

Design and Feasibility of an International Study Assessing the Prevalence of Contact Allergy to Fragrances in the General Population: The European Dermato-Epidemiology Network Fragrance Study

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Key Words

Fragrance · Contact allergy · Survey

Abstract

Background/Aims: Data on contact allergy to fragrances in the general population are limited. Data from allergological services suggest that the frequency of contact allergy to fragrances is increasing. The European Dermato-Epidemiology Network (EDEN) Fragrance Study aims to obtain reliable data on the prevalence of contact allergy to fragrances and other sensitizers of the European baseline series, in the general population of different geographical areas of Europe. We report the methodology and the reliability of instruments adopted and discuss the feasibility based on a pilot phase. **Methods:** Descriptive epidemiology survey. A random sample from the general population is selected and interviewed, and is offered patch testing in a randomized way. We specifically enquire about any skin rash reported during the pre-

vious year, and any history of reactions to products that may contain the sensitizer and/or a history of avoidance of the same products. Patch test data are linked to the questionnaire information to define clinical relevance. **Results:** The questionnaire showed high test-retest reliability in 94 individuals. Patch test reading also showed a high level of inter-rater reliability. During the pilot phase, a total of 589 participants were recruited. **Conclusions:** The EDEN Fragrance Study is feasible and able to provide useful data on fragrance allergy.

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Introduction

The existing data on the prevalence of allergies from contact with fragrances in the general population are very limited [1]. Data originating from allergological services concerning what is known as the 'patch test popula-

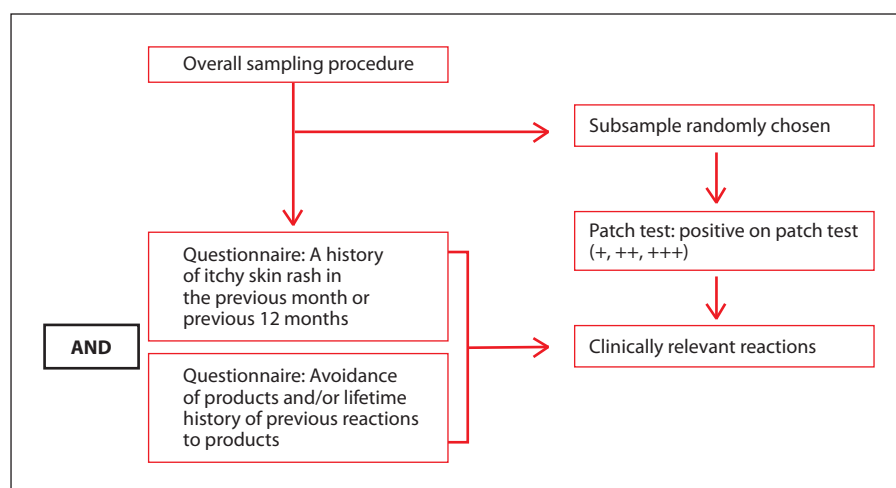


Fig. 1. Schematic representation of the design of the EDEN Fragrance Study.

tion' suggest that the frequency of allergies to fragrances is continuously increasing [2, 3]. Given the widespread use of substances containing fragrances (e.g. detergents, shampoos, deodorants) in the general population, this increase may be relevant to public health.

Epidemiology can contribute crucially to evaluating the importance of allergy to fragrances by estimating the frequency of the disease in the general population and/or subgroups and by assessing the role of potential risk factors. The lack of standardization in the studies conducted so far limits the validity of spatial and temporal comparisons [4]. In groups of unselected individuals, the frequency of positive patch test reactions to fragrances has been estimated at around 1.1% in a study from Denmark [5] and 1.8% in a study from Norway [6].

The European Dermato-Epidemiology Network (EDEN) has designed the 'EDEN International Study on the Prevalence of Contact Allergy to Fragrances' (EDEN Fragrance Study) [1, 3], which aims to obtain reliable data on the prevalence of contact allergy to fragrances in the general population in different geographical areas. By using standardized study methods, the project goal is to finally provide useful data for public health. Here we report the methodology and the reliability of instruments adopted in our study and discuss the feasibility based on our experience in the pilot clinical phase.

