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Characteristics of patients receiving allergy vaccination: to which extent do socio-economic factors play a role?

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Background: Little is known about characteristics of patients receiving allergen-specific immunotherapy. Identifying obstacles to appropriate treatment according to guidelines may facilitate the development of strategies aiming at improved treatment of patients with allergic respiratory diseases. The objective of this study was to investigate differences in disease severity, demographic and socioeconomic status between allergic rhinitis patients receiving allergen-specific immunotherapy and allergic rhinitis patients not receiving allergen-specific immunotherapy. **Methods:** A total of 366 patients were studied of whom 210 were going to receive subcutaneously administrated immunotherapy (SIT) against grass pollen and/or house dust mite allergy. The severity of rhino-conjunctivitis (hay fever) and/or asthma was classified according to international guidelines. The questionnaires included an EQ-5D visual analogue scale instrument and some socio-economic questions. **Results:** Severity of disease, young age, high level of education as well as greater perceived impairment of health-related quality of life due to allergic symptoms were significantly associated with use of SIT. Somewhat unexpectedly, household income was not associated with use of SIT. **Conclusion:** Use of SIT was associated with both disease severity measures and educational level, but not income level. These results suggest social inequality as reflected by lower use of SIT among patients with lower educational level may represent an obstacle to treatment with SIT.

Keywords: asthma, hay fever, health services needs and demand, immunological desensitization, quality of life

Introduction

In Europe, ~25% of the population suffers from respiratory allergy. Thus, allergies constitute a major public health problem, and is associated with impairment of health-related quality of life (HRQL).[1–3] Allergen-specific treatment targets the specific allergic immune response that triggers symptoms and the underlying inflammatory condition of the airways. There are two main options for allergen-specific treatment: allergen avoidance and allergy-specific immunotherapy. While the efficacy of allergen avoidance is debated, there is strong evidence that immunotherapy using inhalant allergens are clinically effective in the treatment of allergic respiratory diseases (ARD).[4] Allergen-specific subcutaneous injection immunotherapy (SIT) with Alutard SQ induces clinical and immunological tolerance, has long-term efficacy, and may prevent the progression of allergic disease. This treatment also improves the HRQL of allergic patients.[5,6] The clinical efficacy of SIT is well established for both allergic rhinitis and allergic asthma.[7–9] There is evidence that under-diagnosis and under-treatment of allergic rhinitis patients are substantial[1,10–12] despite internationally approved guidelines and available effective treatments. In Denmark, few persons with grass pollen allergic rhinitis in the general population have ever received grass pollen SIT.[13] Data from the Danish Medicines Agency show that <0.1% of people allergic to grass pollen and/or house dust mites were treated with SIT in Denmark in the year 2007. In addition, there were great variations in the vaccination rates and turnover between the five administrative regions in Denmark.[14] The primary health care sector in Denmark includes general practitioners (GPs) and specialist doctors. The observed variation is likely to be explained by variations in need, supply and demand. Differences in need will arise to the extent that there are differences in the prevalence and severity of allergy between urban and rural areas, for example.[15] Lack of specialist doctors and GPs in some areas may be an obstacle to health care and could explain low vaccination rates in these areas. This notion is supported by the fact that the number of practising specialists per 10 000 inhabitants in Danish counties varies from 0.8 in the county of Ringkøbing to 3.6 in the county of the Capital.

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Subcutaneously administered SIT is a time-consuming treatment involving weekly injections during the up-dosing phase followed by maintenance doses given at 6 ± 2 weeks intervals for 3–5 years depending on vaccine properties and disease factors. Little is known about characteristics of patients receiving SIT. Identifying obstacles to appropriate treatment according to guidelines may facilitate the development of strategies for the public health policy and practice aiming at improved treatment of patients with ARD.

According to the human capital theory,[16,17] individuals invest in their own health through education, physical exercise and health care in order to feel better and increase future earnings. Thus, the demand for health care is complex, since health care can be regarded as a consumption good as well as an investment good.[18] Willingness to invest in health care in order to gain positive health outcomes in the longer run is a function of individuals' time preference, and thus the rate at which they discount future outcomes. Since SIT is a treatment programme which requires significant resource investments (in terms of time, effort and out-of-pocket payments) at present with the prospect of future gains, individuals who operate with high discount rates are less likely to demand SIT. Results have shown that there is a correlation between education and time preferences.[19] Thus, we would expect that individuals with higher levels of education would be more prone to demand SIT. Other relevant demand side factors could be age, gender and income. Younger age is associated with a higher expected outcome of SIT due to a longer life expectancy. Younger individuals may also perceive allergy and asthma to impact more significantly on the HRQL, due to higher expectations and a more active life. Hence, we expect that younger individuals will be more likely to demand SIT. The out-of-pocket payment for SIT is 4500 DK (~€600) over a period of 3 years, and may thus represent a barrier for consuming SIT, especially for those with a lower income, since for these people such an out-of-pocket expense would constitute a higher opportunity cost. Consequently, we hypothesize that individuals with lower income will be underrepresented amongst those individuals who demand SIT. Furthermore, we expect that patients with the greatest objective need for SIT, i.e. those with the most severe diagnoses will be more prone to demanding SIT and those patients with a low subjective perceived HRQL as measured by a large difference in the visual analogue scale (VAS) scores will be more likely to use a SIT treatment.

