

## Asthma in Light of Patient Documents. A Factor Analytic Study

P A Hahtola,\**MD, PhD*, K H Hahtola,\*\**PhD Forestry*

### Abstract

**Introduction:** The aims of the study were to elucidate the disease spectrum of asthma in clinical practice, the interplay of symptoms, tests and background factors in the diagnosis of asthma and the applicability of exploratory factor analysis in analysing patient documents. **Materials and Methods:** The data in this retrospective cross-sectional study included 195 suspect asthma patients from a systematic sample of 2877 outpatients examined in the Pulmonary Clinic of the Tampere University Hospital from 1983 to 1993 and some statistics on the place of residence and place of birth of the patients. The materials on 73 variables were reduced to 9 factors explaining 40% of the variance in a rotated principal component analysis. **Conclusions:** The factorial description of the patient documents revealed four types of asthma: "allergic", "seasonal", "nasal" and "obstructive" asthma. These phenotypes became more dominant in this order with increasing age. Skin prick reactions to pollen diminished, whereas reactions to epithelia and house dust mite increased from allergic to obstructive asthma. Some slight differences in the patient characteristics were also found with respect to place of residence and place of birth. The use of factor analysis in clinical practice and organisation was demonstrated.

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**Key words:** Age, Factor analysis, House dust mite, Patient documents, Phenotypes of asthma

### Introduction

The lack of uniform criteria for asthma handicaps the diagnosis, the systematic documentation of cases and the consistent reporting of studies addressing asthma.<sup>1-3</sup> It restricts also the use of patient documents of asthmatics especially in detailed causal analysis, although they could give important information for research and administration.

The objectives of this study were to elucidate the disease spectrum of asthma in clinical practice, the interplay of symptoms, tests and background factors in the diagnosis and the applicability of exploratory factor analysis<sup>4</sup> in analysing patient documents.

In order to simplify the terminology, only the term "allergic" is used in this report to refer to states defined by reactivity in skin prick tests (SPTs) or by immunoglobulin E (IgE) findings.<sup>5</sup>

### Materials and Methods

#### Region of Study

The study was carried out in an inland area in the middle of the southern half of Finland. The size of the population

in the Pirkanmaa Hospital District was about 430,000, spread over 35 municipalities. The core municipality, Tampere, was an industrial and service centre with 170,000 residents. The population of the other municipalities ranged from 2000 to 30,000 inhabitants. Tampere has 11 health centres, whereas some small municipalities have a common health centre. The total number of health centres in Pirkanmaa Hospital District is 31. The region also has numerous occupational health care units, private practices and some regional hospitals.<sup>6</sup>

#### Subjects

In Finland, the National Social Insurance Institution provides compensation for most asthma medication, whereas in cases of work-related asthma, insurance companies cover it all. A confirmed diagnosis is necessary for all these forms of compensation. Thus, most local patients suspected of having asthma, especially those with suspected work-related asthma, are examined in the Pulmonary Clinic of the Tampere University Hospital.

The subjects were patients of the adult outpatient clinic of the Tampere University Hospital during an 11-year

\* Consultant, Pulmonology and Allergology  
Department of Pulmonary Diseases  
Tampere University Hospital, Finland

\*\* Professor Emeritus, Land Use Economics  
Department of Economics and Management  
Helsinki University, Finland

Address for Reprints: Dr Paula Hahtola, Kaukolankuja 22, 36200 Kangasala, Finland.  
E-mail: hahtola@sci.fi

period from 1983 to 1993. The basic population consisted of the 2877 new patients who were examined because of suspected asthma and had, at least once, visited one of the authors of this report (PH), who was solely in charge of cases of work-related asthma. In 55% of the cases, this physician also made the diagnosis. Therefore, in comparison with all new asthma patients of the clinic, the patients suspected of having work-related asthma were somewhat over-represented.

With the use of a simple systematic sampling system, every 13<sup>th</sup> patient was included in our study. Ten cases were excluded due to too many missing data. The final number of subjects was 195; 36% were male and 64% were female, with a mean age of 40 years.

### Clinical Examinations

The main clinical tests were the bronchodilator (Brd) test, the measurement of forced expiratory volume in 1 second (FEV<sub>1</sub>) before and after the inhalation of 200 µg of salbutamol, the methacholine (Mch) test, serial peak flow (PEF) recording, skin prick tests (SPTs) for standard allergens and immunoglobulin E (IgE) determinations. The concentration-based Mch test changed in 1989 to a quantitative procedure.<sup>7,8</sup> Forced vital capacity (FVC) with FEV<sub>1</sub> was usually used to determine the initial status of the patient, but it was also used to help evaluate the effect of treatment.

The SPTs were made with the same of extracts (alder, birch, timothy, blue grass, mugwort, horse, dog, cat, cow, *Dermatophagoides pteronyssinus* and *farinae*, *Aspergillus fumigatus*, *Alternaria alternata* and *Cladosporium* from ALK Laboratories, Denmark) throughout the study. SPT was regarded as positive if the longest weal diameter was at least 3 mm larger than the negative control (solvent). Histamine hydrochloride (10 mg/mL) was used as a positive control. A test for IgE was done irregularly, primarily in order to define the grade of atopy. The Brd and Mch tests and PEF recordings were optional, and their use depended on the clinical state of the patient.

Owing to the lack of standard diagnostic criteria, the terms fixed by the National Social Insurance Institution for the compensation of medical treatment for asthma served as essential landmarks. The terms included the increase of PEF or FEV<sub>1</sub> at least 15% (50 L/min or 0.15 L) in the Brd test, the decrease of PEF or FEV<sub>1</sub> at least 15% (50 L/min or 0.15 L) in an exercise stress test or the diurnal PEF change at least 20% (50 L/min). An exercise stress test was seldom done.

### Data

The patient characteristics collected included records on referrals and visits, demographic data, family history,

living conditions, diseases and symptoms, diagnostic tests and diagnoses. In cases where the patients had visited any of the clinics of the Tampere University Hospital up to 1998 after the initial examinations for asthma, the available information on the later status of asthma was also included.

In an attempt to provide information on possible environmental effects, some municipal statistics on the place of residence and the place of birth of the patients were also included. They included data on age structure, income, urbanisation grade, and employment of the municipality of residence and the location and degree of urbanisation of the birthplace.

Some variables available in the patient documents were excluded because of a great number of missing data and a skewed distribution. In addition, we eliminated some variables with similar factor structure in the preliminary analyses. The final factor description thus consisted of 64 variables from the patient documents and 9 variables from the municipal statistics.

The numbers and some statistics of 13 ratio and interval variables are shown in Table I and the numbers and coding of 60 ordinal and dichotomous variables in Table II. Forty-three percent of the 191 tested patients had at least one SPT reaction. This is comparable to other studies.<sup>9,10</sup> The proportion of patients diagnosed as definitely asthmatic was 51%, for 22% the diagnosis was uncertain, and 27% were not asthmatics.

