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Accidental food allergic reactions are associated with higher costs and more sick leave but not with quality of life

Short title:

Influence of food allergic reactions on costs and HRQL

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To the editor,

The prevalence of IgE-mediated food allergy diagnosed by clinical history and positive serology in adults across Europe ranges from 0.3-6% (1). Almost half of the food allergic adults are confronted with accidental allergic reactions yearly (2). Especially moderate and severe reactions require medical consultation and treatment, which can have a high impact on economic costs (3). A retrospective study in the United States showed that food-induced allergic reactions are a financial burden, where ambulatory visits are responsible for more than half of the costs (4). More insight into the impact of accidental food allergic reactions on economic costs seems important to develop effective and efficient health care policies and guidelines (5). Having food allergy impairs HRQL (6). It is unknown to what extent the occurrence of accidental allergic reactions contribute to this. Since almost half of the food allergic adults experiences on average two accidental allergic reactions per year (2), it is important to have insight in the impact of these reactions on costs, sick leave and HRQL. Therefore, we investigated the influence of food-induced accidental allergic reactions during one year on costs, sick leave and HRQL in adults.

A prospective cohort study with one year follow-up was conducted in a tertiary referral center for food allergy in the Netherlands. In this study, forty-six adults with a doctor-diagnosed food allergy were included. Of them, forty (87%) patients had a severe food allergy. The most common food allergies were for tree nuts (76%, 35/46) and peanut (70%, 32/46). Patient characteristics are shown in table S1. Patients reported every food-induced accidental allergic reaction using an online questionnaire. Furthermore, patients completed questionnaires about HRQL at baseline and after 12 months and about costs after 12 months. Differences between patients with and without accidental allergic reactions regarding total yearly direct, indirect and intangible costs, sick leave due to accidental allergic reactions and specific and generic HRQL were analyzed using descriptive statistics and the Mann-Whitney u test. For details on the methods of the study, see Data S1.

A total of 121 accidental allergic reactions was reported during the 1-year follow-up. Of all patients, 36 (78%) patients reported one or more accidental allergic reactions (range: 1-19), with varying severity: 22% (27/121) mild, 59% (71/121) moderate and 19% (23/121) severe.

Patients with accidental allergic reactions during the one-year follow-up (n=36) had higher total yearly direct and indirect costs compared to patients without accidental allergic reactions (n=10) (mean €1186 (bootstrap 95% CI: €609-1845) vs €158 (bootstrap 95% CI: €68-266), p=0.01). In all subcategories (primary care consultations, outpatient consultations, hospital admissions, travel costs to health care facilities and sick leave costs due to accidental reactions) patients with accidental allergic reactions had higher costs than patients without accidental allergic reactions. (table 1) Three patients had extremely high costs due to hospital admissions or high numbers of primary care or outpatient consultations. (table S2) When excluding

these three patients, the total yearly direct and indirect costs were still significantly higher in patients with accidental allergic reactions compared to patients without accidental allergic reactions (mean €673 (bootstrap 95% CI: €414-967) vs €158 (bootstrap 95% CI: €69-280)), $p=0.03$). With regard to intangible costs, patients with accidental allergic reactions reported more problems on all EQ-5D dimensions compared to patients without accidental allergic reactions: mobility (19% vs 0%), self-care (6% vs 0%), usual activities (28% vs 0%), pain/discomfort (50% vs 20%) and anxiety/depression (19% vs 0%). (table 1)

Of the patients who experienced accidental allergic reactions, 22% (8/36) reported sick leave due to a total of eleven accidental allergic reactions during the 1-year follow-up: five patients reported sick leave for one reaction and three patients for two reactions. Severity of accidental allergic reactions in which sick leave was reported, was in 8 cases moderate (duration of sick leave: few hours ($n=6$), one day ($n=1$), >two days ($n=1$)) and in 3 cases severe (duration of sick leave: few hours ($n=1$), one day ($n=2$)).

