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Institut für Sozialmedizin, Epidemiologie und Gesundheitsökonomie
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Habilitationsschrift

Longitudinale Analysen von Beobachtungsstudien und Interventionsstudien bei allergischen Atemwegserkrankungen

zur Erlangung der Lehrbefähigung
für das Fach Epidemiologie und Biometrie

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von

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Abkürzungen

ACUSAR	Acupuncture in Seasonal Allergic Rhinitis
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ISAAC	International Study of Asthma and Allergies in Childhood
MeDALL	Mechanisms of the Development of Allergy
QALY	Quality-adjusted life-year
RKI	Robert Koch-Institut
RMS	Rescue medication score
RQLQ	Rhinitis Quality of Life Questionnaire
SF-36	Short form 36

1. Einleitung

1.1. Allergische Erkrankungen

Asthma und allergische Rhinitis gehören zu den häufigsten allergischen Erkrankungen und gehen mit belastenden Symptomen im Alltag wie beispielsweise Atemnot, Konjunktivitis und einer eingeschränkten Lebensqualität einher (International Rhinitis Management Working Group, 1994, Reddel et al., 2015). So zeigte die Global Burden of Disease Study 2015, dass Asthma die häufigste der chronischen Atemwegserkrankungen mit ca. 358 Millionen Betroffenen weltweit ist (GBD 2015 Chronic Respiratory Disease Collaborator, 2017). Daten des Robert Koch-Instituts (RKI) zeigten für Deutschland, dass die 12-Monats-Prävalenz für Asthma bronchiale bei Erwachsenen im Zeitraum 2014/2015 bei 6,2% lag (Stepphuhn et al., 2017). Von allergischer Rhinitis waren in Deutschland 14,8% der Erwachsenen und 10,7% der Kinder und Jugendlichen betroffen (Bergmann et al., 2016). Die Lebensqualität ist sowohl bei Patienten mit Asthma oder allergischer Rhinitis als auch bei deren Angehörigen deutlich eingeschränkt (Stucky et al., 2015, Juniper et al., 2004, Luskin et al., 2014, Halterman et al., 2004, Roncada et al., 2018, Canonica et al., 2008, Sikorska-Szaflik and Sozańska, 2020).

1.2. Einflussfaktoren für allergische Erkrankungen

Zu den Ursachen für die Entstehung von allergischen Erkrankungen gehören insbesondere Umweltfaktoren (z. Bsp. Luftschadstoffe), Lebensstilfaktoren (z. Bsp. Rauchen) sowie genetische Komponenten (Subbarao et al., 2009, Laußmann et al., 2012, Wang, 2005). Der mögliche Einfluss von Haustierhaltung im Kindesalter auf die Entstehung allergischer Erkrankungen wurde bereits in mehreren epidemiologischen Studien untersucht, konnte jedoch lange nicht eindeutig geklärt werden. Verschiedene Beobachtungsstudien kamen dabei sowohl zum Ergebnis, dass Haustiere als Risikofaktor für die Entstehung von Allergien gelten können, als auch, dass sie ein protektiver Faktor sein können (Almqvist et al., 2003, Brussee et al., 2005, Al-Mousawi et al., 2004, Bener et al., 2004, Hesselmar et al., 1999, Custovic et al., 2003, Anyo et al., 2002, Svanes et al., 2003, Lau et al., 2000, Lau et al., 2005, Chen et al., 2007, Chen et al., 2008, Abdulrazzaq et al., 1995, McConnell et al., 2002, Bornehag et al., 2003, Jaakkola et al., 2002, Campo et al., 2006, Litonjua et al., 2002, Remes et al., 2001, Arif et al., 2004, Perzanowski et al., 2002, Ownby et al., 2002, Celedón et al., 2002, Wegienka et al., 2011). Daher konnte insbesondere bei der Geburt eines Kindes die sich häufig stellende Frage für Familien, ob ein Haustier abgeschafft (Risikofaktor) oder angeschafft (protektiver Faktor) werden sollte, nie zufriedenstellend beantwortet werden. Aus primär-präventiver Sicht bzgl. der Entstehung von

allergischer Rhinitis und Asthma ist die Empfehlung bzgl. einer Vermeidung oder eines Umgangs mit Haustieren für Ärzte und Familien jedoch bedeutsam.

Als einer der relevanten biologischen Faktoren wird zudem das Geschlecht des bzw. der Erkrankten im Zusammenhang mit allergischen Erkrankungen gewertet. So waren unter den Erwachsenen in Deutschland Frauen mit 7,1% häufiger von Asthma betroffen als Männer mit 5,4% (Stepphuhn et al., 2017). Ebenso war die Prävalenz der allergischen Rhinitis bei Frauen höher als bei Männern (16,5% vs. 13,0%) (Bergmann et al., 2016). Diese Geschlechtsunterschiede unter Erwachsenen sind im Kindesalter (vor der Pubertät) jedoch umgekehrt anzutreffen. So zeigte das RKI, dass Jungen in Deutschland mit 7,5% deutlich häufiger von Asthma betroffen waren als Mädchen mit 4,5% (Thamm et al., 2018). Auch bei allergischer Rhinitis war die Prävalenz bei Jungen relevant höher als bei Mädchen (13,0% vs. 8,9%) (Thamm et al., 2018). Die Ursachen für diesen im Vergleich zu anderen Krankheiten ungewöhnlichen „Wechsel“ der geschlechtsspezifischen Prävalenz bei Atemwegsallergien um die Pubertät herum sind unklar. Ein besseres Verständnis könnte möglicherweise helfen, altersabhängige, geschlechtsspezifische Präventionsstrategien zu entwickeln.

1.3. Behandlung allergischer Rhinitis

Als Behandlungsmöglichkeiten für die allergische Rhinitis stehen in erster Linie eine allergenspezifische Immuntherapie (Hyposensibilisierung) sowie die medikamentöse Behandlung der Symptome zu Verfügung (van Cauwenberge et al., 2000, Stuck et al., 2017). Zusätzlich werden Karenzmaßnahmen (Vermeidung des Kontakts mit Allergenen) empfohlen. Ebenso könnte sich das aus der Chinesischen Medizin stammende Verfahren der Akupunktur als nicht-medikamentöses Verfahren zur Symptombehandlung anbieten. So zeigten Querschnittstudien, dass 17-19% der Patienten mit Rhinitis bzw. Allergien Akupunktur zur Behandlung nutzen (Krouse and Krouse, 1999, Schafer et al., 2002). Unter den komplementärmedizinische Verfahren scheint die Akupunktur ein gewisses Potenzial als Therapieoption zu haben (Senna et al., 2000). Dennoch war die vorhandene Evidenz zu ihrer Wirksamkeit bei Allergien und Asthma noch begrenzt.

1.4. Statistische Methoden

In den vorliegenden Arbeiten wurden einige methodisch-statistische Besonderheiten verwendet, auf die im Folgenden eingegangen werden soll.

1.4.1. Metaanalytische Verfahren

Für die Untersuchung von Einflussfaktoren für allergische Erkrankungen wie Geschlecht oder Haustierhaltung ist die Durchführung von randomisiert kontrollierten Interventionsstudien nicht möglich. Daher können für diese Fragestellungen nur Beobachtungsstudien (z. Bsp. prospektive Kohortenstudien) herangezogen werden. Die beste verfügbare Evidenz liefern Metaanalysen, wenn mehrere große und qualitativ gute Beobachtungsstudien bereits vorliegen. Dabei sind grundsätzlich zwei methodische Metaanalyse-Ansätze möglich:

- die Verwendung aggregierter Ergebnisse aus Publikationen zur Berechnung eines gepoolten Gesamtergebnisses („klassische“ Metaanalyse)
- die Verwendung von Rohdaten der einzelnen Studien für die standardisierte Auswertung und Berechnung der Gesamtergebnisse (individual patient (or participant) data (IPD) Metaanalyse) (Tierney et al., 2015, Tierney et al., 2019).

IPD-Metaanalysen könne wiederum unterteilt werden in

- einstufige IPD-Metaanalyse (one-stage IPD meta-analysis)
- zweistufige IPD-Metaanalyse (two-stage IPD meta-analysis).

Bei der einstufigen IPD-Metaanalyse werden die Rohdaten der einzelnen Studien zu einem einzigen gemeinsamen Datensatz zusammengefügt. Eine zusätzliche Variable wird erzeugt, die anzeigt, aus welcher der Studien die Daten der einzelnen Teilnehmer stammen. Der Datensatz wird mit gängigen statistischen Methoden ausgewertet. Eine Adjustierung für potentielle Confounder (wenn in jeder Studie vergleichbar erhoben) ist dabei möglich. Die Studienzugehörigkeit der Teilnehmer kann als Zufallseffekt bei der Auswertung berücksichtigt werden (hierarchisches oder Multi-Level-Modell).

Bei der zweistufigen IPD-Metaanalyse wird zunächst jede Studie mit gängigen statistischen Methoden separat ausgewertet. Eine Adjustierung für potentielle Störgrößen (Confounder) kann individuell auf Studienebene erfolgen. Dies ist insbesondere dann von Vorteil, wenn Studien einzelne Variablen sehr unterschiedlich erhoben haben, wenn Variablen gar nicht vorliegen oder wenn viele fehlende Werte (missing values) in einzelnen Variablen vorhanden sind. Nach der Auswertung auf Studienebene werden die Einzelergebnisse der Studien mit üblichen metaanalytischen Methoden zu einem Gesamtergebnis zusammengefasst. Eine graphische Darstellung der Einzelergebnisse und des Gesamtergebnisses erfolgt meist als Forest-Plot.

In den vorliegenden Arbeiten dieser Habilitationsschrift kamen alle hier beschrieben Metaanalyse-Methoden zur Anwendung.

1.4.2. Gemeinsame Betrachtung von klinischen Endpunkten und Bedarfsmedikation

In vielen klinischen Studien, die als randomisiert, kontrollierte Studie durchgeführt werden, ist es den Studienteilnehmern erlaubt, während der Studie gewisse, vorab festgelegte Medikamente als Notfall- bzw. Bedarfsmedikation einzunehmen. Damit soll, insbesondere für die Kontrollgruppe aber auch für die Interventionsgruppe bei nicht oder nicht ausreichend wirksamer Intervention, gewährleistet sein, dass kein Studienteilnehmer durch die Studienteilnahme unbehandelt bleibt, falls eine zusätzliche Behandlung erforderlich ist; es muss vielmehr jedem Studienteilnehmer auch bei Studienteilnahme eine adäquate Therapie zukommen.

Diese aus ärztlicher und ethischer Sicht notwendige Maßnahme der verfügbaren Notfall- bzw. Bedarfsmedikation, bringt jedoch Nachteile für die Methodik, bzw. die Interpretation der Ergebnisse mit sich. Zum einen kann eine wirksame Intervention als unwirksam erscheinen, falls der klinische Endpunkt bei Studienende in Interventionsgruppe und Kontrollgruppen ähnlich ist (d.h. kein signifikanter bzw. relevanter Unterschied zwischen den beiden Gruppen vorhanden ist), dies jedoch in der Kontrollgruppe nur dadurch erreicht wurde, dass die Teilnehmer deutlich mehr Bedarfsmedikation verwendet hatten. Zum anderen kann eine unwirksame Intervention als wirksam erscheinen, falls eine Überlegenheit der Interventionsgruppe im klinischen Endpunkt nur erreicht wurde, weil in dieser Gruppe mehr Bedarfsmedikation verwendet wurde. Auch in Nicht-Unterlegenheitsstudien kann dieses Phänomen auftreten, wenn als Kontrolle eine etablierte, gut wirksame Standardtherapie verwendet wird und die zu testende Intervention nur durch die deutlich höhere Verwendung von Notfall- oder Bedarfsmedikation eine vergleichbare Wirksamkeit gezeigt hat.

Diese Problematik wird bei den gängigen Studiendesigns mit der Betrachtung von einem einzigen primären klinischen Endpunkt nicht adäquat berücksichtigt. Die Bedarfsmedikation wird in der Regel getrennt vom primären Endpunkt, lediglich als sekundärer Endpunkt betrachtet. Eine Lösung besteht darin, den klinischen Endpunkt und die Verwendung von Bedarfsmedikation als co-primäre Endpunkte zu definieren und gemeinsam zu betrachten. Ein positives Studienergebnis ist damit nur dann gegeben, wenn sich in mindestens einem dieser beiden primären Endpunkte eine Überlegenheit der Intervention gegenüber der Kontrollgruppe zeigt UND der andere Endpunkt zumindest nicht unterlegen ist. Damit ist gewährleistet, dass eine Intervention nur dann als wirksam angesehen wird, wenn ihre klinische Überlegenheit nicht allein auf Unterschieden in der Bedarfsmedikation basiert. In der im Rahmen dieser Habilitationsschrift vorliegenden Interventionsstudie kam die gemeinsame Betrachtung von klinischem Endpunkt und Bedarfsmedikation zur Anwendung.

1.5. Fragestellungen

In den vorliegenden Arbeiten dieser Habilitationsschrift wurden spezifische Risikofaktoren zu allergischen Erkrankungen untersucht. Insbesondere wurde die Haltung von Haustieren in den ersten Jahren nach der Geburt und der Zusammenhang zwischen dem Auftreten von allergischen Erkrankungen im Schulalter bestimmt.

Ebenfalls ist dargestellt, ob und wie sich das Geschlechterverhältnis bei allergischen Erkrankungen in den Phasen vor bzw. nach der Pubertät verändert. Als Behandlungsoption sollte zudem die Wirksamkeit der Akupunktur im Vergleich zu einer Scheinakupunktur bzw. alleiniger Bedarfsmedikation bei Patienten mit saisonaler allergischer Rhinitis untersucht werden; ebenso sollte die gemeinsame Betrachtung von Kosten und Nutzen der Akupunkturbehandlung erfolgen.

Im Einzelnen werden folgende Fragestellungen untersucht:

- Gibt es einen Zusammenhang zwischen der Haustierhaltung im Kleinkindalter und dem Auftreten von Asthma oder Allergien im Grundschulalter?
- Gibt es einen Unterschied im Geschlechterverhältnis der Häufigkeit von Asthma oder allergischer Rhinitis von der Kindheit und Jugend bis ins Erwachsenenalter?
- Wie sind Wirksamkeit (bezogen auf Lebensqualität und Bedarfsmedikation), Kosten und Kosteneffektivität von Akupunktur bei der Behandlung von allergischer Rhinitis?

2. Eigene Arbeiten

2.1. Metaanalysen von Beobachtungsstudien zu Risikofaktoren allergischer Erkrankungen

2.1.1. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts

Lødrup Carlsen KC*, **Roll S***, Carlsen KH, Mowinckel P, Wijga AH, Brunekreef B, Torrent M, Roberts G, Arshad SH, Kull I, Krämer U, von Berg A, Eller E, Høst A, Kuehni C, Spycher B, Sunyer J, Chen CM, Reich A, Asarnoj A, Puig C, Herbarth O, Mahachie John JM, Van Steen K, Willich SN, Wahn U, Lau S, Keil T, GALEN WP 1.5 'Birth Cohorts' working group. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. PLoS One. 2012;7(8):e43214. https://doi.org/10.1371/journal.pone.0043214 (*Contributed equally to this work)

Um den Zusammenhangs zwischen Haustierhaltung in den ersten beiden Lebensjahren und der Entwicklung von Asthma bzw. allergischen Erkrankungen im Alter von 6 bis 10 Jahren (frühe Schulzeit) zu bestimmen, wurden longitudinale, individuelle Rohdaten aus 11 europäischen Geburtskohorten mit mehr als 22.000 Kindern zusammengeführt und ausgewertet. Als Risikofaktor (Exposition) wurde die Haltung von Hunden, Katzen, Vögel oder Nagetieren in den ersten beiden Lebensjahren untersucht. Asthma bronchiale im Alter von 6 bis 10 Jahren war der primäre Endpunkt. Zudem wurden allergisches Asthma, nicht-allergisches Asthma, allergische Rhinitis sowie eine allergische Sensibilisierung (jeweils im Alter von 6 bis 10 Jahren) als sekundäre Endpunkte betrachtet.

In einer zweistufigen Metaanalyse (two-stage individual participant data meta analysis) wurden zunächst adjustierte Odds Ratios für jede Geburtskohorte getrennt berechnet. Diese wurden im Anschluss in einer Metaanalyse mit zufälligen Effekten zu einem Gesamtergebnis zusammengefasst. Dabei zeigte sich insgesamt kein Zusammenhang zwischen der Haustierhaltung in den ersten zwei Lebensjahren und allergischen Erkrankungen im Grundschulalter. Für Familien mit zu erwartendem Nachwuchs bzw. Säuglingen oder kleinen Kindern bedeutet dies, dass Haustiere nicht abgeschafft werden müssen. Die Haltung eines Haustiers scheint jedoch auch keinen eindeutig protektiven Effekt auf die Entstehung von Asthma oder allergische Rhinitis bei Kindern zu haben.

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Does Pet Ownership in Infancy Lead to Asthma or Allergy at School Age? Pooled Analysis of Individual Participant Data from 11 European Birth Cohorts

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Abstract

Objective: To examine the associations between pet keeping in early childhood and asthma and allergies in children aged 6–10 years.

Design: Pooled analysis of individual participant data of 11 prospective European birth cohorts that recruited a total of over 22,000 children in the 1990s.

Exposure definition: Ownership of only cats, dogs, birds, rodents, or cats/dogs combined during the first 2 years of life.

Outcome definition: Current asthma (primary outcome), allergic asthma, allergic rhinitis and allergic sensitization during 6–10 years of age.

Data synthesis: Three-step approach: (i) Common definition of outcome and exposure variables across cohorts; (ii) calculation of adjusted effect estimates for each cohort; (iii) pooling of effect estimates by using random effects meta-analysis models.

Results: We found no association between furry and feathered pet keeping early in life and asthma in school age. For example, the odds ratio for asthma comparing cat ownership with ''no pets'' (10 studies, 11489 participants) was 1.00 (95% confidence interval 0.78 to 1.28) ($I^2 = 9\%$; $p = 0.36$). The odds ratio for asthma comparing dog ownership with ''no pets'' (9 studies, 11433 participants) was 0.77 (0.58 to 1.03) ($I^2 = 0\%$, $p = 0.89$). Owning both cat(s) and dog(s) compared to ''no pets'' resulted in an odds ratio of 1.04 (0.59 to 1.84) ($I^2 = 33\%$, $p = 0.18$). Similarly, for allergic asthma and for allergic rhinitis we did not find associations regarding any type of pet ownership early in life. However, we found some evidence for an association between ownership of furry pets during the first 2 years of life and reduced likelihood of becoming sensitized to aero-allergens.

Conclusions: Pet ownership in early life did not appear to either increase or reduce the risk of asthma or allergic rhinitis symptoms in children aged 6–10. Advice from health care practitioners to avoid or to specifically acquire pets for primary prevention of asthma or allergic rhinitis in children should not be given.

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Introduction

The causes of the worldwide asthma and allergy epidemic over recent decades remain uncertain. Environmental and lifestyle factors, possibly interacting with genetic variants, may play a role however clear evidence for a predominant risk factor is lacking. Pet exposure as a common indoor environmental exposure particularly in families with young children has been of increasing public health concern with regard to recommendations for primary prevention of respiratory and allergic disease. Considerable controversy exists as to whether particularly cat and dog exposure may be a risk or even a protective factor for developing asthma, allergic symptoms or allergic sensitization [1–24]. The conferred risks of pet exposure may be limited to individuals with allergic parents [25–27].

Previous results have come predominantly from cross-sectional studies and may therefore be skewed due to recall bias with regards to pet keeping [7], and early symptoms [28]; in addition, pet avoidance behaviour may distort the associations between pets and allergic diseases [15,29,30]. The heterogeneity of results might also be explained by differences in exposure classifications without ''clean'' categories of single pets and differences in the prevalence of pets in the community [31]. Furthermore, the climate may influence indoor versus outdoor pet keeping and its association with allergic outcomes [3,32].

Primary care practitioners are uncertain about respiratory health risks or benefits of furry pet ownership particularly in early childhood and what advice to give to parents. The objective of this study was to improve the evidence on the primary prevention of asthma and allergies in relation to pet keeping in early life, using data from a large data base of European birth cohort studies. The primary aim was to determine whether pet keeping in the first two years of life was associated with asthma in school-aged children (age 6 to 10 years). Secondarily, we aimed to assess whether pet-keeping was associated with other allergic diseases (allergic or non-allergic asthma, allergic sensitization or allergic rhinitis).

Methods

Design and included birth cohort studies

As part of the Global Allergy and Asthma European Network (GA^2LEN, www.ga2len.net) all population-based European birth cohort studies with a special focus on asthma and allergy were identified, contacted and their methods described and compared [33,34].

For the present combined data analyses, three inclusion criteria were defined: (i) European population-based observational birth cohort studies focusing on allergy and asthma (with ethical approval from local review boards); (ii) recruitment of subjects in pregnancy, at birth or during the first year of life; (iii) at least 1 prospective assessment during 6–10 years of age (early school age); (iv) data on pet ownership assessed prospectively during the first 2 years. To avoid recall bias about early childhood exposures, cross-sectional studies of school-children were not considered. For each included study the raw individual level participant data was available for data analysis.

Ethics statement

This meta-analysis was conducted according to the principles stated in the Declaration of Helsinki. All included birth cohort studies were approved by their local Institutional Review Boards and all participants' parents provided written informed consent. The Institutional Review Boards were for MAS: Ethical Review Board Charité – Universitätsmedizin Berlin, Berlin (Germany); BAMSE: Regional Ethical Review Board, Karolinska Institutet, Stockholm (Sweden); ECA: The regional committee for medical and health profession research ethics, South-East, (Norway); PIAMA-NHS: Ethical Review Boards Utrecht CCMO P04.0071C, Rotterdam MEC 2004-152, Groningen M 4.019912 (The Netherlands); LISA: Ethics committees of the Bavarian General Medical Council, the University of Leipzig, and the Medical Council of North-Rhine-Westphalia (Germany); GINI-B: Ethics committees of the Bavarian General Medical Council, the University of Leipzig, and the Medical Council of North-Rhine-Westphalia (Germany); ARC: The Regional Scientific Ethical Committee for Southern Denmark (Denmark); AMICS-Barcelona: Clinical Research Ethical Committee of the Parc de Salut Mar, IMIM, Barcelona (Spain); AMICS-Menorca: Comite etic d'investigacio clinica de les Illes Balears (Spain); Leicester: Leicestershire, Northamptonshire and Rutland Research Ethics Committees 1 and 2 (UK); Isle of Wight: lsle of Wight, Portsmouth & SE Hants HA Local Research Ethics Committee (UK).

Definition of primary outcome

Since current ''wheeze'' is not very specific for asthma [35], we chose the primary outcome to be ''current asthma'' for the last available follow-up during 6–10 years defined as satisfying at least 2 out of 3 parent-reported conditions (from self-report questionnaires or interviews): (i) doctor-diagnosed asthma ever; (ii) asthma symptoms/wheezing (last 12 months) according to the International Study of Asthma and Allergy in Childhood (ISAAC) core questions [36]; (iii) using asthma medication (last 12 months) [35]. For two studies (DARC, ECA) the study physician's asthma diagnosis was used.