### Factor Analysis

The complex field of asthma is reflected in patient

TABLE I: RATIO AND INTERVAL VARIABLES

| No                   | Variable                                                                | Mean | SD  | Mv |
|----------------------|-------------------------------------------------------------------------|------|-----|----|
| Patient documents    |                                                                         |      |     |    |
| 1                    | Year of first visit                                                     | 1987 | 3.9 | 0  |
| 2                    | Year of diagnosis                                                       | 1986 | 6.4 | 0  |
| 11                   | Age (y)                                                                 | 40   | 14  | 0  |
| 13                   | Height (cm)                                                             | 169  | 9   | 2  |
| 14                   | Weight (kg)                                                             | 74   | 16  | 6  |
| 52                   | FEV <sub>1</sub> (l/s percent of expected)                              | 88   | 16  | 28 |
| 53                   | FVC (l best value of the period)                                        | 3.9  | 1.0 | 30 |
| 60                   | Visit (no. before the confirmed diagnosis)                              | 3.1  | 1.4 | 8  |
| Municipal statistics |                                                                         |      |     |    |
| 65                   | Number of cars per thousand persons                                     | 382  | 25  | 0  |
| 66                   | % of population in urbanised areas                                      | 80   | 19  | 0  |
| 67                   | % of population of 0 to 14 years                                        | 18   | 2.2 | 0  |
| 68                   | % of population of 65 years or more                                     | 16   | 3.5 | 0  |
| 69                   | Mean yearly income of households [Fmk x 1000 ( <i>Euro about</i> )]     | 161  | 16  | 0  |
| 70                   | Employment (self-sufficiency % of workplaces in the residential region) | 98   | 18  | 0  |

FEV<sub>1</sub>: forced expiratory volume in 1 second; FVC: forced vital capacity; Mv: missing values

TABLE II: ORDINAL AND DICHOTOMOUS VARIABLES

| No     | Variable Content and Class Codes                                                         | % of classes 0-4 |    |    |    |    | Mv |
|--------|------------------------------------------------------------------------------------------|------------------|----|----|----|----|----|
|        |                                                                                          | 0                | 1  | 2  | 3  | 4  |    |
|        | Patient documents                                                                        |                  |    |    |    |    |    |
| 3-6    | Admission months                                                                         |                  |    |    |    |    |    |
|        | XI-II: 1, III-IV: 2, V-VIII: 3, IX-X: 4                                                  |                  | 37 | 14 | 34 | 15 | 0  |
| 7-10   | Referred from health centre: 1, private practice: 2, hospital: 3, occupational health: 4 |                  | 46 | 22 | 13 | 19 | 0  |
| 12     | Sex, male: 0, female: 1                                                                  | 36               | 64 |    |    |    | 0  |
| 15     | Married, no: 1, yes: 2                                                                   |                  | 35 | 65 |    |    | 10 |
| 16     | Born in summer/winter months, X-IV: 1, V-IX: 2                                           |                  | 43 | 57 |    |    | 0  |
| 17     | Asthma in father, mother and/or other relatives: 0-3                                     | 61               | 35 | 4  | 1  |    | 4  |
| 18     | Smoking pack-years, no: 0, <10: 1, ≥10: 2                                                | 66               | 20 | 15 |    |    | 2  |
| 19     | Recently non-smoking, <1 month: 0, 1 month-10 years: 1, >10 years: 2                     | 18               | 10 | 72 |    |    | 0  |
| 20     | Urban type dwelling, farmhouse: 1, detached: 2, semi-detached: 3, block of flats: 4      |                  | 9  | 41 | 10 | 40 | 11 |
| 21     | Pet at home, 0, 1                                                                        | 70               | 30 |    |    |    | 4  |
| 22-25  | Occupational class, home*: 1, service: 2, industry: 3, farming: 4                        |                  | 18 | 35 | 42 | 11 | 0  |
|        | Diseases in last 2 years                                                                 |                  |    |    |    |    |    |
| 26, 28 | Digestive organs: 1, skin: 2                                                             |                  | 11 | 26 |    |    | 1  |
| 27     | Heart, vessels and/or muscles, skeleton: 0-2                                             | 71               | 24 | 5  |    |    | 1  |
| 29     | Sum of diseases 26-28, and nervous or mental, genitourinary and hormonal: 0-6            | 41               | 36 | 16 | 5  | 2  | 1  |
| 30     | Nasal polyp and/or cavity infection ever: 0-2                                            | 80               | 18 | 3  |    |    | 4  |
| 31     | Nasal hypersensitivity ever: 0, 1                                                        | 19               | 81 |    |    |    | 4  |
| 32     | Seasonal nasal symptoms, no: 0, unclear: 1, yes: 2                                       | 63               | 9  | 28 |    |    | 33 |
| 33     | Recently nasal symptoms, no: 0, <3 months: 1, 3-12 months: 2, 1-3 years: 3, >3 years: 4  | 18               | 3  | 12 | 18 | 48 | 9  |
| 34     | Common colds yearly, <1: 0, 1-2: 1, >2: 2                                                | 81               | 9  | 10 |    |    | 1  |
| 35     | Pulmonary symptoms, Breathlessness: 1                                                    |                  | 91 |    |    |    | 3  |
| 36     | Wheezing: 1                                                                              |                  | 58 |    |    |    | 6  |
| 37     | Cough: 1                                                                                 |                  | 77 |    |    |    | 7  |
| 38     | Phlegm: 1                                                                                |                  | 52 |    |    |    | 1  |
| 39     | Sum of symptom classes, 35-38: 0-4                                                       |                  | 10 | 34 | 30 | 26 | 2  |
| 40     | Seasonal pulmonary symptoms, no: 0, unclear: 1, yes: 2                                   | 80               | 12 | 8  |    |    | 2  |
| 41     | Recently pulmonary symptoms, <3 months: 1, 3-12 months: 2, 1-3 years: 3, >3 years: 4     |                  | 8  | 26 | 31 | 35 | 0  |
| 42     | Symptoms to pollen, house dust, animal dust, work air: 0-4                               | 11               | 44 | 26 | 16 | 3  | 1  |
| 43     | Symptoms to food, drink and/or drug: 0-3                                                 | 81               | 15 | 3  | 1  |    | 1  |
| 44     | Pulmonary symptoms to exertion: 0, 1                                                     | 51               | 49 |    |    |    | 17 |
| 45-48  | SPT positive, pollen: 1, epithelia: 2, house dust mite: 3, mould: 4                      |                  | 29 | 27 | 15 | 8  | 4  |
| 49     | Positive SPT classes, 45-48: 0-4                                                         | 56               | 19 | 15 | 7  | 2  | 3  |
| 50     | IgE U/L, <30: 1, 30-100: 2, >100: 3                                                      |                  | 40 | 24 | 37 |    | 72 |
| 51     | B-eos 10 <sup>9</sup> l <sup>-1</sup> , <0.2: 1, 0.2-0.4: 2, >0.4: 3                     |                  | 54 | 30 | 16 |    | 26 |
| 54     | Positive bronchodilator test: 1                                                          |                  | 22 |    |    |    | 92 |
| 55     | Methacholine test: 1                                                                     |                  | 56 |    |    |    | 38 |
| 56     | Peak flow home recording: 1                                                              |                  | 59 |    |    |    | 98 |
| 57     | Wheezing in auscultation: 1                                                              |                  | 21 |    |    |    | 1  |
| 58     | Positive asthma test classes, 54-57: 0-4                                                 | 33               | 32 | 25 | 9  | 2  | 0  |
| 59     | Performed SPT (0, 1) and asthma tests 54-56: 0-4                                         | 0                | 9  | 27 | 41 | 24 | 0  |
| 60     | Visit number before the confirmed diagnosis**                                            | 0                |    | 44 | 31 | 11 | 8  |
| 61     | No asthma: 0, uncertain asthma: 1, certain: 2                                            | 27               | 22 | 51 |    |    | 0  |
| 62     | Diagnosis made by PH: 1, by other physicians: 0                                          | 45               | 55 |    |    |    | 8  |
| 63     | Guidance concerning home, work, medication: 0-3                                          | 14               | 49 | 32 | 5  |    | 0  |
| 64     | Asthma later, better: 0, stable: 1, worse: 2                                             | 53               | 28 | 19 |    |    | 48 |
|        | Municipal statistics                                                                     |                  |    |    |    |    |    |
| 71     | Born outside the residential province: 0, inside: 1                                      | 44               | 55 |    |    |    | 0  |
| 72     | Birthplace, urban: 1, densely populated: 2, rural: 3                                     |                  | 47 | 15 | 39 |    | 0  |
| 73     | Birthplace, coastal: 0, inland: 1                                                        | 13               | 87 |    |    |    | 0  |

B-eos: first value of blood eosinophil count; IgE: immunoglobulin E; Mv: missing values

\*home work, student or retired; \*\*visit number, 5: 9%, 6: 6%

documents, which as data source means a great number of variables with varying degrees of quantification and conceptual validity, the result being low correlation.