At baseline there was no difference in food allergy specific and generic HRQL between patients with and without accidental allergic reactions. After one year follow-up there were still no significant differences in either food allergy specific HRQL (total score FAQLQ-AF, domain Risk of accidental exposure) and generic HRQL (physical functioning, social functioning, physical role limitations, emotional role limitations, mental health, vitality, pain, general health and health change). (table 2)

We showed that accidental allergic reactions in food allergic adults are associated with higher direct and indirect costs. In our study, primary care consultations, outpatient consultations and hospital admissions were responsible for relatively comparable amounts of costs, whereof the highest costs came from primary care consultations. Patel et al. (4) reported that in the United States more than half of the costs of food-induced allergic reactions come from office-based physician visits and that almost half of the costs come from acute treatment. In addition, in the Netherlands patients visit a general practitioner just as often as an emergency department in case of accidental allergic reactions (7). Furthermore, we found that the occurrence of accidental allergic reactions is an important factor that even leads to sevenfold higher healthcare costs. Assuming that 2.1% of the Dutch adults has food allergy (1) whereof 46% experiences accidental allergic reactions yearly (2), a rough estimation of the total yearly costs for all food allergic Dutch adults with accidental allergic reactions would be 160 million euro and without accidental allergic reactions 25 million euro. This shows the large economic burden of accidental allergic reactions. There are several causes for accidental allergic reactions, of which the most important are: not adequately managing the elimination diet, incorrect and confusing food labelling caused by e.g. the limited credibility of precautionary labelling and misunderstandings in restaurants (2). Investment in more preventive strategies to avoid accidental allergic reactions, e.g. by giving more dietary advice and by improving regulation of the

food industry and restaurants, seems important to reduce the occurrence of accidental allergic reactions and related economic impact.

We demonstrated that patients with accidental allergic reactions reported more problems with regard to mobility, self-care, usual activities, pain/discomfort and anxiety/depression compared with patients without accidental allergic reactions. This suggests that patients with accidental allergic reactions might have higher intangible costs. More research with a larger sample size is required to confirm this.

We demonstrated that 22% of the patients who experiences one or more accidental allergic reaction per year reports sick leave due to 1-2 accidental allergic reactions. There is no literature about the extent to which workplace circumstances contribute to accidental allergic reactions. Further investigation into sick leave due to accidental allergic reactions and the influence of workplace circumstances would make a valuable contribution to the current knowledge on this subject.

Food allergic patients have an impaired HRQL (6). The food allergy specific HRQL in our study population was lower, compared with the Dutch food allergic population showed by Goossens et al. (8) ($p=0.04$). This difference might be caused by the higher percentage of milk allergic patients in our study population compared with Goossens et al. (8) (35% vs 15%), which is known as a predictor for greater HRQL impairment (9). Scores of our study population on generic HRQL were comparable with the Dutch food allergic population (10) with exception of the RAND-36 dimension General health which was less impaired in our study ($p=0.037$). We found that experiencing accidental allergic reactions has no additional impact on HRQL. In our study, most patients had food allergy for a long period (mean: 24 years), which probably led to a relatively stable HRQL.

A limitation of this study was the relatively small sample size. Furthermore, our study population had a relatively high percentage of patients with severe food allergy, which might be caused by our third line population. These limitations restrict the generalizability of the data to the general food allergic population.

The results were strengthened by the prospective design, use of validated questionnaires and inclusion of a well-defined patient-set. More research in a larger study population is needed to get more insight in the impact of accidental food allergic reactions on economic costs and HRQL.

In conclusion, accidental allergic reactions are associated with higher direct and indirect costs and more sick leave, but not with HRQL.

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Author contributions

AK, ADMH, GFH, VMB and HOM designed the study. ADMH and HOM collected the data. AV, ACK, TML and HOM, analyzed the data and wrote the manuscript. All authors contributed to interpretation of results and manuscript revision and approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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Data availability statement

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions.

Table

1.