Definition of secondary outcomes

''Allergic asthma'' was defined as the presence of the primary outcome ''asthma'' and a positive serum specific immunoglobulin E (s-IgE)>0.35 kU/l to (i) any aero- and/or food allergen. Further

Table 1. Birth cohort acronym, study setting, year of recruitment, number of children recruited, and pet ownership during the first 2 years of life in 11 European birth cohorts (sorted from north to south).

Birth cohort acronym	Study setting/first year of recruitment	Children initially recruited, N	Pet ownership at age 0–2 y					
			%					
			(n/N)					
			Cat(s) only[1]	Dog(s) only[1]	Cat(s) and dog(s) only[1]	Bird(s) only[1]	Rodent(s) only[1]	No furry or feathered pets
ECA	Oslo	3754	7.9	8.8	0.9	4.3	1.5	76.6
	Norway, 1992	(1877)[2]	(222/2810)	(247/2810)	(24/2810)	(122/2810)	(42/2810)	(2153/2810)
BAMSE	Stockholm	4089	9.6	4.4	1.5	2.4	1.6	80.6
	Sweden, 1994		(355/3719)	(163/3719)	(54/3719)	(89/3719)	(60/3719)	(2998/3719)
DARC	Odense	562	16.2	11.0	4.0	3.6	2.3	62.9
	Denmark, 1998		(72/445)	(49/445)	(18/445)	(16/445)	(10/445)	(280/445)
Leicester 1998	Leicester	566[3]	16.4	16.4	4.4	1.5	6.5	54.8
	UK, 1998		(86/524)	(86/524)	(23/524)	(8/524)	(34/524)	(287/524)
Isle of Wight	Isle of Wight	1456	25.5	18.5	11.5	3.5	2.5	38.5
	UK, 1989		(274/1074)	(199/1074)	(123/1074)	(38/1074)	(27/1074)	(413/1074)
PIAMA-NHS	Multicenter	3291	27.8	8.7	5.7	6.1	6.2	45.5
	The Netherlands, 1996		(729/2620)	(228/2620)	(148/2620)	(160/2620)	(163/2620)	(1192/2620)
MAS	Multicenter	1314	11.6	6.1	1.6	8.5	3.4	68.8
	Germany, 1990		(108/933)	(57/933)	(15/933)	(79/933)	(32/933)	(642/933)
LISA	Multicenter	3097	9.6	6.1	1.5	4.7	5.4	72.7
	Germany, 1997		(232/2406)	(147/2406)	(37/2406)	(112/2406)	(129/2406)	(1749/2406)
GINI-B	Multicenter	3739	6.8	7.2	1.9	4.8	4.3	75.0
	Germany, 1996		(162/2377)	(172/2377)	(44/2377)	(113/2377)	(103/2377)	(1783/2377)
AMICS-Barcelona	Barcelona	487	6.2	9.8	1.0	21.8	4.2	57.0
	Spain, 1996		(12/193)	(19/193)	(2/193)	(42/193)	(8/193)	(110/193)
AMICS-Menorca	Menorca	485	4.3	18.3	6.5	18.1	2.0	50.8
	Spain, 1997		(17/398)	(73/398)	(26/398)	(72/398)	(8/398)	(202/398)
Total		**22840**	**13.0**	**8.2**	**2.9**	**4.9**	**3.5**	**67.5**
			(2269/17499)	**(1440/17499)**	**(514/17499)**	**(851/17499)**	**(616/17499)**	**(11809/17499)**

ECA: Environment and Childhood Asthma Study. BAMSE: Children, Allergy, Milieu, Stockholm, Epidemiological Survey. DARC: Danish Allergy Research Council Study. PIAMA-NHS: The Prevention and Incidence of Asthma and Mite Allergy – Natural History Study. MAS: Multi-center Allergy Study. LISA: Lifestyle-related Factors on the Immune System and Development of Allergies in Childhood Study. GINI-B: German Infant Nutritional Intervention Study (observational part). AMICS: Asthma Multicentre Infant Cohort Study.

[1]and no other furry or feathered pet.

[2]3754 initially recruited and followed-up until 2 years; for ECA: 1877 invited for longer follow-up.

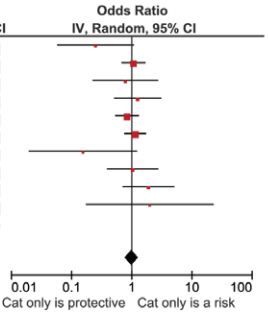
[3]More children are part of the Leicester 1998 cohort, but for the present meta-analyses on early pet ownership we included only children who were recruited during the 1st year of life.

doi:10.1371/journal.pone.0043214.t001

A) Cat only vs. no pet ownership (n=11489)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	-1.38926	0.74904	2.8%	0.25 [0.06, 1.08]
02 BAMSE	0.06549	0.233868	22.9%	1.07 [0.68, 1.69]
03 DARC	-0.24532	0.64068	3.7%	0.78 [0.22, 2.75]
04 Leicester 1998	0.22495	0.462662	7.0%	1.25 [0.51, 3.10]
05 IoW	-0.17955	0.232458	23.1%	0.84 [0.53, 1.32]
06 PIAMA-NHS	0.131478	0.214131	26.2%	1.14 [0.75, 1.74]
07 MAS	-1.86792	1.058258	1.4%	0.15 [0.02, 1.23]
08 LISA	0.030791	0.502159	6.0%	1.03 [0.39, 2.76]
09 GINI-B	0.639162	0.504988	5.9%	1.89 [0.70, 5.10]
10 AMICS_Barcelona	0.690047	1.247262	1.0%	1.99 [0.17, 22.98]
11 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**1.00 [0.78, 1.28]**

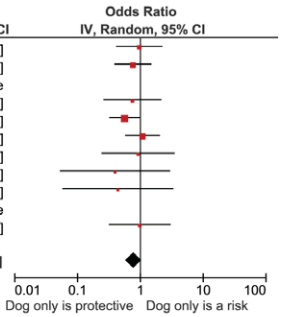
Heterogeneity: Tau² = 0.01; Chi² = 9.90, df = 9 (P = 0.36); I² = 9%
Test for overall effect: Z = 0.03 (P = 0.98)



B) Dog only vs. no pet ownership (n=11433)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	-0.04326	0.43198	11.7%	0.96 [0.41, 2.23]
02 BAMSE	-0.27454	0.345922	18.2%	0.76 [0.39, 1.50]
03 DARC	0	0		Not estimable
04 Leicester 1998	-0.29403	0.541124	7.4%	0.75 [0.26, 2.15]
05 IoW	-0.58088	0.285038	26.8%	0.56 [0.32, 0.98]
06 PIAMA-NHS	0.078887	0.325356	20.6%	1.08 [0.57, 2.05]
07 MAS	-0.08591	0.684455	4.7%	0.92 [0.24, 3.51]
08 LISA	-0.93055	1.031189	2.0%	0.39 [0.05, 2.98]
09 GINI-B	-0.82314	1.036619	2.0%	0.44 [0.06, 3.35]
10 AMICS_Barcelona	0	0		Not estimable
11 AMICS_Menorca	-0.02431	0.576874	6.5%	0.98 [0.32, 3.02]
Total (95% CI)			**100.0%**	**0.77 [0.58, 1.03]**

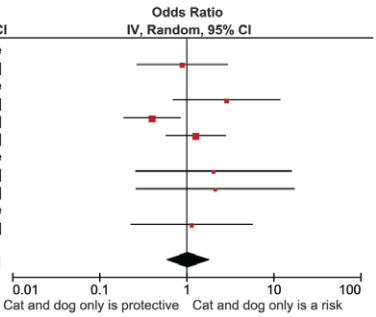
Heterogeneity: Tau² = 0.00; Chi² = 3.56, df = 8 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.75 (P = 0.08)



C) Cat and dog only vs. no pet ownership (n=10262)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	0	0		Not estimable
02 BAMSE	-0.12168	0.615334	15.2%	0.89 [0.27, 2.96]
03 DARC	0	0		Not estimable
04 Leicester 1998	1.049028	0.725995	12.0%	2.85 [0.69, 11.85]
05 IoW	-0.91739	0.386488	25.5%	0.40 [0.19, 0.85]
06 PIAMA-NHS	0.237058	0.4069	24.4%	1.27 [0.57, 2.81]
07 MAS	0	0		Not estimable
08 LISA	0.706859	1.05465	6.6%	2.03 [0.26, 16.02]
09 GINI-B	0.750712	1.071991	6.4%	2.12 [0.26, 17.32]
10 AMICS_Barcelona	0	0		Not estimable
11 AMICS_Menorca	0.127794	0.824672	9.9%	1.14 [0.23, 5.72]
Total (95% CI)			**100.0%**	**1.04 [0.59, 1.84]**

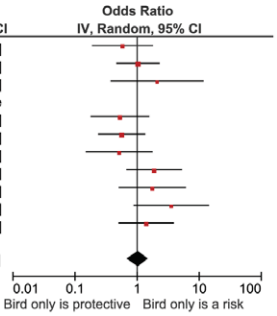
Heterogeneity: Tau² = 0.19; Chi² = 8.95, df = 6 (P = 0.18); I² = 33%
Test for overall effect: Z = 0.13 (P = 0.90)



D) Bird only vs. no pet ownership (n=11591)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	-0.54348	0.577799	9.6%	0.58 [0.19, 1.80]
02 BAMSE	0.031446	0.409978	15.9%	1.03 [0.46, 2.30]
03 DARC	0.739018	0.880764	4.7%	2.09 [0.37, 11.77]
04 Leicester 1998	0	0		Not estimable
05 IoW	-0.63859	0.556314	10.2%	0.53 [0.18, 1.57]
06 PIAMA-NHS	-0.57313	0.44661	14.1%	0.56 [0.23, 1.35]
07 MAS	-0.66675	0.632707	8.3%	0.51 [0.15, 1.77]
08 LISA	0.630741	0.526519	11.1%	1.88 [0.67, 5.27]
09 GINI-B	0.562666	0.636335	8.2%	1.76 [0.50, 6.11]
10 AMICS_Barcelona	1.267583	0.714401	6.8%	3.55 [0.88, 14.41]
11 AMICS_Menorca	0.337066	0.524852	11.2%	1.40 [0.50, 3.92]
Total (95% CI)			**100.0%**	**1.03 [0.69, 1.52]**

Heterogeneity: Tau² = 0.08; Chi² = 11.44, df = 9 (P = 0.25); I² = 21%
Test for overall effect: Z = 0.13 (P = 0.90)



E) Rodent only vs. no pet ownership (n=9484)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	0	0		Not estimable
02 BAMSE	-0.08652	0.535769	21.1%	0.92 [0.32, 2.62]
03 DARC	0	0		Not estimable
04 Leicester 1998	-0.19907	0.725861	11.5%	0.82 [0.20, 3.40]
05 IoW	0	0		Not estimable
06 PIAMA-NHS	-0.08448	0.41839	34.5%	0.92 [0.40, 2.09]
07 MAS	0.334738	0.85331	8.3%	1.40 [0.26, 7.44]
08 LISA	-0.39439	0.754564	10.6%	0.67 [0.15, 2.96]
09 GINI-B	0.800816	0.657044	14.0%	2.23 [0.61, 8.07]
10 AMICS_Barcelona	0	0		Not estimable
11 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**1.03 [0.64, 1.66]**

Heterogeneity: Tau² = 0.00; Chi² = 2.04, df = 5 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)

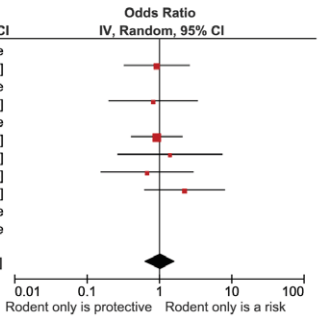


Figure 1. Current asthma. Meta-analyses of the adjusted odds ratios of **asthma** at 6–10 years of age and pet ownership in the first 2 years of life for: A), cat only vs. no pets; B), dog only vs. no pets; C) cat and dog only vs. no pets; D) bird only vs. no pets; E) rodents only vs. no pets.
doi:10.1371/journal.pone.0043214.g001

definitions of allergic asthma were specified as asthma with a positive s-IgE to: (ii) any aero-allergen (in- or outdoor); (iii) cat allergen; (iv) dog allergen. "Non-allergic asthma" was defined as the presence of "asthma" without sensitization to any tested aero-/food allergen (s-IgE≤0.35 kU/l). The reference groups were non-asthmatic children without allergic sensitization.

"Allergic sensitization" regardless of symptoms was defined as a positive s-IgE test >0.35 kU/l for the following categories: cat, dog, any indoor, any outdoor, any aero-, and any aero-/food allergen.

"Allergic rhinitis" included parent-reported symptoms during the last 12 months (ISAAC core questions: sneezing, runny or blocked nose without a cold or flu) plus s-IgE>0.35 kU/l against at least 1 aero-allergen.

Definition of household pet keeping

Based on parent-completed questionnaires or interviews between the children's birth (or during pregnancy) and second birthday, we defined 6 pet ownership categories: (i) cat(s) only; (ii) dog(s) only; (iii) cat(s) and dog(s) only; (iv) rodent(s) only; (v) bird(s) only; (vi) and no furry or feathered pets ("no pets") as the reference category. Six percent of families could not be classified into one of the categories above because they had a combination of different types of pets and were thus excluded from the analyses. Information on pet contact outside the home or outdoor pet keeping was not available in most cohorts. Other pets such as reptiles or amphibians were not considered.

Our primary aim was to examine the effect of pet ownership at any time between birth and the 2nd birthday. In addition, to

Table 2. Prevalence of current asthma, allergic asthma (sensitized to ≥1 aero-allergen), allergic rhinitis (sensitized to ≥1 aero-allergen) and allergic sensitization (≥1 aero-allergen >0.35 kU/L) at last follow-up assessment between 6 to 10 years in 11 European birth cohorts.

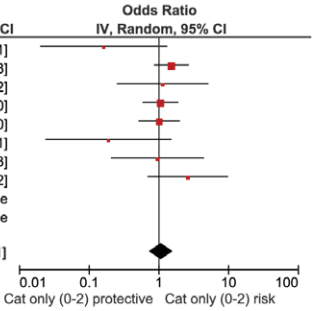
Birth cohort, country (sorted from north to south)	Age of children at follow-up (years)	Follow-up rate	Asthma	Allergic asthma	Allergic rhinitis	Allergic sensitisation
			%	%	%	%
			(n/N)	(n/N)	(n/N)	(n/N)
ECA	10	84%	11.9	7.6	13.9	33.2
Norway			(120/1010)	(73/963)	(135/972)	(325/979)
BAMSE	8–9	84%	9.3	5.2	8.0	26.0
Sweden			(308/3330)	(165/3187)	(255/3202)	(637/2451)
DARC	6	81%	7.7	4.3[1]	4.1[1]	35.9[1]
Denmark			(35/457)	(19/441)	(18/441)	(168/468)
Leicester 1998	6	57%	18.7	n.a.	n.a.	n.a.
UK			(66/353)			
Isle of Wight	10	94%	16.3	8.8	11.9	33.0
UK			(223/1370)	(110/1257)	(142/1196)	(314/952)
PIAMA-NHS	8	83%	7.1	2.7	5.5	29.7
The Netherlands			(194/2720)	(70/2596)	(131/2374)	(383/1289)
MAS	10	58%	11.2	9.1	20.0	48.1
Germany			(68/606)	(54/592)	(147/735)	(343/713)
LISA	6	71%	3.0	1.2	5.5	26.7
Germany			(66/2185)	(25/2144)	(109/1988)	(318/1193)
GINI-B	6	59%	2.9	1.3	4.5	27.2
Germany			(64/2179)	(28/2143)	(90/2020)	(257/945)
AMICS-Barcelona	6	64%	12.5	3.9[1]	5.8[1]	18.9[1]
Spain			(39/312)	(11/284)	(15/259)	(54/286)
AMICS-Menorca	6	94%	7.9	3.0[1]	0.5[1]	12.3[1]
Spain			(36/458)	(13/435)	(2/438)	(43/349)
Total			**8.1**	**4.0**	**7.7**	**29.5**
			(1219/14980)	**(568/14042)**	**(1044/13625)**	**(2842/9625)**

n.a. = not assessed.
[1]in DARC, AMICS-Barcelona and AMICS-Menorca, sensitization data were only available for the age of 4 years.
doi:10.1371/journal.pone.0043214.t002

A) Cat only vs. no pet ownership (n=10722)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	-1.82568	1.071096	3.3%	0.16 [0.02, 1.31]
02 BAMSE	0.411179	0.292656	26.7%	1.51 [0.85, 2.68]
03 DARC	0.122402	0.771266	6.0%	1.13 [0.25, 5.12]
04 IoW	0.050543	0.301335	25.8%	1.05 [0.58, 1.90]
05 PIAMA-NHS	0.009139	0.34829	21.5%	1.01 [0.51, 2.00]
06 MAS	-1.66934	1.062186	3.3%	0.19 [0.02, 1.51]
07 LISA	-0.04759	0.784017	5.8%	0.95 [0.21, 4.43]
08 GINI-B	0.954976	0.678498	7.6%	2.60 [0.69, 9.82]
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**1.09 [0.74, 1.61]**

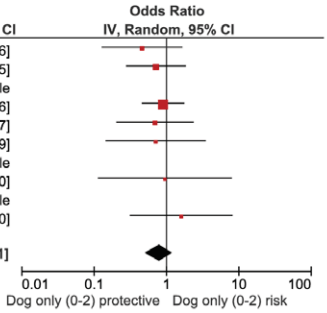
Heterogeneity: Tau² = 0.06; Chi² = 8.84, df = 7 (P = 0.26); I² = 21%
Test for overall effect: Z = 0.43 (P = 0.66)



B) Dog only vs. no pet ownership (n=9032)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	-0.77927	0.655481	10.9%	0.46 [0.13, 1.66]
02 BAMSE	-0.33712	0.485282	19.9%	0.71 [0.28, 1.85]
03 DARC	0	0		Not estimable
04 IoW	-0.11097	0.345308	39.4%	0.89 [0.45, 1.76]
05 PIAMA-NHS	-0.36691	0.627912	11.9%	0.69 [0.20, 2.37]
06 MAS	-0.34497	0.813654	7.1%	0.71 [0.14, 3.49]
07 LISA	0	0		Not estimable
08 GINI-B	-0.05194	1.087249	4.0%	0.95 [0.11, 8.00]
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0.467794	0.834649	6.7%	1.60 [0.31, 8.20]
Total (95% CI)			**100.0%**	**0.79 [0.52, 1.21]**

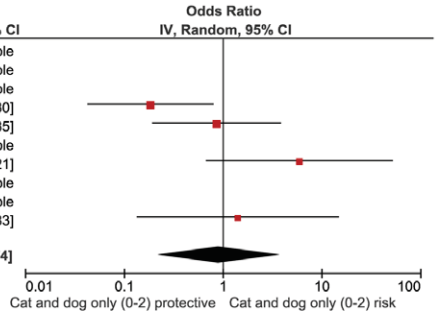
Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 6 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)



C) Cat and dog only vs. no pet ownership (n=4941)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	0	0		Not estimable
02 BAMSE	0	0		Not estimable
03 DARC	0	0		Not estimable
04 IoW	-1.69665	0.750651	29.6%	0.18 [0.04, 0.80]
05 PIAMA-NHS	-0.15392	0.766807	29.2%	0.86 [0.19, 3.85]
06 MAS	0	0		Not estimable
07 LISA	1.775589	1.11211	21.4%	5.90 [0.67, 52.21]
08 GINI-B	0	0		Not estimable
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0.339847	1.202612	19.8%	1.40 [0.13, 14.83]
Total (95% CI)			**100.0%**	**0.91 [0.22, 3.74]**

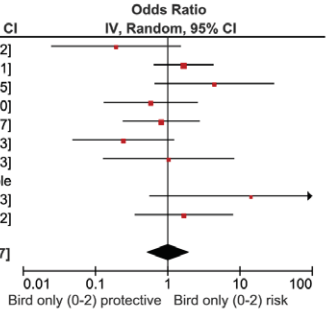
Heterogeneity: Tau² = 1.21; Chi² = 7.26, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 0.14 (P = 0.89)



D) Bird only vs. no pet ownership (n=9446)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	-1.64797	1.054183	8.0%	0.19 [0.02, 1.52]
02 BAMSE	0.505781	0.487067	19.9%	1.66 [0.64, 4.31]
03 DARC	1.484952	0.973438	9.0%	4.41 [0.66, 29.75]
04 IoW	-0.54306	0.764655	12.5%	0.58 [0.13, 2.60]
05 PIAMA-NHS	-0.20958	0.626591	15.7%	0.81 [0.24, 2.77]
06 MAS	-1.41616	0.828251	11.3%	0.24 [0.05, 1.23]
07 LISA	0.026801	1.067653	7.9%	1.03 [0.13, 8.33]
08 GINI-B	0	0		Not estimable
09 AMICS_Barcelona	2.651278	1.651767	3.8%	14.17 [0.56, 360.93]
10 AMICS_Menorca	0.51327	0.800364	11.8%	1.67 [0.35, 8.02]
Total (95% CI)			**100.0%**	**1.01 [0.51, 1.97]**

Heterogeneity: Tau² = 0.35; Chi² = 12.36, df = 8 (P = 0.14); I² = 35%
Test for overall effect: Z = 0.02 (P = 0.99)



E) Rodent only vs. no pet ownership (n=7212)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	0	0		Not estimable
02 BAMSE	0.057211	0.748493	26.6%	1.06 [0.24, 4.59]
03 DARC	0	0		Not estimable
04 IoW	0	0		Not estimable
05 PIAMA-NHS	0.037544	0.625838	38.0%	1.04 [0.30, 3.54]
06 MAS	-0.41795	1.116857	11.9%	0.66 [0.07, 5.88]
07 LISA	0.728799	0.795091	23.5%	2.07 [0.44, 9.85]
08 GINI-B	0	0		Not estimable
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**1.16 [0.55, 2.48]**

Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 3 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.70)

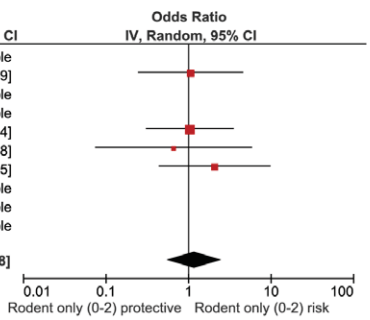


Figure 2. Allergic asthma. Meta-analyses of the adjusted odds of **allergic asthma** (sensitized to at least 1 aero-allergen; secondary endpoint) in early school age and ownership of pets in the first 2 years of life for: A), cat only vs. no pets; B), dog only vs. no pets; C) cat and dog only vs. no pets; D) bird only vs. no pets; E) rodents only vs. no pets.
doi:10.1371/journal.pone.0043214.g002

evaluate whether the timing of pet ownership is relevant, we examined different exposure periods: at time of birth; between birth and 1st birthday, and between 1st and 2nd birthdays.