According to Thurstone,<sup>4</sup> no field of research is so chaotic as it seems at first sight, but rather somehow structured. As a correlational method, the factor analysis rests on the assumption that a substantial part of the common variance included in the correlation matrix can be explained by a reduced number of linear transformations, called factors, which represent this underlying structure. The factorial structures thus revealed have proved to be relatively invariant with respect to changes in subjects and the set of variables.

In the case of this study material, we considered that the underlying factor structure might reveal types of asthma or asthmatics, that would enhance a parsimonious description of the field. The second author of the study, alike, had in his earlier work<sup>11</sup> delineated by factor analysis a typology of farming in different socio-economic environments, to explain the forest owner's predispositions, rationale, and attitudes in forest management.

Factor analysis proceeds in three stages: factorisation, rotation and interpretation.<sup>12-14</sup>

*Factorisation* is where the number of dimensions (factors) are decided and the factors extracted. From the two main methods available: 1) principal axes factorising based on common variance and 2) principal component factorising using the total variance of variables, we used principal components. For exploratory, i.e. more in theory-generating than in theory-testing purposes, these methods do not have any substantial difference.

Using screen-test, arranging eigenvalues, i.e. percent of total variance of the principal components successively extracted, in a simple plot (5.38, 4.30, 3.81, 3.46, 3.07/ 2.69, 2.59/ 2.31, 2.27/ 2.05, 2.05, 1.91), we found the number of components 5, 7 and 9 being proper cutting points, where the decrease of eigenvalues seems to level off. Thus, the proposed underlying structure would be 5, 7 or 9 dimensional. On proceeding by both 7 and 9 principal components, we found the 9-dimensional factor-description most compelling. The clear cutting point in screen-test gives a hint of possible underlying "simple structure" in the correlation matrix, which would enhance the clear interpretation of factors or principal components.

*Rotation*, by which, in order to make the interpretation as easy as possible, one tries to locate the factor axes according to the "simple structure" of factor space. Then, each factor will tend to have either large or small loadings of particular variables. Orthogonal Varimax rotation is the most common rotation method.

*Interpretation* is the crucial stage in the analysis,

because it confers empirical meaning to the mathematical formalism, which is constructed in factorisation and rotation. Owing to the inevitable subjectivity of interpretation this stage presupposes experience and acquaintance of the field of study.<sup>12-14</sup>

The factor analysis in our study (Table III), using principal component solution with Varimax rotation (SPSS 8.0 for Windows), was carried out in two phases. First, the 9 rotated components, factors FI-FIX, were interpreted. In the interpretation, the variables with variance clearly concentrating on one factor, the "pure indicators" of factors, received the most attention. However, the total behaviour of the variables was emphasised rather than single loadings.<sup>11</sup> Then, the factor structures of the variables were scrutinised in detail. In the detailed analysis, in order to provide additional insight into patient characteristics and the role of clinical tests and symptoms in diagnostics, factor scores (Fig. 1) calculated separately for patients with certain, uncertain and no asthma, were also used.

## Results

### Factor Interpretation

The loadings of the central variables depicting the nasal and pulmonary symptoms (30-44), the results of the sensitivity and asthma tests (45-58), the certainty of the asthma diagnosis (61), the treatment (63) and the later asthma status (64) were concentrated into factors FI, FIII, FVIII, and FIX. (The numbers of variables referred to in factor analysis are given in brackets throughout the text.) These 4 factors can be interpreted as *phenotypes of asthma* or *asthmatics* and, with respect to the tests of obstruction, they could be put in the following order: FI, FVIII, FIX and FIII. Factors FV and FVI seemed to represent some patient

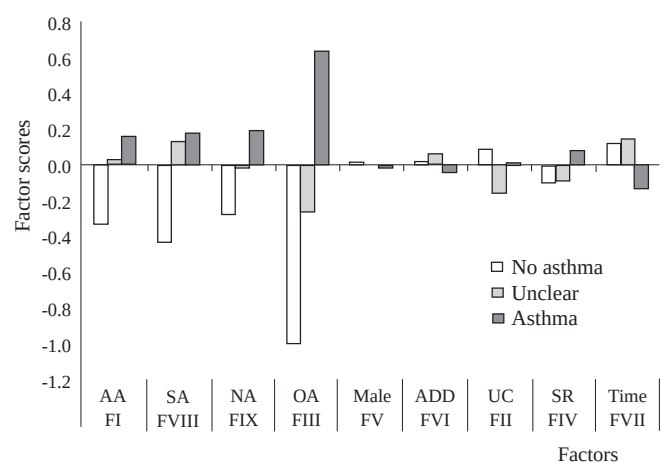


Fig. 1. Factor (FI-FIX) scores related to the certainty of asthma. AA: allergic asthma; ADD: age dependent diseases; Male: male sex; NA: nasal asthma; OA: obstructive asthma; SA: seasonal asthma; SR: surrounding region, Time: changes during the study period; UC: urban centre

TABLE III: FACTOR ANALYSIS, ROTATED COMPONENTS (FI-FIX)