Materials and Methods

Design of the Study

The EDEN Fragrance Study is a descriptive epidemiology survey. A random sample from the general population is invited to answer a questionnaire and offered patch testing in a randomized

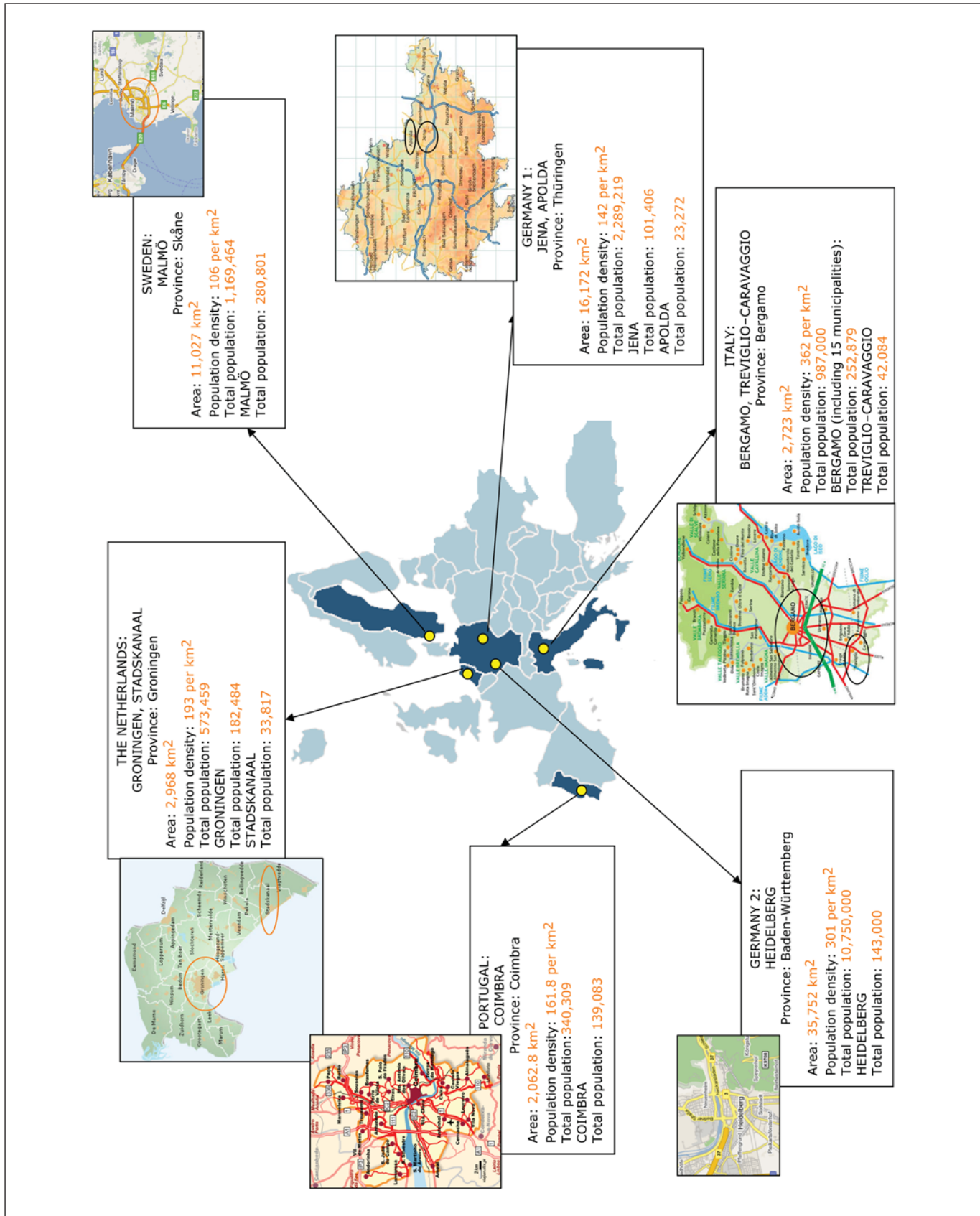
way. Figure 1 shows the study design, which yields two sets of information: (1) by a questionnaire, (a) any history of clinically relevant skin reactions independent of the nature of the reaction, during the month and/or the year preceding the interview, (b) any history of skin reactions to products commonly containing the allergens of interest and (c) any history of avoidance of such products because of a skin reaction at any time during the person's lifetime; (2) by patch testing, any positive skin reaction to tested allergens. In addition to estimates of positive reaction prevalence, we can also obtain estimates of the prevalence of clinically relevant reactions to fragrances (or to other substances of interest) by combining the above information for a randomly chosen subsample undergoing patch testing. In this study, a clinically relevant reaction is considered to be any skin rash reported during the previous month and/or the previous year, associated with a positive patch test reaction to a contact sensitizer and with a previous history of reactions to products that may contain the sensitizer and/or a history of avoidance of the same products.