Definition of possible confounding factors

Eleven variables, if available, collected by parental questionnaires or interviews, were considered as possible confounders in the adjusted analyses of the individual birth cohorts: 1. family history (parents and siblings) of asthma and/or allergic rhinitis (yes versus no); 2. family history of pet allergy (yes versus no); 3. maternal smoking during pregnancy (yes versus no); 4. postnatal maternal smoking from after birth to last follow-up between 6 to 10 years of age ('regular smoker' and 'irregular smoker' versus 'never smoke' as reference category); 5. educational level of parents at birth of child (by tertile according to school years as proxy for socio-economic status); 6. one or more older siblings (yes versus no); 7. home/apartment with convenient ground access (ground or 1st floor versus 2nd floor or higher); 8. crowding at home (number of persons per square meter or room; in quintiles, with the lowest quintile as reference category); 9. gender (boys versus girls); 10. breast feeding duration (in months); 11. doctor's diagnosed eczema any time between birth and 2 years (yes versus no).

Statistical analyses

For each cohort, a multivariable logistic regression analysis was used to calculate the adjusted odds ratio (OR) and 95% confidence intervals (CI) to estimate the effect of pet exposure in the first 2 years on the primary (current asthma) and secondary outcomes at age 6 to 10 years. Adjustment was performed for 7 potential confounders that were available for all studies (these were factors 1, 4–6, and 9–11 as listed above) and in addition, for all factors available for the respective cohort. Furthermore, we performed sensitivity analyses using (i) only the 7 potential confounders available for all studies, and (ii) using a propensity score approach for adjustment [37,38]. For the latter, all available covariates as listed above (except gender of the child) were used for each study separately to estimate scores indicating the propensity of pet ownership for each participant using logistic regression analysis; subsequently these propensity scores plus gender were used as adjustment variables for modelling pet ownership and outcomes. For the primary outcome, we additionally analyzed possible two-way interactions (effect modification) between pet exposure and (i) parental allergy status, (ii) smoking in pregnancy and (iii) postnatal maternal smoking.

The combining of results from all cohorts was done by random-effect meta-analyses with the inverse-variance method, based on the assumption that the associations in the different cohorts are not identical, estimating the average of the associations [39,40]. As further sensitivity analyses for the primary outcome, we calculated fixed-effect meta-analyses, where it is assumed that the association is the same across all cohorts [39].

In subgroup analyses, we assessed the associations for the following groups: (i) parents with and (ii) without asthma or allergic rhinitis ever; (iii) parents with and (iv) without pet allergies ever; (v) parents with asthma and/or allergic rhinitis, but without pet allergies; and (vi) parents without any allergies. Furthermore, we analyzed studies with high and those with low prevalence of pet ownership separately, and compared cohorts from major climatic regions in Europe (Nordic, Maritime, Central, and South).

In all analyses, a level of 0.05 was considered as statistically significant, without adjustment for multiple testing. Heterogeneity among the studies was tested using chi-squared Q-statistic and I^2. We performed meta-analyses with Review Manager version 5.0 (German Cochrane Centre, Freiburg, Germany) and all other analyses with SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

11 European studies, including the largest and oldest birth cohorts that were specifically designed to examine asthma and allergies, expressed interest and were included in the combined analyses. The recruitment of newborns and their families took place from 1989 (Isle of Wight, UK) to 1998 (DARC, Denmark and Leicester, UK) (Table 1). During age 6 to 10 years most cohorts achieved a follow-up rate of over 75%, this being the highest in the Isle of Wight and the three Scandinavian cohorts (Table 1).

Pet ownership

Pet ownership ranged from around 60% (Isle of Wight, UK) to around 20% (BAMSE, Stockholm, Sweden), only cat ownership from 28% (Dutch PIAMA-NHS) to 4% (Menorca, Spain), and only dog ownership from 18% (the 2 islands Menorca and Isle of Wight) to 4% (BAMSE) (Table 1). Keeping both cat(s) and dog(s) but no other pets was particularly common on the Isle of Wight (UK), keeping birds only in the 2 Spanish cohorts, and keeping rodents only in Leicester, UK, and the Dutch PIAMA-NHS cohort, respectively. Data to define the pet ownership categories was available for 40% (Menorca, Spain) to 93% (Leicester, UK).

Primary endpoint

The prevalence of current asthma at 6–10 years ranged from 2.9%–18.7% (Table 2). There were no significant associations between any type of pet ownership during the first 2 years and asthma during 6–10 years in the adjusted estimates of the main meta-analyses or in any of the individual cohorts (Figure 1). The meta-analysis odds ratio (OR) for asthma when owning a cat was 1.00 (95% confidence interval 0.78–1.28) and 0.77 (0.58–1.03) when owning a dog. Owning both cat and dog resulted in an OR for asthma of 1.04 (0.59–1.84). The OR of bird ownership was 1.03 (0.69–1.52), and 1.03 (0.64–1.66) for rodents. Heterogeneity across the cohorts was not significant.

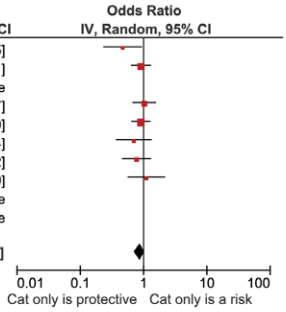
Main results were similar when analyzing shorter pet exposure time periods (e.g. around birth or during first 12 months) or in sensitivity analyses using a propensity score to control for potential confounding. Also, meta-analyses in subgroups showed no significant association of pet ownership and asthma among parents with or among those without asthma/allergies, in cohorts with only high or those with only low pet prevalence, or in subgroups of cohorts from 4 major climatic regions in Europe.

No significant associations that would suggest effect modification were found when we analyzed two-way interactions between pet exposure and parental allergies, maternal prenatal smoking, or postnatal maternal smoking. Results were similar for fixed compared with random effect meta-analyses.

A) Cat only vs. no pet ownership (n=6978)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	-0.76013	0.359863	6.4%	0.47 [0.23, 0.95]
02 BAMSE	-0.09375	0.185211	24.2%	0.91 [0.63, 1.31]
03 DARC	0	0		Not estimable
04 IoW	0.025157	0.218014	17.5%	1.03 [0.67, 1.57]
05 PIAMA-NHS	-0.09758	0.178439	26.1%	0.91 [0.64, 1.29]
06 MAS	-0.35486	0.33194	7.5%	0.70 [0.37, 1.34]
07 LISA	-0.25458	0.27098	11.3%	0.78 [0.46, 1.32]
08 GINI-B	0.101556	0.347143	6.9%	1.11 [0.56, 2.19]
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**0.87 [0.73, 1.04]**

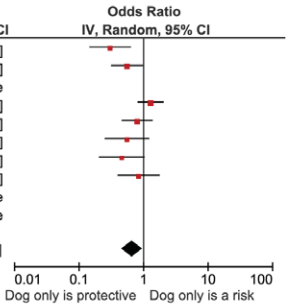
Heterogeneity: Tau² = 0.00; Chi² = 4.74, df = 6 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.55 (P = 0.12)



B) Dog only vs. no pet ownership (n=6978)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	-1.19438	0.378103	12.8%	0.30 [0.14, 0.64]
02 BAMSE	-0.59241	0.289784	16.2%	0.55 [0.31, 0.98]
03 DARC	0	0		Not estimable
04 IoW	0.249487	0.237813	18.4%	1.28 [0.81, 2.05]
05 PIAMA-NHS	-0.23053	0.281618	16.5%	0.79 [0.46, 1.38]
06 MAS	-0.59333	0.404246	11.9%	0.55 [0.25, 1.22]
07 LISA	-0.77988	0.416801	11.5%	0.46 [0.20, 1.04]
08 GINI-B	-0.17793	0.382876	12.6%	0.84 [0.40, 1.77]
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**0.65 [0.45, 0.95]**

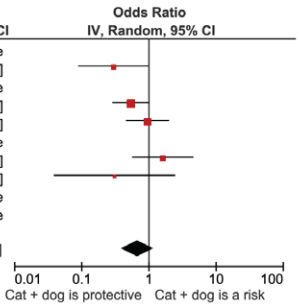
Heterogeneity: Tau² = 0.14; Chi² = 13.85, df = 6 (P = 0.03); I² = 57%
Test for overall effect: Z = 2.23 (P = 0.03)



C) Cat and dog only vs. no pet ownership (n=5747)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	0	0		Not estimable
02 BAMSE	-1.21112	0.620049	14.9%	0.30 [0.09, 1.00]
03 DARC	0	0		Not estimable
04 IoW	-0.621	0.324449	32.4%	0.54 [0.28, 1.02]
05 PIAMA-NHS	-0.0482	0.376387	28.1%	0.95 [0.46, 1.99]
06 MAS	0	0		Not estimable
07 LISA	0.474752	0.535369	18.4%	1.61 [0.56, 4.59]
08 GINI-B	-1.1827	1.061252	6.1%	0.31 [0.04, 2.45]
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**0.68 [0.40, 1.18]**

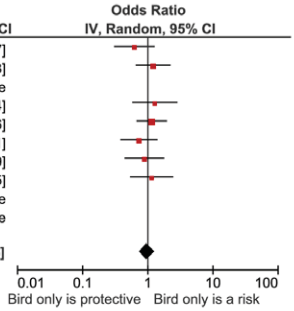
Heterogeneity: Tau² = 0.13; Chi² = 6.25, df = 4 (P = 0.18); I² = 36%
Test for overall effect: Z = 1.37 (P = 0.17)



D) Bird only vs. no pet ownership (n=6978)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	-0.47694	0.366235	12.4%	0.62 [0.30, 1.27]
02 BAMSE	0.187539	0.314402	16.8%	1.21 [0.65, 2.23]
03 DARC	0	0		Not estimable
04 IoW	0.244861	0.407242	10.0%	1.28 [0.58, 2.84]
05 PIAMA-NHS	0.136105	0.274714	22.0%	1.15 [0.67, 1.96]
06 MAS	-0.31451	0.334908	14.8%	0.73 [0.38, 1.41]
07 LISA	-0.12163	0.358562	12.9%	0.89 [0.44, 1.79]
08 GINI-B	0.134043	0.389523	11.0%	1.14 [0.53, 2.45]
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**0.98 [0.76, 1.26]**

Heterogeneity: Tau² = 0.00; Chi² = 3.75, df = 6 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)



E) Rodent only vs. no pet ownership (n=5585)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	0	0		Not estimable
02 BAMSE	-0.63831	0.463083	15.7%	0.53 [0.21, 1.31]
03 DARC	0	0		Not estimable
04 IoW	0	0		Not estimable
05 PIAMA-NHS	-0.70599	0.343225	28.6%	0.49 [0.25, 0.97]
06 MAS	-0.29067	0.520234	12.4%	0.75 [0.27, 2.07]
07 LISA	-0.04576	0.351511	27.2%	0.96 [0.48, 1.90]
08 GINI-B	-0.34605	0.456928	16.1%	0.71 [0.29, 1.73]
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**0.67 [0.47, 0.95]**

Heterogeneity: Tau² = 0.00; Chi² = 2.13, df = 4 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.21 (P = 0.03)

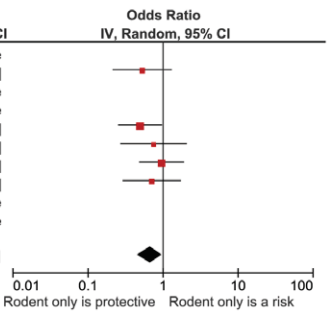


Figure 3. Allergic sensitization. Meta-analyses of the adjusted odds of **allergic sensitization** (sensitized to at least 1 aero-allergen) in early school age and pet ownership in the first 2 years of life for: A), cat only vs. no pets; B), dog only vs. no pets; C) cat and dog only vs. no pets; D) bird only vs. no pets; E) rodents only vs. no pets. (There were no IgE data available for Leicester 1998 cohort.)
doi:10.1371/journal.pone.0043214.g003

Secondary endpoints

Allergic asthma. The overall prevalence of allergic asthma (defined as current asthma and sensitization to ≥1 aero-allergen) in early school age was 4.0%, ranging from 1.2% at six years to 9.1% at 10 years (Table 2). Pet ownership was not associated with asthma in combination with sensitization to ≥1 aero-allergen (Figure 2), to ≥1 indoor-, to ≥1 outdoor, or to ≥1 aero- or food allergen in the meta-analyses of all cohorts (data not shown). Based on results from only 3 cohorts with data available, owning a dog was not associated with asthma in combination with sensitization to dog (OR 1.14, 95% CI 0.57–2.28) or to cat. However, owning cats increased the odds of having asthma combined with sensitization to dog (OR 2.59, 95% CI 1.49–4.49) and to cat (OR 1.91, 95% CI 1.16–3.12).

Non-allergic asthma. Asthma without sensitization to any aero- or food allergen (''non-allergic asthma'') was not significantly associated with cat (OR 0.99, 0.51–1.94), dog (OR 1.35, 0.71–2.57), bird (OR 1.80, 0.80–4.04) or rodent ownership (OR 1.70, 0.53–5.44) in the meta-analyses of all cohorts. Results from the only 2 cohorts with sufficient data regarding both cat and dog ownership (BAMSE and PIAMA-NHS) showed that owning both cat(s) and dog(s) increased the odds of non-allergic asthma (OR 3.66, 1.50–8.93).

Allergic sensitization and rhinitis. The prevalence of sensitization to ≥1 aero-allergen ranged from 26%–33% during 6–10 years (Table 2). Having dogs or rodents during the first 2 years significantly reduced the odds of sensitization to ≥1 aero-allergen (OR 0.65, 0.45–0.95 for dog; OR 0.67, 0.47–0.95 for rodent; Figure 3). Cat ownership showed a similar trend (OR 0.87, 0.73–1.04). The prevalence of parent-reported rhinitis during 6–10 years plus sensitization to ≥1 aero-allergen was 7.7% (Table 2). Allergic rhinitis was not associated with any pet ownership (Figure 4).

Insufficient data for the definition of the primary endpoint ranged from 5% (AMICS-Menorca) to 54% (MAS) of the participants; from 10% (AMICS-Menorca) to 55% (MAS) for defining allergic asthma; 10% (AMICS-Menorca) to 48% (ECA) for allergic rhinitis, and 17% (DARC) to 75% (GINI-B) for the definition of allergic sensitization.

Discussion

Principal findings

Our meta-analyses showed that ownership of single types of furry pets or birds in the first 2 years of life neither increased nor decreased the risk of asthma, non-allergic asthma (not sensitized to any aero- or food-allergen), allergic asthma or allergic rhinitis (both included sensitization to at least 1 aero-allergen) in school-aged children. However, living with furry pets in the first 2 years appeared to reduce the likelihood of becoming sensitized to aero-allergens in early school-age regardless of respiratory symptoms.

Comparison with other studies

An older meta-analysis, mainly with cross-sectional studies from the 1990s, showed a slightly increased risk of asthma or wheezing for children >6 years in relation to any pet exposure, but did not analyze different types of pets [41]. A more recent meta-analysis of 9 cohort studies (including children of all ages) showed a protective effect for asthma related to cat exposure [42]. Both previous meta-analyses were based on published risk estimates with the disadvantage that exposure, potential confounders and outcome could not be harmonized across the included studies compared to our analyses using individual raw data from 11 birth cohort studies with long-term prospective assessments.

The reduced sensitization to aero-allergens related to furry pet ownership is consistent with similar findings in several previous studies, particularly for dogs [7,21,22,24,43]. We found that rodent ownership showed this protective effect too, and that dog ownership was associated with reduced risk of sensitization to common food allergens (data not shown).

Strengths of present analyses

Our approach was different than a previous meta-analysis on this topic because we were able to collect, harmonize, and combine the individual participant data from 11 birth cohorts instead of using published risk estimates based on heterogeneous outcome and exposure definitions and age groups [42].

The large sample allowed the definition of mutually exclusive pet exposure categories: ownership of ''only cat(s)'', ''only dog(s)'', ''only rodent(s)'', and ''only bird(s)''. This is another unique feature of our collaborative study compared to previous studies, which did not separate potential effects of ''clean'' pet exposure categories. Furthermore, analyzing the time at birth, the first and the second year of life separately, the results were very similar compared with the whole period of the first 2 years. This suggests that our results are robust, and do not point towards a narrow post natal period with increased susceptibility to pet exposure in the home.

For the outcome definition, previous studies used single variables such as parent-reported wheezing or doctor's-diagnosed asthma, which may have over- or underestimated the real prevalence of asthma. To avoid a potential over-estimation of asthma prevalence we used a more stringent definition for the primary outcome asthma based on at least 2 out of the 3 conditions parent-reported wheezing, doctor's-diagnosed asthma and asthma medication [35]. Also, pet ownership was not assessed in relationship to severity of asthma since our aim was to investigate the possible role of pets in primary prevention of asthma. Our definition of allergic rhinitis was not only based on typical symptoms but also included detection of serum IgE.

A limitation of previous studies may have been the lack of sufficient adjustment for potential confounding. The size of our sample had enough statistical power to take into account potential confounders including family, social and domestic factors in most cohorts [31].

Although the birth cohorts come from different climatic European regions, include children born in different years (between 1989–1998), have urban and rural/island study settings, different prevalences of allergies and patterns of pets, the statistical tests for heterogeneity were rarely significant, which strengthens the findings and generalizability of our analyses.

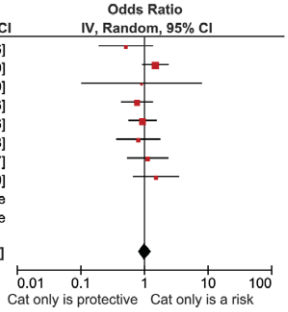
Possible limitations

Avoidance behavior in families with allergies could be an explanation for the ''protective effect'' of pet keeping seen in some previous studies (reverse causation) [7]; however reasons for avoiding pets were not assessed in most birth cohorts. We addressed the issue of avoidance behavior due to parental allergies to some extent by running meta-analyses in several subgroups.

A) Cat only vs. no pet ownership (n=10384)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	-0.67639	0.501368	6.1%	0.51 [0.19, 1.36]
02 BAMSE	0.392466	0.246638	25.0%	1.48 [0.91, 2.40]
03 DARC	-0.10536	1.114757	1.2%	0.90 [0.10, 8.00]
04 IoW	-0.27036	0.295177	17.5%	0.76 [0.43, 1.36]
05 PIAMA-NHS	-0.07109	0.262067	22.2%	0.93 [0.56, 1.56]
06 MAS	-0.22374	0.408098	9.1%	0.80 [0.36, 1.78]
07 LISA	0.115347	0.381555	10.5%	1.12 [0.53, 2.37]
08 GINI-B	0.418294	0.426352	8.4%	1.52 [0.66, 3.50]
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**1.02 [0.80, 1.30]**

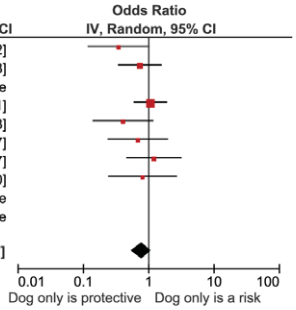
Heterogeneity: Tau² = 0.00; Chi² = 6.60, df = 7 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)



B) Dog only vs. no pet ownership (n=10107)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	-1.06541	0.555887	9.4%	0.34 [0.12, 1.02]
02 BAMSE	-0.31299	0.392624	18.9%	0.73 [0.34, 1.58]
03 DARC	0	0		Not estimable
04 IoW	0.057685	0.300076	32.4%	1.06 [0.59, 1.91]
05 PIAMA-NHS	-0.90777	0.546903	9.8%	0.40 [0.14, 1.18]
06 MAS	-0.3844	0.541887	9.9%	0.68 [0.24, 1.97]
07 LISA	0.18112	0.496888	11.8%	1.20 [0.45, 3.17]
08 GINI-B	-0.21846	0.617938	7.6%	0.80 [0.24, 2.70]
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**0.77 [0.55, 1.07]**

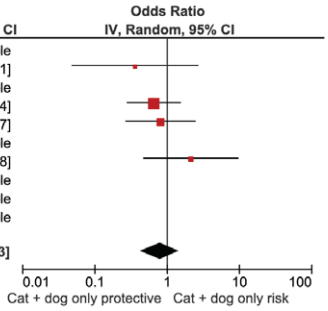
Heterogeneity: Tau² = 0.00; Chi² = 5.49, df = 6 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.54 (P = 0.12)



C) Cat and dog only vs. no pet ownership (n=7233)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	0	0		Not estimable
02 BAMSE	-1.02606	1.031364	8.7%	0.36 [0.05, 2.71]
03 DARC	0	0		Not estimable
04 IoW	-0.42907	0.439454	47.7%	0.65 [0.28, 1.54]
05 PIAMA-NHS	-0.21377	0.570991	28.3%	0.81 [0.26, 2.47]
06 MAS	0	0		Not estimable
07 LISA	0.753601	0.773981	15.4%	2.12 [0.47, 9.68]
08 GINI-B	0	0		Not estimable
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**0.79 [0.43, 1.43]**

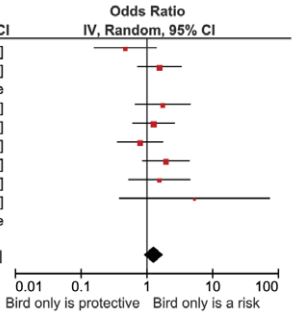
Heterogeneity: Tau² = 0.00; Chi² = 2.42, df = 3 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.78 (P = 0.43)



D) Bird only vs. no pet ownership (n=10207)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	-0.75927	0.562268	9.1%	0.47 [0.16, 1.41]
02 BAMSE	0.439752	0.397255	17.5%	1.55 [0.71, 3.38]
03 DARC	0	0		Not estimable
04 IoW	0.551957	0.498724	11.4%	1.74 [0.65, 4.62]
05 PIAMA-NHS	0.235576	0.379267	19.1%	1.27 [0.60, 2.66]
06 MAS	-0.23942	0.412431	16.3%	0.79 [0.35, 1.77]
07 LISA	0.665511	0.423832	15.5%	1.95 [0.85, 4.46]
08 GINI-B	0.435031	0.553889	9.4%	1.55 [0.52, 4.58]
09 AMICS_Barcelona	1.666596	1.347377	1.6%	5.29 [0.38, 74.25]
10 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**1.28 [0.91, 1.80]**

Heterogeneity: Tau² = 0.01; Chi² = 7.40, df = 7 (P = 0.39); I² = 5%
Test for overall effect: Z = 1.43 (P = 0.15)



E) Rodent only vs. no pet ownership (n=8648)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
01 ECA	0	0		Not estimable
02 BAMSE	0.152112	0.618027	20.7%	1.16 [0.35, 3.91]
03 DARC	0	0		Not estimable
04 IoW	0	0		Not estimable
05 PIAMA-NHS	-0.4315	0.540119	27.1%	0.65 [0.23, 1.87]
06 MAS	-0.00262	0.665343	17.8%	1.00 [0.27, 3.67]
07 LISA	-0.42465	0.616796	20.8%	0.65 [0.20, 2.19]
08 GINI-B	-0.06079	0.759995	13.7%	0.94 [0.21, 4.17]
09 AMICS_Barcelona	0	0		Not estimable
10 AMICS_Menorca	0	0		Not estimable
Total (95% CI)			**100.0%**	**0.83 [0.48, 1.45]**

Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 4 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)

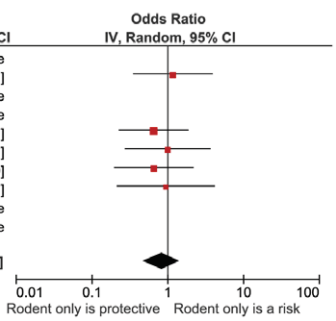


Figure 4. Allergic rhinitis. Meta-analyses of the adjusted odds of **allergic rhinitis** (sensitized to at least 1 aero-allergen; secondary endpoint) in early school age and pet ownership in the first 2 years of life for: A), cat only vs. no pets; B), dog only vs. no pets; C) cat and dog only vs. no pets; D) bird only vs. no pets; E) rodents only vs. no pets.
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The results were very similar among children from parents *without* allergies (asthma, allergic rhinitis, pet allergy) compared to children from parents *with* allergies. Furthermore, keeping certain types of pets may be associated with different life-styles that we were unable to account for in the present meta-analyses.