The aim of the present study is to investigate 'differences' between allergic rhinitis patients receiving SIT and allergic rhinitis patients not receiving SIT. The focus will be to investigate whether socio-economic factors have any explanation, when controlling for disease severity (both subjectively and objectively). We believe more knowledge of the relative importance of these factors may be of great importance when developing strategies for improving the treatment of allergic patients.

Methods

The allergen SIT group

For this case–control study, we recruited patients from 13 clinics specialized in specific allergy management. These clinics were positioned all over the country of Denmark, although the greatest proportion was from the metropolitan areas and especially the region of Copenhagen with 172 patients (68%). Patients recruited for the control group were all from the region of Copenhagen (see 'The control group' section). The patients were consecutively invited to participate as they were referred to SIT from their GP. The patients were referred to the specialist clinics for treatment of grass pollen and/or house dust mite allergy, during September 2005 to December 2006. Data were collected immediately before SIT was initiated. The patients had to be at least 16 years of age to be included in the SIT group. Data were collected by using specifically designed questionnaires for the doctors and for the patients, respectively. A total of 254 participants completed the questionnaire. Of these, 210 (82.7%) had detectable serum-specific positive blood test for specific Immunoglobulin E (IgE) to grass pollen and/or house dust mites (IgE $\geq$ 0.35 k U/l) and were to start SIT. The specialist doctors provided information about the patients' general health, disease duration and data on lung function as well as specificity of allergy and immunotherapy treatment. Furthermore, the doctors classified hay fever severity according to the allergic Rhinitis and its impact on asthma (ARIA) as intermittent or persistent.[20,21] Doctors also classified an eventual asthma according to the Global Initiative for Asthma (GINA guideline).[22,23]

The control group

A group of persons reporting allergic rhinitis symptoms and IgE sensitized to grass and/or house dust mites were established from a general population study, the Health2006 Study. The Health2006 study took place between June 2006 and June 2008 and included 3471 persons aged 18–69 years randomly selected from the general population in the region of Copenhagen. Blood samples from all participants were analysed for specific IgE against the four most clinically important allergens in Denmark, i.e. birch, grass, cat and house dust mite. Persons, who had received any forms of immunotherapy, were not included in the study. Persons, who reported hay fever/asthma symptoms in the questionnaire and who had a positive test for specific IgE against grass pollen and/or house dust mite were selected for this study. These persons completed the same questionnaire as the patient's questionnaire used in the SIT group. In addition, the participants in the Health2006 group classified their hay fever severity according to the ARIA guidelines and their asthma (if relevant) according to the GINA guidelines, thereby making it possible to compare the socio-economic burden of ARD and HRQL across the two groups.

Between June 2006 and September 2007, a total of 452 consecutive participants in the Health2006 who reported symptoms of allergic rhinitis were asked to complete the questionnaire (see below). A total of 317 (70.1%) participants completed the questionnaire. Of these, 156 had detectable serum specific IgE to grass pollen and/or house dust mites.

Patients' questionnaires

The patient questionnaire included a EQ-5D VAS instrument[24,25] and socio-economic questions. The evaluation period was the 12 months before the day the patients were filling in the questionnaires. The EQ-5D VAS is a generic instrument, which allow researchers to compare outcomes across a range of different diseases and in different domains.[26] The VAS instrument offers a simple method for measurement of self-rated current health status. The VAS used is a vertical 20 cm 'thermometer', it has endpoints of 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom. The respondent rated his/her health state on the VAS by drawing a line from the top box marked 'your health state on a typical day with no allergy symptoms' to the appropriate point on the VAS, and from the base box 'your health state on a typical day with allergy symptoms' on the VAS, thereby making it possible to calculate the difference in the two VAS scores (referred to as delta-VAS). Asking participants to report their HRQL in both settings

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enables estimation of the potential impact of allergy interventions in a later stage, and it enables the calculation of a possible impact of allergen exposure.