Sampling Strategy

The EDEN Fragrance Study is an international and multicentric study that involves various geographic areas in 5 European countries: Germany, Italy, The Netherlands, Portugal and Sweden (fig. 2). In each area, a random population sample is recruited.

In Germany, 2 different geographical areas are included: the province of Thüringen, with Jena and Apolda, and the province of Baden-Württemberg, including Heidelberg. In the Netherlands, areas are the province of Groningen with the city of Groningen and the municipality of Stads kanaal. In Italy, the province of Bergamo is sampled with the city of Bergamo and its 15 municipalities, and the towns of Treviglio and Caravaggio. The included area in Portugal is the district of Coimbra with the city of Coimbra. In Sweden, the province of Skåne is targeted, including the city of Malmö (fig. 2).

Fig. 2. Geographical areas where each centre will perform a sampling plan.



To obtain a representative sample of the population within each geographical area, we are using a stratified proportional sampling design with replacement. In the sampling plan, the distribution of the population by age, gender and geographical location are accounted for. The final sample is expected to be well balanced in terms of the main demographic variables and representative of the final target population for these variables. All individuals aged 18–74 years are eligible. We are also using the same stratified proportional sampling design with replacement to obtain the subsample of participants to whom we will offer patch testing.

Recruitment Procedures

We are contacting by letter participants selected through the sampling procedure. A second letter and a phone call follow in case of non-response. Sampled individuals are asked to send back a reply pre-stamped card to accept or refuse participation in the study. Participants, who are free to withdraw from the study at any time, receive more detailed information by e-mail or by phone, and an operator contacts them to set a date for a face-to-face interview conducted at home or at a hospital. Participants also selected to undergo patch testing are asked to set a date for application, removal and reading of the patch test. Specialized and trained nurses apply and remove patches at the individual homes of participants in the Netherlands and in Italy, and in the hospital in the other countries; expert dermatologists in the hospitals do the readings.

Questionnaire

The questionnaire consists of 3 parts. The demographic part gathers general information on age, gender, ethnic group, occupation and marital status. The section on medical history focuses on history of skin problems characterized by localized erythema and itching lasting for more than 3 days during the past year and the past month. Other information collected includes any previous dermatological diagnoses, with a special focus on contact dermatitis, and any allergy test carried out. The history of exposure to products containing fragrances focuses on the frequency with which the participant uses certain products, characterized by their fragrance content. This part also records any possible problem related to a skin contact with these products. Questions on the use of topical medications are also included. In each country, trained interviewers conduct the interviews, using the relevant language questionnaire (derived from the English version by the translation/backtranslation technique).

In 2005, we undertook a study to estimate reproducibility of the questionnaire. This study involved comparison of the results for 60 items from the questionnaire, which was administered twice at an interval of 1–8 weeks (median = 1 week) to 94 volunteers (31 males and 64 females, median age = 40 years) from 3 European regions: Italy (Bergamo, 40 people), The Netherlands (Groningen, 34 people) and Sweden (Malmö, 21 people).

Patch Tests

Patch testing is performed according to the International Contact Dermatitis Research Group guidelines. Weak (+), strong (++) and extreme (+++) reactions with an allergic morphology are considered as positive reactions. Both thin-layer rapid-use epicutaneous (TRUE) test and Finn chambers® are used, testing for a total of 47 allergens. TRUE test standard series include panel 1, panel

2 and panel 3 containing 29 allergens. In Finn chambers, we test as petrolatum preparations fragrance mix 1, fragrance mix 2, their 14 individual fragrance allergens and the emulsifier sorbitan sesquileate in fragrance mix 1 as well as sesquiterpene lactone mix. This testing using TRUE test panels and petrolatum preparations tests for all contact sensitizers in the European baseline series except primin and methyldibromoglutaronitrile [7].

Two courses have been held at the Department of Occupational and Environmental Dermatology at the University Hospital in Malmö to improve the patch test procedure by standardizing the application of a defined amount of the petrolatum preparation on a Finn chamber and reading of the patch test. Twelve specialized nurses from all participating centres were taught and practiced applying the amount of petrolatum preparation recommended by the European Society of Contact Dermatitis for application onto a Finn chamber [8].