| Variables                       | No | FI           | FVIII        | FIX          | FIII        | FV           | FVI          | FII          | FIV          | FVII         | C    |
|---------------------------------|----|--------------|--------------|--------------|-------------|--------------|--------------|--------------|--------------|--------------|------|
|                                 |    | AA           | SA           | NA           | OA          | MALE         | ADD          | UC           | SR           | TIME         |      |
| Patient documents               |    |              |              |              |             |              |              |              |              |              |      |
| Year of first visit             | 1  |              |              |              |             |              | 0.18         |              |              | <b>0.61</b>  | 0.41 |
| Year of diagnosis               | 2  |              | -0.13        | -0.13        |             |              |              |              | -0.16        | <b>0.63</b>  | 0.47 |
| Admission                       |    |              |              |              |             |              |              |              |              |              |      |
| November-February               | 3  | 0.11         | <b>-0.51</b> |              |             |              | -0.12        |              | -0.12        |              | 0.31 |
| March-April                     | 4  |              | 0.13         |              |             |              | 0.11         | 0.19         | 0.10         | -0.16        | 0.12 |
| May-August                      | 5  |              | <b>0.48</b>  | <b>-0.24</b> |             |              | 0.16         |              |              | <b>0.24</b>  | 0.38 |
| September-October               | 6  |              |              | <b>0.34</b>  | -0.11       |              | -0.16        | -0.16        |              | -0.11        | 0.21 |
| Referred by                     |    |              |              |              |             |              |              |              |              |              |      |
| Health centre                   | 7  |              | -0.18        | 0.14         | -0.13       |              |              | <b>-0.58</b> |              | <b>0.21</b>  | 0.46 |
| Private practice                | 8  | -0.13        |              |              |             |              |              | <b>0.31</b>  |              | <b>-0.49</b> | 0.36 |
| Hospital                        | 9  | 0.17         | <b>0.35</b>  |              | 0.18        | -0.14        |              |              |              |              | 0.23 |
| Occupational health             | 10 | -0.12        | -0.12        | -0.18        |             | 0.18         |              | <b>0.37</b>  |              | <b>0.32</b>  | 0.33 |
| Age                             | 11 | <b>-0.40</b> | <b>-0.24</b> |              | 0.17        | -0.18        | <b>0.48</b>  | -0.18        |              |              | 0.55 |
| Sex                             | 12 |              |              |              |             | <b>-0.81</b> |              |              |              |              | 0.70 |
| Height                          | 13 |              |              |              |             | <b>0.83</b>  | -0.11        |              |              | -0.13        | 0.73 |
| Weight                          | 14 | -0.16        | -0.13        |              |             | <b>0.53</b>  | <b>0.24</b>  | -0.11        |              |              | 0.41 |
| Marital status                  | 15 | -0.14        | <b>-0.32</b> |              |             | -0.11        | <b>0.28</b>  | <b>-0.32</b> |              |              | 0.33 |
| Born in summer/winter           | 16 |              |              | 0.12         | -0.15       | -0.19        | <b>0.21</b>  |              | -0.15        | 0.12         | 0.16 |
| Asthma in family                | 17 |              |              |              |             | -0.13        |              |              |              | 0.18         | 0.07 |
| Smoking pack-years              | 18 | <b>-0.25</b> |              |              | 0.13        | <b>0.22</b>  | <b>-0.20</b> | 0.11         | <b>0.21</b>  | <b>0.27</b>  | 0.30 |
| Non-smoking time                | 19 | 0.16         |              |              |             | <b>-0.20</b> | <b>0.25</b>  | -0.11        | -0.18        | <b>-0.34</b> | 0.29 |
| Urban type dwelling             | 20 |              |              |              |             | -0.13        | -0.10        | <b>0.72</b>  |              |              | 0.56 |
| Pet at home                     | 21 |              | <b>-0.30</b> |              |             |              | -0.13        | <b>-0.27</b> | 0.12         | <b>0.21</b>  | 0.25 |
| Home work                       | 22 | <b>0.26</b>  | <b>0.29</b>  | 0.19         | -0.13       |              |              |              |              |              | 0.23 |
| Service                         | 23 |              | 0.16         |              |             | <b>-0.58</b> | <b>-0.30</b> | 0.18         |              | -0.11        | 0.50 |
| Industrial work                 | 24 | -0.13        | <b>-0.31</b> |              |             | <b>0.49</b>  | <b>0.35</b>  | <b>0.22</b>  |              | <b>0.25</b>  | 0.59 |
| Farm work                       | 25 |              |              |              |             |              |              | <b>-0.69</b> |              | -0.14        | 0.52 |
| Digestive diseases              | 26 | 0.14         |              |              |             |              | <b>0.38</b>  |              | 0.14         |              | 0.21 |
| Functional diseases             | 27 | -0.18        |              | 0.14         |             |              | <b>0.69</b>  |              |              | -0.10        | 0.56 |
| Skin diseases                   | 28 |              | <b>0.43</b>  | <b>-0.21</b> |             |              | <b>0.20</b>  |              | 0.19         | 0.17         | 0.33 |
| Non-respiratory disease classes | 29 | -0.14        | 0.19         |              |             | 0.14         | <b>0.75</b>  |              |              |              | 0.66 |
| Nasal history                   |    |              |              |              |             |              |              |              |              |              |      |
| Polyps                          | 30 |              | 0.13         | 0.15         | 0.18        |              |              |              |              | -0.18        | 0.11 |
| Hypersensitivity                | 31 | 0.12         | 0.13         | <b>0.58</b>  |             |              |              | 0.18         | <b>-0.22</b> | <b>0.20</b>  | 0.49 |
| Seasonal                        | 32 | <b>0.33</b>  | <b>0.37</b>  |              |             |              | <b>-0.29</b> |              |              |              | 0.35 |
| Duration                        | 33 | <b>0.21</b>  | <b>0.22</b>  | <b>0.60</b>  |             |              |              | 0.15         | <b>-0.23</b> |              | 0.55 |
| Frequency of flu                | 34 |              | 0.11         |              | 0.14        | 0.13         |              |              |              |              | 0.07 |
| Pulmonary symptoms              |    |              |              |              |             |              |              |              |              |              |      |
| Breathlessness                  | 35 |              |              | <b>0.39</b>  |             |              |              |              |              | -0.16        | 0.21 |
| Wheezing                        | 36 |              |              | <b>0.38</b>  | <b>0.33</b> |              |              |              | 0.11         |              | 0.28 |
| Cough                           | 37 | <b>-0.35</b> | -0.17        | 0.12         |             |              | <b>-0.21</b> |              |              | <b>0.34</b>  | 0.33 |
| Phlegm                          | 38 | <b>-0.29</b> |              | <b>0.45</b>  |             | -0.10        | -0.15        |              |              | <b>0.31</b>  | 0.43 |
| Sum of classes                  | 39 | <b>-0.34</b> | -0.17        | <b>0.59</b>  | 0.16        |              |              |              | 0.10         | <b>0.27</b>  | 0.62 |
| Seasonal symptoms               | 40 | <b>0.28</b>  | <b>0.36</b>  |              | -0.12       |              |              |              |              |              | 0.25 |
| Duration                        | 41 |              | <b>0.39</b>  | 0.10         |             |              |              |              | -0.11        | <b>-0.24</b> | 0.25 |
| Pulmonary symptoms to           |    |              |              |              |             |              |              |              |              |              |      |
| Inhaled allergens               | 42 | <b>0.31</b>  | <b>0.32</b>  | 0.14         |             |              | 0.12         |              | -0.15        | <b>0.34</b>  | 0.37 |
| Oral allergens                  | 43 |              | 0.13         |              |             |              | <b>0.26</b>  |              |              |              | 0.10 |
| Exertion                        | 44 | 0.11         | <b>0.20</b>  | <b>0.38</b>  | 0.10        |              |              |              |              |              | 0.22 |