Mean
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	Total	Patients with allergic reactions (n=36)	Patients without allergic reactions (n=10)
	Mean (bootstrap 95% CI)	Mean (bootstrap 95% CI)	Mean (bootstrap 95% CI)
<i>Total costs</i>	€962 (505-1476)	€1186 (609-1845)	€158 (68-266)
Direct costs			
<i>Consultations</i>			
Primary care consultations	€360 (179-550)	€443 (233-689)	€64 (34-102)
Outpatient consultations	€270 (114-483)	€322 (124-628)	€81 (17-166)
Hospital admissions	€241 (47-522)	€308 (57-663)	€0 (0-0)
<i>Travel costs to healthcare facilities</i>	€42 (25-59)	€50 (29-74)	€13 (5-24)
Indirect costs			
<i>Sick leave costs due to accidental allergic reactions</i>	€49 (3-115)	€62 (5-149)	€0 (0-0)
	n (%)	n (%)	n (%)
Intangible costs			
<i>Frequency of reporting problems per EQ-5D dimension¹:</i>			
Mobility	7 (15)	7 (19)	0 (0)
Self-care	2 (4)	2 (6)	0 (0)
Usual activities	10 (22)	10 (28)	0 (0)
Pain/discomfort	20 (44)	18 (50)	2 (20)
Anxiety/depression	7 (15)	7 (19)	0 (0)

problems) + 3 (extreme problems)

Table 2. Scores FAQLQ-AF and RAND-36 in patients with and without accidental allergic reactions

	Scores at baseline			Scores after 12 months follow-up		
	Patients with reactions n=33 (missing: n=3)	Patients without reactions n=10	Test of difference between patients with vs without reactions	With reactions n=36	Without reactions n=10	Test of difference between patients with vs without reactions
	Median (bootstrap 95% CI)	Median (bootstrap 95% CI)	P-value	Median (bootstrap 95% CI)	Median (bootstrap 95% CI)	P-value
FAQLQ-AF^a:						
Total score	4.3 (3.9-4.7)	3.2 (2.1-5.1)	0.12	4.1 (3.4-4.6)	3.7 (2.4-4.9)	0.41
Domain Allergen avoidance-dietary restrictions	4.0 (3.5-4.6)	2.6 (2.2-4.5)		3.8 (3.0-4.5)	3.5 (2.6-4.6)	
Domain Emotional impact	4.4 (4.1-4.7)	3.1 (2.0-5.3)		4.2 (3.7-4.7)	3.7 (2.3-4.9)	
Domain Risk of accidental exposure	5.0 (4.6-5.6)	4.1 (2.4-6.1)	0.36	4.8 (4.4-5.3)	4.2 (2.4-5.8)	0.50
Domain Food allergy-related health	3.0 (2.7-3.8)	2.3 (1.7-3.7)		3.0 (2.3-3.5)	2.5 (1.8-3.7)	
RAND-36^b:						
Physical functioning	100 (90-100)	100 (93-100)	0.52	95 (90-100)	98 (90-100)	0.35
Social functioning	88 (75-100)	100 (44-100)	0.90	50 (50-50)	50 (38-50)	0.17
Physical role limitations	100 (75-100)	100 (100-100)	0.44	100 (75-100)	100 (100-100)	0.25
Emotional role limitations	100 (100-100)	100 (100-100)	0.64	100 (100-100)	100 (100-100)	0.72
Mental health	80 (72-88)	80 (68-88)	0.83	60 (60-66)	60 (58-64)	0.72
Vitality	60 (55-70)	70 (50-90)	0.25	45 (43-50)	50 (43-55)	0.34
Pain	90 (84-100)	95 (78-100)	0.62	20 (0-22)	5 (0-10)	0.13
General health	65 (55-75)	73 (60-78)	0.49	50 (50-50)	50 (45-55)	0.80
Health change	50 (50-50)	50 (38-50)	0.34	50 (50-50)	50 (50-50)	0.63

^a The total score ranges from 1 "no impairment" to 7 'maximal impairment'. MCID: 0.5

^b The total score ranges from 0 "maximum disability" to 100 "no disability". MCID: 3-5

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Data S1. Methods

Study design, setting, study population and ethics

A prospective cohort study with one year follow-up was conducted at the Department of Allergology/Dermatology, a tertiary referral center for food allergy in the Netherlands. Inclusion of patients took place from 2016 to 2017. This study was part of a larger study (1) which focused on the food consumption of 73 doctor-diagnosed food allergic patients who had a food allergy for peanut, hazelnut, milk and/or hen's egg. We included those patients who completed the Food Allergy Socio-Economic Questionnaire (FA-ECOQ) after 12 months.