Another possible limitation of our analyses is that for some birth cohorts the outcome was only available for 6 years of follow-up (at this age asthma may not have been fully developed in some subjects), whereas for others we could include the 8 and 10 year follow-up data. Comparing the effect estimates of the individual birth cohorts, we did not find that cohorts with a 6 year follow-up differed from the older cohorts; instead we found rather homogeneous results across the cohorts.

Some cohorts assessed more potential confounding variables than others. However, when we repeated our analyses with only those confounders that were assessed in all studies our results did not change considerably. Since most cohorts did not ask for the number of pets at home, we could not examine the possibility of a dose-response relationship of pet keeping.

A risk of participation bias in each included study could be present and it could be different for each study (e.g. due to regional differences in disease awareness or in recruitment strategies). However, while this might influence the observed prevalences for allergic diseases, this should less influence any association between pet ownership and allergic disease. On the other hand, each cohort had different numbers of observations available to define the primary and secondary outcomes, and some kind of selection bias cannot be excluded.

Assessing total exposure to pet allergens in early life was outside the aim and scope of the present study. Furthermore, total allergen exposure, which is virtually impossible to measure, would not influence the scientific evidence for giving advice on pet keeping or not.

When interpreting the results, the reliance upon parents' questionnaire data should be kept in mind. It should be noted, however, that standardized ISAAC questions were used to assess allergic symptoms and diseases. In addition, the quality of data might not be equal across the included studies due to data collection timing and methods.

We examined various secondary endpoints while performing over a hundred additional explorative analyses of the whole dataset and of subgroups. Some of these subgroups included only 2 or 3 birth cohorts if these were the only ones with sufficient exposure and/or outcome data. Almost all analyses showed no associations between exposure and secondary outcomes with a few exceptions, e.g. a positive association between cat ownership and asthma in combination with sensitization to dog or cat allergens, however dog ownership was not associated with asthma in combination with dog or cat allergens. Another positive association was found between ownership of both cat(s) and dog(s) and non-allergic asthma; however cat and dog ownership alone was not associated with non-allergic asthma. Since we did not correct for multiple testing, the statistically significant results in some of the subgroup analyses should be interpreted cautiously and as results of explorative analyses keeping in mind the possibility of false positive findings.

Conclusions

This pooled analysis of individual participant data from 11 European birth cohorts found no association between ownership of single types of furry and feathered pets in the first 2 years of life and asthma or allergic rhinitis in school children aged 6–10. For primary prevention of asthma and allergy, we found no evidence for health care practitioners to give parents specific advice on avoiding or acquiring pets in early childhood. To evaluate the effect of pet keeping in early childhood on e.g. developing eczema, further pooled birth cohort data analyses are needed rather than single birth cohort analyses.

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Author Contributions

Conceived and designed the experiments: KCLC SR SL TK. Performed the experiments: KCLC SR TK. Analyzed the data: SR AR PM JMMJ KVS. Contributed reagents/materials/analysis tools: KHC AW BB MT GR SA IK AvB EE AH CK BS JS CMC AA CP OH SW UW UK. Wrote the paper: SR KCLC TK.

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2.1.2. The sex-shift in single disease and multimorbid asthma and rhinitis during puberty - a study by MeDALL

Keller T, Hohmann C, Standl M, Wijga AH, Gehring U, Melén E, Almqvist C, Lau S, Eller E, Wahn U, Christiansen ES, von Berg A, Heinrich J, Lehmann I, Maier D, Postma DS, Antó JM, Bousquet J, Keil T*, **Roll S***. The sex-shift in single disease and multimorbid asthma and rhinitis during puberty - a study by MeDALL. Allergy. 2018 Mar;73(3):602-614. https://doi.org/10.1111/all.13312 (*Contributed equally to this work)

Die Frage nach Unterschieden im Geschlechterverhältnis in der Prävalenz von Asthma und/oder Rhinitis vor der Pubertät gegenüber dem Zeitraum nach Beginn der Pubertät wurde in diesem Projekt gezielt untersucht. Dazu wurden Metaanalysen mit Rohdaten aus sechs europäischen Geburtskohorten mit 19013 Kindern und Jugendlichen von der Geburt bis zum Alter von 14-20 Jahren verwendet. Als Endpunkte wurden die Prävalenz von Asthma (ohne Rhinitis), Rhinitis (ohne Asthma), sowie Asthma und Rhinitis (gemeinsam) betrachtet. Einflussfaktoren waren Geschlecht und Pubertätsstatus (vor vs. nach Beginn der Pubertät; erfasst mit einem validierten Instrument) sowie die Interaktion (Wechselwirkung) zwischen den beiden Faktoren Geschlecht und Pubertätsstatus. Es wurden sowohl einstufige als auch zweistufige Metaanalysen mit individuellen, longitudinalen Teilnehmerdaten durchgeführt. In einstufigen Metaanalysen wurden adjustierte Odds Ratios für Geschlecht und Pubertätsstatus sowie die Wechselwirkung in den gepoolten Daten bestimmt. Dabei wurden die Analysen für potentielle Confounder (Alter, elterliche Allergien, Raucher der Mutter während der Schwangerschaft) adjustiert. Als Sensitivitätsanalyse wurde zusätzlich mittels zweistufigen Metaanalysen die Ergebnisse zunächst für jede Kohorte getrennt berechnet und anschließend zu einem Gesamtergebnis zusammengefasst. Am deutlichsten zeigte sich bei den Ergebnissen eine Verschiebung zwischen Mädchen und Jungen in der Prävalenz von Asthma mit gleichzeitiger allergischer Rhinitis. Während die Prävalenz vor der Pubertät bei Jungen deutlich höher war, bestand nach der Pubertät ein eher ausgeglichenes Geschlechterverhältnis. Für die Prävalenz von Asthma (ohne Rhinitis) sowie Rhinitis (ohne Asthma) war dieser Unterschied im Geschlechterverhältnis deutlich weniger ausgeprägt.

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The sex-shift in single disease and multimorbid asthma and rhinitis during puberty - a study by MeDALL

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Abstract

Background: Cross-sectional studies suggested that allergy prevalence in childhood is higher in boys compared to girls, but it remains unclear whether this inequality changes after puberty. We examined the sex-specific prevalence of asthma and rhinitis as single and as multimorbid diseases before and after puberty onset in longitudinal cohort data.

T. Keil and S. Roll contributed equally.

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Methods: In six European population-based birth cohorts of MeDALL, we assessed the outcomes: current rhinitis, current asthma, current allergic multimorbidity (ie, concurrent asthma and rhinitis), puberty status and allergic sensitization by specific serum antibodies (immunoglobulin E) against aero-allergens. With generalized estimating equations, we analysed the effects of sex, age, puberty (yes/no) and possible confounders on the prevalence of asthma and rhinitis, and allergic multimorbidity in each cohort separately and performed individual participant data meta-analysis.

Findings: We included data from 19 013 participants from birth to age 14-20 years. Current rhinitis only affected girls less often than boys before and after puberty onset: adjusted odds ratio for females vs males 0.79 (95%-confidence interval 0.73-0.86) and 0.86 (0.79-0.94), respectively (sex-puberty interaction $P = .089$). Similarly, for current asthma only, females were less often affected than boys both before and after puberty onset: 0.71, 0.63-0.81 and 0.81, 0.64-1.02, respectively (sex-puberty interaction $P = .327$). The prevalence of allergic multimorbidity showed the strongest sex effect before puberty onset (female-male-OR 0.55, 0.46-0.64) and a considerable shift towards a sex-balanced prevalence after puberty onset (0.89, 0.74-1.04); sex-puberty interaction: $P < .001$.

Interpretation: The male predominance in prevalence before puberty and the "sex-shift" towards females after puberty onset were strongest in multimorbid patients who had asthma and rhinitis concurrently.

KEYWORDS
allergic multimorbidity, asthma, birth cohort, puberty, rhinitis

1 | INTRODUCTION

The prevalence of two of the most common chronic diseases globally, asthma and rhinitis, remains at a high level or is still increasing in some parts of the world.[1-3] At around puberty, considerable sex-specific differences in the prevalence of allergic diseases have been identified.[4-6] For asthma, the prevalence is higher in boys than in girls before puberty, but after puberty, there is a female predominance persisting in adulthood.[7-10]

In rhinitis, sex-specific prevalence differences before and after puberty onset are less clear.[11] A recent meta-analysis of cross-sectional population-based studies suggested a "sex-switch" around puberty from male to female predominance in rhinitis prevalence.[12] However, longitudinal sex-specific evaluations from early childhood to adolescence regarding rhinitis as well as asthma prevalence are lacking. Long-term birth cohort studies are essential to understanding the life course and childhood predictors of allergies including sex-specific differences.[13] As the statistical power of individual cohorts is often insufficient to allow stratified analyses,[14] the European Commission funded MeDALL (Mechanisms of the Development of ALLergy; EU FP7-CP-IP; Project No: 261357; 2010-2015) with the aim to integrate 14 European birth cohorts including 44 010 participants for combined and harmonized analyses.[15]

This large data set allowed examining a potential sex-shift in the prevalence of less common but more severe allergic phenotypes such as multimorbidity of asthma and rhinitis and their association with and without allergen-specific immunoglobulin E (IgE) antibodies with the sufficient statistical power.[15]

Asthma and rhinitis are both heterogeneous diseases with many forms and phenotypes of different aetiologies; thus, we differentiated between asthma only and rhinitis only as single entities and multimorbidity.[15,16]

In the present analyses, we aimed to examine and compare a possible "sex-shift" in prevalence of asthma, rhinitis and multimorbidity (asthma and concurrent rhinitis) during puberty using the pooled MeDALL cohort data.

2 | METHODS

2.1 | Study design, setting and included birth cohorts

This study is based on the six older population-based birth cohorts from the MeDALL project.[15,17] We chose the following inclusion criteria: (i) at least one prospective assessment of asthma and rhinitis before puberty (ie, from birth to 10 years of age) and after possible puberty onset (11-18 years); (ii) at least one assessment of allergic sensitization based on specific antibodies against aero-allergens in serum; (iii) at least one prospective assessment of the puberty status at 10 years or older. The included birth cohorts were PIAMA (The Netherlands), BAMSE (Sweden), DARC (Denmark) and MAS, GINIplus and LISAplus (all Germany). All participating birth cohorts had obtained ethical approval from their local review boards. Recruitment, study design and data collection for the birth cohort studies have been described in detail previously.[18-22]

Information on health outcomes and puberty status has been collected at several time points. The number of time points and exact ages of the participants at follow-up differed between cohorts. When combining the cohorts, we had data for a total of 14 possible follow-up time points (Table S1).

A panel of experts within the MeDALL consortium followed a stringent process[23] for data harmonization between the participating cohorts. For each variable to be harmonized, a reference definition was agreed and each cohort then evaluated how their own cohort definition matched the reference definition as complete, partial or impossible. All single evaluations were then reviewed in a joint workshop to create the final harmonized data set.

2.2 | Outcome variables

2.2.1 | Primary outcomes

We defined three primary outcome measures: current asthma only, current rhinitis only and current allergic multimorbidity.

Current asthma only

"Current asthma only" was defined as a positive answer to at least two of the three following questions:

- "Has your child *ever* been diagnosed by a doctor as having asthma?"
- "Has your child (/Have you) taken any medication for asthma (including inhalers, nebulizers, tablets or liquid medicines) or breathing difficulties (chest tightness, shortness of breath) in the last 12 months?"
- "Has your child (/Have you) had wheezing or whistling in your chest at any time in the last 12 months?"[24]

and a negative "current rhinitis" status. If two of these three questions were answered with "no" at the respective follow-up, asthma status was negative.

Current rhinitis only

The occurrence of "current rhinitis only" at the respective follow-up assessment was defined by a positive (parent or self-reported) answer to the question "Has your child had/Did you have problems with sneezing, or a runny, or blocked nose when s/he/you did not have a cold or flu in the past 12 months?" (yes/no) based on the International Study of Asthma and Allergy in Childhood (ISAAC)[24] and a negative current asthma status. A negative answer to the question above defined a negative current rhinitis status.

Current allergic multimorbidity

A positive "current allergic multimorbidity" status was defined as concurrent asthma and rhinitis. If either rhinitis or asthma was negative, allergic multimorbidity status was defined as negative.

2.2.2 | Secondary outcomes

To investigate possible effects of puberty status on allergic sensitization, we included the following six secondary outcomes:

- "IgE-associated current rhinitis"
- "Non-IgE associated current rhinitis"
- "IgE-associated current asthma"
- "Non-IgE associated current asthma"
- "IgE-associated current allergic multimorbidity (asthma and rhinitis)"
- "Non-IgE associated current allergic multimorbidity (asthma and rhinitis)".

A positive allergic sensitization status was defined as specific immunoglobulin E (IgE) $\geq$ 0.35 kU/L in serum against at least one common aero-allergen (dog, cat, house dust mite or birch pollen, as they were assessed in all included cohorts) at the same follow-up at which the clinical phenotypes were assessed or, if serum samples were missing, at the preceding follow-up. A negative allergic sensitization status was defined as s-IgE $<$ 0.35 kU/L against all four common aero-allergens.

As a sensitivity analysis, we defined the six secondary outcomes including sensitization status based on IgE against food and aero-allergens, defined as s-IgE $\geq$ 0 .35 kU/L against at least one common food (cow's milk, hen's egg, peanut) or aero-allergen. A negative allergic sensitization status was defined as s-IgE $<$ 0.35 kU/L against all of the seven allergens.

2.3 | Definition of main exposure variable puberty

Puberty categories were defined using the Puberty Development Scales (PDS).[25,26] For boys, the following items were included: (i) body hair growth, (ii) voice change and (iii) facial hair growth. For girls, the Puberty Category Scores (PCS) was based on (i) body hair growth, (ii) breast development and (iii) menstruation.

For each item (except menstruation) four response categories indicate the extent of puberty from "not yet started" up to "seems complete". These were coded with values of 1 to 4 and summed up for each participant. According to these sum scores (and the stage of menstruation in girls) PCS was defined as Prepubertal, Early Pubertal, Midpubertal, Late Pubertal, Postpubertal. For the final binary analysis variable 'puberty' Midpubertal, Late Pubertal, and Postpubertal were considered as a positive puberty status.

Additionally, to gain more insight into possible effects of the age at puberty-onset in relation to the sex-shift of allergic diseases during puberty, we conducted a sensitivity analysis including the information of the time point of puberty-onset by using the age period 10-12 years for early and 13-16 years for late puberty-onset.

2.4 | Definition of possible confounders

Based on results from previous studies, we considered the following variables in the analyses as possible confounders: age (categorical (for all cohort-specific models except for MAS) or continuous (for models in the MAS cohort and in pooled data set)—depending on number of available follow-ups per cohort), history of parental allergies (yes = at least one parent with asthma and/or rhinitis diagnosis/no = two nonallergic parents) and maternal smoking during pregnancy (yes/no).[27,28]

2.5 | Statistical methods

For categorical variables, absolute and relative frequencies are presented. Results of all descriptive analyses are presented separately by cohort and pooled for all cohorts and sex. We pooled relative frequencies using random-effect meta-analyses.

We used generalized estimating equations (GEE) to estimate adjusted odds ratios (OR) and 95% confidence interval (CI) for the associations of the primary and secondary outcome variables with sex and puberty (and the interaction thereof) adjusting for the possible confounders described above, and age as the longitudinal time variable. The focus was on the interaction of puberty and sex as an indicator of sex-specific changes in outcome prevalence before vs after puberty onset. With GEE models, outcomes and exposure of the participants are analysed over time, taking the longitudinal design and thus the repeated measurements of one individual, which are not independent of each other, into account.

Initially, we pooled the harmonized cohort data sets to perform a one-stage Individual Participant Data (IPD) meta-analysis.[29] We used the GEE model described above on the combined data set of all cohorts with a birth cohort identifier variable included as an additional covariable in the model with participants nested in cohorts to account for the clustering in each cohort.

Additionally, as a comparative sensitivity analysis, we conducted a two-stage IPD meta-analysis, which consisted of the estimation of the adjusted odds ratios with the GEE model described above for each cohort separately as first stage and a subsequent random-effect meta-analyses with the inverse-variance method combining as second stage the adjusted effect estimates from all cohorts. Heterogeneity across the studies was assessed using the chi-squared Q-statistic and I^2.[30]

All our analyses are of explorative nature and we did not adjust for multiple testing. Missing values were not imputed. Thus, the number of included participants varied for more complex analyses including several variables and different number of missings per variable. We performed the meta-analyses in R version 3.1.2

(R Foundation for Statistical Computing) and all other analyses with SAS version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Description of cohorts

We included six birth cohorts with a total of 19 013 recruited participants: PIAMA (the Netherlands, 1996, n = 3963), BAMSE (Sweden, 1994, n = 4089), DARC (Denmark, 1998, n = 562) and three German birth cohorts (GINIplus, 1995, n = 5991; LISAplus, 1997, n = 3094; and MAS, 1990, n = 1314). We used data from birth to age 14-20 years (depending on the cohort). The number of observations used varied over follow-up time points due to dropouts and nonresponse. For analyses concerning the three GEE models for the primary outcomes, all necessary information (at least at one time point) was available for 14 533 participants.

3.2 | Puberty and exposure variables

In total, approximately 50% of the participants were female. Puberty started earlier in girls than in boys (eg, 62% vs 3% at age 11 in PIAMA, the Netherlands) with boys catching up in later teenage years (across the cohorts, except DARC), about 90%-99% of the participants had reached puberty according to our definition at the last included follow-up. Exposures such as self-reported parental allergies (ever) and maternal smoking differed slightly between the cohorts, but not considerably between boys and girls (Table 1).

3.3 | Prevalence of primary outcomes

3.3.1 | Current rhinitis only

Prevalence of current rhinitis only (ie, without coexisting asthma) varied between the cohorts. Among boys, it was generally higher than girls in earlier childhood, but this difference became smaller with increasing age (Figure 1; Table S1).

3.3.2 | Current asthma only

Prevalence of current asthma only differed slightly between the cohorts, with the highest prevalence in BAMSE across the follow-ups. At a younger age, more boys than girls had asthma but in teenage years these differences were smaller or even disappeared such as in GINIplus and BAMSE (Figure 2; Table S2).

3.3.3 | Allergic multimorbidity

Current allergic multimorbidity prevalence was higher among boys than girls especially in earlier childhood. These differences decreased as the participants grew older to smaller or even no differences between males and females (Figure 3; Table S3).

3.4 | Primary outcomes in relation to puberty

3.4.1 | Current rhinitis only

For current rhinitis only, the male predominance before puberty remained but was less pronounced after the onset of puberty. There was some degree of heterogeneity among the cohorts after puberty onset (I^2 = 39.6%) but not before puberty (Table 2). The pooled one-stage IPD meta-analysis also indicated this trend towards a female-male ratio decline (interaction sex*puberty onset P = .089) (Figure 4).

3.4.2 | Current asthma only

For current asthma only, we found a male predominance before puberty that decreased slightly after puberty onset. There was no heterogeneity among the cohorts (Table 2; Figure 4).

3.4.3 | Allergic multimorbidity

The strongest male predominance before puberty was found for allergic multimorbidity (OR: 0.55, 95%-CI 0.46-0.64). Furthermore, this outcome showed a clear shift towards a sex-balanced prevalence after puberty onset (0.89, 0.74-1.07), sex-puberty onset interaction term $P < .001$ (Figure 4). There was no considerable heterogeneity among the cohorts (Table 2).

3.5 | Sensitivity analyses: two-stage IPD meta-analyses

The additional two-stage IPD meta-analyses, which we performed as a sensitivity analyses, showed similar effect estimates for all three primary outcomes as the pooled one-stage IPD approach. The two-stage approach also allowed us to calculate I^2 for the assessment of potential heterogeneity between the cohorts. There was no considerable statistical heterogeneity for the primary outcomes apart for current rhinitis only with some moderate heterogeneity (Table 2).

3.6 | Sensitivity analyses: differentiating early and late puberty onset

Differentiating between early (age 10-12 years) and late puberty onset (age 13-16 years) did not change the effect estimates and the corresponding P-values for the interaction "pubertytime*sex" considerably compared to our primary analyses (Table S5).

3.7 | IgE- and non-IgE associated outcomes

3.7.1 | IgE- and non-IgE associated current rhinitis only and current asthma only

Prevalence estimates of IgE-associated current rhinitis only and asthma only were higher in male than in female participants before and to a lesser extent after puberty onset.