The second course focused on standardizing the patch test reading. After approval of the Ethical Committee, 11 dermatologists from the participating centres took part in this study at the Department of Occupational and Environmental Dermatology in Malmö. The dermatologists were not informed about the study until the morning when the patch test reading took place. They were told that 6 patients with suspected allergic contact dermatitis had been patch tested 3 days earlier with sensitizers from the baseline test series and supplemented with other chemicals from their own environment. Dermatologists performed the scoring independently and without communication with the patients or among themselves.

Six patients with known contact allergies within the groups of fragrances, metals and preservatives as well as 2 well-known irritants were patch tested. Every patient was patch tested with dilutions of the sensitizers and irritants to ascertain that allergic and irritant reactions were obtained of various strengths, including negative, doubtful and positive reactions. The application of the Finn chambers with the test preparations onto the individual backs of the 6 patients was randomized.

After the initial reading, there was a lecture on patch test reading based on the International Contact Dermatitis Research Group classification and with emphasis on the distinction among irritant, doubtful and allergic reactions as well as the requirements for grading into the different allergic groups (+, ++, +++).

Following the lecture, the dermatologists performed a second reading of the patient findings. We then evaluated the agreement of the readings before and after the lecture, using as the gold standard the answers from an expert dermatologist from the Department of Occupational and Environmental Dermatology.

Data Collection and Monitoring

The study group developed a Web-based electronic form to collect data from the questionnaire and from patch testing. Cross-reference checks in the electronic form enable reduction of input errors, missing data and inconsistencies. To improve standardization, the group also developed a video presentation for the study, which is available for download at http://area-lavoro.centrostudigised.it/EDEN_Fragrance_Study/Patch_Test_film.wmv.

Study Pilot Phase

The pilot phase of the study took place between January 2006 and August 2007. During this phase, each national team applied

the study methods as indicated above with the exception of adopting a simple randomization plan for recruiting the sample of 100 people. Preliminary estimates of the prevalence of contact allergy to fragrances were obtained to calculate the final sample size and to optimize the study design.

Sample Size

Using data from the pilot clinical phase, we estimated that the 1-year prevalence of a clinically relevant reaction to fragrances was not lower than 1%. Based on this estimate, we performed a power analysis to identify the cut-off for adequate power to investigate the prevalence of contact allergy to fragrances and to document possible differences among countries. Using the exact (Clopper-Pearson) confidence interval method [9], we estimated that a sample size of 3,000 produces a 2-sided 95% confidence interval with a width equal to 0.08 and a relative standard error of 17% when the sample prevalence is 1.00% (95% confidence interval, 0.06–1.40%; fig. 3). We thus require a sample of 500 individuals interviewed and patch tested per centre, for a total of 3,000 individuals. We further sample about 1,500 individuals for the interviews per centre (a total of a further 12,000 individuals interviewed).

Data Analyses

To assess agreement in the reproducibility studies, we calculated Cohen's kappa coefficient for categorical items and the intraclass correlation coefficient for quantitative data. Values from 0.41 to 0.60 indicate moderate agreement, values from 0.61 to 0.80 substantial agreement, and values from 0.81 to 1.00 almost perfect agreement.

We calculate weighted estimates of the prevalence of positive reactions to allergens and of clinically relevant reactions to allergens, taking into account the age and gender distribution of the population in the different geographical areas. To estimate possible selection biases in the selection of the subsample, we compare the characteristics (obtained by the questionnaire) of individuals undergoing the interview with those of the subsample also undergoing patch testing.

Finally, we calculate the prevalence of contact allergies overall and in different geographical areas and assessed geographical variations and potential risk factors. Control for confounding factors requires standardization procedures and appropriate multivariate analysis methods (e.g. logistic regression analysis).

All participant centres got approval for the study from their ethical committees.

