which would be more consistent with our data. This suggests that the association between different clinical manifestations of allergy within individuals reflects acquired phenotypes rather than common or linked genotypes.

We conclude that there is consistent evidence from studies of twin concordance that genetic factors influence susceptibility to aeroallergen sensitization and clinical allergic disease. However, genetically identical twins often vary in their expression of atopy, and it is environmental rather than genetic factors that are of prime importance in determining the pattern of sensitization and associated allergic diseases in individuals with a genetic predisposition to atopy.

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## REFERENCES

1. Hrubec Z, Robinette CD. The study of human twins in medical research. *N Engl J Med* 1984;310:435-41.
2. Koppelman GH, Los H, Postma DS. Genetics and environment in asthma: the answer of twin studies. *Eur Respir J* 1999;13:2-4.
3. Hopp RJ, Bewtra AK, Watt GD, Nair NM, Townley RG. Genetic analysis of allergic disease in twins. *J Allergy Clin Immunol* 1984;73:265-270.
4. Sistonen P, Johnsson V, Koskenvuo M, Aho K. Serum IgE in twins. *Hum Hered* 1980;30:155-8.
5. Wüthrich B, Baumann E, Fries RA, Schnyder UW. Total and specific IgE (RAST) in atopic twins. *Clin Allergy* 1981;11:147-54.
6. Townley RG, Guirgis H, Bewtra A, Watt G, Burke K, Carney K. IgE levels and methacholine inhalation responses in monozygous and dizygous twins. *J Allergy Clin Immunol* 1976;57:227.
7. Bazaral M, Orgel A, Hamburger RN. Genetics of IgE and allergy: serum IgE levels in twins. *J Allergy Clin Immunol* 1974;54:288-304.
8. Boomsma DI. Twin registers in Europe: an overview. *Twin Res* 1998;1:34-51.
9. Spector TD, Keen RW, Arden NK, Morrison NA, Major PJ, Nguyen TV, et al. Influence of vitamin D receptor genotype on bone mineral density in postmenopausal women: a twin study in Britain. *BMJ* 1995;310:1357-60.
10. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. *BMJ* 1996;312:940-4.
11. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;9:687-95.
12. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483-91.
13. Strachan DP, Harkins LS, Golding J, ALSPAC Study Team. Sibship size and self-reported inhalant allergy among adult women. *Clin Exp Allergy* 1997;27:151-5.
14. Sarna A, Kaprio J, Sistonen P, Koskenvuo M. Diagnosis of twin zygosity by mailed questionnaire. *Hum Hered* 1978;28:241-54.
15. SAS System Inc. SAS/STAT user's guide, version 6. 4th ed. Cary (NC): SAS System; 1990.
16. Ramakrishnan V, Goldberg J, Henderson WG, Eisen SA, True W, Lyons MJ, et al. Elementary methods for the analysis of dichotomous outcomes in unselected samples of twins. *Genet Epidemiol* 1992;9:273-87.
17. Jensen AR. Estimation of the limits of heritability of traits by comparison of monozygotic and dizygotic twins. *Proc Natl Acad Sci U S A* 1967;58:149-56.
18. Schlesselman JJ. Case-control studies: design, conduct, analysis. Oxford: OUP; 1982. p. 207-13.
19. Lykken DT, Tellegen A, DeRubies R. Volunteer bias in twin research: the rule of two-thirds. *Soc Biol* 1978;25:1-9.

20. Andrew T, Hart DJ, Snieder H, de Lange M, Spector TD, MacGregor AJ. Are twins and singletons comparable? A study of disease-related and lifestyle characteristics in adult women. *Twin Res* 2001. In press.
21. Chinn S, Jarvis D, Luczynska C, Burney P. Individual allergens as risk factors for bronchial responsiveness in young adults. *Thorax* 1998;53:662-7.
22. Bråbäck L, Hedberg A. Perinatal risk factors for atopic disease in conscripts. *Clin Exp Allergy* 1998;28:936-42.
23. Strachan DP, Moran SE, McInnery K, Smalls M. Reduced risk of hospital admission for childhood asthma among Scottish twins: record linkage study. *BMJ* 2000;321:732-3.
24. Edfors-Lubs ML. Allergy in 7000 twin pairs. *Acta Allergol* 1971;26:249-85.
25. Holm NV. A note on ascertainment probability in the Allen/Hrubec twin model. *Acta Genet Med Gemellol (Roma)* 1983;32:37-47.
26. Duffy DL, Martin NG, Battistutta D, Hopper JL, Mathews JD. Genetics of asthma and hay fever in Australian twins. *Am Rev Respir Dis* 1990;142:1351-8.
27. Harris JR, Magnus P, Samuelson SO, Tambs K. No evidence for effects of family environment on asthma. A retrospective study of Norwegian twins. *Am J Respir Crit Care Med* 1997;156:43-9.
28. Lichtenstein P, Svantengren M. Genes, environments and sex: factors of importance in atopic diseases in 7-9-year-old Swedish twins. *Allergy* 1997;52:1079-86.
29. Laitinen T, Rasanen M, Kaprio J, Koskenvuo M, Laitinen LA. Importance of genetic factors in adolescent asthma. *Am J Respir Crit Care Med* 1998;157:1073-8.
30. Skadhauge LR, Christensen K, Kyvik KO, Sigaard T. Genetic and environmental influence on asthma: a population-based study of 11,688 Danish twin pairs. *Eur Respir J* 1999;13:8-14.
31. Nieminen MM, Kaprio J, Koskenvuo M. A population-based study of bronchial asthma in adult twin pairs. *Chest* 1991;100:70-5.
32. Sarafino EP, Goldfeder J. Genetic factors in the presence, severity and triggers of asthma. *Arch Dis Child* 1995;73:112-6.
33. Räsänen M, Laitinen T, Kaprio J, Koskenvuo M, Laitinen LA. Hay fever, asthma and number of older siblings. *Clin Allergy* 1997;27:515-8.
34. Schultz Larsen F, Holm NV, Henningsen K. Atopic dermatitis. A genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol* 1986;15:487-94.
35. Svartengren M, Ericsson CH, Mossberg B, Camner P. Bronchial reactivity and atopy in asthma discordant monozygotic twins. *Ann Allergy* 1990;64:124-8.
36. Ericsson CH, Svartengren M, Mossberg B, Pedersen N, Camner P. Bronchial reactivity and allergy-promoting factors in monozygotic twins discordant for allergic rhinitis. *Ann Allergy* 1991;67:53-9.
37. Falliers CJ, Cardoso RRdeA, Bane HN, Coffey R, Middleton E. Discordant allergic manifestations in monozygotic twins: genetic identity versus clinical, physiologic and biochemical differences. *J Allergy* 1971;47:207-19.
38. Strachan DP. Lifestyle and atopy. *Lancet* 1999;353:1457-8.
39. Hopper JL, Hannah MC, Macaskill GT, Mathews JD. Twin concordance for a binary trait: III. A bivariate analysis of hay fever and asthma. *Genet Epidemiol* 1990;7:277-89.
40. Huovinen E, Kaprio J, Laitinen LA, Koskenvuo M. Incidence and prevalence of asthma among adult Finnish men and women of the Finnish twin cohort from 1975 to 1990, and their relation to hay fever and chronic bronchitis. *Chest* 1999;115:928-36.
41. Duffy DL, Mitchell CA, Martin NG. Genetic and environmental risk factors for asthma. A cotwin-control study. *Am J Respir Crit Care Med* 1998;157:840-5.