TABLE 1 Baseline characteristics and presence of puberty by age for each birth cohort and pooled

	PIAMA (n = 3963)		BAMSE (n = 4089)		GINIplus (n = 5991)		LISAplus (n = 3094)		DARC (n = 562)		MAS (n = 1314)		Total	
	Male n/N (%)	Female n/N (%)	Male n/N (%)	Female n/N (%)	Male n/N (%)	Female n/N (%)	Male n/N (%)	Female n/N (%)	Male n/N (%)	Female n/N (%)	Male n/N (%)	Female n/N (%)	Male %	Female %
Sex	2054/3963 (51.8%)	1909/3963 (48.2%)	2065/4089 (50.5%)	2024/4089 (49.5%)	2991/5830 (51.3%)	2839/5830 (49.7%)	1584/3094 (51.2%)	1510/3094 (48.8%)	285/562 (50.7%)	277/562 (49.3%)	684/1314 (52.1%)	630/1314 (48.0%)	51.3	48.8
Parental allergy	885/2025 (43.7%)	805/1889 (42.6%)	1001/2050 (48.8%)	976/2007 (48.6%)	1022/2340 (43.7%)	998/2214 (45.1%)	738/1470 (50.2%)	710/1384 (51.3%)	142/254 (55.9%)	143/255 (56.1%)	275/643 (42.8%)	300/601 (49.9%)	47.0	48.4
Maternal smoking during pregnancy	356/2037 (17.5%)	344/1889 (18.2%)	272/2065 (13.2%)	259/2023 (12.8%)	383/2474 (15.5%)	356/2327 (15.3%)	262/1524 (17.2%)	274/1450 (18.9%)	108/285 (37.9%)	75/277 (27.1%)	154/627 (24.6%)	154/584 (26.4%)	20.0	19.2
Puberty at age 10	-	-	-	-	63/1593 (3.9%)	170/1372 (12.4%)	31/853 (3.6%)	85/702 (12.1%)	-	-	0/394 (0%)	58/326 (17.8%)	1.9	13.6
Puberty at age 11	40/1316 (3.0%)	796/1295 (61.5%)	-	-	-	-	-	-	-	-	1/368 (0.3%)	147/299 (49.2%)	1.4	55.6
Puberty at age 12	-	-	424/1390 (30.5%)	1184/1353 (87.5%)	-	-	-	-	-	-	21/361 (5.8%)	261/346 (75.4%)	16.3	82.0
Puberty at age 13	-	-	-	-	-	-	-	-	-	-	117/373 (31.4%)	369/387 (95.4%)	31.4	95.4
Puberty at age 14	1092/1264 (86.4%)	1363/1366 (99.8%)	-	-	-	-	-	-	103/162 (63.6%)	199/212 (93.9%)	-	-	76.2	97.9
Puberty at age 15	-	-	-	-	1148/1268 (89.1%)	1316/1370 (96.1%)	683/741 (92.2%)	678/723 (93.8%)	-	-	289/315 (91.8%)	390/393 (99.2%)	90.8	96.6
Puberty at age 16	-	-	1231/1318 (93.4%)	1594/1623 (98.2%)	-	-	-	-	-	-	-	-	93.4	98.2

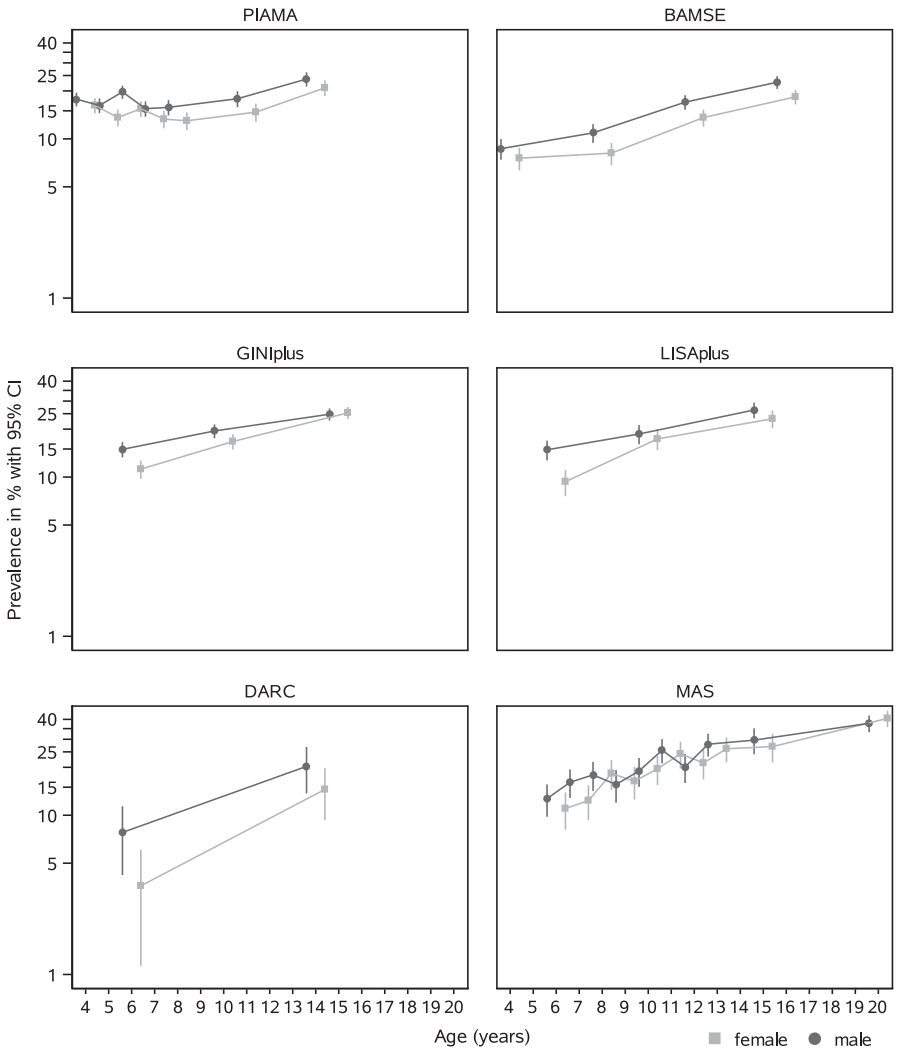

FIGURE 1 Sex-specific prevalence with 95% CI of current rhinitis only (on a logarithmic scale) in six European birth cohorts by age

In contrast, both non-IgE associated rhinitis only and asthma only showed sex-balanced prevalence estimates before puberty and a slight female predominance in the prevalence after puberty onset, corresponding sex-puberty interaction terms $P = .074$ and $P = .141$, respectively (Table 2).

3.7.2 | IgE- and non-IgE associated allergic multimorbidity

For IgE-associated allergic multimorbidity, we found a sex-shift from a strong male predominance before puberty towards a sex-balanced prevalence after puberty onset (sex-puberty interaction term $P < .001$). Similarly, non-IgE associated allergic multimorbidity showed also a sex-shift in the prevalence from a clear male predominance before puberty towards a sex-balanced occurrence of this phenotype after puberty onset (Table 2).

3.8 | Sensitivity analyses: allergic sensitization including IgE against aero- and food allergens

Including IgE against the common aero- and food allergens showed similar effect estimates for IgE- and non-IgE associated current rhinitis only, current asthma only and allergic multimorbidity compared to our primary definition of allergic sensitization status based only on common aero-allergens (Table S6).

4 | DISCUSSION

4.1 | Key results

Our individual participant data meta-analyses of six large European birth cohorts showed a strong male predominance before puberty for the prevalence of current allergic multimorbidity and to a lesser extent for current rhinitis and current asthma as single entities. After puberty onset, the sex-specific odds ratio shifted towards females in all phenotypes resulting in a rather sex-balanced prevalence for asthma only and particularly for allergic multimorbidity.

Considering allergic sensitization status, we found that for IgE-associated rhinitis only and asthma only, the clear male predominance decreased slightly, but remained significant after puberty onset, whereas for IgE-associated multimorbidity, we found a much stronger shift towards females with rather sex-balanced prevalence after puberty onset.

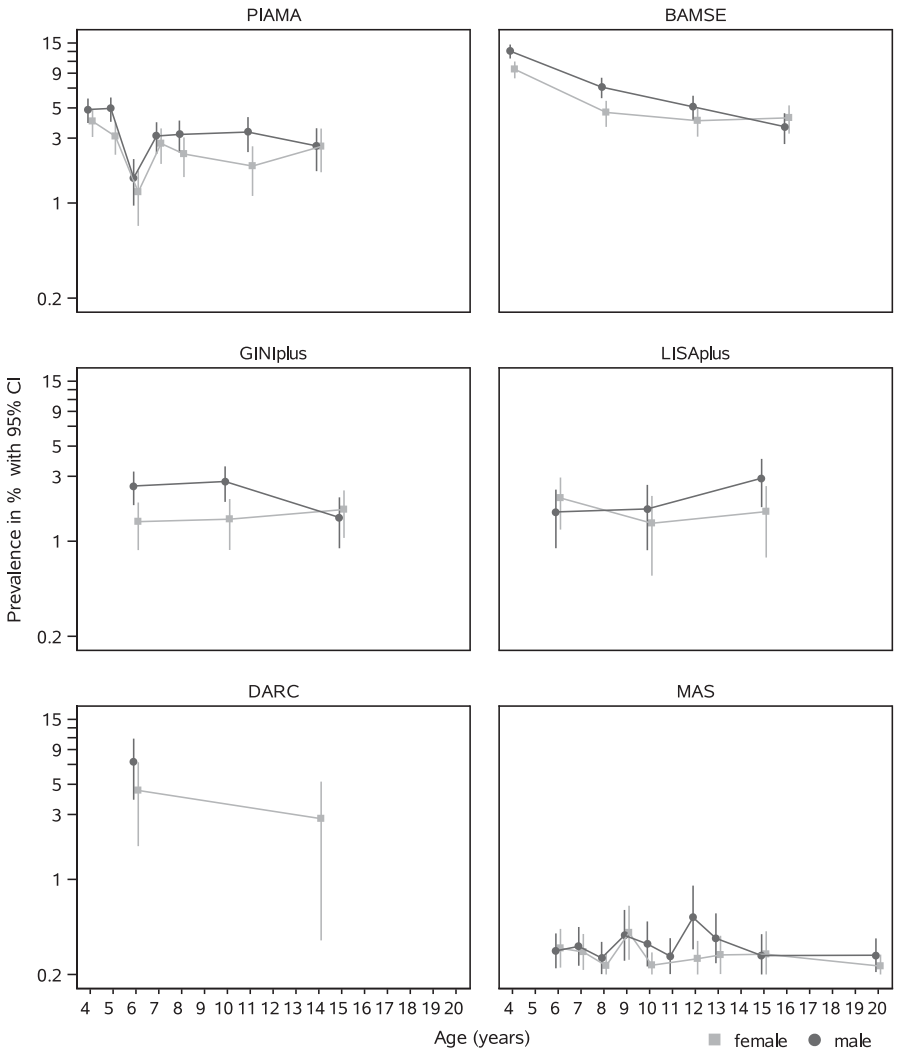

FIGURE 2 Sex-specific prevalence with 95% CI of current asthma only (on a logarithmic scale) in six European birth cohorts by age

The non-IgE associated (single and multimorbid) phenotypes showed a slight female predominance after puberty onset, which was strongest for non-IgE associated rhinitis.

4.2 | Strengths and limitations

Based on validated puberty assessments, this is the first longitudinal evaluation of birth cohort data assessing the sex-shift in prevalence at around puberty not only for rhinitis or asthma as single entities, but also for allergic multimorbidity. We combined prospectively collected data from six European birth cohorts from early childhood through adolescence up to age 20. For the IPD meta-analysis, we used pooled raw original data, which allowed us to define outcome and exposure variables, confounding variables and interactions consistently across the cohorts. Previous sex-shift evaluations had almost exclusively cross-sectional designs and used heterogeneous methods. This limited the comparability of sex-ratios before and after puberty onset between these studies, because the participants were not the same in the two groups (ie, before and after puberty). Due to the longitudinal character of the data in our study with homogeneous prospective assessments, comparability of sex-specific prevalence estimates before and after puberty onset can be considered more robust. Our findings gained external validity from the combination of several large cohorts showing similar results in different European regions and recruitment settings.

One limitation of (birth) cohort studies is that they are dynamic and prone to missing values during the course of repeated follow-up assessments as some participants, in particular teenagers, drop out or participate irregularly. This may cause selection bias and potentially limits the representativeness of the results.

Furthermore, at the time of the last follow-up included in our present analyses, some participants (PIAMA, the Netherlands, and DARC, Denmark) were just 14 years old and may not have reached puberty. The proportion of girls not in puberty was 0.2% (PIAMA) and 4.1% (DARC), which was comparable to the other cohorts with older participants at last follow-up, and for boys approximately 35% (DARC) and 15% (PIAMA). We cannot rule out a potential bias, especially if single cohorts will be analysed separately, but consider this risk of bias negligible in our large meta-analyses, where the absolute number of prepubertal participants at the last follow-up was comparatively small (eg, DARC represented <3% of all children recruited for

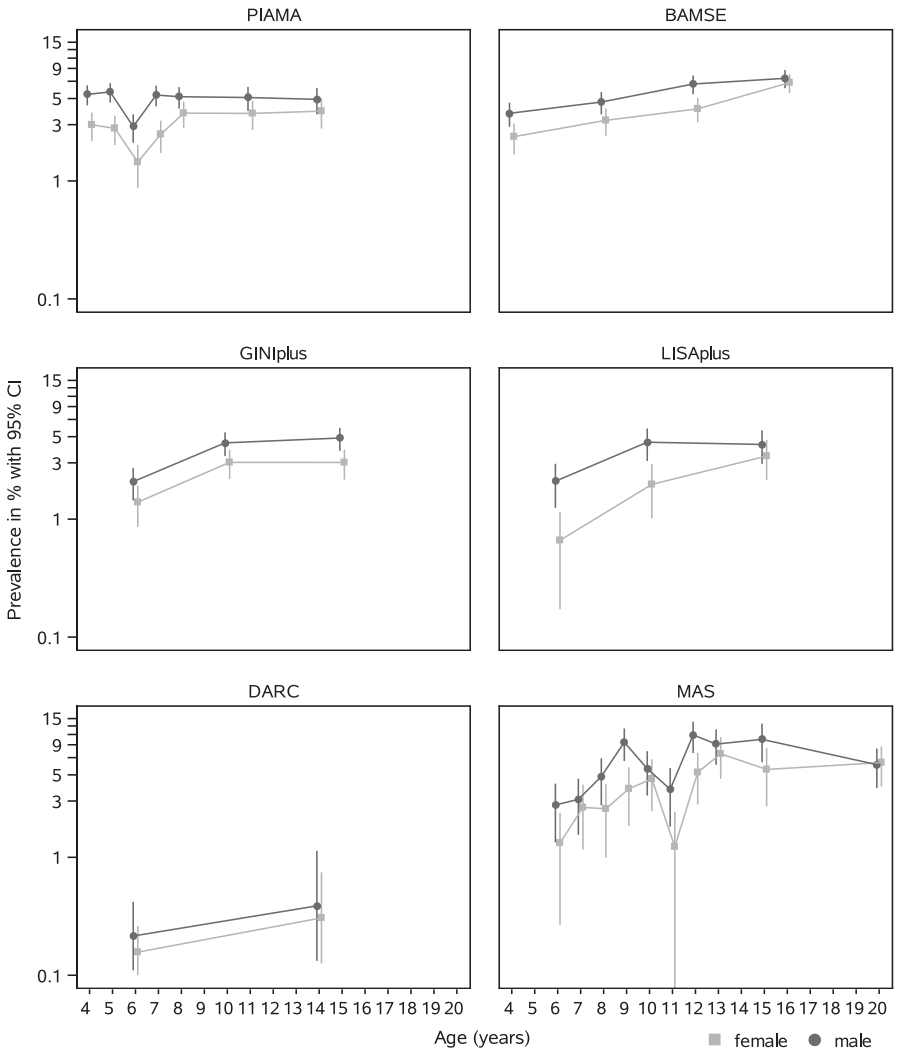

FIGURE 3 Sex-specific prevalence with 95% CI of current allergic multimorbidity (on a logarithmic scale) in six European birth cohorts by age

TABLE 2 Adjusted odds ratios[a] with 95% confidence intervals (CI) for sex effect (female vs male) before and after puberty for two-stage meta-analysis incl. assessment of heterogeneity among the cohorts using I^2

	Two-stage IPD meta-analysis Adjusted OR[a] (95%-CI) Heterogeneity I^2	
Outcome	**Before puberty onset**	**After puberty onset**
Current rhinitis only	0.78 (0.72-0.84) I^2 = 0%	0.90 (0.80-1.02) I^2 = 39.6%
Current asthma only	0.71 (0.62-0.82) I^2 = 0%	0.82 (0.64-1.06) I^2 = 4%
Current allergic multimorbidity	0.54 (0.46-0.65) I^2 = 11%	0.85 (0.71-1.03) I^2 = 0%
IgE-associated current rhinitis only (without asthma)	0.66 (0.52-0.84) I^2 = 54.9%	0.75 (0.66-0.86) I^2 = 22.1%
IgE-associated current asthma only (without rhinitis)	0.53[b] (0.40-0.70) I^2 = 0%	0.62[b] (0.42-0.91) I^2 = 2%
IgE-associated current allergic multimorbidity	0.52 (0.42-0.66) I^2 = 0%	0.84 (0.68-1.05) I^2 = 0%
Non-IgE associated current rhinitis only (without asthma)	0.94 (0.83-1.06) I^2= 0%	1.17 (1.02-1.34) I^2 = 0%
Non-IgE associated current asthma only (without rhinitis)	0.84[b] (0.69-1.03) I^2 = 0%	1.17[b] (0.81-1.72) I^2 = 0%
Non-IgE associated current allergic multimorbidity	0.73[b] (0.42-1.27) I^2 = 57.8%	0.97[b] (0.53-1.79) I^2 = 34.6%

[a]Adjusted for age, parental allergy and maternal smoking during pregnancy.
[b]Due to small prevalence in some cohorts not including all cohort estimators.

the 6 birth cohorts in total). We aimed to examine possible effects of the age at which puberty started by defining two main categories of early (age 10-12 years) and late onset (age 13-16 years) based on the assessment time points of the cohorts. We did not find a considerable impact of the timing of puberty with this approach. To analyse this aspect in more detail than in our sensitivity analysis was not

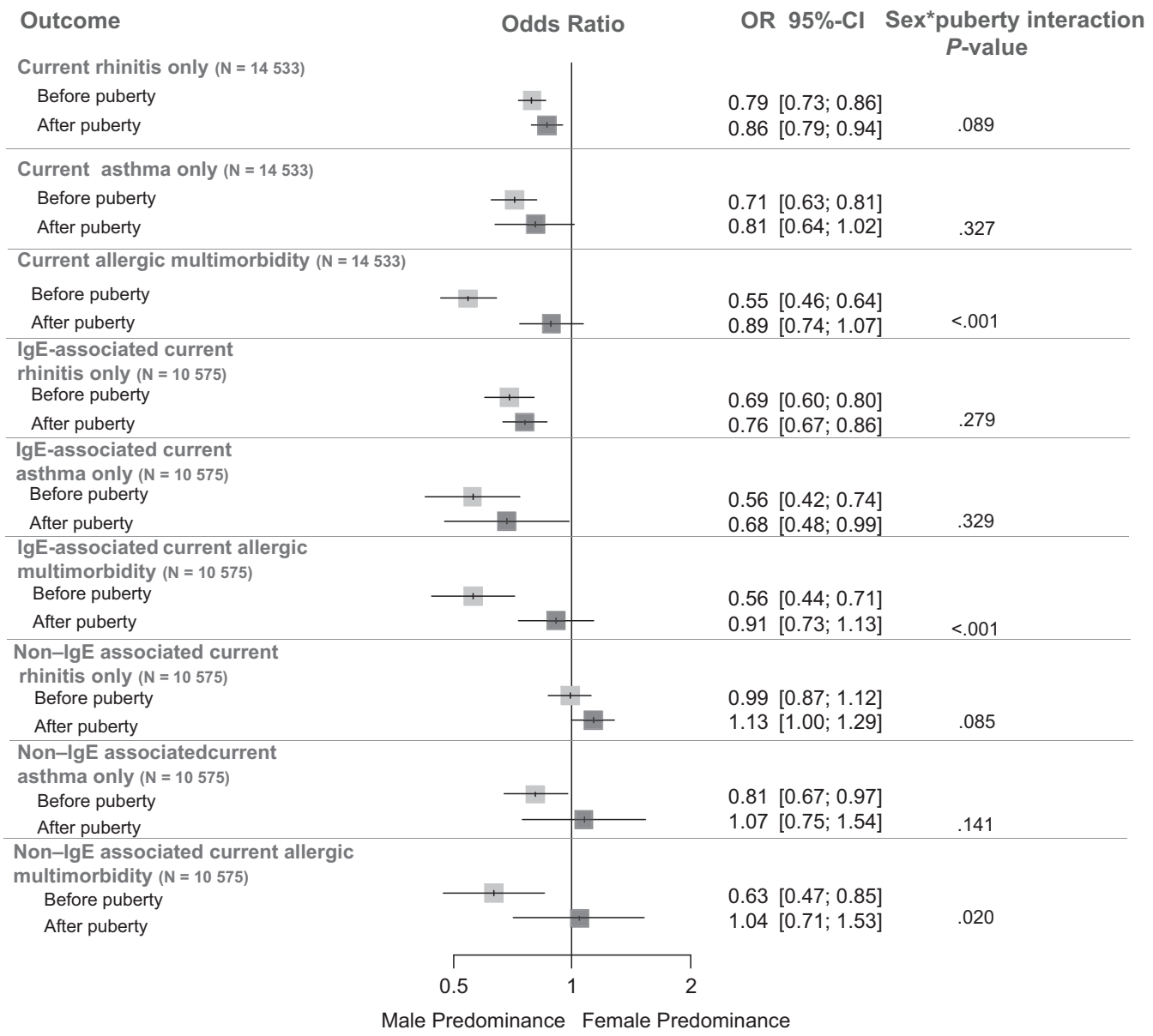

FIGURE 4 Odds Ratios from one-stage IPD meta-analysis of sex effect (female vs male) before and after puberty for all outcomes

possible because the cohorts differed in terms of the ages and follow-up intervals at which pubertal stage was assessed.

4.3 | Comparison to other studies

Pinart et al found a sex-switch for current (allergic) rhinitis prevalence from male to female predominance in their recent meta-analysis of published cross-sectional studies comparing childhood populations with adolescent and adulthood populations including mainly middle-aged participants. Participants of all birth cohorts included in our IPD meta-analyses except one had not reached adulthood yet. Therefore, we may have only found an indication towards a sex-shift but not a complete "sex-switch" in the prevalence of rhinitis as Pinart et al.'s analyses suggested. However, our findings point towards such an effect. Pinart et al.'s study differed further from ours as their meta-analyses focused on cross-sectional studies that mostly did not measure IgE sensitization, thus could not distinguish between IgE-associated and non-IgE associated rhinitis phenotypes.[31,32] Furthermore, the differentiation between rhinitis as a single or as part of a multimorbid phenotype was not made by Pinart et al[12] either.

In the Isle-of-Wight birth cohort study from the UK, which started in 1989, prevalence of sensitized and nonsensitized rhinitis in childhood and early adulthood showed a similar pattern to our findings. Concerning the differences in sensitization status of rhinitis patients, they showed a male predominance in rhinitis during early childhood as well as at 18 years of age only in subjects with rhinitis who were sensitized. For nonsensitized rhinitis, females in the UK cohort had a significantly higher prevalence at age 18 years.[33] Our results showed sex-balanced prevalence both before and after

puberty onset in teenage adolescents who were on average slightly younger. The theory that allergic sensitization might play a crucial role in the natural history of rhinitis can be reaffirmed considering sex differences.[34]

For asthma prevalence, several mostly cross-sectional evaluations showed a sex-switch from childhood to adolescence towards a female predominance.[5,7] We could not confirm a complete prevalence sex-shift for asthma prevalence, but a rather sex-balanced prevalence for asthma only after puberty. However, our statistical power was decreased when examining asthma without coexisting rhinitis and stratifying it by sensitized and nonsensitized subtypes. Therefore, we were not able to determine more precisely sex-specific prevalence differences in these strata. The TRAILS study from the Netherlands found a sex-shift between 11 and 16 years, but no association with pubertal stages as an explanation for the shift was found.[35] Other than in our study, they investigated asthma regardless of the presence of rhinitis which may explain the different findings.

Due to the common coexistence of asthma and rhinitis,[36] we aimed at evaluating sex-specific prevalence patterns in multimorbid patients to reduce the knowledge gap for these more severely affected patients. In particular, population-based research on sex-specific prevalence differences among multimorbid patients is scarce. The few earlier evaluations such as in the MAS[37] and BAMSE[38] cohorts showed an increasing prevalence of allergic multimorbidity with age. BAMSE found a male predominance in the prevalence of multimorbidity until the age of 12 that was confirmed by our analyses of multiple European cohorts. Regardless of allergic sensitization status, we found a stronger male predominance in the prevalence of allergic multimorbidity before puberty onset than for the single entities. In puberty, this clear sex-specific prevalence predominance decreased and shifted clearly towards a sex-balanced prevalence of multimorbidity after puberty onset. Based on the difference between prevalence in both individual morbidities and in multimorbidity, we hypothesize that this is not an additive effect but that due to the double burden different mechanisms may play a role.

