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The Development of the MeDALL Core Questionnaires for a Harmonized Follow-Up Assessment of Eleven European Birth Cohorts on Asthma and Allergies

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Key Words

European birth cohorts · Asthma · Allergy · Questionnaire assessment · Harmonization · MeDALL

Abstract

Background: Numerous birth cohorts have been initiated in the world over the past 30 years using heterogeneous methods to assess the incidence, course and risk factors of asthma and allergies. The aim of the present work is to provide the stepwise proceedings of the development and current version of the harmonized MeDALL-Core Questionnaire (MeDALL-CQ) used prospectively in 11 European birth cohorts. ***Methods:*** The harmonization of questions was accomplished in 4 steps: (i) collection of variables from 14 birth cohorts, (ii) consensus on questionnaire items, (iii) translation and back-translation of the harmonized English MeDALL-CQ into 8 other languages and (iv) implementa-

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tion of the harmonized follow-up. ***Results:*** Three harmonized MeDALL-CQs (2 for parents of children aged 4–9 and 14–18, 1 for adolescents aged 14–18) were developed and used for a harmonized follow-up assessment of 11 European birth cohorts on asthma and allergies with over 13,000 children. ***Conclusions:*** The harmonized MeDALL follow-up produced more comparable data across different cohorts and countries in Europe and will offer the possibility to verify results of former cohort analyses. Thus, MeDALL can become the starting point to stringently plan, conduct and support future common asthma and allergy research initiatives in Europe.

Introduction

Numerous cohorts focusing on asthma and allergy have been initiated in the world over the past 30 years, most of them focusing on the evaluation of incidence, course and risk factors of asthma and allergies [1, 2]. In Europe, the costs of persistent asthma were estimated at EUR 19.3 billion and most costs were due to young patients aged 15–30 years [3]. The questionnaires used by many cohorts to assess symptoms of asthma and rhinitis included several questions based on those developed and validated in the worldwide International Study of Asthma and Allergies in Childhood (ISAAC) [4]. Although the order and/or wording of the ISAAC questions were usually slightly modified, questions on asthma and allergic rhinitis were homogeneously assessed across European birth cohorts. On the other hand, the assessment of other allergic phenotypes (e.g. eczema, sensitization to aero- and food allergens), pulmonary development and possible determinants of allergic diseases, including dietary habits and environmental exposures, were rather heterogeneous [1, 2]. MeDALL attempts to increase the amount of harmonized questions beyond those included in the ISAAC questionnaire or those which might have been included in the ISAAC questionnaire but were not frequently used by the cohorts in the last years.

Since 2004, several research initiatives funded under the EU Framework Program for Research and Technological Development FP6-FP7 have attempted to identify, compare and evaluate pooled data from existing European birth cohorts [5]: GA^{2}LEN (Global Allergy and European Network, FP6) [6], ENRIECO (Environmental Health Risks in European Birth Cohorts, FP7) [7], CHICOS (Developing a Child Cohort Research Strategy for Europe, FP7) and MeDALL (Mechanisms of the Development of Allergy, FP7) [8–10]. Combined analyses across birth cohorts result in larger sample sizes and increased statistical power, and broaden the diversity of environmental exposure assessments and facilitate research on underlying mechanisms explaining heterogeneous results among the cohorts [11].

Combining birth cohort data can be done retrospectively on historical data or prospectively by using the same core questionnaire and standard operating procedures for physical examinations. The collaborative MeDALL project aims to integrate epidemiological and clinical research and to identify inherited and environmental factors associated with the onset of allergy in children [8, 9]. Within this project, combined analyses of historical data from 14 European birth cohorts are underway. Moreover, MeDALL harmonizes a core assessment for follow-up of 11 birth cohorts in order to prospectively collect data on asthma and allergies. It is of importance that historical and prospective questions are interoperable to compare data.

Questionnaires for birth cohorts are collected according to the age at examination. In adolescents questionnaires are completed by the participants and their parents, whereas in school children (under 10 years) questionnaires are given to the parents only. In MeDALL, participants of 8 birth cohorts are older than 13 years (in the following referred to as the 'older birth cohorts') and participants of 6 others are younger than 10 years (in the following referred to as the 'younger birth cohorts') at the time of the harmonized follow-up.