All patients gave written informed consent prior to inclusion. The local Medical Ethics Review Committee confirmed at 5 July 2016 that the Medical Research Involving Human Patients Act (WMO) did not apply to the study (protocol number: 16/421).

Outcome measures and data collection

Outcome measures were mean yearly direct and indirect costs, sick leave and HRQL.

Patients had to report every accidental allergic reaction to food during one year, using an online questionnaire. Each reported reaction was reviewed by the research team determining whether the reaction was compatible with a food allergic reaction. Furthermore, patients had to complete the baseline questionnaire, regarding patient characteristics; the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF) (2) and the RAND-36 (3) at baseline and after 12 months the FA-ECOQ (4) and EQ-5D-3L (5) after 12 months. The Dutch validated versions of the FAQLQ-AF, RAND-36, FA-ECOQ and EQ-5D-3L and were used (2-5).

The online questionnaire about accidental allergic reactions consisted of items about the causes, severity and sick leave due to the accidental allergic reaction. The severity of accidental allergic reactions was classified using an adapted version of the Mueller severity score. Reactions with local oral symptoms (Mueller 0) were classified as being mild, reactions with symptoms from skin and mucous membranes (Mueller 1) and/or gastro-intestinal tract (Mueller 2) were classified as moderate and reactions with respiratory symptoms (Mueller 3) and/or cardiovascular symptoms (Mueller 4) were classified as being severe (6,7).

The FAQLQ-AF consisted of four domains (Risk of accidental exposure, Emotional impact, Allergen avoidance-dietary restrictions and Food allergy-related health) including 29 items about food allergy specific HRQL. The total score ranged from 1 "no impairment" to 7 'maximal impairment' (2). The minimal clinically important difference (MCID) was 0.5 (8).

The RAND-36 consisted of eight health concepts (Physical functioning, Social functioning, Physical role limitations, Emotional role limitations, Mental health, Vitality, Pain, General health and Health change),

including 36 questions about generic HRQL. The total score ranged from 0 “maximum disability” to 100 “no disability”(3). The minimal clinically important difference (MCID) is 3-5 (9).

The FA-ECOQ measured direct and indirect costs (4). Costs were calculated based on the Dutch guidelines for economic evaluations in health care (10) and were corrected for inflation using the consumer price index for 2017 (11). (table 3) Direct costs included costs for primary care consultation, outpatient consultations, hospital admissions, travel costs to health care facilities for all purposes and indirect costs included costs for sick leave due to accidental allergic reactions.¹

The EQ-5D-3L measures health status and consisted of five dimension: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain had three levels: no problems (level 1), some problems (level 2) and extreme problems (levels 3). (12)

Analysis

In this study 46 patients were included, which was a subgroup of a larger study (1). In the main study a sample size of 70-80 patients was determined to be representative for the aim of the main study; ultimately 73 patients were included (1). For the current study no further sample size calculation was performed.

The FAQLQ-AF, RAND-36, FA-ECOQ and EQ-5D-3L scores were calculated using standardized methods (2, 3, 4, 12). For outcome data regarding yearly direct and indirect costs, the mean and 95% bootstrap confidence interval were calculated.

Outcome data regarding sick leave due to accidental allergic reactions and HRQL were analyzed using descriptive statistics. To calculate duration of sick leave, the shortest possible duration per answer option (answer options: a few hours, 1 day, 2 days, >2 days) was used (e.g. for answer option >2 days, we assumed 3 days). Based on level of measurement, frequencies (n/%) or median (bootstrap 95% confidence interval) were used.

Differences regarding total yearly direct, indirect and intangible costs, sick leave due to accidental allergic reactions and HRQL (The food allergy specific (total score and domain Risk of accidental exposure) and generic (total score per dimension) HRQL) between patients with and without accidental allergic reactions were analyzed using descriptive statistics and the Mann-Whitney u test. A p-value <0.05 was considered statistically significant.

Data were analyzed using IBM SPSS Statistics 25 (IBM Corporation, Armonk, NY, USA).