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TABLE III. Cont'd

| Variables                      | No | FI          | FVIII        | FIX          | FIII         | FV          | FVI          | FII          | FIV          | FVII         | C    |
|--------------------------------|----|-------------|--------------|--------------|--------------|-------------|--------------|--------------|--------------|--------------|------|
|                                |    | AA          | SA           | NA           | OA           | MALE        | ADD          | UC           | SR           | TIME         |      |
| Positive SPT to                |    |             |              |              |              |             |              |              |              |              |      |
| Pollen                         | 45 | <b>0.75</b> | 0.14         |              |              |             |              | 0.18         |              |              | 0.63 |
| Epithelia                      | 46 | <b>0.71</b> | 0.13         | 0.12         | 0.11         | -0.10       |              |              |              |              | 0.56 |
| House dust mite                | 47 | <b>0.54</b> | -0.19        |              | <b>0.25</b>  |             |              | <b>-0.21</b> |              |              | 0.45 |
| Mould                          | 48 | <b>0.54</b> | -0.12        |              |              |             |              |              | 0.16         |              | 0.34 |
| Sum of classes                 | 49 | <b>0.92</b> |              |              | 0.10         |             |              |              |              |              | 0.87 |
| IgE                            | 50 | <b>0.53</b> |              |              |              |             |              |              | 0.19         |              | 0.34 |
| B-eos                          | 51 | 0.16        |              | <b>0.36</b>  | 0.18         |             |              |              | 0.11         |              | 0.22 |
| FEV <sub>1</sub>               | 52 |             |              | <b>-0.23</b> | <b>-0.34</b> | 0.10        | <b>-0.34</b> | 0.16         | -0.16        |              | 0.35 |
| FVC                            | 53 | 0.17        |              |              | -0.17        | <b>0.71</b> | <b>-0.37</b> |              |              | -0.11        | 0.73 |
| Positive asthma tests          |    |             |              |              |              |             |              |              |              |              |      |
| Bronchodilator                 | 54 |             | 0.14         | 0.15         | <b>0.27</b>  |             | 0.17         |              |              | -0.17        | 0.18 |
| Methacholine                   | 55 |             |              | 0.13         | <b>0.66</b>  |             | -0.11        |              |              |              | 0.48 |
| Peak flow recording            | 56 |             | 0.14         |              | <b>0.61</b>  |             |              |              |              | -0.10        | 0.42 |
| Auscultation                   | 57 |             | <b>-0.25</b> |              | <b>0.45</b>  |             | 0.11         |              | 0.15         | <b>-0.20</b> | 0.35 |
| Sum of classes                 | 58 |             | -0.11        |              | <b>0.90</b>  |             |              |              |              |              | 0.83 |
| Sum of performed SPT and 55-57 | 59 | -0.17       | <b>-0.23</b> |              | <b>0.44</b>  |             |              |              |              | <b>0.28</b>  | 0.38 |
| Number of visits               | 60 | -0.12       | 0.12         | -0.18        | <b>0.30</b>  | 0.16        |              |              |              | <b>0.26</b>  | 0.25 |
| Certainty of asthma            | 61 | <b>0.21</b> | <b>0.25</b>  | 0.18         | <b>0.72</b>  |             |              |              |              | -0.12        | 0.68 |
| Physician                      | 62 |             |              |              | -0.12        |             |              |              | 0.15         | <b>0.33</b>  | 0.16 |
| Treatment quantity             | 63 | <b>0.22</b> |              |              | <b>0.56</b>  |             |              | -0.12        | -0.10        |              | 0.39 |
| Later asthma status            | 64 |             | <b>0.30</b>  |              | <b>0.21</b>  |             |              |              |              | -0.12        | 0.17 |
| Municipal statistics           |    |             |              |              |              |             |              |              |              |              |      |
| Number of cars                 | 65 |             | 0.17         |              |              |             |              | <b>-0.51</b> | <b>0.66</b>  |              | 0.73 |
| Rate of urbanisation           | 66 | 0.10        | -0.17        | 0.13         |              |             |              | <b>0.86</b>  |              |              | 0.80 |
| Children <14 years %           | 67 | 0.13        |              |              |              |             |              |              | <b>0.90</b>  |              | 0.84 |
| Persons >64 years %            | 68 | -0.15       | 0.15         | -0.14        |              |             | -0.12        | <b>-0.67</b> | <b>-0.53</b> |              | 0.82 |
| Annual income                  | 69 | <b>0.20</b> |              |              |              |             | 0.11         | <b>0.42</b>  | <b>0.75</b>  |              | 0.80 |
| Employment, self-sufficiency   | 70 |             | -0.14        |              |              |             |              | 0.28         | <b>-0.77</b> |              | 0.71 |
| Born in present living region  | 71 | <b>0.23</b> |              | -0.15        |              | 0.14        |              | -0.12        | <b>-0.23</b> |              | 0.17 |
| Born in rural region           | 72 | -0.18       |              | -0.17        | 0.17         |             | 0.15         | <b>-0.39</b> |              | -0.18        | 0.30 |
| Born in inland                 | 73 |             |              | <b>-0.25</b> |              |             |              |              |              | 0.18         | 0.11 |
| Eigenvalue                     |    | 4.33        | 2.64         | 2.55         | 3.7          | 3.07        | 2.69         | 3.95         | 3.27         | 2.64         | 29.9 |

Factors: AA: allergic asthma; ADD: age dependent diseases; MALE: male sex; NA: nasal asthma; OA: obstructive asthma; SA: seasonal asthma; SPT: skin prick test; SR: surrounding region; TIME: changes during the study period; UC: urban centre

Loadings under [10] are not signed, over [19] are in boldface

B-eos: blood eosinophil count; C: communality; FEV<sub>1</sub>: forced expiratory volume in 1 second; FVC: forced vital capacity; IgE: immunoglobulin E

characteristics not directly related to asthma. Two factors, FII and FIV, were associated with regional conditions. Factor FVII depicted changes during the study period.

### Types of Asthma

The number of positive asthma tests (58) proved to be a rather pure measurer of factor FIII. Loadings of all the single tests for obstructive tendency (54-58) and the certainty of asthma diagnosis (61) were also concentrated into this factor. Factor FIII could thus be interpreted as "obstructive asthma" (OA). Many tests (59) and visits before the diagnosis (60) and multiple treatment forms (63) were also associated with this type of asthma. Wheezing, a worsening later course and the SPT reaction to house dust mite were other characteristics of this phenotype (36, 64, 47).<sup>15</sup>

Factor FIX included prominent pulmonary symptoms, breathlessness, wheezing and phlegm (35, 36, 38). Because of the accentuation of several nasal symptoms (31, 33), factor FIX was named "nasal asthma" (NA).

Seasonal (32, 40) and repeated (33, 41) nasal and pulmonary symptoms were characteristic of factor FVIII. Being based on the seasonal symptoms and on the concentration of the clinic admissions to summer (3, 5), factor FVIII was interpreted as "seasonal asthma" (SA). Skin problems (28) and the later worsening of asthma (64) were notable.<sup>15</sup> The clear negative loading of auscultation (57) and a negative association between perennial allergens and the seasonal-type asthma agrees also with the total picture of this factor (SA, 21).

Because of its rather pure measurer, the number of positive SPT reactions (49), factor FI was interpreted as “allergic asthma” (AA). The reactions to single SPT allergens and the results of the IgE test (45-49) were also concentrated into this factor. These allergic features with seasonal nasal (32, 33) and pulmonary (40) symptoms proved to be characteristic, especially for young patients (11). Some of the youngest patients, because of their increasing age, had probably come from a paediatric clinic to an adult clinic for instruction (63). In addition to the allergic type of asthma, the dimension FI seemed to differentiate allergic symptoms from the typical smoking-related (19, 20) symptoms (37, 38) of older people.

#### *Patient Characteristics not Related to Asthma*

A pure measurer of factor FV was male sex (12). In addition the variables depicting height and weight (13, 14), good lung function (53) and industrial occupation (23, 24) were the most highly loaded on this factor. Factor FV thus represented male sex and the relative size of the patients, and it was named “male sex” (Male).

The best indicator of factor VI was the number of non-respiratory (29) diseases, such as those of the digestive system (26), heart, vessels, muscles, skeleton (27) and also skin (28). On the other hand, the factor was associated with decreased pulmonary function (52, 53). Furthermore, because of the high loadings on age and weight (11, 14) and the perennial nature of the symptoms (32), factor VI was interpreted as “age-dependent diseases” (ADD). The accentuation of industrial occupation (24) refers also to work-related diseases.