The aim of the present work is to provide the stepwise proceedings of the development and current version of the MeDALL-Core Questionnaire (MeDALL-CQ) used prospectively in over 13,000 children. More specifically: (1) different working steps and the item selection process for the harmonized MeDALL-CQ are described and (2) the 3 English MeDALL-CQs, namely the parental (MeDALL-PQ, 14–18 years) and adolescent (MeDALL-AQ, 14–18 years) versions for the older birth cohorts and the parental questionnaire (MeDALL-PQ, 4–9 years) for the younger birth cohorts are presented in the online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000357732). (3) Translations in 8 languages and standard operating procedures for clinical examinations are available but not included in the present paper. They can be retrieved by contacting the corresponding author. The harmonized MeDALL follow-up is ongoing and resulting data will be presented in following publications.

Table 1. The eight birth cohorts (participant age 14–18 years) that took part in the development of a harmonized MeDALL-CQ

Birth cohort	Country/region	Year of recruitment	Size at recruitment, n	Age at MeDALL follow-up, years	Size at MeDALL follow-up (expected), n
BAMSE	Sweden/Stockholm	1994–1996	4,089	16–18	3,300
PIAMA-NHS	The Netherlands/North, West and Central	1996–1997	3,963	15–17	2,500
GINIplus	Germany/Munich, Wesel	1996–1998	5,991	14–17	2,050
LISAplus	Germany/Munich, Wesel, Leipzig, Bad Honnef	1997–1998	3,097	15–17	1,050
AMICS-Menorca	Spain/Menorca	1997–1998	485	14–15	380
DARC	Denmark/Odense	1998–1999	562	14–15	450
ECA	Norway/Oslo	1992–1993	3,754	16–17	550
MAS	Germany/Berlin, Düsseldorf, Mainz, Freiburg, Munich	1990	1,314	20	790

Six of the cohorts took part in the common MeDALL follow-up assessment and two birth cohorts (ECA, MAS) had a follow-up based on own funding.

Table 2. The six birth cohorts (participant age 4–9 years) that took part in the development of a harmonized MeDALL-CQ and the common MeDALL follow-up assessment

Birth cohort	Country/region	Year of recruitment	Size at recruitment, n	Age at MeDALL follow-up, years	Size at MeDALL follow-up (expected), n
BiB	UK/Bradford	2007–2010	13,776	4	1,500
INMA	Spain/Valencia, Sabadell, Guipuzkoa	2004–2008	3,768	4–7	1,100
PARIS	France/Paris	2003–2006	4,115	8	900
RHEA	Greece/Heraklion, Crete	2007–2008	1,497	4	900
ROBBIC	Italy/Rome,	2003	709	8–9	700
	Italy/Bologna	2003	654		
EDEN	France/Nancy, Poitiers	2003–2006	1,896	5	900

Five of the cohorts took part in the common MeDALL follow-up assessment and one birth cohort (EDEN) had a follow-up based on own funding, which did not use the MeDALL-CQ.

Materials and Methods

Members of MeDALL-CQ

Members of 8 older European MeDALL birth cohorts (AMICS-Menorca, BAMSE, DARC, ECA, GINIplus, LISAplus, MAS and PIAMA-NHS) developed and approved a common harmonized MeDALL-CQ for adolescent participants (MeDALL-AQ, 14–18 years) and their parents (MeDALL-PQ, 14–18 years; table 1).

Members of 6 younger European MeDALL birth cohorts (BiB, EDEN, INMA, PARIS, ROBBIC and RHEA) developed and approved a common harmonized MeDALL-PQ, for children aged 4–9 years (table 2).

Development of MeDALL-CQ

The harmonization of questions was conducted for 8 major sections (table 3) in 4 steps: (i) collection of variables from 14 birth cohorts, (ii) consensus on questionnaire items, (iii) translation and back-translation of the harmonized English MeDALL-CQ in 8 other languages and (iv) implementation of the harmonized follow-up (fig. 1).

During the process, it was important to reach a consensus on the inclusion of the questionnaire items by achieving a maximal harmonization between the cohorts and, at the same time, not to endanger longitudinal comparisons within each cohort. The MeDALL-CQ included core questions but also shared additional questions and gave the cohorts the opportunity to include a number of their own individual questions. This questionnaire, available in 9 different languages, was used prospectively by 11 MeDALL birth cohorts.