Table 3. Overview of reference prices used for calculating costs^a

	Reference price (in euros)
Primary care consultations	
General practitioner	€34
General practitioner, consultation at home	€52
Physiotherapy consultations	€34
Outpatient consultations	
Physicians	€95
Dieticians	€34
Hospital admissions (per day)	
Day care	€287
General hospital	€461
Academic hospital	€668
First aid	€269
Travel costs to health care facilities	
Per kilometer	€0.20
Parking per visit	€1.56

^a Costs were calculated based on the Dutch guidelines for economic evaluations in health care (10) and were corrected for inflation using the consumer price index for 2017 (11).

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Table S1. Patient characteristics

	All patients n=46	Patients with reactions n=36	Patients without reactions n=10
	n (%)	n (%)	n (%)
Gender: female	35 (76)	30 (83)	5 (50)
Mean age, in years (SD, min-max)	42 (13, 24-69)	42 (12, 24-67)	43 (16, 26-69)
Education:			
- Low	3 (7)	2 (6)	1 (10)
- Medium	11 (24)	9 (25)	2 (20)
- High	32 (70)	25 (69)	7 (70)
Atopic comorbidities:			
- Allergic rhinitis	38 (83)	30 (83)	8 (80)
- Asthma (missing: n=1)	31 (69)	23 (66)	8 (80)
- Atopic dermatitis (missing: n=1)	33 (73)	30 (86)	3 (30)
Food allergy for:			
- Tree nuts	35 (76)	28 (78)	7 (70)
- Peanut	32 (70)	25 (69)	7 (70)
- Fruit	24 (52)	19 (53)	5 (50)
- Hen's egg	17 (37)	15 (42)	2 (20)
- Cow's milk	16 (35)	14 (39)	2 (20)
- Vegetables	13 (28)	11 (31)	2 (20)
- Soy	8 (17)	6 (16)	2 (20)
- Celery	7 (15)	6 (17)	1 (10)
- Sesame	5 (11)	4 (11)	1 (10)
- Fish, crustaceans and/or molluscs	2 (4)	1 (3)	1 (10)
- Lupin	2 (4)	2 (6)	0 (0)
- Other food allergies	3 (7)	3 (8)	0 (0)
Mean number of confirmed food allergies (SD, min-max) ^b	5 (2, 1-11)	5 (2, 1-11)	4 (3, 1-11)
Years of having food allergy (SD, min-max)	24 (11, 2-50)	24 (11, 2-50)	25 (13, 2-38)
Most severe previous reaction:			
- Mild (Mueller ^c 0)	1 (2)	1 (3)	0 (0)
- Moderate (Mueller 1-2)	5 (11)	4 (11)	1 (10)
- Severe (Mueller 3-4)	40 (87)	31 (86)	9 (90)

^a Educational level: low, elementary education; medium, high school or middle-level applied education; high, higher professional or academic education;

^b Fruit, vegetables, other food allergy each considered as 1.

^c Reactions with local oral allergy symptoms (Mueller 0) were classified as being mild, reactions with symptoms from skin and mucous membranes (Mueller 1) and/or gastro-intestinal tract (Mueller 2) were classified as moderate and reactions with respiratory symptoms (Mueller 3) and/or cardiovascular symptoms (Mueller 4) were classified as being severe (1,2)

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Table S2. Details of patients with reactions with relatively high costs

	Patients with reactions		
	Patient 1	Patients 2	Patients 3
Total costs	€7553	€4957	€7951
Primary care consultations: costs (frequency)	€2664 (72)	€1734 (51)	€1820 (53)
Outpatient consultations: costs (frequency)	€4560 (48)	€414 (5)	€1140 (12)
Hospital admissions: costs (frequency in days, ambulance)	€0 (0, 0)	€2672 (4, 0)	€4817 (10, 1)
Travel costs to healthcare facilities	€329	€137	€174
Costs sick leave due to accidental allergic reactions	€0	€0	€0
Age in years	53	50	61
Number of accidental allergic reactions (Mueller scores)	3 (2, 3, 2)	2 (2,3)	1 (2)
Severity of food allergy (Mueller)	3	4	3
Atopic comorbidity ^a	Yes	Yes	Yes
Food allergy specific HRQLQ (total score FAQLQ-AF) at baseline	3.9	4.5	4.9

^a *pollinosis, asthma and/or atopic dermatitis*