Information about the participant's personal income and household income for the year 2006 was collected from Statistics Denmark for both the SIT and the Health2006 groups.

Analysis

Statistical analyses were performed using STATA 9.2 (StataCorp LP, College Stadion, TX, USA) and SPSS (SPSS Inc. Chicago, IL, USA) for windows 15.0. Continuous variables were described as mean ± 1 SD and categorical variables were described as frequencies. Student's *t*-test and chi-squared test were used to test differences between the SIT and control group for continuous and categorical variables, respectively. *P* values of less than 0.05 were considered statistically significant.

To further investigate differences between the SIT group and the Health2006 group, we performed logistic regression analyses with a dichotomous variable indicating whether the individual belonged to the SIT group (=1) or control group (=0) as dependent variable, and the following independent variables, respectively: gender, age, severity of allergy and asthma diagnosis, highest-attained education, delta VAS score as well as household income from the year 2006.[27,28]

We controlled for possible interaction between severity of diagnoses and other personal characteristics, by running a similar regression analysis including only those respondents with a severe allergy diagnosis or an asthma diagnosis. Furthermore, since age may correlate with income and education, we ran a regression which included respondents under or equal to the age of 45 years and analysed the impact of the remaining variables on SIT demand.

Subjective need as measured by respondents' perceived decrease in HRQL (delta-VAS score) may depend on life expectations. Such expectations may be a function of age and education. In order to test whether a possible impact of these person characteristics on SIT may be explained by different subjective perceptions of HRQL, we tested whether HRQL differed statistically significantly across these groups when holding severity of allergy diagnosis constant.

Results

Table 1 shows that participants in the SIT group were significantly younger, were more likely to have an upper secondary school education and they were more likely to have a short or medium high education or a university degree than participants from the Health2006 group. Participants in the SIT group also had a significantly lower personal income and household income than participants from the Health2006 group.

As shown in table 2, the predominant part of the participants in the SIT group was classified as having persistent rhino conjunctivitis (RC) (96.2%) when compared with the Health2006 group (55.8%). Approximately half of the participants in the SIT group were diagnosed with asthma, as compared with 18.6% in the Health2006 group. Interestingly, participants from the SIT group reported fewer years with allergy/asthma symptoms when compared with the Health2006 group, but participants from the SIT group had been bothered significantly more months during the last year compared with participants from the Health2006 group. Participants from the SIT group had been in contact with emergency rooms significantly more often than participants from the Health2006 group.

Table 2 also shows that participants in the SIT group had lower HRQL than participants in the Health2006 group on days with allergy symptoms measured on the VAS instrument ($P < 0.001$), whereas it was higher on days with no allergy symptoms. The mean delta-VAS score (i.e. the perceived decrease in HRQL) was significantly higher in the SIT group as compared with the Health2006 group.

Table 3 shows the logistic regression analysis of participants selecting a SIT treatment with respect to gender, age, RC severity, an asthma diagnosis, highest attained education, household income and delta-VAS. Patients in the Health2006 group were more likely to be younger of age, have persistent RC and concomitant asthma, when compared with the patients in the SIT group. In a preliminary analysis, we

Table 1 Demographic and socio-economic characteristics of the patients

	Health2006 group *n* = 156	SIT group *n* = 210	*P*-value
Gender[a]			
Male	77 (49.4)	111 (52.9)	0.508
Age in years[b]			
Mean (SD)	44.6 (12.0)	33.4 (10.9)	<0.001
Range in year	19.2–68.3	16.1–66.3	
School education[a]			
Basic school (7–10 years)	74 (47.4)	52 (24.8)	<0.001
Upper secondary school (12 years)	72 (46.2)	143 (68.1)	<0.001
Other school education (9 years + additional school education)	10 (6.4)	15 (7.1)	0.784
Highest attained education[a]			
Vocational education and training	32 (20.5)	31 (14.8)	<0.149
Short or medium high education	84 (53.9)	68 (32,4)	<0.001
University degree	16 (10.3)	68 (32.4)	<0.001
Other education or unknown	9 (5.8)	13 (6.2)	0.867
No education	15 (9.6)	30 (14.3)	0.178
Smoking status[a]			
Current smoker	28 (18.0)	27 (12.9)	0.178
Former smoker	39 (25.0)	44 (21.0)	0.360
Never smoker	89 (57.1)	139 (66.2)	0.074
Mean (SD) personal income in DKK in the year 2006[b]	371 389 (242 818)	288 225 (245 685)	0.001
Mean (SD) household income in DKK in the year 2006[b]	628 789 (340 907)	546 167 (349 230.5)	0.025