Sections and Item Selection for the MeDALL-CQ

Health Outcomes

The definitions for asthma, rhinitis and eczema were based on a MeDALL consensus meeting held in Barcelona, June 2011 [12].

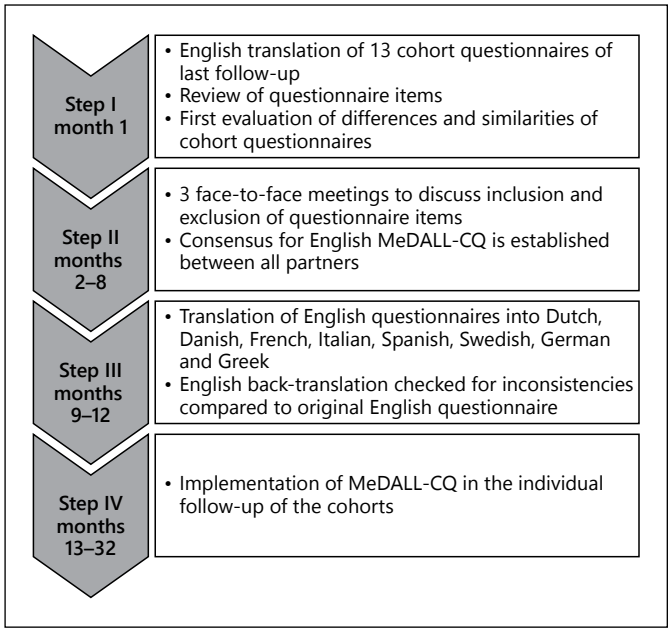

Fig. 1. Overview of the different working steps of the development of the harmonized MeDALL-Core Questionnaires (CQ) currently used by 11 European birth cohorts.

Table 3. Major sections of the common MeDALL questionnaire

1. Asthma
2. Allergic rhinitis
3. Eczema
4. Socio-demographic questions
5. Nutrition
6. Indoor environment (dampness/mold, tobacco smoke exposure, air pollution)
7. Lifestyle factors (physical activity, smoking, alcohol and drugs)
8. Puberty development

Asthma. ISAAC questions on wheezing symptoms [4], questions on doctor's diagnosis, hospital visits and medication intake were chosen to assess the prevalence and severity of asthma. Based on the decisions of the working group the adolescent core questionnaire, AQ, contained additional questions on tightness of chest and shortness of breath since these symptoms are also considered as 'key indicators for considering a diagnosis of asthma' [13]. The triad of respiratory symptoms (wheezing and/or tightness of chest and/or shortness of breath), doctor's diagnosis and medication intake was used for a questionnaire-based definition of asthma in children and adolescents [8, 14, 15]. In the MeDALL-AQ, a visual analog scale was used to estimate asthma and its impact on daily life, as these scales are more sensitive to small outcome differences than, for example, ordinal scales are [16], and may be relevant to assess the control of asthma [8]. Depending on country-specific differences, the wording of the question regarding an asthma diagnosis by a doctor might be adapted (e.g. additional questions for doctor's diagnosis of obstructive, asthmatic or spastic bronchitis for German-speaking countries). Questions for which it was unclear whether the judgment about the illness was based on a doctor's diagnosis or on self-diagnosis were not incorporated. Moreover, the MeDALL-CQs gave the cohorts the opportunity to include a number of cohort-specific questions to allow for consistency with earlier follow-ups. For the asthma section, this comprises questions on seasonal variations of symptoms, chronic obstructive lung disease and further details of medication intake. These questions were included in the section for optional use.

Rhinitis. The presence of rhinitis can be assessed by questionnaire assessment, while allergic rhinitis can be assessed by a questionnaire on nasal symptoms and the demonstration of an IgE-mediated sensitization to specific allergens (using skin-prick testing and/or specific serum IgE assays) only. Seasonal and perennial rhinitis were distinguished by the inclusion of ISAAC questions on current (last 12 months) and seasonal rhinitis symptoms [4]. In addition, questions about medication use and prior allergen-specific immunotherapy were included. If only current symptoms are assessed, children with medication intake might wrongly be categorized as healthy because the extent of their currently experienced symptoms might be profoundly reduced by the treatment received. Questions based on ARIA were used to assess the duration and severity of allergic rhinitis [17]. In the MeDALL-AQ, 14–18 years, questions on rhinosinusitis were included based on suggestions in the European Position Paper on Rhinosinusitis and Nasal Polyps (EP^3OS) emphasizing the importance of the current lack of knowledge about the incidence and prevalence of rhinosinusitis in European countries, and the need for 'large-scale epidemiologic research' [18, 19].