#### *Other Factors*

The loadings of the variables depicting the place of residence of the patients were concentrated into factors FII and FIV. According to its best measurers, especially a high rate of urbanisation in the municipality of residence (66) and urban dwelling and occupations (20, 25), factor FII depicted the centres with the most urban way of life and could be interpreted as the “urban centre” (UC). In addition, factor FII represented the dimension farming versus non-farming occupation (25).

The best regional indicators of factor FIV were the high proportion of children (67) and the parallel low proportion of elderly persons in the population (68). Other regional characteristics of the factor were the high income of households (69), high number of cars (65) and low self-sufficiency of employment in the municipality of residence (70). Thus, this factor points to regions where commuting to workplaces outside one's own place of residence is typical and it can be interpreted as “surrounding region” (SR).

Factor VII was named “TIME” since its best measurers were the times of the first visit and diagnosis (1, 2). It illuminates the changes that occurred in patient characteristics during the study period.

#### *Detailed Analysis*

##### Patient referral and seasonal variation

Nasal asthmatics tended to be admitted in the autumn (NA, 6), while the proportion of seasonal asthmatics was clearly accentuated in the summer (SA, 3, 5). A tendency towards admissions in the spring or summer months was also discernible for patients with age-dependent diseases (ADD, 4, 5) and those from the urban centres (UC) or their surroundings (SR). The weighting of the admissions in summer seemed to increase during the study period (TIME, 5).

Patients referred by a hospital (9) had been diagnosed as asthmatics, especially seasonal, obstructive or allergic asthmatics (SA, OA, AA), more often than those referred by others. Nasal asthmatics tended to come from health centres (NA, 7). The patients coming from occupational health units had seldom an allergic, seasonal or nasal phenotype of asthma (AA, SA, NA, 10).

As for regional differences, private practices and occupational health units were accentuated as referral sources in urban regions, and health centres were the commonest referral sources in rural regions (UC, 8, 10, 9).

##### Demographics of the patients

The patient characteristics were mostly related to age and occupation (11, 22-25). The features of the four phenotypes of asthma, allergic, seasonal, nasal and obstructive asthma (AA, SA, NA, OA, 11), emerged in this order with age. The higher proportion of unmarried (15) among the allergic and seasonal asthmatics (AA, SA) than among the nasal or obstructive asthmatics (NA, OA) may also have depended on age.

Working at home (22) was more common among the allergic, seasonal and nasal asthmatics (AA, SA, NA), but working outside home was more common among obstructive asthmatics (OA, 22-25). Industrial work was common for both young male (MALE, 11, 24) and elderly patients with age-related disorders (ADD), but it was seldom found among allergic or seasonal asthmatics (AA, SA, 24).

The only sign of smoking as an aggravating factor for asthma<sup>16</sup> in this material was indicated by the slight loading of smoking for obstructive asthmatics (OA, 18). Smoking seemed to be more common among male industrial workers (MALE, 18-19) and among patients living in urban centres (UC, 18-19) and in the surrounding regions (SR).

Patients with age-dependent diseases tended to have been born in summer (ADD, 16), whereas the obstructive asthmatics were primarily born in winter (OA, 16).<sup>17</sup> The low communality and scattered loadings of this variable discourage, however, further hypothesising. Any consistent association of asthma with sex (12),<sup>18,19</sup> asthma in relatives (17), pets (21), or type of residence (20) could not be found either by the group of variables and subjects used in our study.

#### Symptoms and sensitivity tests

Both the reactions to the skin prick tests and the symptoms related to inhaled allergens (42, 45-49) indicated that allergy plays a role in all four types of asthma.<sup>20-22</sup> Especially, the SPT reaction to epithelia (46) seemed to be associated with all the asthma phenotypes.<sup>23</sup>

The concentration of SPT reactions and the increased IgE values in factor FI (AA, 49, 50) confirmed that, especially this type of asthma represents allergic sensitisation. The reaction to mould, especially, seems to indicate allergic asthma (AA, 48). The respiratory symptoms of seasonal asthmatics had lasted longer than the seasonal symptoms of allergic asthmatics (SA, AA, 32, 40, 41). Signs of skin problems and sensitivity to pollen (45) are other characteristics of the seasonal asthmatics (SA, 28, 45).<sup>24,25</sup>

Nasal asthmatics are characterised by long-lasting nasal and pulmonary symptoms (NA, 27, 35-40), and they suffer from breathlessness and phlegm (35, 38) even more than obstructive asthmatics do. Possible differences in respect to how the patients' symptoms are presented should, however, be taken into consideration.<sup>26</sup> Also, the possible effects of perennial allergens may remain unobserved.<sup>27</sup> Especially, wheezing and sensitivity to house dust mite are features pointing to the asthma type with heaviest pulmonary obstruction (OA, 36, 39, 47).

#### Other tests and the certainty of diagnosis

The overall picture of the results of the functional asthma tests (52-58) gave an impression of increasing obstruction from allergic to obstructive asthma (AA-SA-NA-OA) although the B-eos test had its highest loading for the nasal phenotype (NA, 51).

The negative results of auscultation and functional asthma tests (57, 58) for seasonal asthmatics (SA), as well as the few asthma tests (59) made for this group of patients in relation to the number of visits (60), deviated from the overall picture. It reflects the difficulty to observe seasonal asthma in auscultation or to arrange for Brd tests and PEF recordings (54, 56) to be made in the proper season. The same problem of seasonality concerns the B-eos test (SA, 51).<sup>28,29</sup> The examinations had probably

taken place after the season and the treatment of the symptoms.<sup>30</sup>

The results of Brd test and wheezing on auscultation revealed a tendency to obstruction also with respect to the age-dependent diseases (ADD, 54, 57), in addition to the reduced lung function (52, 53) these patients had. The difficulty of differentiating asthmatic obstruction from age-dependent diseases has probably increased the number of tests and visits needed for the diagnosis (OA, 59, 60). One example of possible respiratory problems, which becomes worse with age but is not related to asthma, is gastroesophageal reflux connected to overweight (ADD, 14).<sup>31,32</sup> Skin and digestive symptoms of these older patients (11, 26, 28) and respiratory symptoms associated with oral or inhaled allergens (42, 43) handicap also the differentiation between asthma and age-dependent diseases. Of the asthma tests used in this study, the Mch test seemed to be the best for differentiating obstructive asthma from age-dependent diseases (OA, ADD, 55).

According to factor scores (Fig. 1) the obstructive type of asthma (OA) differentiated best the certain asthmatics from the non-asthmatics or uncertain asthmatics and that the diagnosis was primarily based on asthma tests. Patients with uncertain asthma tended to have features of seasonal asthma (SA) or age-dependent diseases (ADD). The proportion of certain asthma patients decreased during the study period and those with an uncertain or no asthma diagnosis increased.

#### Regional variation of the patients

Both allergic and nasal asthma tended to be urban phenomena (AA, NA, 66, 31, 33), the seasonal asthmatics living in more rural areas (SA, 66, 65). However, the reactions to pollen diminished and those to house dust mite increased from the urban to the rural regions (UC, 45, 47). Since the urban patients were younger (11) than others, the differences may partially be age-related.<sup>20,33</sup>

The allergic asthmatics seemed to have lived their entire life in the same region (AA, 71)<sup>34,35</sup> whereas many of the patients with nasal asthma were born in coastal cities (NA, 71-73). The obstructive asthmatics (OA, 72), like the patients with age-dependent diseases (ADD, 72), had primarily been born in rural municipalities. The aforementioned regional variation in patient characteristics with respect to place of residence and birth can also be explained by differences in the age structures of patients and the municipalities in question.