Values are number of participants (%), if not stated otherwise

a: Pearson Chi-square test

b: Student's *t*-test were used to test differences between the allergen specific immunotherapy group and the control group for continuous variables and categorical variables, respectively

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Table 2 RC (hay fever), asthma and HRQL classification of the participants

	Health2006 group $n=156$	SIT group $n=210$	*P*-value
Positive test for specific IgE to grass pollen	138 (88.5)	184 (87.6)	0.806
Positive test for specific IgE to House dust mite	60 (38.5)	65 (31.0)	0.134
RC classification			
No RC classification (intermittent or persistent)	9 (5.8)	5 (2.4)	0.095
Intermittent RC	60 (38.5)	3 (1.4)	<0.001
Persistent RC	87 (55.8)	202 (96.2)	<0.001
Asthma diagnosis	29 (18.6)	103 (49.1)	<0.001
Self reported duration of allergy/asthma in years			
Mean (SD)	23.2 (13.8)	17.3 (11.4)	<0.001
Range in year	0–57	0–54	
Number of months uncomfortable because of allergy/asthma symptoms in the last year			
Mean (SD)	3.3 (3.3)	6.5 (4.0)	<0.001
Range in month	0–12	0–12	
Emergency room visit during the last year because of allergy/asthma	6 (3.9)	30 (14.3)	0.001
HRQL			
VAS on days with no allergy symptoms, mean (SD)	0.87 (0.11)	0.91 (0.09)	0.001
VAS on days with allergy symptoms, mean (SD)	0.70 (0.18)	0.50 (0.20)	<0.001
Delta-VAS, mean (SD)	0.17 (0.15)	0.41 (0.20)	<0.001

Values are number of patients (%), if not stated otherwise

Table 3 Logistic regression analysis with SIT[a] (=1) or not (=0) as the dependent variable ($n=351$)

SIT treatment (number of observations)	Odds ratio	95% CI
Gender (366)		
Female (178)	1.00	Reference
Male (188)	1.98	0.92–4.26
Age (366)	0.92	0.89–0.95
RC severity (366)		
No RC or intermittent RC diagnosis (77)	1.00	Reference
Persistent RC (289)	32.92	9.16–118.35
Asthma (366)		
No asthma diagnosis (234)	1.00	
Asthma diagnosis (132)	4.19	1.86–9.44
Highest attained education (366)		
No education (45)	1.00	Reference
Vocational education and training (63)	2.25	0.56–8.99
Short or medium high education (152)	3.46	0.99–12.09
University degree (84)	51.79	10.38–258.33
Other education or unknown (22)	6.50	0.87–48.55
Household income in 2006 in DKK 100 000 (363)	1.00	0.89–1.11
Delta-VAS score (354)	1.11	1.08–1.15

CI: confidence interval
a: Allergen-specific subcutaneous injection immunotherapy

controlled for smoking status and interaction between education and respiratory symptoms. Patients in the SIT group were more likely to have a university degree, and a greater delta-VAS score, indicating that their self-perceived need for SIT was significantly higher. The regression analysis showed that household income did not influence the patient choice of SIT treatment when taking into account differences in age between the SIT and Health2006 groups.

In order to control for any correlation that may occur between the objective need variables and other explanatory variables, a regression analysis was performed, where the analysis only included patients with persistent RC and/or patients with an asthma diagnosis ('objective need' for SIT was thus held constant); see table 4.

When controlling for severity of disease according to the diagnosis, age, high level of education as well as subjective perception of HRQL remain statistically significant explanatory factors. Having a university degree is, however, associated with lower odds ratios of 28.61. When, in addition, controlling for age by looking at only the younger age group (under or equal to the age of 45 years) the odds ratio for education is reduced to 7.23 (suggesting some correlation between age and level of education). Controlling for age does not change the result that income has no effect on the consumption of SIT. Also a regression analysis was performed which included income but not education as a potential explanatory variable (both in tables 3 and 4). In both cases, income remained statistically insignificant.

Focusing only on patients diagnosed with persistent RC or asthma, it was found that respondents under or equal to the age of 45 ($n=231$) had a mean delta-VAS score of 35.9, while older respondents ($n=69$) had a mean delta-VAS score of 25.7. These scores were statistically significantly different ($P<0.001$). When performing the same analysis for people with university degrees versus all others, there was a tendency to a lower perceived HRQL amongst those with no university degree, but the difference was not statistically significant ($P=0.165$).

Concerning the other independent variables in the model (table 3) we controlled for interactions, but did not find any (e.g. education level, income and age).