Eczema. The diagnosis of eczema by a doctor and the prevalence, severity and seasonal variations of eczema symptoms were assessed by means of items from the ISAAC questionnaire [4] and the Williams' and UK working criteria [20]. Moreover, questions on contact dermatitis were included. Concerning eczema severity, the POEM (Patient-Oriented Eczema Measure) [21] was part of the supplemental questionnaire which assesses self-reported recent eczema severity over the last 7 days. As for wheezing and rhinitis symptoms in epidemiological studies, the corresponding POEM-based eczema severity questions referred to the last 12 months. This method of assessing self-reported eczema severity will be validated by two of the birth cohorts during the course of MeDALL (BAMSE and DARC).

Possible Determinants of Allergic Diseases

Parental Allergies. Family history is a relevant risk factor of allergic diseases and regular assessments of parental allergies are necessary to record different patterns which might influence children's allergies [22]. Thus, the MeDALL-PQ contains questions on the diagnosis of asthma, rhinitis and eczema of both parents, also including age at onset of the disease and the differentiation between the doctor's diagnosis and self-diagnosis. Although information on parental allergies was already collected in former questionnaires (for most cohorts at birth) the differentiation between a self-diagnosis versus a doctor's diagnosis was lacking in most cohorts.

Nutrition. The birth cohorts participating in MeDALL are geographically spread across the European continent from Norway

and Sweden in the north to Spain and Greece in the south, covering various climatic and cultural regions with heterogeneous nutritional habits [23, 24]. Due to these considerable differences in diet among the MeDALL birth cohort study participants, and also reflected by the different instruments used in previous nutritional assessments in each of the cohorts, harmonized food questions could not be identified. However, all MeDALL cohorts assessed data on the food-item level by using cohort-specific food frequency questionnaires. Common questions for the MeDALL-CQs were agreed upon by the MeDALL partners to assess self- and parent-reported allergic reactions to food, including the age at first reaction, the type of allergic reaction and current allergic reactions to food items.

Indoor Environment. 'Cooking with gas' was included in the MeDALL-PQ and the inclusion of variables such as kitchen ventilation or the 'presence of other sources of combustion products' were not expected to explain additional variance when investigating respiratory health outcomes [25]. Three questions on 'dampness and/or mold within the home' were adapted from the LISAplus and GINIplus cohorts aiming to follow-up a previous meta-analysis that suggested a possible link with wheezing and allergic rhinitis [15]. The parents were considered to be a more reliable source of information concerning the indoor environment at home than the adolescents. Active and passive tobacco smoke exposure, however, needed to be included in both the parental MeDALL-PQ as well as the adolescent MeDALL-AQ, since parents are not likely to know (exactly) their teenaged children's tobacco exposure outside the home.

Lifestyle Factors. In the MeDALL-AQ, 14–18 years, questions on physical activity, smoking, alcohol and drug consumption were included. For this purpose, the International Physical Activity Questionnaire (IPAQ) [26] was adapted to the needs of an epidemiological study. Instead of asking for physical activity during the last 7 days, which could be useful in cross-sectional or short-term intervention studies, the corresponding IPAQ-based MeDALL questions asked for physical activity during a typical week in the last 12 months in summer and, separately, in winter. It is planned to validate this assessment in the German LISA birth cohort by using accelerometers. Besides active smoking, questions on passive smoking at indoor locations were added to the MeDALL-PQ, distinguishing between second-hand smoke exposures 'at home' and 'not at home'. Alcohol and drug consumption were assessed each by two questions asking for the type of alcohol/drug and the amount of intake as glasses per week or times of intake in the last 12 months, adapted from the KiGGS survey [27]. The unit 'number of sips' used before by some of the cohorts was not considered as a valid proxy for current drinking behavior in adolescents. No consensus was reached about questions on binge drinking, but the following 2 questions were recommended for optional use: 'have you ever drunk that much alcohol that you have been dizzy or sick afterwards? If yes, how often in the last 12 months?' and 'have you ever drunk that much alcohol that you could not remember everything from the day before?', which have been used in former questionnaires by the cohorts GINIplus and LISAplus.