Living in the surroundings of centres (SR) slightly tended to increase pulmonary symptoms (36, 39) and obstruction (52, 57), as well as some non-respiratory diseases (26, 28). In Finnish conditions these pulmonary symptoms could reflect mould problems of new housing built in the

surroundings of developing centres (SR, 48, 50).<sup>36-38</sup> The other living conditions of this type of region possibly related to pulmonary symptoms include smoking (18, 19), exposure to traffic pollution and possible work-related allergens (62). The factor scores (Fig. 1) also revealed some tendency for certain asthmatics to live in regions characterised as “surrounding regions” (SR), whereas the non-asthmatics resided in urban centres (UC).

#### Change in patient characteristics

According to the loading of the date of the first visit (1) on factor ADD, the age-dependent diseases increased during the study period. The parallel increase in skin symptoms (TIME, 28) and the low level of forced vital capacity (TIME, 53) supports this assumption. Smoking and nasal hypersensitivity (18, 19, 31) also increased. Smoking was accompanied by an increase in cough and phlegm production (37, 38). All these changes made the diagnosing of asthma more difficult, as is reflected in the decrease of the certainty of the asthma diagnoses (61).

Negative loadings on breathlessness, wheezing on auscultation and on the Brd test reactions confirmed that asthma had actually decreased among patients (TIME, 35, 57, 54, 61). The duration of pulmonary symptoms had also decreased and the later asthma status of patients had improved (41, 64). However, the number of pulmonary symptoms, visits and clinical tests before diagnosis (39, 59, 60) increased. These changes can be considered the results of improved health care. The drop in the number of patients with nasal polyps and nasal cavity infections (30) suggests that a greater number of these patients have been directed to rhinologists.

The number of patients with an industrial occupation increased (TIME, 24), as did referrals from occupational health units (7-10). In addition, an increasing proportion of patients seemed to have been examined on the basis of the suspicion of work-related respiratory symptoms (62). The increase in respiratory symptoms, associated with inhaled allergens (42), may also reflect the growing interest in these issues.

The increase in the number of pets (TIME, 21, 72) and in urban birthplace can be interpreted as a sign of the continuing urbanisation of Finnish society. Records of asthma in the family also increased (17, 21). Despite a real increase in the number of asthmatic relatives, there may also be a growing awareness of heredity as a risk factor for asthma.<sup>39</sup>

#### **Discussion**

The data source consisting of patient documents is reflected by the great number of variables with varying levels of quantification and conceptual validity, the result being low correlation. Exploratory factor analysis has

some advantages when such a complex research field is approached. In data reduction by factor analysis, the unique and error variance of correlation matrix can be reduced, and the conceptual validity of the variables can be partially controlled.<sup>12</sup> The requirements for measurement are not so strict as those aimed at detailed causal analyses.<sup>14</sup> Especially, the construction of “phenotypes” of asthma by factor analysis may give a useful conceptual scheme for diagnosis, clinical practice and management and produce fruitful hypotheses for more detailed studies.

Factor analysis of the patient documents of suspect asthma patients used in the study revealed four phenotypes of asthma: “allergic”, “seasonal”, “nasal” and “obstructive” asthma. These types become more dominant in this order with increasing age. SPT reactions are concentrated among younger allergic asthmatics and then decrease with age while the signs of obstruction increase.<sup>22</sup> The phenotypes form a series of worsening distress from seasonal, nasal and respiratory symptoms into perennial distress and increasing airway obstruction.

Allergy, especially the SPT reaction to epithelia, seemed to play a role in all asthma types.<sup>23</sup> Parallel with the series from allergic asthma to obstructive asthma, the accentuation of the SPT reaction to pollen tended to shift to epithelia and house dust mite. In this study the reaction to moulds indicated allergic asthma best, reaction to pollen pointed to seasonal asthma and the sensitivity to house dust mite was the best predictor of obstructive asthma.

Concerning other tests, results of the functional asthma tests implied an increasing obstruction from allergic to obstructive asthma (AA-SA-NA-OA). Probably, owing to the difficulty in arranging auscultation or PEF-recording to be done in the proper season, the seasonal asthmatics deviated from this overall picture.<sup>30</sup> The marker of inflammatory aspect of asthma, B-eos test seemed to be the best marker for nasal asthma.

Whether these four types should be considered as separate diseases or as a series of the same strengthening process remains open. Asthma typology may, however, facilitate the weighting of medication and the control of possible allergens. Awareness of different types of asthma may also encourage the detailed research of underlying mechanisms and the possible markers of different types.<sup>1,2</sup>

Factor analysis also revealed a group of patient characteristics not related to asthma, especially age-dependent distresses and smoking. In the case of the elderly patients, the suspicions of asthma seemed to have been based on respiratory symptoms in association with some allergens, wheezing on auscultation and also skin symptoms. For male patients, a tendency towards flu, possibly owing to smoking might have awakened suspicions of asthma. Gastroesophageal reflux, which is often connected to

overweight, handicaps also the differentiation between asthma obstruction and age-dependent diseases. In this study, the Mch test seemed to be the best for differentiating obstructive asthma from age-dependent diseases.<sup>31,32</sup> Despite the seasonality of asthma, the characteristics of age-dependent diseases seemed to increase the uncertainty of diagnosis.

The allergic and nasal asthma seemed to be more common in urban environments, while seasonal asthmatics often lived in more rural regions. Nasal asthmatics tended to be born in coastal towns, while obstructive asthmatics often originated from more rural regions. The overlapping of the regional variation of patient characteristics with the age structure of municipalities, overall urbanisation of society and the referral policy of health care units handicapped the regional analysis, which would have required a more extensive regional scope and a greater subject material and set of variables.

The age-dependent diseases and smoking increased during the study period. Both of these changes made the diagnosing more difficult and are reflected in the decrease of the certainty of the asthma diagnosis. A proper asthma, instead, decreased, but the number of visits and clinical tests made before the diagnosis increased. These changes can be considered results of improvements in health care, the greater division of labour between clinics and efforts to make thorough examinations of asthmatics as early as possible.<sup>15</sup>

For other administrative aspects, an increasing proportion of patients seems to have been examined on the basis of work-related respiratory symptoms, indicating a growing concern about work conditions. Growing interest in inhaled allergens points to the same direction. The weighting of the admissions in summer seems to have increased during the study period, probably due to the administrative strategy to refer the growing group of patients with age-dependent diseases to examinations in the summer vacation period.

## Conclusion

Continuous systematic analysis of patient characteristics by factor analysis would offer an efficient device for monitoring clinical practice and management. In addition, a better formulation and standardisation of patient documents and their utilisation in research and administration would be facilitated.