4.4 | Potential mechanisms

Physiological changes during puberty such as endogenous[39] or exogenous sexual hormones (birth control pills)[40] have been proposed as potential determinants. Possible explanations include anatomical differences,[41] differences in the immune response profile such as increased IgE levels and enhanced cytokine responses in boys compared to girls in early childhood,[41,42] whereas in puberty and adulthood, female sex steroids are in general associated with enhanced immune responses and testosterone with dampening inflammatory responses.[43]

Sociocultural factors such as different symptom reporting behaviour between men and women[41] have been suggested as mechanisms behind the gender shift in allergic diseases. These are less of a concern in childhood as symptoms were parent reported but may play a role from school age on as teenagers fill out their own study questionnaires.

5 | CONCLUSIONS

In conclusion, we found the strongest male predominance before puberty for the prevalence of current allergic multimorbidity and also, but less pronounced, for current rhinitis and current asthma as single entities. With increasing age, we saw a "sex-shift" towards females resulting in a rather sex-balanced prevalence after puberty onset. This effect was much stronger in multimorbid children who had both current rhinitis and coexisting asthma than in those with rhinitis or asthma alone. We observed a larger prevalence shift towards females in nonsensitized than sensitized subjects.

Further cohort follow-up assessments are required to examine the hypothesized prevalence sex-switch to a female predominance regarding the different allergic phenotypes in adulthood.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

TKeller wrote the initial draft under supervision of SR and TKeil. TKeller developed the statistical analysis plan, conducted and interpreted the statistical analyses with supervision of SR. CH, TKeil, JMA and JB coordinated the harmonized follow-up assessment of all birth cohorts including the development of a common standardized questionnaire at age 14-20 and participated in the development of the statistical analysis plan. MS, AvB (GINIplus), JH, IL (LISAplus), UG, AW (PIAMA), EM, CA (BAMSE), SL, TKeil, UW (MAS), EE, ESC (DARC) coordinated the local follow-up assessments, and provided the newly as well as all the relevant previously collected birth cohort data. DM coordinated the harmonization of all previously collected data for the integration in a new common birth cohort database, provided harmonized data sets and participated in the coordination of the follow-up assessment. All authors read the different versions of the manuscript, provided comments, participated in the critical revision of the manuscript and the interpretation of the results, and approved the final version.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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2.1.3. Sex-specific incidence of asthma, rhinitis and respiratory multimorbidity before and after puberty onset: individual participant meta-analysis of five birth cohorts collaborating in MeDALL

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Um die Unterschiede zwischen Mädchen und Jungen bei aktuell bestehenden allergischen Erkrankungen (Prävalenz) besser zu verstehen, ist es von Interesse zu untersuchen, ob sich auch die Fälle von Neuerkrankungen (Inzidenz) im Verlauf der Pubertät geschlechtsspezifisch ändern. Dazu standen die Daten von 18451 Kindern und Jugendlichen aus fünf europäischen Geburtskohorten zu Verfügung. Diese individuellen Rohdaten wurden harmonisiert und mittels einstufigen Metaanalysen ausgewertet. Als Endpunkte wurden die Inzidenz von Asthma, bzw. allergischer Rhinitis sowie die Inzidenz des Auftretens von Asthma in Kombination mit allergischer Rhinitis untersucht. Als Einflussfaktor wurden Geschlecht und Pubertätsstatus sowie die Interaktion zwischen Geschlecht und Pubertätsstatus betrachtet. Alle Analysen wurden für Alter, elterlichen Allergiestatus und Rauchen der Mutter in der Schwangerschaft adjustiert. Ähnlich wie bei den Ergebnissen zur Prävalenz, zeigte sich auch bei den Neuerkrankungen ein deutliches Muster. Für den Zeitraum vor der Pubertät zeigten sich bei den Ergebnissen für alle Endpunkte höhere Inzidenzen bei Jungen als bei Mädchen. Auch nach Pubertätsbeginn gab es mehr Neuerkrankungen bei Jungen, jedoch war der Unterschied zu Mädchen geringer ausgeprägt.

BMJ Open Respiratory Research

Sex-specific incidence of asthma, rhinitis and respiratory multimorbidity before and after puberty onset: individual participant meta-analysis of five birth cohorts collaborating in MeDALL

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ABSTRACT

Introduction To understand the puberty-related sex shift in the prevalence of asthma and rhinitis as single entities and as respiratory multimorbidities, we investigated if there is also a sex-specific and puberty-related pattern of their incidences.

Methods We used harmonised questionnaire data from 18 451 participants in five prospective observational European birth cohorts within the collaborative MeDALL (Mechanisms of the Development of Allergy) project. Outcome definitions for IgE-associated and non-IgE-associated asthma, rhinitis and respiratory multimorbidity (first occurrence of coexisting asthma and rhinitis) were based on questionnaires and the presence of specific antibodies (IgE) against common allergens in serum. For each outcome, we used proportional hazard models with sex–puberty interaction terms and conducted a one-stage individual participant data meta-analysis.

Results Girls had a lower risk of incident asthma (adjusted HR 0.67, 95% CI 0.61 to 0.74), rhinitis (0.73, 0.69 to 0.78) and respiratory multimorbidity (0.58, 0.51 to 0.66) before puberty compared with boys. After puberty onset, these incidences became more balanced across the sexes (asthma 0.84, 0.64 to 1.10; rhinitis 0.90, 0.80 to 1.02; respiratory multimorbidity 0.84, 0.63 to 1.13). The incidence sex shift was slightly more distinct for non-IgE-associated respiratory diseases (asthma 0.74, 0.63 to 0.87 before vs 1.23, 0.75 to 2.00 after puberty onset; rhinitis 0.88, 0.79 to 0.98 vs 1.20, 0.98 to 1.47; respiratory multimorbidity 0.66, 0.49 to 0.88 vs 0.96, 0.54 to 1.71) than for IgE-associated respiratory diseases.

Discussion We found an incidence 'sex shift' in chronic respiratory diseases from a male predominance before puberty to a more sex-balanced incidence after puberty onset, which may partly explain the previously reported sex shift in prevalence. These differences need to be considered in public health to enable effective diagnoses and timely treatment in adolescent girls.

Key messages

- We examined whether the sex-specific incidence of asthma, rhinitis and respiratory multimorbidity differed before and after puberty onset.
- A meta-analysis of longitudinal birth cohorts showed a sex shift from higher incidence in boys before puberty towards a rather sex-balanced incidence after puberty onset.
- The elevated risk of asthma and rhinitis incidences in teenage girls should lead to more consideration of a sex-specific and age-specific focus on diagnosis and treatment of these respiratory diseases in public health.

INTRODUCTION

Meta-analyses of published results from cross-sectional studies suggested a sex shift in the prevalence of allergic rhinitis with and without concurrent asthma around puberty. The prevalence shifted from a clear male predominance in childhood towards a female predominance in adolescence.[1 2] Similar associations were found by individual participant data (IPD) meta-analyses combining harmonised data from large European birth cohorts collaborating in MeDALL (Mechanisms of the Development of Allergy): boys were more likely than girls to have higher prevalence of

asthma, rhinitis and respiratory multimorbidity (defined as concurrent asthma and rhinitis) before puberty; after the onset of puberty, a sex shift towards a sex-balanced estimated prevalence was found.[3]

Reasons for the considerable sex shift in the prevalence of allergic diseases remain unclear. Asthma and rhinitis are chronic diseases that can develop throughout childhood but may not persist into school age or adolescence. Prevalence may be affected by remission and by different sex-specific incidence patterns. Therefore, we aimed to investigate whether the sex-specific incidence patterns of asthma and rhinitis as single entities as well as their co-occurrence change with the onset of puberty.

METHODS

Study design and setting

This study was carried out as part of the MeDALL project, a European research initiative for a better understanding of the development of asthma and allergy. Participating birth cohorts were longitudinal, observational and population-based. For the present analyses, IPD from the five oldest birth cohorts participating in the MeDALL project (BAMSE: Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology, PIAMA: Prevention and Incidence of Asthma and Mite Allergy, GINIplus: German Infant Nutritional Intervention-Program, LISA: Lebensstil, Immunsystem, Allergien and MAS: Multizentrische Allergie Studie[4]) from three European countries (Sweden, the Netherlands and Germany) with follow-up assessments up to 20 years of age were used. Data from the five cohorts were combined by consistent harmonisation rules and processes,[5 6] while data from the most recent follow-up w ɜ derived from a common harmonised MeDALL Core Questionnaire for four of the five birth cohorts.[7] A detailed description of the overall MeDALL collaboration[8 9] and the inclusion and exclusion criteria of the birth cohorts for the current analysis have been reported previously.[3]

Definition of primary outcomes

Incident asthma, rhinitis and respiratory multimorbidity were our primary outcomes. If five or more consecutive years of follow-up of the primary outcome data were missing, the data were censored at the last available follow-up.

Definition of asthma and rhinitis

Asthma was defined as a positive answer to at least two of the three following questions:

- 'Has your child (/Have you) ever been diagnosed by a doctor as having asthma?' (yes/no).
- 'Has your child (/Have you) had wheezing or whistling in your chest at any time in the last 12 months?' (yes/no).
- 'Has your child (/Have you) taken any medication for asthma (including inhalers, nebulisers, tablets or liquid medicines) or breathing difficulties (chest tightness, shortness of breath) in the last 12 months?' (yes/no).

Rhinitis was defined according to the International Study of Asthma and Allergies in Childhood (ISAAC)[10] as a positive response to the following question:

- 'Has your child (/Have you) had problems with sneezing, or a runny, or blocked nose when s/he did not have a cold or flu in the past 12 months?' (yes/no).

For each question the wording 'Has your child' stems from the parental questionnaire, and the wording 'Have you' stems from the adolescent questionnaire.

Definition of incident asthma and incident rhinitis

Incident asthma and rhinitis were rated 'positive' if there was:

- A positive first time ever assessment of the disease at the current follow-up.

Incident asthma and rhinitis were rated 'negative' if:

- The assessment of the disease was negative at the current follow-up and
- The assessment of the disease was not positive at any earlier follow-up.

Definition of incident respiratory multimorbidity

Incident respiratory multimorbidity was rated 'positive' if there was:

- A positive first time ever assessment of both rhinitis and asthma at the current follow-up.

Incident respiratory multimorbidity was rated 'negative' if:

- The assessment of rhinitis and/or asthma was negative at the current follow-up and
- The assessment of both asthma and rhinitis together was not positive at an earlier follow-up.

Definition of secondary outcomes

Allergic sensitisation assessed by specific IgE

All included birth cohorts had information on specific antibodies against common aeroallergens, that is, dog, cat, house dust mite and birch pollen, which were measured as specific IgE in the serum. A participant had a positive allergic sensitisation status if at least one of the four specific IgE measurements was ≥0.7 kU/L serum. Accordingly, a participant had a negative allergic sensitisation status if all of the specific IgE measurements were <0.7 kU/L.

The following were the six secondary outcomes:

- IgE-related and non-IgE-related asthma (defined as a positive incident asthma/questionnaire data in combination with a positive or negative sensitisation status/IgE data, respectively).
- IgE-related and non-IgE-related rhinitis (defined as a positive incident rhinitis/questionnaire data in combination with a positive or negative sensitisation status/IgE data, respectively).

- IgE-related and non-IgE-related respiratory multimorbidity (defined as a positive incident respiratory multimorbidity/questionnaire data in combination with a positive or negative sensitisation status/IgE data, respectively).

If five or more consecutive years of follow-up of the secondary outcome data were missing, the data were censored at the last available follow-up. For these six secondary outcomes, questionnaire incident data were combined with either IgE data assessed at the same follow-up or with IgE data from the most recent available follow-up, and analyses were thus restricted to those with non-missing questionnaire incident and IgE data. Please see online supplementary table 5 for a general overview of available questionnaire and IgE data at different follow-ups.

Definition of the time-dependent covariable puberty

Participant puberty status was self-assessed by the validated Pubertal Development Scale (PDS), which is widely used in population studies, or available data covering information from the PDS using the items 'body hair growth', 'voice change' and 'facial hair growth' for boys, and the items 'body hair growth', 'breast development' and 'menstruation' for girls.[11] Based on these items the dichotomous variable 'onset of puberty' (yes/no) was calculated. Absence of any signs of puberty was rated as a negative onset of puberty status, while mid-pubertal, late pubertal or postpubertal category scores were all summarised as a positive onset of puberty status. Further details of this definition are presented elsewhere.[3]

Definition of confounder variables

The model was adjusted for the following previously identified variables: age (continuous), parental allergies, that is, one or both parents with self-reported rhinitis and/or asthma (yes/no), maternal smoking during pregnancy (yes/no), and cohort.

Statistical analyses

Data were analysed with SAS V.9.4 and R V.3.1.2 (R Foundation for Statistical Computing). In all analyses the missing values were excluded list-wise. Baseline data and incidences of the primary and secondary outcomes were described as frequencies and percentages per age and sex for each cohort and in total.

We used one-stage IPD meta-analyses to combine the data from five European birth cohorts (BAMSE, PIAMA, GINIplus, LISA and MAS). Proportional hazard models including puberty as a time-dependent covariable with the average partial likelihood method for handling ties in the event times were used for analysing the data. Within each proportional hazard model for all primary and secondary outcomes, two adjusted HRs with 95% CIs were presented, one comparing boys versus girls before puberty onset, and one comparing them after puberty onset. P values were reported for the interaction term 'sex*puberty', which reflects the sex-specific changes in outcome incidences before versus after puberty onset in the model. The present clinical questions and data analyses are post-hoc, and we consider the results to be hypothesis-generating rather than confirmatory. Therefore, all results, including p values, are considered exploratory and were not adjusted for any multiple testing. In defining the primary outcome, incidence was rated 'missing' if asthma and/or rhinitis were missing at the current follow-up. If the incidence was rated positive in an earlier follow-up, the participant was no longer at risk and was censored for the incidence calculation at the current follow-up.

Patient and public involvement

We did not include patients, only samples of healthy infants from the general population. Participants and the public were not involved in the development of the research question, outcome measures or study design. The individual birth cohort study teams inform their participants regularly about relevant new results of these long-term prospective studies, mainly via their study-specific websites.

RESULTS

Basic characteristics of the five included birth cohorts

Five birth cohorts collaborating in the MeDALL project with 18 451 recruited participants in total were included. Due to dropouts, the available IPD for analyses of primary and secondary outcomes varied at different follow-ups. At most follow-ups the rate of dropouts was equal between sexes, and only at some follow-ups we found more male than female dropouts (see online supplementary table 1). The included follow-up assessment time points were from 4 to 20 years of age. About half of the participants were male, and positive parental history of allergy ranged from 43% to 56% in the different cohorts. Across the three cohorts with data at age 10 years, 1.9% of male and 13.6% of female participants reported signs of puberty at the 10-year follow-up. These percentages increased to over 90% at the 15-year and 16-year follow-ups for both boys and girls, respectively (table 1).

Incidence and sex shift of asthma

The incidence of asthma was lower for girls than for boys at preschool and early school-age follow-ups. The percentages decreased for both sexes over time (see online supplementary table 2). Before puberty onset, girls were at a considerably lower risk than boys for developing incident asthma (HR 0.67, 95% CI 0.61 to 0.74). After puberty onset, the difference was less distinct (girls vs boys; HR 0.84, 95% CI 0.64 to 1.10). The interaction term 'sex*puberty' described a p=0.122 (figure 1). These findings were similar for IgE-associated asthma, whereas for non-IgE-associated asthma we found a more

Table 1 Baseline characteristics and presence of signs of puberty by sex and age, separately for each birth cohort and pooled

	PIAMA (n=3963)		BAMSE (n=4089)		GINIplus (n=5991)		LISA (n=3094)		MAS (n=1314)		Total	
	Boys n/N (%)	Girls n/N (%)	Boys n/N (%)	Girls n/N (%)	Boys n/N (%)	Girls n/N (%)	Boys n/N (%)	Girls n/N (%)	Boys n/N (%)	Girls n/N (%)	Boys (%)	Girls (%)
Sex	2054/3963 (51.8)	1909/3963 (48.2)	2065/4089 (50.5)	2024/4089 (49.5)	2991/5830 (51.3)	2839/5830 (49.7)	1584/3094 (51.2)	1510/3094 (48.8)	684/1314 (52.1)	630/1314 (48.0)	51.3	48.8
Parental allergy	885/2025 (43.7)	805/1889 (42.6)	1001/2050 (48.8)	976/2007 (48.6)	1022/2340 (43.7)	998/2214 (45.1)	738/1470 (50.2)	710/1384 (51.3)	275/643 (42.8)	300/601 (49.9)	45.9	47.4
Maternal smoking during pregnancy	356/2037 (17.5)	344/1889 (18.2)	272/2065 (13.2)	259/2023 (12.8)	383/2474 (15.5)	356/2327 (15.3)	262/1524 (17.2)	274/1450 (18.9)	154/627 (24.6)	154/584 (26.4)	17.2	17.9
Puberty at age 10	–	–	–	–	63/1593 (3.9)	170/1372 (12.4)	31/853 (3.6)	85/702 (12.1)	0/394 (0)	58/326 (17.8)	1.9	13.6
Puberty at age 11	40/1316 (3.0)	796/1295 (61.5)	–	–	–	–	–	–	1/368 (0.3)	147/299 (49.2)	1.4	55.6
Puberty at age 12	–	–	424/1390 (30.5)	1184/1353 (87.5)	–	–	–	–	21/361 (5.8)	261/346 (75.4)	16.3	82.0
Puberty at age 13	–	–	–	–	–	–	–	–	117/373 (31.4)	369/387 (95.4)	31.4	95.4
Puberty at age 14	1092/1264 (86.4)	1363/1366 (99.8)	–	–	–	–	–	–	–	–	86.4	99.8
Puberty at age 15	–	–	–	–	1125/1268 (88.7)	1274/1330 (95.8)	683/741 (92.2)	678/723 (93.8)	289/315 (91.8)	390/393 (99.2)	90.8	96.6
Puberty at age 16	–	–	1231/1318 (93.4)	1594/1623 (98.2)	–	–	–	–	–	–	93.4	98.2

BAMSE, Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology; GINIplus, German Infant Nutritional Intervention-Program; LISA, Lebensstil, Immunsystem, Allergien; MAS, Multizentrische Allergie Studie; n, number of participants per analysis; N, total number of participants at time of recruitment; PIAMA, Prevention and Incidence of Asthma and Mite Allergy.

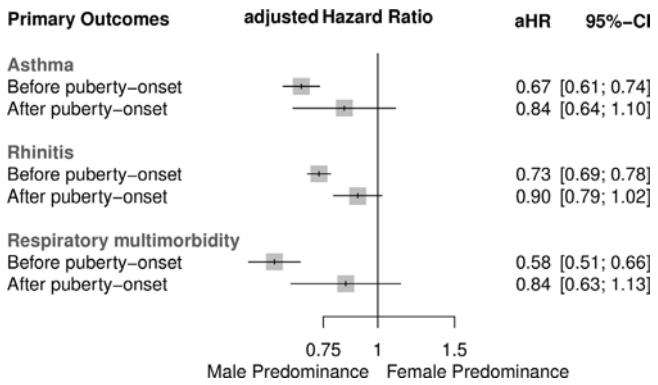

Figure 1 Adjusted HRs and 95% CIs for the risk of the incidence of asthma, rhinitis and respiratory multimorbidity for boys versus girls before and after puberty onset. The presented results are based on analyses of n=14 245, n=14 266 and n=14 233 participants, respectively. aHR, adjusted HR.

pronounced sex shift towards female predominance after puberty onset (HR 0.74, 95% CI 0.63 to 0.87 before vs 1.23, 0.75 to 2.00 after puberty onset) (figure 2).

Incidence and sex shift of rhinitis

In follow-ups during preschool and early school age, rhinitis incidence was more frequently reported in boys than in girls. At the latest follow-up assessments, most cohorts had either similar or slightly higher rhinitis incidences in girls compared with boys (see online supplementary table 3).

Before puberty onset, girls were at a considerably lower risk than boys for incident rhinitis (HR 0.73, 95% CI 0.69 to 0.78), whereas after puberty onset this lower risk was less distinct and almost sex-balanced (HR 0.90, 95% CI 0.79 to 1.02): interaction term 'sex*puberty' p=0.005 (figure 1). Incidences of IgE-associated and non-IgE-associated rhinitis differed considerably considering the effect of puberty onset: the male predominance remained almost identical before and after puberty onset for IgE-associated rhinitis, whereas for the incidence of non-IgE-associated rhinitis we found a sex switch from male to female predominance after puberty onset (HR 0.88, 95% CI 0.79 to 0.98 before vs 1.20, 0.98 to 1.47 after puberty onset) (figure 2).

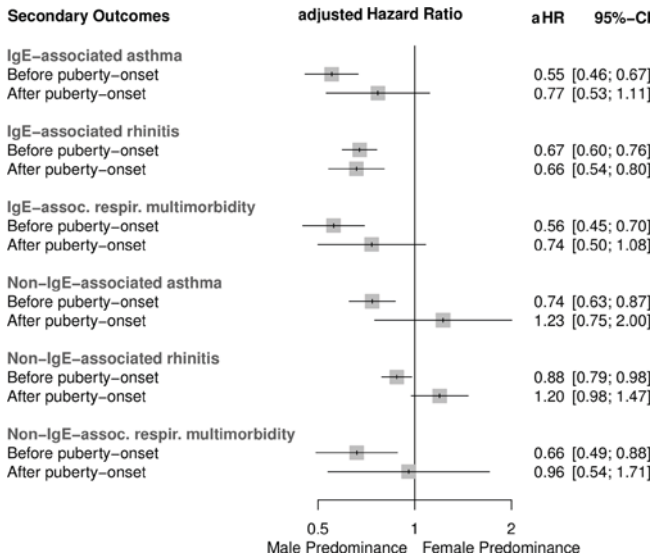

Figure 2 Adjusted HRs and 95% CIs for the risk of the incidence of IgE-associated and non-IgE-associated asthma, rhinitis and respiratory multimorbidity for boys versus girls before and after puberty onset. The presented results are based on analyses of n=10 320, n=10 331 and n=10 304 participants, respectively. aHR, adjusted HR.

Incidence and sex shift of respiratory multimorbidity

Up to the age of 6 years, the incidence of respiratory multimorbidity was higher in boys than in girls in all cohorts. At the last follow-ups, most cohorts had an either similar or higher incidence of respiratory multimorbidity for girls compared with boys (see online supplementary table 4).

Before the onset of puberty, girls were at a considerably lower risk than boys for incident respiratory multimorbidity (HR 0.58, 95% CI 0.51 to 0.66), and this effect was stronger than for asthma and rhinitis as single entities. After puberty onset, the risk for incident respiratory multimorbidity was sex-balanced (HR 0.84, 95% CI 0.63 to 1.13; interaction term 'sex*puberty' p=0.02) (figure 1). Considering allergic sensitisation status, these findings were similar for the incidence of IgE-associated respiratory multimorbidity and more pronounced towards a sex-balanced incidence for non-IgE-associated respiratory multimorbidity (HR 0.66, 95% CI 0.49 to 0.88 before vs 0.96, 0.54 to 1.71 after puberty onset) (figure 2).