Puberty Development. In the MeDALL-ACQ, puberty development was assessed by the Pubertal Development Scale (PDS) [28]. The prospectively collected data since birth in the MeDALL cohorts provides the unique possibility to investigate determinants of the postulated sex-switch in the prevalence of asthma and allergic diseases during puberty [29].

Other Questions. The MeDALL-AQ contained questions on height, weight and school degree/level of schooling of the adolescent participants. Although allergies might play a minor role in adolescents' job choices [30], items inquiring whether the choice of schooling programs is affected by allergic diseases were included so that the prevalence of current allergic symptoms would not be underestimated due to the avoidance of known allergens. Furthermore, this question could give an idea of the severity of the allergic disease and its impact on the choices of the adolescent regarding everyday life. The items of this section were extracted from former cohort questionnaires and agreed on by all MeDALL birth cohorts.

Results

The three MeDALL-CQs consisted of 8 sections, of which each was divided into a core section and supplementary questions which remained optional for the cohorts. The complete MeDALL-CQs are presented in online supplemantary figure 1–3. Please see online supplementary figure 4 for references of the single items of the MeDALL-CQs.

The MeDALL-AQ, 14–18 years, included 66 core-section items and 19 optional items for adolescents (online suppl. fig. 1). The parent-reported MeDALL-PQ, 14–18 years, included 50 core-section items and 5 optional items (online suppl. fig. 2). The parent-reported MeDALL-PQ, 4–9 years, included 56 core-section items and 37 optional items (online suppl. fig. 3).

Discussion

The MeDALL-CQ is, to our knowledge, the first attempt to develop a multilingual common core questionnaire for birth cohorts in allergy and asthma. It has been constructed using a rigorous stepwise process and it is now used in 11 birth cohorts in 9 European countries. It can be expanded to other countries in the world with relatively minor adaptation. This MeDALL-CQ is interoperable with historical data of the 14 MeDALL cohorts, making it possible to compare part of the data across several time points (table 4).

Limitations

In some sections of the questionnaire country-specific differences were so profound, for example in the section on nutrition, that it was decided that harmonization was impossible. Also, questions about educational status had to be adapted for each country. The other sections were judged to be suitable for the harmonization process and

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Table 4. Interoperability table for relevant outcome and exposure variables for historical cohort data and harmonized data (MeDALL follow-up, last column) assessed from all cohorts at the MeDALL follow-up