Results

Reliability of Study Methods

A high level of agreement emerged for all questions assessed in the interview (fig. 4). Cohen's kappa statistics were 0.85–1 for demographic data and around 0.70 for the questions referring to skin problems, previous clinical examinations, allergic tests performed, dry skin and sensitive skin. Data concerning the history of skin diseases were too limited to calculate the kappa statistic, while the

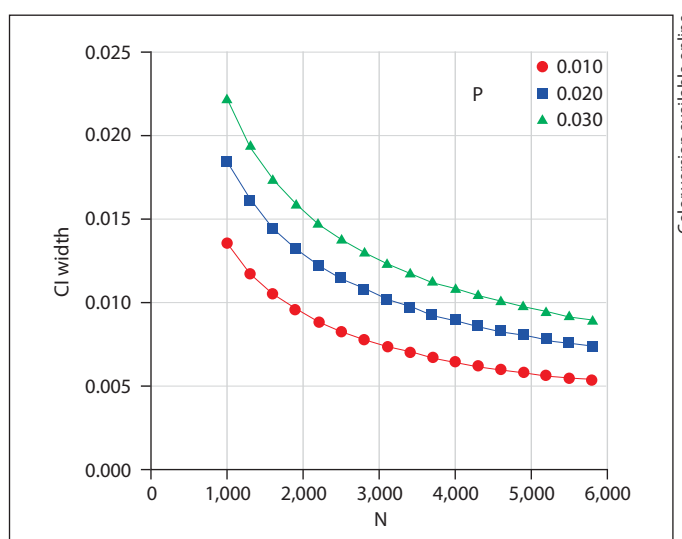


Fig. 3. The graph illustrates the width of the 95% confidence interval (CI), for estimation of a given proportion (P), based on different sample sizes (N).

agreement for the question concerning itchy skin rash was rather low initially (around 0.30). This low agreement prompted a change in the code book for collecting data, which resulted in a much higher value of the coefficient (around 0.70) on a subsequent reliability exercise. The weighted kappa statistic for the questions concerning exposure frequencies to selected products containing fragrances ranged from 0.54 ('shampoos') to 0.91 ('cosmetic product'), with the majority of items yielding kappa values higher than 0.70.

In the course on the standardization of the patch test procedure held in Malmö, the application of the recommended amount of petrolatum preparation on a Finn chamber was highly satisfactory after the training session. Education yielded improvement in patch test reading, but work remains to be done to standardize the reading for weak positive reactions and irritative reactions.

Pilot Study Phase

During the pilot phase, a total of 589 participants were recruited by a simple randomization procedure and interviewed in the centres involved in the study from December 2006 to May 2007 (from June to August 2007 in the Portuguese centre; table 1). There were 117 participants from Italy, 106 and 101 from the 2 German centres, 104 from the Netherlands, 101 from Sweden and 60 from Portugal (the lower number in Coimbra arises from the late start of the study in this centre).