DISCUSSION

Main findings

Our longitudinal birth cohort meta-analyses using harmonised IPD specifically examined the sex-specific incidence in relation to puberty onset for common chronic allergic and respiratory conditions. Our results showed a sex shift from a male predominance before puberty towards a sex-balanced incidence after puberty onset for asthma and rhinitis as single entities and as a respiratory multimorbidity. These findings explain some of the previously described sex shifts in asthma and allergy prevalence from childhood to adulthood. After stratifying for allergic sensitisation, the sex-specific effect seemed stronger for non-IgE-associated conditions.

Comparison with other studies

Similar to our findings, the Isle of Wight study found a male predominance for allergic rhinitis at 4 and 18 years. For non-allergic rhinitis the study reported no sex difference at 4 years but a female predominance at 18 years.[12] Observational population-based prevalence studies have been more common than incidence studies particularly for rhinitis and respiratory multimorbidity. A longitudinal

British birth cohort study found the annual incidence of asthma and wheezing up to 16 years of age was higher in boys than in girls: 0.85% vs 0.58% on average per year. This effect reversed during follow-up at 17–23 years, when the incidence was considerably lower in boys than in girls: 0.56% vs 0.94%.[13] This finding suggested a prevalence sex shift at a slightly older age than that of our study participants. Given the age of effect reversal, it remains unclear if it is puberty onset-related. Puberty status was not specifically evaluated in this UK birth cohort. The participants in the UK cohort were born in 1958, and the pubertal age has been decreasing over the past decades. A more recent cohort study from Canada stated a higher asthma incidence for girls than for boys aged 12–18 years: 13.2% vs 6.6% per 1000 person-years.[14] A large Dutch cohort study based on medical records from a health database found an asthma incidence of 6.7 per 1000 person-years for children and adolescents aged 5–18 years. They confirmed a sex shift in asthma incidence at the age of 13, with a male predominance before and a female predominance thereafter.[15] Another Dutch study found a sex shift with more girls than boys reporting asthma at the age of 16. However, an association with the assessed pubertal status could not be confirmed.[16] Individuals were found to have an increased risk of asthma if they reported an early but not a normal or late puberty onset.[17] A lack of information about early, normal or late puberty onset, as well as not taking into account the differentiation between IgE-associated and non-IgE-associated asthma, could account for some of the differences in the reported study results. Two recent systematic reviews of cross-sectional studies reported a sex-related shift for rhinitis prevalence with and without respiratory comorbidity from a male predominance in childhood towards a female predominance among adolescents.[1 2] Our study adds to previous knowledge by examining incidence data in rhinitis and respiratory multimorbidity, the effect of puberty status, and a differentiation of IgE versus non-IgE-association for all three health outcomes. We were able to show that in the examined cohorts, puberty onset played a considerable role in a shift from male predominance towards a more sex-balanced incidence of asthma, rhinitis and respiratory multimorbidity while controlling for age.

The incidence of asthma, rhinitis and respiratory multimorbidity varied between the cohorts in our combined analyses. Potential explanations include differences in the recruitment procedures, climatic regions (from Scandinavia to Southern Germany) and/or degree of urbanisation of the study areas (from urban to mixed urban-rural). Differences in assessment methods among the included cohorts have been minimised as the specific questions have been previously harmonised (based on the ISAAC questions) and underwent a further harmonisation process for the latest assessment in adolescence.[7 10] Therefore, we consider the outcome and puberty data across the included cohorts to be comparable.

In line with our results, an elevated risk of adult-onset non-IgE-associated asthma in women has been previously reported.[18] Various reasons for the observed increased risk of asthma and rhinitis in women after puberty have been discussed. Contributing factors may include sex-specific and age-related anatomical differences of the lung.[19] Considering puberty and the postpubertal stage, there is strong evidence that the sex hormones oestrogen and progesterone influence the development and outcome of asthma. However, the question of which hormones have protective effects or increase the risk of developing allergy and asthma is not fully understood.[19] Women generally show stronger immune responses than men, which makes them potentially more vulnerable to autoimmunity and allergy. A suppressive effect of androgens on group 2 innate lymphoid cells is supposed have a protective effect for allergic asthma in men after puberty onset.[20]

Strengths and limitations

For this analysis, we aimed to focus on asthma, rhinitis and respiratory multimorbidity incidence data as these have relevant public health implications. An increased incidence in adolescence emphasises the need for a raised awareness for early diagnosis and treatment of formerly healthy female subjects. To date, incident asthma cases are less likely to be diagnosed in adolescence than in childhood. At 16 years, girls reported uncontrolled asthma more often but fewer doctors' diagnoses and they were prescribed fewer medications than boys.[21] As the prevalence of a disease is determined by its incidence and remission, prospectively collected longitudinal data to better understand the interplay of incidence and remission would be of interest in the future.

Among the strengths of the current study is the prospectively collected longitudinal data from five different European population-based cohorts. Furthermore, we were able to include IPD from over 18 000 European birth cohort participants for the pooled analyses rather than performing 'traditional' meta-analyses combining already published effect estimates. Our approach aimed to minimise heterogeneity between the cohorts by harmonising the individual data a priori, where necessary. The construction of a common database, thanks to a close trustful collaboration between the research teams, has led to a unique data source of European birth cohorts. The pooled data set has more statistical power than the individual cohort data sets and allows examination of less common (sub)phenotypes or exposures. This is the first longitudinal birth cohort evaluation of the incidence of asthma and rhinitis as single entities and as respiratory multimorbidities in relation to the puberty status of birth cohort participants.

Several limitations should be considered while interpreting the current study results. The five included European cohort studies are not representative of the general population of their countries. However, to a certain degree, they represent regional, mainly urban populations from where they were recruited.

Four out of five cohorts provided the latest follow-up for age 14–16 years and only one cohort for 20 years of age. Many girls at age 14–16 years were already in puberty at earlier follow-ups. Almost all participants were categorised as being at least in puberty, and many participants, especially the girls, had completed puberty by the last available follow-up. However, this cannot be interpreted as a long-term postpubertal observation period. Therefore, possible long-term effects of puberty-related hormone exposure cannot be evaluated with our sample and have to be subject to future investigations of these cohorts.

Another possible limitation of longitudinal studies such as birth cohorts is the systematic and unsystematic dropouts, resulting in lower participation rates and a possible bias over the time course. However, as this may influence the magnitude of the incidence estimates, we have no clear indication of a systematic sex-related loss of participants (see online supplementary table 1).

Our definition of incidence could not always be restrained to 1 year, which would have been desirable. Among the cohorts, time intervals between the follow-up assessments differed. The longest interval was 5 years. Even if the participants were asked for the occurrence of symptoms within the past 12 months, it could not be excluded that the condition might have already developed at an earlier time point within the time frame without a follow-up. This has to be considered for the definition of the onset of puberty. However, the cohorts all started with 100% prepubertal children, and we were eventually able to detect the onset of puberty in 96% of all participants. Lacking the exact timing of the onset of puberty might be negligible as it may not influence our results considerably. The variables of age and puberty onset are highly related. We aimed to disentangle these two variables by controlling for age while puberty was the time-dependent covariable.

CONCLUSIONS

Our IPD meta-analyses showed an incidence 'sex shift' in chronic respiratory diseases from males to females after puberty onset, which may partly explain the previously and more commonly reported prevalence 'sex shift'. The observed sex shift, especially for non-IgE-related incidences of the diseases, suggests sex-specific and puberty-specific underlying mechanisms. Our results stress the importance of raising alertness among clinicians for incident cases of respiratory diseases in adolescent girls for effective detection and timely treatment.

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Contributors CH wrote the initial draft under the supervision of SR and TKei. TKel developed the statistical analysis plan and conducted the initial analyses. TKel, CH, UG, AW and HS augmented the statistical analyses plan, and TKel conducted and interpreted the statistical analyses with supervision of SR. CH, TKei, JA and JB coordinated the development of common standardised questionnaires and standard operational procedures, coordinated the follow-up assessment of the MeDALL birth cohorts, and participated in the development of the initial statistical analysis plan. MS, AvB (GINIplus), JH, IL (LISA), UG, AW, HS (PIAMA), AB, IK (BAMSE), SL, TKei and UW (MAS) coordinated the local follow-up assessments and provided the data on the harmonised follow-up and the birth cohort data. They, along with DM, participated in the planning of the common database and in the preparation of harmonised data sets for central storage and analyses. DM built the common database. DM was responsible for the correct and safe storage of the data in the common database and the data distribution to different research teams. All authors read the different versions of the manuscript, revised them and provided comments, participated in the revision of the final manuscript, and approved the final version.

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Competing interests None declared.

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2.1.4. Is there a sex-shift in prevalence of allergic rhinitis and comorbid asthma from childhood to adulthood? A meta-analysis

Fröhlich M, Pinart M, Keller T, Reich A, Cabieses B, Hohmann C, Postma DS, Bousquet J, Antó JM, Keil T, **Roll S**. Is there a sex-shift in prevalence of allergic rhinitis and comorbid asthma from childhood to adulthood? A meta-analysis. Clin Transl Allergy. 2017 Dec 5;7:44. https://doi.org/10.1186/s13601-017-0176-5

Eine weitere Fragestellung zu Geschlechtsunterschieden bei allergischer Rhinitis (alleine) bzw. in Kombination mit Asthma bezieht sich auf den Vergleich von aktuell bestehender Atemwegsallergien in der Kindheit und Jugend im Vergleich zum Erwachsenenalter. Hierzu wurde ein systematischer Review mit Metaanalyse basierend auf publizierten Daten durchgeführt. In den Review eingeschlossen wurden bevölkerungsbasierte Beobachtungsstudien weltweit (Längsschnitts- oder Querschnittstudien), die geschlechts- und altersstratifizierte Prävalenzen von allergischer Rhinitis und Asthma untersuchten. Auch hier wurde aus den publizierten Prävalenzen zunächst das Relative Risiko (männlich vs. weiblich) für jede Studie bestimmt. Diese wurden dann über Metaanalysen mit zufälligen Effekten zusammengefasst. Während Jungen ein deutlich erhöhtes Risiko für allergische Rhinitis mit oder ohne Asthma in der Kindheit zeigten, waren Mädchen während des Jugendalters stärker betroffen. Im Erwachsenenalter dagegen schien es keine deutlichen Geschlechtsunterschiede bzgl. des Auftretens allergischer Atemwegsallergien zu geben.

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Clinical and Translational Allergy

REVIEW Open Access

Is there a sex-shift in prevalence of allergic rhinitis and comorbid asthma from childhood to adulthood? A meta-analysis

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Abstract

Background: Allergic rhinitis and asthma as single entities affect more boys than girls in childhood but more females in adulthood. However, it is unclear if this prevalence sex-shift also occurs in allergic rhinitis and concurrent asthma. Thus, our aim was to compare sex-specific differences in the prevalence of coexisting allergic rhinitis and asthma in childhood, adolescence and adulthood.

Methods: Post-hoc analysis of systematic review with meta-analysis concerning sex-specific prevalence of allergic rhinitis. Using random-effects meta-analysis, we assessed male–female ratios for coexisting allergic rhinitis and asthma in children (0–10 years), adolescents (11–17) and adults (> 17). Electronic searches were performed using MEDLINE and EMBASE for the time period 2000–2014. We included population-based observational studies, reporting coexisting allergic rhinitis and asthma as outcome stratified by sex. We excluded non-original or non-population-based studies, studies with only male or female participants or selective patient collectives.

Results: From a total of 6539 citations, 10 studies with a total of 93,483 participants met the inclusion criteria. The male–female ratios (95% CI) for coexisting allergic rhinitis and asthma were 1.65 (1.52; 1.78) in children (N = 6 studies), 0.61 (0.51; 0.72) in adolescents (N = 2) and 1.03 (0.79; 1.35) in adults (N = 2). Male–female ratios for allergic rhinitis only were 1.25 (1.19; 1.32, N = 5) in children, 0.80 (0.71; 0.89, N = 2) in adolescents and 0.98 (0.74; 1.30, N = 2) in adults, respectively.

Conclusions: The prevalence of coexisting allergic rhinitis and asthma shows a clear male predominance in childhood and seems to switch to a female predominance in adolescents. This switch was less pronounced for allergic rhinitis only.

Keywords: Allergic rhinitis, Asthma, Multimorbidity, Prevalence, Systematic review

Background

Increasing prevalence in allergic diseases has been observed in many countries, especially in Western but also many developing countries [1]. Sex specific differences in prevalence of allergic rhinitis and asthma over the life span were recognized, showing a higher prevalence of allergic rhinitis and asthma as single entities in boys than in girls during childhood followed by an equal distribution in adolescence [2, 3]. In adulthood more women than men are affected by asthma [4, 5]. In a prospective cohort study, the prevalence of coexisting eczema, allergic rhinitis, and asthma in the same child was more common than expected by chance alone and was not only attributable to IgE sensitization, suggesting that these diseases share causal mechanisms [6]. In a systematic review of studies across the globe we showed a sex-switch in prevalence of allergic rhinitis in population-based studies [3]. Since research on multimorbidity, i.e. the coexistence of 2 or more allergic diseases in

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the same individual, is sparse, the aim of this systematic review with meta-analyses was to examine sex specific differences in the prevalence of coexisting allergic rhinitis and asthma, from childhood through adolescence into adulthood.

Methods

Data sources, search strategy, and selection criteria

We conducted a systematic literature search using the online databases MEDLINE and EMBASE. MeSH terms were used in conjunction with keywords searched in the title and abstract. We restricted our search to studies published between January 2000 and April 2014. There was no restriction to the language of publication. The protocol for our systematic review was developed with guidance from the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [7]. It can be accessed at PROSPERO (http://www.crd.york.ac.uk/PROSPERO/, registration number CRD42016036105). To manage the identified publications, we used EndNote X7® (Thomson Reuters) bibliographic database.

Inclusion and exclusion criteria

The selection of studies was performed along with pre-set criteria for in- or exclusion. Since the present study is a post hoc analysis of a larger review considering the difference in prevalence for allergic rhinitis only [3], we chose broad inclusion criteria to reach most of the available information and to increase generalisability. The present analysis included studies of the previous comprehensive review that (1) recruited participants of both sexes from the general population, (2) reported the prevalence of coexisting allergic rhinitis and asthma, asthma only, and allergic rhinitis only stratified by sex and age if the population under study included both children and adults, and (3) were designed as longitudinal or cross-sectional studies.

We excluded (1) non-original studies (e.g. reviews or guidelines), (2) studies that selected participants by special occupation, (3) studies with only male or female participants, (4) studies analysing selective patient collectives (e.g. from special allergy clinics), or (5) non-population-based study designs e.g. ecological studies, case reports, case series, case–control studies, experimental studies, intervention studies, and clinical studies.

We evaluated prevalence estimates of allergic rhinitis, asthma and coexisting allergic rhinitis and asthma regarding the following endpoints: allergic rhinitis only was defined as having symptoms of allergic rhinitis (i.e. runny nose without having a cold) without having symptoms of asthma. In analogy, asthma only was defined as having symptoms of asthma (i.e. wheezing or whistling in the chest) but no symptoms of allergic rhinitis. An individual who named both symptoms of allergic rhinitis and symptoms of asthma was included in the group of coexisting allergic rhinitis and asthma. If selected studies reported prevalence rates for having symptoms ever or current, we chose 'current', which was defined as reporting symptoms in the last 12 months.

Study selection, data extraction and quality assessment

A detailed protocol of the selection process for the initial review was published elsewhere [3]. In short a two-step review process was performed with scanning titles of identified studies first independently by two reviewers (MP and CH), followed by a second screening of all abstracts of articles rated as 'include' or 'unclear'. A disagreement between the two reviewers was resolved by discussion to meet a consensus. If consensus was not reached, a third independent reviewer (TKei or MF) was asked to assess the relevance.

Prior to data extraction, two reviewers (MP and MF) independently reviewed full texts of all selected publications rated as 'include' or 'unclear'. A pre-designed data extraction form was piloted with five studies selected from the pool of included studies. At least two reviewers (TKel, CH, BC, TKei, AR, MP and MF) extracted data from the selected full texts independently with disagreements through referral to a third reviewer (TKei).

For data extraction we used a self-designed (MP) SoSci-Survey questionnaire (https://www.soscisurvey.de/) retrieving information on country, study design, description of the process of recruitment of participants, age of participants, sample size, residency, response rate, observation period, definition of disease and measurement, method of data collection, prevalence of allergic rhinitis only (i.e. subjects without asthma) and asthma only (i.e. subjects without allergic rhinitis) as well as coexisting allergic rhinitis and asthma stratified by sex. Prevalences for each study were calculated using the number of participants with the respective disease as numerator and the total number of participants as denominator.

To evaluate the quality of identified literature and the heterogeneity between different studies we used an evaluation score based on previously published studies [8]. For this score every included article was reviewed on sampling method, response rate, sample size, and data collection method. A maximum of five points would account for 'high quality', three to four points would be 'moderate' and zero to two would be 'low quality'.

Quantitative data synthesis

Study populations were divided into age ranges of childhood (0–10 years of age), adolescence (11–17 years), or adulthood (18–79 years). For each study, we extracted the prevalence rates of coexisting allergic rhinitis and

asthma, as well as of allergic rhinitis only, and asthma only separately for male and female participants. We then calculated male–female ratios for each study, as well as pooled male–female-ratio estimates with 95% confidence intervals (95% CI) using random-effects meta-analyses with the inverse variance method (SR). Heterogeneity between the studies was measured by I^2. Statistical analyses were done using Review Manager (RevMan), Version 5.3. Copenhagen (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of included studies

1222 out of 6539 publications were selected by title screening. Of those, 247 studies were eligible for data extraction since they reported prevalence of allergic rhinitis stratified by sex. Finally, 10 studies reporting the prevalence of asthma alone and allergic rhinitis with coexisting asthma were included into the systematic review (Fig. 1, Table 1) [8–16]. Six studies provided sex-specific prevalence of coexisting allergic rhinitis and asthma, allergic rhinitis only, and asthma only in children (0–10 years), two studies in adolescents (11–17 years), and two studies in adults (18–79 years). Studies with a broad age range were categorised as closely as possible to the targeted age groups, using the mean age of the participants for one study [16]. The assessment of allergic symptoms was questionnaire-based, mainly using the International Study of Asthma and Allergies in Childhood (ISAAC) [17] questionnaire for 8 studies in children and adolescents [8, 10–15, 18], or the European Community Respiratory Health Survey (ECRHS) [19] for 2 studies in adults [9, 20]. See Additional file 1: Tables E1–E3 for further description of study characteristics and Additional file 1: Table E5 for study results.

Male–female ratios of coexisting allergic rhinitis and asthma

We included 6 studies with a total of 34,365 males and 31,611 females for children (0–10 years), 2 studies with 1803 males and 2152 females for adolescents (11–17 years) and 2 studies with 11,573 males and 11,979 females for adults (18–79 years). The pooled estimates for the male–female ratio (males vs. females) of the prevalence of coexisting allergic rhinitis and asthma were 1.65 (95% CI 1.52–1.78) in children, 0.61 (0.51–0.72) in adolescents, and 1.03 (0.79–1.35) in adults (Fig. 2).

The studies reported a male predominance of coexisting allergic rhinitis and asthma in children and a female predominance in adolescents. Desalu et al. [9] and Konno et al. [20] showed heterogeneous results for adulthood.

Male–female ratios of allergic rhinitis without asthma

We included 5 studies with 29,775 males and 27,071 females for children (0–10 years), 2 studies with 1803 males and 2152 females for adolescents (11–17 years) and 2 studies that included 11,573 males and 11,979 females for adults (18–79 years). The pooled estimates for the male–female ratio of the prevalence of allergic rhinitis only were 1.25 (1.19–1.32) in children, 0.80 (0.71–0.89) in adolescents and 0.98 (0.74–1.30) in adults.

None of the studies reported a female predominance in the prevalence of allergic rhinitis only among children. In contrast both studies providing information on adolescents showed a female predominance. Concerning the prevalence among adults the two analysed studies again showed heterogeneous results.

Male–female ratios of asthma without allergic rhinitis

We included 5 studies with 29,775 males and 27,071 females for children (0–10 years), 2 studies with 1803 males and 2152 females for adolescents (11–17 years). We found only one study providing information on asthma only in adults. The pooled estimates for the male–female-ratio of the prevalence of asthma only were 1.20 (0.99–1.45) in children and 1.03 (0.62–1.71) in adolescents. Konno et al. [20] reported in a study with 11,132 males and 11,687 females a male–female ratio for the prevalence of asthma only of 1.61 (1.44–1.81) in adults (Fig. 3).

Four of five included studies for asthma only in children reported a male predominance, whereas Nahhas et al. [15] showed a female predominance. Two studies analysed the prevalence of asthma only in adolescents and found heterogeneous results. De Brito et al. [8] reported a female predominance, whereas Luna et al. [14] showed a male predominance.

Heterogeneity and quality of studies

While no statistical heterogeneity was detected among the lower age groups, moderate heterogeneity existed among the studies in the adult group ($I^2_{18-79} = 41\%$) for coexisting allergic rhinitis and asthma. In the meta-analysis for the prevalence of asthma only, considerable heterogeneity was found ($I^2_{0-10} = 75\%$; $I^2_{11-17} = 81\%$) resulting in an overall of $I^2 = 85\%$. Little or no heterogeneity was seen in studies reporting results for allergic rhinitis only in children and adolescents ($I^2_{0-10} = 27\%$; $I^2_{11-17} = 0\%$) compared to studies including adults ($I^2_{18-79} = 73\%$). All studies were of moderate quality (4 points) except from Desalu et al., which was rated as high quality (5 points), see Additional file 1: Table E4.