Variables	Follow-up																
	<1 year	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years	13 years	14 years	15 years	MeDALL follow-up
Asthma																	
Wheeze	Amics-M, BAMSE, DARC, ECA, INMA-S, LISA, MAS, PARIS, PIAMA, RHEA, ROBBIC	Amics-M, BAMSE, DARC, ECA, EDEN, INMA-S, INMA-V, GINI, LISA, MAS, PARIS, PIAMA, ROBBIC	Amics-M, BAMSE, ECA, EDEN, INMA-S, INMA-V, GINI, MAS, PARIS, PIAMA	Amics-M, BAMSE, DARC, EDEN, GINI, MAS, PARIS, PIAMA, ROBBIC	Amics-M, BAMSE, EDEN, GINI, INMA-S, INMA-V, LISA, MAS, PARIS, PIAMA	EDEN, MAS, PARIS, PIAMA	Amics-M, DARC, GINI, LISA, MAS, PARIS, PIAMA	MAS, PIAMA	EDEN, PIAMA, MAS, BAMSE	Amics-M, MAS, BAMSE	LISA, MAS, ECA, BAMSE, GINI	PIAMA, BAMSE	BAMSE	MAS		MAS	✓
Chest tightness, shortness of breath	INMA-S, RHEA, ROBBIC	BIB, INMA-S, ROBBIC	INMA-S, ROBBIC	PARIS, PIAMA	INMA-S, PARIS, PIAMA	PARIS, PIAMA	PARIS, PIAMA	PIAMA	PIAMA			PIAMA					✓
Asthma medication	BAMSE, BIB, DARC, ECA, EDEN	Amics-M, BAMSE, BIB, DARC, ECA, EDEN, PIAMA	Amics-M, BAMSE, BIB, ECA, EDEN, PARIS, PIAMA	Amics-M, BAMSE, BIB, DARC, EDEN, GINI, PIAMA, ROBBIC	Amics-M, BAMSE, EDEN, GINI, PIAMA	EDEN, INMA-V, PIAMA	Amics-M, DARC, GINI, LISA, PIAMA	PIAMA	BAMSE, EDEN, MAS, PIAMA	Amics-M, MAS	ECA, GINI, MAS	BAMSE, MAS, PIAMA	BAMSE, MAS	MAS			✓
Doctor's diagnosis	BAMSE, BIB, DARC, ECA, EDEN, MAS, RHEA, ROBBIC	Amics-M, BAMSE, BIB, DARC, ECA, EDEN, GINI, LISA, MAS, PARIS, PIAMA, ROBBIC	Amics-M, BAMSE, BIB, ECA, EDEN, GINI, LISA, MAS, PARIS, PIAMA	Amics-M, BAMSE, BIB, DARC, EDEN, GINI, LISA, MAS, PARIS, PIAMA, ROBBIC	Amics-M, BAMSE, EDEN, GINI, INMA-V, LISA, MAS, PARIS, PIAMA	BAMSE, EDEN, INMA-V, LISA, GINI, PARIS, PIAMA	Amics-M, BAMSE, DARC, GINI, LISA, MAS, PARIS, PIAMA	BAMSE, GINI, LISA, MAS, PIAMA	BAMSE, EDEN, GINI, LISA, MAS, PIAMA	Amics-M, BAMSE, GINI, LISA, MAS	BAMSE, ECA, GINI, LISA, MAS	BAMSE, MAS, PIAMA	BAMSE, MAS	MAS		MAS	✓
Eczema																	
Dry skin	BAMSE, DARC, INMA-S	Amics-M, BAMSE, DARC, INMA-S	BAMSE, Amics-M, INMA-S, INMA-V, PARIS	Amics-M, DARC	Amics-M, INMA-V		Amics-M, DARC		BAMSE,	Amics-M							✓
Itchy rash	Amics-M, BAMSE, EDEN, DARC, INMA-S, MAS, LISA, PIAMA, RHEA, ROBBIC	Amics-M, BAMSE, EDEN, DARC, GINI, INMA-S, MAS, LISA, PARIS, PIAMA, ROBBIC	Amics-M, BAMSE, BIB, EDEN, GINI, INMA-S, INMA-V, MAS, LISA, PARIS, PIAMA	Amics-M, DARC, EDEN, GINI, MAS, PARIS, PIAMA, ROBBIC	Amics-M, BAMSE, EDEN, GINI, INMA-V, LISA, MAS, PARIS, PIAMA	EDEN, MAS, PARIS, PIAMA	Amics-M, DARC, GINI, LISA, MAS, PARIS, PIAMA	MAS, PIAMA	BAMSE, EDEN, MAS, PIAMA	Amics-M, MAS	GINI, LISA, MAS	MAS	BAMSE, MAS	MAS		MAS	✓

Table 4. (continued)