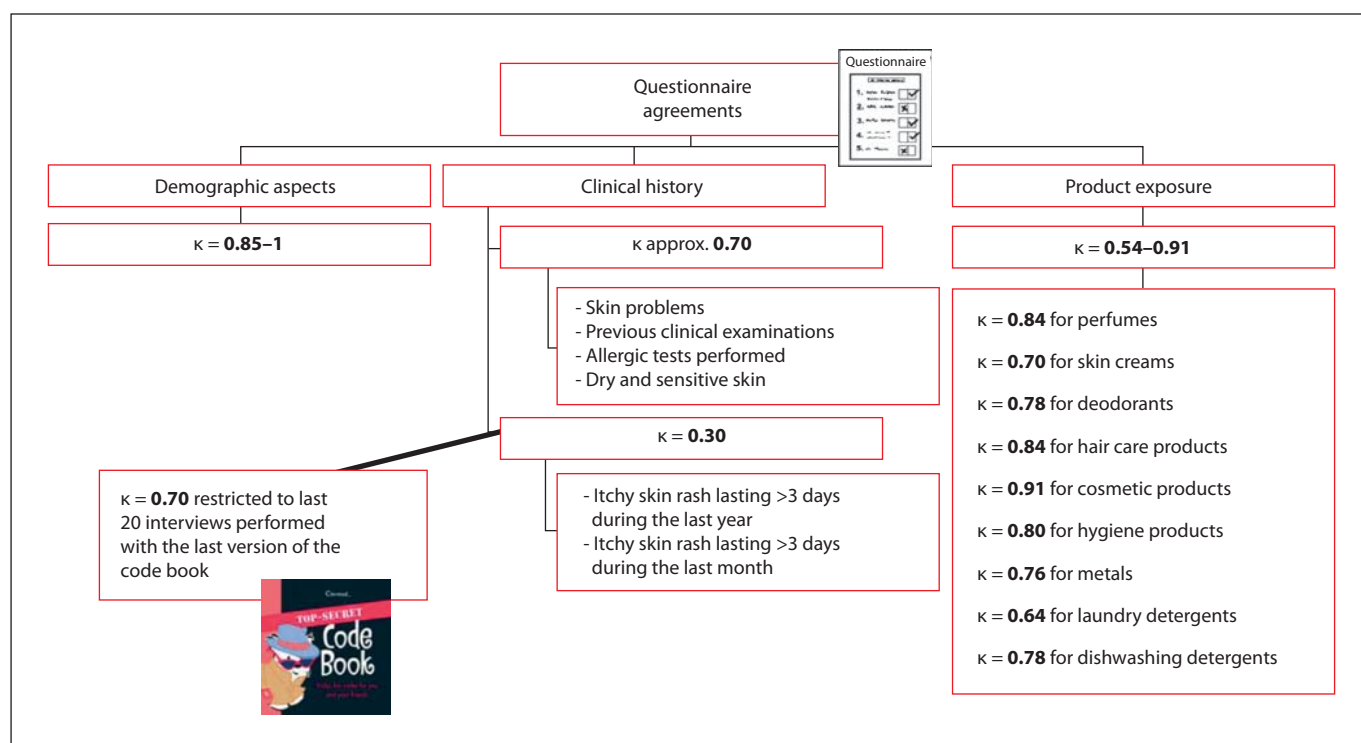


Fig. 4. Reproducibility estimates of the questionnaire.

We obtained participation rates from the Italian (approx. 50%) and Dutch (20%) centres. Among the reasons for non-participation were the fact that the study was too time consuming (approx. 38%), fear of being tested (approx. 24%), unsatisfactory reward for participation and the presence of a severe skin disease (7%). In Italy and similarly in other countries, about 25% of individuals representing 'potential cases' who agreed initially to be patch tested refused later on to do so (50% changed their minds, 29% refused because of schedule incompatibility; data not shown).

Table 2 shows the baseline characteristics of the sample overall and by centre. Participants were mainly women (59%), younger than 30 or older than 60 years (59%), and married (57%). Half were still working (51%). Distribution of gender, marital status and occupational status was similar among all the study centres, except for Heidelberg and Portugal. In Heidelberg, 61% of participants were younger than 30 years, 50% were still students, and only 27% were married, reflecting the distribution of a university town. The Portuguese population was mainly older (52%) and retired (47%). The Italian sample is characterized by a high portion of participants aged between

Table 1. Pilot clinical phase data on 589 participants interviewed, by study centre

Centre	Participants interviewed	Participants tested
Total	589	364 (61.8)
Italy, Bergamo	117	53 (45.3)
Germany, Jena	106	44 (41.5)
Germany, Heidelberg	101	80 (79.2)
The Netherlands, Groningen	104	104 (100.0)
Sweden, Malmö	101	58 (57.4)
Portugal, Coimbra	60	25 (41.7)

Figures in parentheses are percentages.

40 and 49 years, while in all the other centres, except Heidelberg, the highest percentage of the participants was older than 59 years.

A total of 364 individuals were patch tested, with 115 (32%) presenting a positive reaction to at least 1 allergen and 28 (8%) to at least 1 fragrance allergen. Overall, 55

Table 2. Overall and by centre distribution of the baseline sociodemographic characteristics of the study population (n = 589)