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## REFERENCES

1. Kauffmann F, Dizier M-H, Pin I, Paty E, Gormand F, Vervloet D, et al. Epidemiological study of the genetics and environment of asthma, bronchial hyperresponsiveness, and atopy. Phenotype issues. *Am J Respir Crit Care Med* 1997; 156:123-9.
2. Koppelman G H, Meijer G G, Postma D S. Defining asthma in genetic studies. *Clin Exp Allergy* 1999; 29:1-4.
3. Marsh D G. Approaches toward the genetic analysis of complex traits: asthma and atopy. *Am J Respir Crit Care Med* 1997; 156:133-8.
4. Thurstone L L. Multiple-Factor Analysis. Chicago: University of Chicago Press, 1947:55-9, 176-81, 503.
5. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999; 54:268-72.
6. Klaukka T. Pirkanmaan sairaanhoitopiiriä ja sen kuntia koskevia tilastotietoja väestön terveydestä. Tampere: Kansaneläkelaitos, 1994.
7. Muittari A. The value of the metacholine test as a diagnostic method in bronchospastic disorders. *Ann Med Intern Fenn* 1968; 57:197-203.
8. Nieminen M M. Unimodal distribution of bronchial hyperresponsiveness to methacholine in asthmatic patients. *Chest* 1992; 102:1537-43.
9. Bailey W C, Richards J M Jr., Manzella B A, Brooks C M, Windsor R A, Soong S. Characteristics and correlates of asthma in a university clinic population. *Chest* 1990; 98:821-8.
10. Hedman J, Poussa T, Nieminen M M. A rapid dosimetric methacholine challenge in asthma diagnostics: a clinical study of 230 patients with dyspnoea, wheezing or a cough of unknown cause. *Respir Med* 1998; 92:32-9.
11. Hahtola K. The rationale of decision-making by forest owners. *Acta Forest Fenn* 1973; 130:9-29.
12. Darlington R B. Factor Analysis. Department of Psychology, Cornell University. [Accessed 14 June 2002 (and 17 April 2003), at <http://comp9.psych.cornell.edu/Darlington/factor.htm>]
13. Stapleton C D. Basic Concepts in Exploratory Factor analysis (EFA) as a Tool to Evaluate Score Validity: A Right-Brained Approach. Texas A&M University Homepage. January 1997. [Accessed 8 July 2002 (and 17 April 2003), at <http://ericae.net/ft/tamu/Efa.htm>]
14. Factor analysis. PA 765. Quantitative Research in Public Administration. NC State University. [Accessed 8 July 2002 (and 17 April 2003), at <http://www2.chass.ncsu.edu/garson/pa765/factor.htm>]
15. Panhuysen C I M, Vonk J M, Koëter G H, Schouten J P, van Altena R, Bleecker E R, et al. Adult patients may outgrow their asthma. A 25-year follow-up study. *Am J Respir Crit Care Med* 1997; 155:1267-72.
16. Siroux V, Pin I, Oryszczyn M P, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. *Eur Respir J* 2000; 15:470-7.
17. Nilsson L, Björkstén B, Hattevig G, Kjellman B, Sigurs N, Kjellman N-IM. Season of birth as predictor of atopic manifestations. *Arch Dis Child* 1997; 76:341-4.
18. Prescott E, Lange P, Vestbo J, and The Copenhagen City Heart Study Group. Effect of gender on hospital admissions for asthma and prevalence of self-reported asthma: a prospective study based on a sample of general population. *Thorax* 1997; 52:287-9.
19. De Marco R, Locatelli F, Sunyer J, Burney P and the European Community Respiratory Health Survey Study Group. Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. *Am J Respir Crit Care Med* 2000; 162:68-74.
20. Sunyer J, Antó J M, Kogevinas M, Barceló M A, Soriano J B, Tobias A, et al and the Spanish Group of the European Community Respiratory Health Survey. Risk factors for asthma in young adults. *Eur Respir J* 1997; 10:2490-4.
21. Tschopp J M, Sistek D, Schindler C, Leuenberger P, Perruchoud A P, Wüthrich B, et al and SAPALDIA team. Current allergic asthma and allergic rhinitis: diagnostic efficiency of three commonly used atopic markers (IgE, skin prick tests, and Phadiatop®). Results from 8329 randomized adults from the SAPALDIA study. *Allergy* 1998; 53: 608-13.

22. Niemeijer N R, de Monchy J G R. Age-dependency of sensitization to aero-allergens in asthmatics. *Allergy* 1992; 42:431-5.
23. Magnan A, Fourre-Jullian C, Jullian H, Badier M, Lanteaume A, Vervloet D, et al. Rhinitis alone or rhinitis plus asthma: what makes the difference? *Eur Respir J* 1998; 12:1073-8.
24. Fabrizi G, Corbo G M, Ferrante E, Macciocchi B, Romano A, Agabiti N, et al. The relationship between allergy, clinical symptoms and bronchial responsiveness in atopic dermatitis. *Acta Derm Venereol* 1992; 71:68-73.
25. Brinkman L, Raaijmakers J A M, Bruijnzeel-Koomen C A F M, Koenderman L, Lammers J-WJ. Bronchial and skin reactivity in asthmatic patients with and without atopic dermatitis. *Eur Respir J* 1997; 10: 1033-40.
26. Bijl-Hofland I D, Folgering HThM, van den Hoogen H, Cloosterman S G M, Van Weel C, Donkers J M, et al. Perception of bronchoconstriction in asthma patients measured during histamine challenge test. *Eur Respir J* 1999; 14:1049-54.
27. Rietveld S, Everaerd W. Perceptions of asthma by adolescents at home. *Chest* 2000; 117:434-9.
28. Vignola A M, Chanez P, Campbell A M, Souques F, Lebel B, Enander I, et al. Airway inflammation in mild intermittent and in persistent asthma. *Am J Respir Crit Care Med* 1998; 157:403-9.
29. Louis R, Lau L C K, Bron A O, Roldaan C, Radermecker M, Djukanovic R. The relationship between airways inflammation and asthma severity. *Am J Respir Crit Care Med* 2000; 161:9-16.
30. Metso T, Kilpiö K, Björkstén F, Kiviranta K, Haahtela T. Can early asthma be confirmed by laboratory tests? *Allergy* 1996; 51:226-31.
31. Astarita C, Gargano D, Cutajar M, Napolitano A, Manguso F, Abbate G F. Gastroesophageal reflux disease and asthma: an intriguing dilemma. *Allergy* 2000; 55:52-5.
32. Schachter L M, Salome C M, Peat J K, Woolcock A J. Obesity is a risk for asthma and wheeze but not airway hyperresponsiveness. *Thorax* 2001; 56:4-8.
33. Wieringa M H, Weyler J J, Van Bastelaer F J, Nelen V J, Van Sprundel M P, Vermeire P A. Higher asthma occurrence in an urban than a suburban area: role of house dust mite skin allergy. *Eur Respir J* 1997; 10:1460-6.
34. Nilsson L, Castor O, Löfman O, Magnusson A, Kjellman N-IM. Allergic disease in teenagers in relation to urban or rural residence at various stages of childhood. *Allergy* 1999; 54:716-21.
35. Kilpeläinen M, Terho E O, Helenius H, Koskenvuo M. Farm environment in childhood prevents the development of allergies. *Clin Exp Allergy* 2000; 30:201-8.
36. Savilahti R, Uitti J, Roto P, Laippala P, Husman T. Increased prevalence of atopy among children exposed to mold in a school building. *Allergy* 2001; 56:175-9.
37. Williamson I J, Martin C J, McGill G, Monie R D H, Fennerty A G. Damp housing and asthma: a case-control study. *Thorax* 1997; 52: 229-34.
38. Koskinen O M, Husman T M, Meklin T M, Nevalainen A I. The relationship between moisture or mould observations in houses and the state of health of their occupants. *Eur Respir J* 1999; 14:1363-7.
39. Rönmark E, Jönsson E, Platts-Mills T, Lundbäck B. Different pattern of risk factors for atopic and nonatopic asthma among children - Report from the Obstructive Lung Disease in Northern Sweden Study. *Allergy* 1999; 54:926-35.