Discussion

In this study, it was found that measures of severity of RC on days with hay fever symptoms, concomitant asthma, HRQL and socio-economic status (educational level) were significantly associated with receiving a SIT treatment. These results indicate that participants from the SIT group were more severely affected by their allergy/asthma disease as compared with the Health2006 group. In addition we found that increasing age was associated with a lower probability of receiving a SIT treatment, which supports our hypothesis that older people, who have fewer years in which they can enjoy the positive health outcomes associated with SIT, are more willing to cope with their allergy symptoms as compared with younger people. The study also showed that not only objective need for SIT but also self-perceived HRQL (delta-VAS score) impacted on the demand for SIT. Amongst the younger group of patients (≤45 years) with a severe diagnosis, the detriment HRQL due to allergy/asthma was perceived as being lower; suggesting that an additional motivation for younger individuals to demand SIT is that their HRQL are affected more severely by allergy.

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Table 4 Logistic regression analysis with SIT[a] (=1) or not (=0) as the dependent variable

SIT treatment (number of observations N_1/N_2)	Severe diagnoses only $n_1 = 297$		Severe diagnoses and young $n_2 = 229$	
	Odds ratio	95% CI	Odds ratio	95% CI
Female (151/121)	1.00	Reference	1.00	Reference
Male (160/118)	1.71	0.84–3.51	2.23	0.97–5.08
Age (311/239)	0.92	0.89–0.95	n.a.	
Highest attained education (311/239)				
No education (44/36)	1.00	Reference	1.00	Reference
Vocational education and training (52/40)	2.01	0.56–7.22	0.53	0.14–2.06
Short or medium high education (123/84)	2.57	0.82–8.04	1.09	0.32–3.71
University degree (74/63)	28.61	6.90–118.69	7.23	1.67–31.21
Other education or unknown (18/16)	5.29	0.70–39.91	3.41	0.41–28.14
Household income in 2006 in DKK 100 000 (308/237)	1.00	0.91–1.10	0.98	0.87–1.10
Delta-VAS score (300/231)	1.11	1.08–1.14	1.11	1.07–1.15

CI: confidence interval. All included patients were diagnosed as persistent RC and/or had an asthma diagnosis. In second analyses, an age requirement (≤45 years) is added
a: Allergen-specific subcutaneous injection immunotherapy
n.a.: not applicable

Our results suggest that income does not impact on the use of SIT, which implies that out-of-pocket payment does not constitute a significant barrier. Patients with a high level of education receive SIT to a greater extent than those with lower levels of education, which may be an indication of other types of barriers to treatment access. For example, educated persons tend to live in regions with a higher frequency of specialists and/or GPs with an interest in immunology. Since those living in metropolitan areas are higher educated and there is a higher availability of providers of SIT in these regions, these factors may in combination provide an explanation for the great variations in the vaccination rates and turnover between the five administrative regions in Denmark. Alternatively, there may be an information availability bias that favours the more highly educated.

The study may also be biased by the selection process since the patients in the SIT group have first been persuaded to SIT by their GP (assuming uninformed patients) or have persuaded their GP (assuming informed patients) to prescribe SIT. Second, patients in the SIT group have adhered to the prescription by the GP and have attended the specialist clinic. Third, they have agreed to respond to the questionnaire.

We cannot exclude the possibility that the observed differences in socio-economic variables may be an artefact of the samples selected. This is, however, highly unlikely since the control cohort and the main part of the intervention cohort (68%) are very similar in geography. Although there might be other known and unknown factors, which contribute to the difference of both groups, we do not have a clear explanation for this. This topic may be interesting to study in future research where a qualitative approach could possibly be the most appropriate choice.

The study participants in the SIT group were interviewed just prior to the start of SIT treatment. To the extent that participants have an inclination to justify their choice of SIT by exaggerating their symptoms on a day with allergy symptoms, this may bias the presented results.

The study required that the respondents recalled a typical day with allergic symptoms during the past 12 months; hence our results may be affected by recall bias.

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Conflicts of interest: None declared.

Key points

- The consumption of allergy-vaccination is complex, since the characteristics of patients receiving SIT are dependent not only on the patients' objective need, but equally important, on the patients' own perceived HRQL.
- Household income does not impact on which patients receive SIT.
- Patients with the highest levels of education, especially those with a university degree, are significantly more likely to seek SIT as compared with patients having other educational levels, suggesting the existence of social inequality in allergy treatment in Denmark.
- Our results represent valuable information which may guide future attempts to develop strategies for public health policy and practice to decrease under-treatment of ARD.
- Some barriers to treatment may be reduced by future introduction of sublingual and tablet-based immunotherapy which can be administered at home and requires fewer visits to the doctor.

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