	Italy (n = 117)	Germany, Jena (n = 106)	Germany, Heidelberg (n = 101)	The Nether- lands (n = 104)	Sweden (n = 101)	Portugal (n = 60)	Total (n = 589)
Gender							
Male	53 (45.3)	53 (50.0)	37 (36.6)	42 (40.4)	43 (42.6)	15 (25.0)	243 (41.3)
Female	64 (54.7)	53 (50.0)	64 (63.3)	62 (59.6)	58 (57.4)	45 (75.0)	346 (58.7)
Age group							
18–29 years	17 (14.5)	25 (23.6)	62 (61.4)	15 (14.4)	11 (10.9)	8 (13.3)	138 (23.4)
30–39 years	29 (24.8)	12 (11.3)	13 (12.9)	17 (16.4)	16 (15.8)	3 (5.0)	90 (15.3)
40–49 years	35 (29.9)	19 (17.9)	11 (10.9)	17 (16.4)	23 (22.8)	11 (18.3)	116 (19.7)
50–59 years	18 (15.4)	20 (18.9)	5 (4.9)	25 (24.0)	18 (17.8)	7 (11.7)	93 (15.8)
60–75 years	18 (15.4)	30 (28.3)	10 (9.9)	30 (28.9)	33 (32.7)	31 (51.7)	152 (25.8)
Marital status							
Married	83 (70.9)	63 (59.4)	27 (26.7)	62 (59.6)	74 (73.3)	29 (48.3)	337 (57.2)
Unmarried	28 (24.0)	34 (32.1)	71 (70.3)	32 (30.8)	19 (18.8)	17 (28.3)	202 (34.3)
Divorced/widowed	4 (4.3)	9 (8.5)	3 (3.0)	9 (8.7)	8 (7.9)	14 (23.3)	48 (8.1)
Missing	1 (0.8)	–	–	1 (0.9)	–	–	2 (0.3)
Occupational status							
Working	73 (62.4)	48 (45.3)	31 (30.7)	52 (50.0)	68 (67.3)	24 (40.0)	272 (51.4)
Student	6 (5.1)	16 (15.1)	51 (50.5)	10 (9.6)	5 (5.0)	6 (10.0)	88 (16.6)
Unemployed	1 (0.9)	10 (9.4)	5 (4.9)	4 (3.9)	1 (1.0)	–	21 (4.0)
Retired	16 (13.7)	22 (20.8)	7 (6.9)	20 (19.2)	24 (23.8)	28 (46.7)	89 (16.8)
Homemaker	19 (16.2)	3 (2.8)	3 (2.9)	15 (14.4)	1 (1.0)	2 (3.3)	41 (7.8)
Other	2 (1.7)	7 (6.6)	4 (3.9)	3 (2.9)	2 (2.0)	–	18 (3.4)

Figures in parentheses are percentages.

(15%) were positive to nickel with the highest frequencies in the Netherlands (22 subjects; 21%) and Italy (13 individuals; 25%; data not shown).

Discussion

The results of the pilot phase suggest that the EDEN Fragrance Study is feasible. In spite of some limitations mainly arising from differences with data collection among the centres, the study on the reproducibility of the questionnaire showed a good level of reproducibility.

Patch testing procedures showed a high level of reproducibility concerning the preparation phase. With regard to patch test reading, the need for better standardization of readings became obvious even though all readers were already supposed to be using the same classification system when reading the patient findings initially. However, the general consensus is that patch testing is fairly reliable when the same patch test material is used [10].

Although the pilot study is important for optimizing methodology based on experience [3], the results of this

pilot study phase should not be overinterpreted. Because of the limited size of the sample to be collected, the study group adopted a simple randomization procedure so that the sample obtained was not necessarily fully representative of the target population. Moreover, the short study duration did not allow for arranging a suitable time for patch testing for a number of sampled individuals who, in principle, were willing to participate but were not available for patch testing on the proposed dates. The full study phase will last much longer.

Recently, a systematic review of studies on contact sensitization to fragrances in the general population found 13 studies performed among adults [10]. Sample size varied between 82 and 2,545 tested individuals, for a total of 11,648 tested. Based on these studies, the weighted average prevalence of fragrance mix 1 was 3.7%. The major limitations of that study are those that are typical of a meta-analysis study [11], and also include the exclusion of fragrance mix 2 from the investigation. In fact, to our knowledge, no previous studies have investigated the prevalence of fragrance mix 2 sensitization in the general population. The frequency of contact sensitization to fra-

grances strictly depends on the number of allergens tested, and patch testing with fragrance mix 2 detects additional patients sensitive to perfumes and missed by fragrance mix 1 testing [7, 12, 13]; thus, we would expect that the overall prevalence of contact sensitization to fragrances would be higher than prevalence estimates so far. This inclusion could account, at least in part, for the relatively high frequency of contact sensitization to fragrances we found in the pilot investigation. However, more data from the general population, such as those we will collect during the full phase of the study in selected regions of Europe, are needed to obtain more reliable and valid estimates of the prevalence of contact sensitization to fragrances in line with the new regulations concerning the use of fragrances in commercial products [7, 14]. These data will provide relevant information to the European Union Cosmetics Directive 76/768/EEC, which has been amended more than 50 times. Furthermore, they will allow reduction of misleading results in which the contact allergy was found to be responsible only for a minority of all reactions to cosmetics and toiletries on sale [15]. They are also expected to reduce the frequency of situations in which the concentration of allergens in perfume products was much higher than the maximum tolerable concentration considered safe by the EU Scientific Committee [16]. Postmarketing surveillance studies are also required to integrate and compare different sources of data and to establish safety [17].