Variables	Follow-up																
	<1 year	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years	13 years	14 years	15 years	MeDALL follow-up
Itchy rash at flexural body parts	Amics-M, BAMSE, DARC, EDEN, INMA-S, LISA, PIAMA	Amics-M, BAMSE, DARC, EDEN, GINI, INMA-S, LISA, PARIS, PIAMA	Amics-M, BAMSE, GINI, INMA-S, INMA-V, PARIS, PIAMA	Amics-M, DARC, EDEN, GINI, PARIS, PIAMA	BAMSE, EDEN, GINI, INMA-V, LISA, MAS, PARIS, PIAMA	Amics-M, EDEN, MAS, PIAMA	DARC, LISA, MAS, PARIS, PIAMA	PIAMA	BAMSE, EDEN, PIAMA	Amics-M,	GINI, LISA	PIAMA	BAMSE				✓
Rhinitis																	
Sneezing, runny or blocked nose without cold or flu	DARC, MAS, RHEA, ROBBIC	Amics-M, DARC, GINI, LISA, MAS, PARIS, ROBBIC	BIB, EDEN, GINI, LISA, MAS, PARIS	Amics-M, DARC, EDEN, GINI, MAS, PARIS, PIAMA, ROBBIC	Amics-M, BAMSE, EDEN, GINI, LISA, MAS, PARIS, PIAMA	MAS, PARIS, PIAMA	Amics-M, DARC, GINI, LISA, MAS, PARIS, PIAMA	MAS, PIAMA	BAMSE, EDEN, MAS, PIAMA	Amics-M, MAS	GINI, LISA, MAS	MAS, PIAMA	BAMSE, MAS	MAS			✓
Food allergy	BAMSE, DARC, EDEN, INMA-S, LISA, MAS, PARIS, RHEA	BAMSE, DARC, EDEN, GINI, INMA-S, INMA-V, LISA, MAS, PARIS, PIAMA	Amics-M, EDEN, GINI, INMA-S, INMA-V, LISA, MAS, PARIS, PIAMA	Amics-M, DARC, EDEN, GINI, LISA, MAS, PARIS, PIAMA	BAMSE, EDEN, GINI, INMA-V, LISA, MAS, PARIS, PIAMA	BAMSE, EDEN, GINI, LISA, MAS, PARIS, PIAMA	BAMSE, DARC, GINI, LISA, MAS, PARIS, PIAMA	BAMSE, GINI, LISA, MAS, PIAMA	BAMSE, EDEN, GINI, LISA, MAS, PIAMA	GINI, LISA, MAS	GINI, LISA, MAS	MAS, PIAMA	MAS	BAMSE, MAS		MAS	✓
Smoking																	
Passive smoke exposure	Amics-M, BAMSE, BIB, DARC, EDEN, GINI, LISA, MAS, PARIS, PIAMA, ROBBIC, RHEA	Amics-M, BAMSE, BIB, DARC, EDEN, GINI, INMA-S, INMA-V, LISA, MAS, PARIS, PIAMA, ROBBIC	Amics-M, BAMSE, BIB, EDEN, GINI, INMA-S, INMA-V, LISA, MAS, PARIS, PIAMA	Amics-M, DARC, EDEN, GINI, MAS, PARIS, PIAMA, ROBBIC	Amics-M, BAMSE, EDEN, GINI, INMA-S, INMA-V, LISA, MAS, PARIS, PIAMA	EDEN, MAS, PARIS, PIAMA	Amics-M, DARC, GINI, LISA, PARIS, PIAMA	MAS, PIAMA	BAMSE, EDEN, PIAMA	Amics-M, GINI, LISA, MAS, PIAMA	MAS	PIAMA	BAMSE				✓
Smoking of adolescent												PIAMA	BAMSE				✓
Physical activity			INMA-S	BIB	INMA-S, INMA-V, LISA	PIAMA	Amics-M, GINI	PIAMA	PIAMA	Amics-M	GINI, LISA	PIAMA	BAMSE				✓

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Table 4. (continued)

Variables	Follow-up														
	<1 year	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years	13 years	14 years	15 years	MeDALL follow-up
Cooking with gas	Amics-M, BAMSE, DARC, EDEN, LISA, MAS, PARIS, PIAMA, ROBBIC	Amics-M, BIB, DARC, EDEN, GINI, INMA-S, INMA-V, LISA, PARIS, PIAMA	Amics-M, BIB, EDEN, GINI, INMA-S, INMA-V, LISA, PARIS, PIAMA	Amics-M, DARC, EDEN, PARIS, PIAMA, ROBBIC	Amics-M, INMA-S, INMA-V, LISA, PARIS, PIAMA	PARIS, PIAMA	Amics-M, DARC, GINI, LISA, PARIS		BAMSE, EDEN		GINI, LISA	PIAMA				✓
Dampness/ mold	Amics-M, BAMSE, BIB, DARC, EDEN, LISA, MAS, PARIS, PIAMA, ROBBIC, RHEA	Amics-M, BIB, DARC, EDEN, GINI, INMA-S, INMA-V, LISA, PARIS, ROBBIC	Amics-M, BIB, BAMSE, EDEN, INMA-S, GINI, INMA-S, INMA-V, LISA, PARIS, PIAMA	Amics-M, DARC, EDEN, PARIS, PIAMA, ROBBIC	Amics-M, INMA-S, INMA-V, LISA, PARIS, PIAMA	DARC, PARIS, PIAMA	Amics-M, GINI, LISA, PARIS, PIAMA	PIAMA	BAMSE, EDEN, PIAMA	Amics-M, MAS	MAS, GINI, LISA	PIAMA	BAMSE			✓