Further difficulties in establishing estimates of contact sensitizations to fragrances are related to the variability in the concentrations of allergens in solution (or petrolatum) [12, 18]. Moreover, one controversial issue is the reliability of reactions to a fragrance mix [18–20]. On one hand, a fragrance mix represents recognized fragrance materials; on the other hand, there are concerns that positive reactions to the fragrance mix really reflect contact sensitization to individual constituents. Studies suggest that positive reactions to the fragrance mix do not guarantee that one or more of its components will give reactions in subsequent or concomitant patch tests [18]. It has been suggested that allergens in combination have a synergistic effect on the elicitation response [21]. Our study will allow estimation of the correlation between a positive reaction to a fragrance mix and to single allergens for both fragrance mix 1 and fragrance mix 2. Moreover, because our study uses two tests, the TRUE test and the Finn chamber, we will be able to estimate their agreement. Previous studies on this issue are inconsistent; in addition, they have limitations in terms of assessing prevalence or incidence variations of positive reactions in

populations defined with some basic characteristic and may suffer from the ‘floating numerator’ effect [18]. Our pilot study data, in spite of some limitations, have already provided relevant results on this issue (data not presented).

A new method based on information about patch test sales in a given geographical region has been proposed to assess the prevalence of contact allergy in the general population [22]. Although this method may be an inexpensive alternative for obtaining reliable estimates, a descriptive epidemiological survey in which participants represent the general population of the collecting regions, like the EDEN Fragrance Study, is currently the best method of estimating changing patterns of contact sensitizations arising from environmental pressure and also of discovering new associations and risk factors [10]. We will be able to perform cross-analyses on patch test results and general participant characteristics, including skin medical history and frequency of exposure to fragrance-containing products, as well as any possible problem related to skin contact with these products. In particular, the pilot study phase allowed the construction of an algorithm for the standardized assessment of the clinical relevance of positive reactions, based on the questionnaire. The algorithm results provided an unambiguous case definition, a major requirement in any epidemiological study [18], and the instruments to investigate how a positive reaction correlates with clinically relevant manifestations [18].

Of course, ultimately any algorithm for the standardized assessment of the clinical relevance of a positive reaction based on the questionnaire should be validated. Such validation can be achieved with randomized and controlled repeated open application. Evaluation according to anatomical site, modalities of exposure, pattern of reaction and disease severity will be made using our questionnaire, which showed a satisfactory level of reproducibility, in spite of the difficulties in developing questionnaires for previous occupational investigations [23]. Estimates will be sex and age adjusted to avoid differences in prevalence arising from an imbalance of data in terms of these variables. Previous studies, for example, have reported a higher prevalence of contact allergy to fragrances in women and in aged people [10, 24].

Other strengths of the EDEN Fragrance Study are that it is multicentric, thus allowing comparisons within and between countries. In addition, the sample size was computed to provide adequate power to the study.

In conclusion, the EDEN Fragrance Study will fully satisfy the needs that previous studies have exposed [1, 3,

10, 18]. The framework we developed in this study, including the reproducible questionnaire, the informative material, the patch test courses on application and reading, the video on patch test procedures and the clinical relevance definition, will provide useful tools for standardizing methodology for this multicentre and international study, as well as for future investigations on contact allergies and dermatitis in the general population.

Acknowledgements

The EDEN Fragrance Study is conducted in collaboration with the European Society of Contact Dermatitis. The Research Institute on Fragrance Materials initiated the study and gave the

mission to EDEN. The study is reviewed by the Expert Panel of the Research Institute on Fragrance Materials and is coordinated by the Centro Studi GISED, Ospedali Riuniti di Bergamo. Additional support for the study in the Netherlands was obtained from the Netherlands Institute for Public Health and the Environment, and from the Foundation of Occupational and Environmental Dermatology. This work was mainly supported by the Research Institute on Fragrance Materials.

Disclosure Statement

Magnus Bruze is a member of REXPAN, an independent expert panel to the Research Institute on Fragrance Materials.

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