Variables were asked for the last 12 months.

the translations and back-translations of questionnaires were found to be correctly translated into the 8 other languages. However, it cannot be excluded that slightly different wording chosen in other languages has led to different interpretations. This might not be the case for questions about factual knowledge, such as 'how many cigarettes do you smoke?', but rather for questions on medical conditions such as 'wheeze', for which the general public understanding might be limited, and could lead to different answering behavior among participants. Also, asking for eczema – 'have you (mother or father) ever had eczema?' – highly depends on the patients' understanding of the actual wording, which might also differ depending on the language used.

Moreover, the order of the harmonized questions within the questionnaire differs between the cohorts. As the cohorts should have the possibility to include their own questions, the harmonized questions are not asked in one exclusive part of the questionnaire, but are instead integrated in different sections of the cohorts' own questionnaires. Not only the order, but also the way in which the questionnaires can be filled out varies in terms of using paper and pencil versus online completion. Furthermore, the age of the adolescents to which the questionnaire is given showed a discrepancy between the cohorts (14–18 years). No data will be retrieved for the age group 11–13 years within the MeDALL project. If the MeDALL-CQ is used in future studies, different ages of participants and the order of questions should be considered as one source of variability of the results.

The questionnaires were developed by the extraction of questions from former questionnaires, clinical experience, experience with specific questions in the cohort questionnaires and consensus in the research group, and, so far, a validation of the core questionnaires is missing. The MeDALL-CQ is an instrument under constant development and will be modified according to future experience and results.

Strengths and Generalizability

The harmonized MeDALL questionnaire, measuring a variety of health outcomes and possible determinants of allergies in childhood and adolescence, is publicly available in 9 different languages (Danish, Dutch, English, French, German, Greek, Italian, Spanish and Swedish) and has been used for the age groups 4–9 and 14–18 years.

For the 6 older birth cohorts, historical childhood data and the MeDALL-CQ will be harmonized to analyze longitudinal exposure-response relationships from childhood up to adolescence within the MeDALL project. The

separated parental and adolescent questionnaire versions allowed detailed use of the knowledge of each participant. While the parents were expected to give more reliable data on questions referring to conditions throughout the adolescent's life, housing situation and topics such as parental allergies, the adolescents were thought to be the more reliable source for information on current allergy symptoms, which can also occur without the knowledge of the parent, and on environmental exposures such as smoke exposure, which do not take place at home.

The 6 younger birth cohorts provided data up to 9 years of age in the current MeDALL follow-up. If the MeDALL-CQ is continuously used in the coming years, in the long-run these will be the cohorts with prospectively harmonized data, available from early childhood up to adolescence. Time-consuming data harmonization processes will be unnecessary in the future.

The construction of the ISAAC questionnaire was a major achievement in the field of asthma and allergy assessment, it encouraged networking between European cohorts, as in GA^{2}LEN, and was the base on which many data harmonization projects such as ENRIECO have been built. MeDALL is taking this approach one step further by including a bigger pool of harmonized variables and using existing European birth cohorts as a data source with already existing historical data and further follow-ups planned for the coming years. MeDALL will offer a harmonized assessed multicountry sample of over 13,000 parent-child pairs.

Conclusion

The harmonized follow-up of 11 European birth cohorts in MeDALL will produce more comparable data across different cohorts and countries in Europe. In addition, all participating cohorts are allowed to include additional questions and instruments following their own special research interests, so that focused knowledge about specific local issues is obtained. The harmonized follow-up, however, does not reduce the need to harmonize historical data of the participating cohorts for combined longitudinal analyses.

Understanding geographical and time patterns of allergic diseases is a challenge. Results from the harmonized MeDALL follow-up will provide more insight into true differences or similarities between cohorts and/or countries in Europe. This new harmonized assessment will offer the possibility to verify results of former combined analyses for which otherwise extensive efforts of data harmonization are necessary. Thus, MeDALL can become the starting point to stringently plan, conduct and support future common asthma and allergy research initiatives in Europe.

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