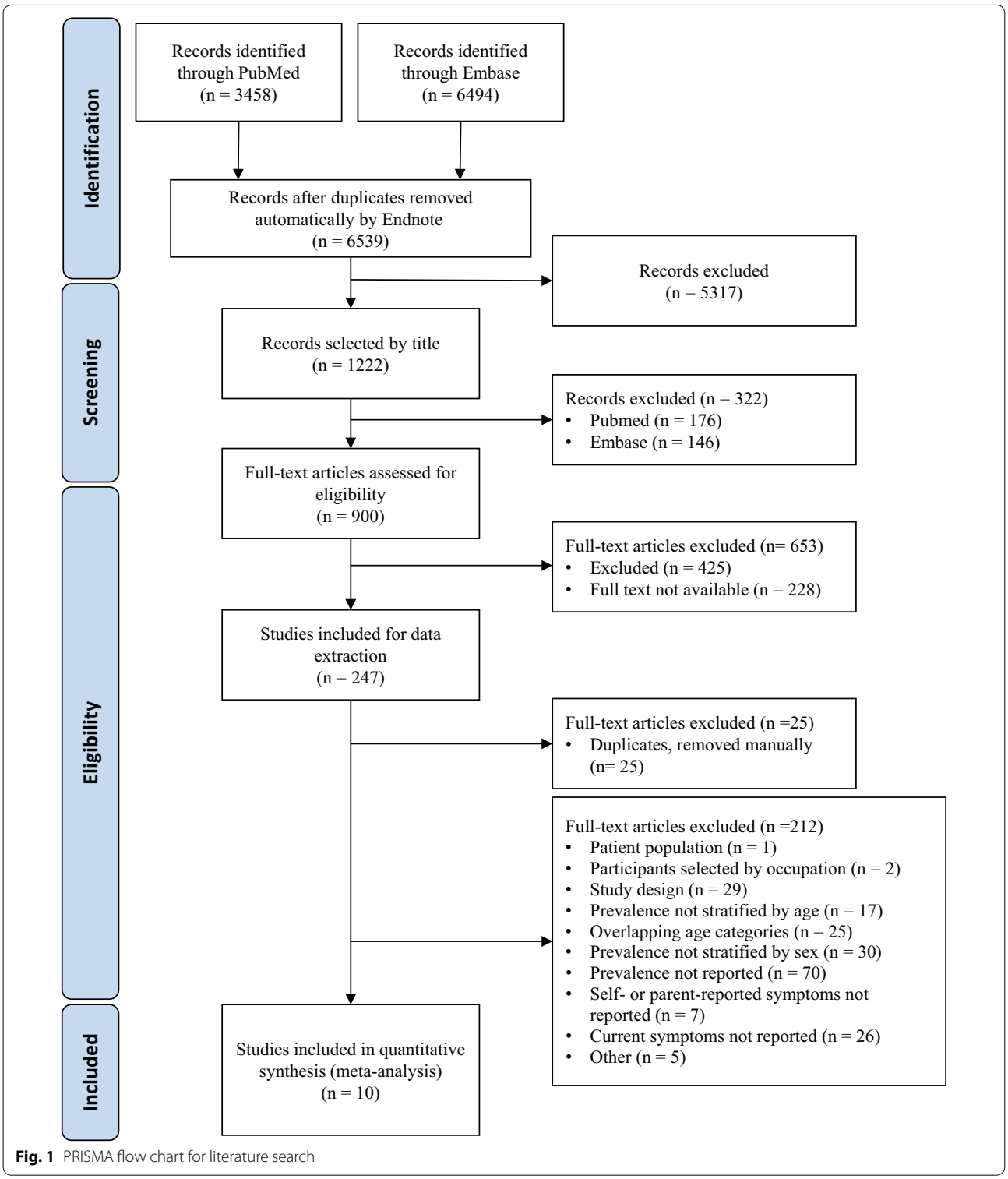

Fig. 1 PRISMA flow chart for literature search

Discussion

Main findings

We found a clear 'sex-switch' in the prevalence of coexisting allergic rhinitis and asthma from a male predominance in childhood to a female predominance in adolescence. Similar trends of these sex-specific prevalence patterns were observed in participants with asthma only and those with allergic rhinitis only. Two

studies in adults showed similar prevalence rates in both sexes.

Comparison with other studies

In a global systematic review with meta-analysis we showed sex-related differences in rhinitis prevalence with a prevalence shift from a male predominance at around puberty to a female predominance thereafter [3]. Similarly, a retrospective analysis of the ECRHS data from 16 European countries showed a transition for asthma from a male predominance in childhood (0–10 years) followed by an equal gender distribution in adolescence (10–15 years) leading to a female predominance in adults (> 15 years) [21]. Sex-specific rhinitis and comorbid asthma prevalence data for older men and women are very scarce. Interestingly, according to a large observational all-female cohort, the Nurses' Health Study in USA, the age-adjusted risk of asthma seems to be increased in postmenopausal women who ever or currently used hormone replacement therapy (i.e. conjugated estrogens with or without progesterone) compared to those who never used such hormones. However, allergic rhinitis with and without comorbid asthma has not been examinated [22]. In a cohort study of 509 children with allergic rhinitis from Turkey (mean age 7.2 ± 3.5 years, age range 1.5–18 years) Dogru showed that asthma was prevalent in the majority (53.2%) of these children [23]. In a French observational study of patients with asthma more than 50% of participants had concomitant allergic rhinitis [24]. Several narrative reviews showed this change in sex predominance favoring females during the transition from childhood to adulthood for diverse allergy-related diseases [4, 5, 25, 26]. Therefore, and since asthma and rhinitis coexist more often than expected [6], we hypothesized that also concomitant allergic rhinitis and asthma may undergo a similar sex-shift in prevalence during puberty.

Our results support this hypothesis to some extent. However, the limited number of studies found in adults did not allow us to clearly establish a clear tendency towards a male or female predominance but rather a balance between the sexes. Our pooled estimates relied only upon data from studies conducted in Asia (N = 7), South America (N = 2) and Africa (N = 1). In Pinart et al. a sex switch for allergic rhinitis prevalence around puberty was not found in studies conducted in Asia [3]. Five of six studies in the youngest age group (0–10 years) were from Asia, whereas no Asian studies were found for adolescents (11–17 years), suggesting a considerable bias.

Concerning possible mechanisms underlying a higher prevalence of allergic diseases in women during and after adolescence, higher levels of sex hormones such as estrogen and progesterone were suggested to be of central importance [27]. Sex hormones play a role in the homeostasis of immunity [28]. Estrogen and progesterone enhance type 2 and suppress type 1 responses in females, whereas testosterone suppresses type 2 responses in males [29]. Experiments in rodents showed an effect of estrogens on mast cell activation and the development of allergic sensitization, while progesterone can suppress histamine release but potentiate IgE induction [28]. Similarly for asthma sex differences have been reported for different phenotypes and symptom profiles in epidemiological, clinical and experimental studies, however, the aetiology remains largely unclear [30–33].

Table 1 Main characteristics of studies included in the systematic review

Study characteristics	Number of studies
Total	10
Study period	
2000–2007	7
2008–2014	3
Region	
Africa	1
Asia	7
South America	2
Sample size analysed	
< 1000	2
1001–5000	1
5001–10,000	3
10,001–100,000	4
Age category (in years)	
0–10	6
11–17	2
18–79	2
Urbanicity	
Urban	7
Rural/urban	1
Unclear/not reported	2
Method for assessing prevalence	
ISAAC questionnaire	8
ECHRS questionnaire	2

ISAAC International Study of Asthma and Allergies in Childhood, *ECRHS* European Community Respiratory Health Survey

Risk of bias

We tried to identify all population based studies reporting prevalence of coexisting allergic rhinitis and asthma. Given that such observational studies require large samples, it seems unlikely that a study of this dimension will have been published and not identified by our search. Furthermore, in population-based prevalence studies publication bias seems to be less of a concern than e.g. in interventional studies. Thus, we believe that a bias due to unpublished data is unlikely.

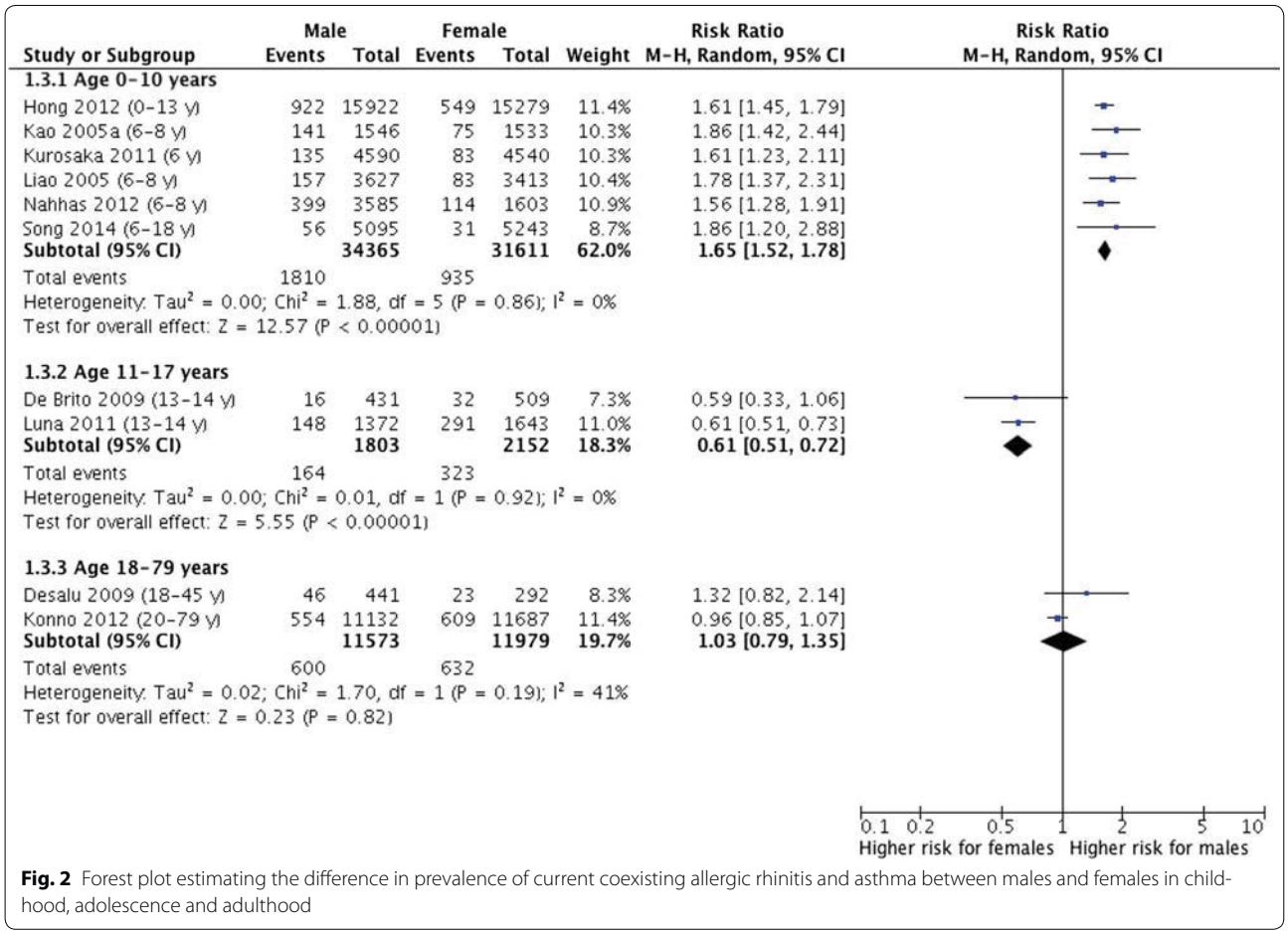

Fig. 2 Forest plot estimating the difference in prevalence of current coexisting allergic rhinitis and asthma between males and females in childhood, adolescence and adulthood

Our systematic review was embedded in a larger review considering the difference in prevalence for rhinitis only [3]. Although we used broad inclusion criteria, we may have missed studies that provided information on prevalence of having allergic rhinitis and asthma but did not provide information of having allergic rhinitis only or were published in journals that are not listed in the 2 major databases of medical literature, MEDLINE and EMBASE. Primary care-based studies including e.g. only out-patients were excluded because of a possible gender-related bias considering that women seek medical treatment, screening programs and other health care offers more often than men [34]. Restricting our search to studies published between 2000 and 2014 does not allow us to conclude on possibly different findings from earlier studies. The prevalence of allergies has dramatically increased in the second half of the twentieth century but reasons for these temporal trends are not clear [35]. We therefore wanted to avoid the rather speculative comparisons of prevalence studies across 5 and more decades and focused our evaluation on the 2 recent decades where the prevalence of allergies may have reached a plateau in many regions around the world [36].

Most of the included studies, especially in children, were conducted in Asia, which may limit the generalisability of the results, because of specific genetic differences between ethnic groups as well as different environmental factors for allergic diseases such as air pollution.

Our results showed that a sex switch from a male to a female predominance in the coexistence of allergic rhinitis and asthma is reported in population-based studies; however, further research is needed to study the underlying mechanisms. The definition of allergic rhinitis and asthma in our study is based on answers to validated questions from the ISAAC and ECRHS projects. Though these instruments are widely used globally and well validated in many languages especially for asthma, a possible overestimation of asthma or allergic rhinitis prevalence cannot be excluded. However, we do not think that this affects the male–female-ratios of the prevalence estimates used in our analysis since there is no indication for different overestimation between male and female responders of the included questions.

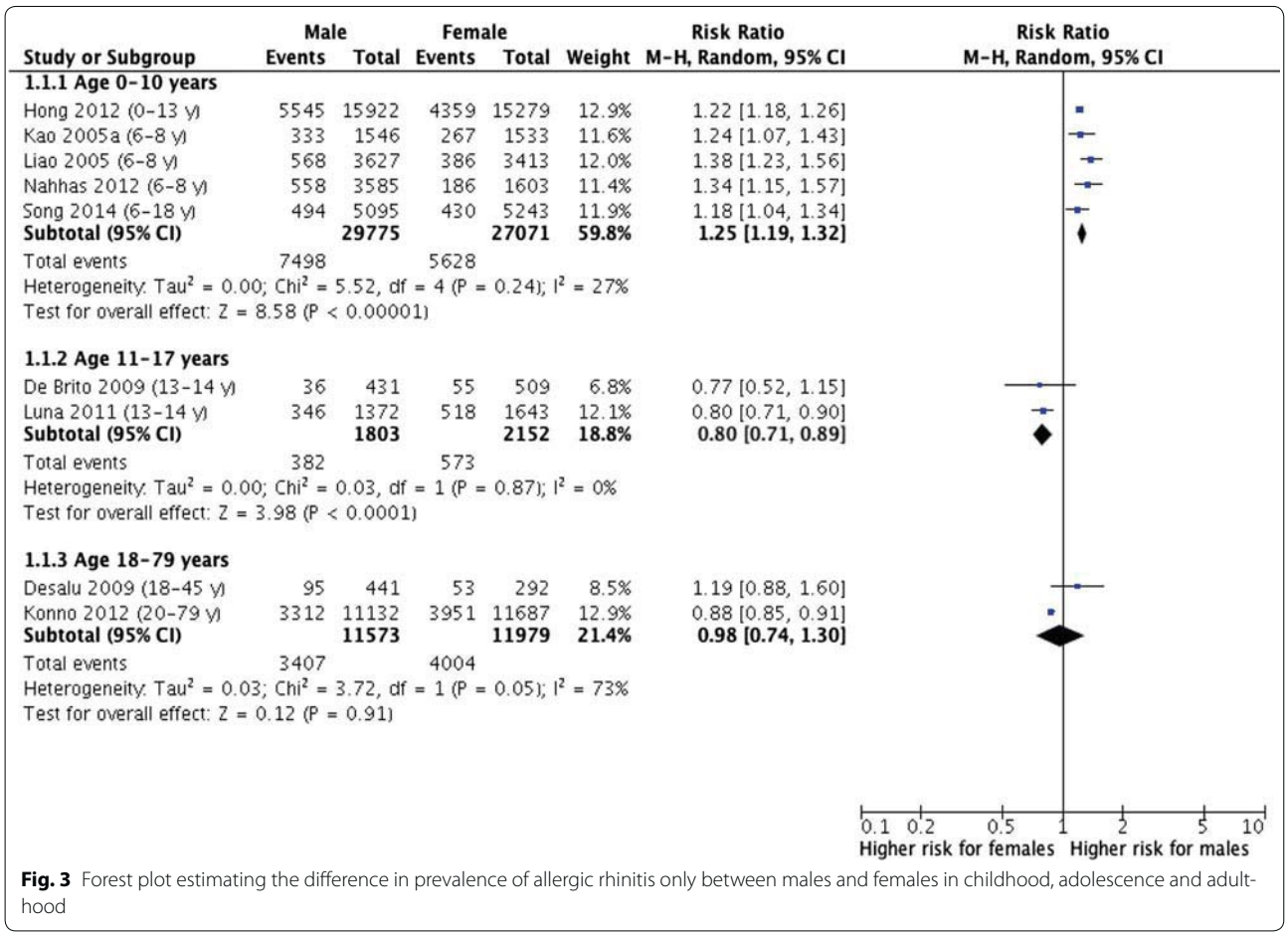

Fig. 3 Forest plot estimating the difference in prevalence of allergic rhinitis only between males and females in childhood, adolescence and adulthood

Using *current symptoms* of asthma and allergic rhinitis as outcome definition may cause misclassification if classifying individuals without symptoms because of successful symptom control for example as negative. However, we consider it unlikely that a person using e.g. anti-obstructive medication on a daily basis would answer negative to the question for having wheeze during the last 12 months. While, on the contrary, we judge the usage of doctor's diagnosis to result in an underestimation of the number of subjects with allergic diseases.

Though there were many studies using the ISAAC study-design only few studies fulfilled our stringent inclusion criteria. This shows that there is a need for a more multimorbid perspective in population-based studies. For this work, we identified only cross-sectional studies. Although this study design is adequate for estimating population-based prevalences, longitudinal studies would be of interest to examine possible mechanisms underlying these differences in prevalence. Therefore, birth cohort studies in particular, are currently being evaluated regarding sex-specific allergy prevalence differences in childhood and early adolescence within the MeDALL project [37, 38].

Considerable inconsistency was found solely in our meta-analyses for asthma only and for the 2 adult studies as indicated by the Higgins' I^2-tests. These summary measures of the meta-analyses should be interpreted with extra caution. Potential sources of heterogeneity include study design, study area or analysed age groups, but the specific influence cannot be examined due to the limited number of studies.

Conclusions

Based on a systematic review with meta-analysis of cross-sectional population-studies from across the globe we found a clear male predominance for the prevalence of coexisting allergic rhinitis and asthma in childhood. This seems to shift towards a female predominance in adolescents. Such a shift was less pronounced for allergic rhinitis as a single entity. Our results suggest that the effect of puberty seems to be particularly present in the most severely affected patients who have both allergic rhinitis and concurrent asthma. However, sex- and gender-specific evaluations beyond 14 years of age are scarce and further allergic multimorbidity studies in different

population settings, particularly in adults, are required. In clinical, epidemiological and basic research more sex- and gender-specific analyses are needed to develop better prevention and treatment strategies.

Additional file

Additional file 1: Search terms. Search terms and equations used for the original review [3] in PubMed and Embase databases. **Table E1** Characteristics of the included studies assessing prevalence of coexisting allergic rhinitis and asthma in children (0 – 10 y). **Table E2** Characteristics of the included studies assessing prevalence of coexisting allergic rhinitis and asthma in adolescents (11 – 17y). **Table E3** Characteristics of the included studies assessing prevalence of coexisting allergic rhinitis and asthma in adults (18 – 79 y). **Table E4** Study quality assessment of the included studies. **Table E5** Main results of included studies.

Abbreviations
ECRHS: European Community Respiratory Health Survey; ISAAC: International Study of Asthma and Allergies in Childhood; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Authors' contributions
Conceived and designed the experiments: MF, MP, TKei and SR. Performed the experiments: MF, MP, CH, AR, TKel, BC. Data analysis and/or interpretation of the systematic review: MF, TKel, AR, Tkei and SR. Wrote the paper: all authors. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
As data for our meta-analysis we used only previously published results and information from the included studies but no raw data, i.e. individual participant data. Therefore, only meta-analysis data would be available.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Not applicable.

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2.2. Akupunktur als Behandlung bei allergischen Erkrankungen

2.2.1. Acupuncture in patients with seasonal allergic rhinitis: a randomized trial

Brinkhaus B, Ortiz M, Witt CM, **Roll S**, Linde K, Pfab F, Niggemann B, Hummelsberger J, Treszl A, Ring J, Zuberbier T, Wegscheider K, Willich SN. Acupuncture in patients with seasonal allergic rhinitis: a randomized trial. Ann Intern Med. 2013 Feb 19;158(4):225-34. https://doi.org/10.7326/0003-4819-158-4-201302190-00002

Ziel der Studie war die Bestimmung der Wirksamkeit von Akupunktur bzgl. der Rhinitis-bezogenen Lebensqualität sowie des Verbrauchs an Bedarfsmedikation bei Patienten mit saisonaler allergischer Rhinitis.

In diese randomisiert kontrollierte, dreiarmige, multizentrische Studie wurden zu Beginn der Pollensaison 422 Patienten mit allergischer Rhinitis im Verhältnis 2:1:1 randomisiert zugeteilt zu einer der drei Gruppen:

- Akupunktur und Bedarfsmedikation (n=212),
- Scheinakupunktur und Bedarfsmedikation (n=102),
- nur Bedarfsmedikation (n=108).

Eingeschlossen wurden Patienten im Alter von 16 bis 45 Jahren mit klinisch manifester und positiv getesteter saisonaler allergischer Rhinitis bzgl. Birken- und Gräserpollen.

Patienten der Akupunktur- und Scheinakupunkturgruppe erhielten innerhalb von 8 Wochen 12 Behandlungen. Die Akupunktur erfolgte semi-standardisiert mit verschiedenen obligatorischen sowie fakultativen Akupunkturpunkten, jeweils mit manueller Stimulation. Die Scheinakupunktur (auch Sham-Akupunktur genannt) erfolgte an Nicht-Akupunkturpunkten mit nur oberflächlicher Einbringung und ohne manuelle Stimulation der Nadel.

Patienten der Akupunktur- und Scheinakupunkturgruppe waren verblindet gegenüber ihrer Behandlung (Akupunktur vs. Scheinakupunktur). Patienten der Bedarfsmedikationsgruppe erhielten keine spezifische Behandlung. Patienten aller drei Gruppen konnten bei Bedarf orale Antihistaminika bzw. orale Steroide verwenden.

Die beiden co-primären Endpunkte waren Rhinitis-bezogene Lebensqualität (Rhinitis Quality of Life Questionnaire, RQLQ) und die Verwendung von Bedarfsmedikation (Rescue medication score, RMS) nach 8 Wochen. Sekundäre Endpunkte beinhalteten Symptome der allergischen Rhinitis und allgemeine gesundheitsbezogene Lebensqualität (SF-36). Endpunkte wurden nach 8 und 16 Wochen, sowie zu Woche 8 ein Jahr nach der Intervention (Woche 60) erhoben.

Es zeigte sich eine Verbesserung der Rhinitis-bezogenen und allgemeinen Lebensqualität sowie eine Verringerung der Bedarfsmedikation der Akupunkturgruppe gegenüber der Schein- und der reinen Bedarfsmedikationsgruppe. Zusätzlich verbesserten sich die Symptome in der Akupunkturgruppe gegenüber der Scheinakupunkturgruppe und der Gruppe ohne Akupunktur nach 8 Wochen. Positive Effekte wurden in leicht abgeschwächter Form zum Teil sogar im nachfolgenden Jahr gesehen. Für Patienten mit saisonaler allergischer Rhinitis bzgl. Birken- und Gräserpollen bedeutet dies, dass sich durch eine relativ sichere, nicht-medikamentöse Behandlung sowohl eine Verbesserung ihrer Lebensqualität und ihrer Symptome erreichen lässt, bei gleichzeitiger Reduktion der Einnahme von oralen Antihistaminika.

Brinkhaus B, Ortiz M, Witt CM, Roll S, Linde K, Pfab F, Niggemann B, Hummelsberger J, Treszl A, Ring J, Zuberbier T, Wegscheider K, Willich SN. Acupuncture in patients with seasonal allergic rhinitis: a randomized trial. Ann Intern Med. 2013 Feb 19;158(4):225-34. https://doi.org/10.7326/0003-4819-158-4-201302190-00002

2.2.2. Cost-effectiveness for acupuncture in seasonal allergic rhinitis: economic results of the ACUSAR trial

Reinhold T, **Roll S**, Willich SN, Ortiz M, Witt CM, Brinkhaus B. Cost-effectiveness for acupuncture in seasonal allergic rhinitis: economic results of the ACUSAR trial. Ann Allergy Asthma Immunol. 2013 Jul;111(1):56-63. https://doi.org/10.1016/j.anai.2013.04.008

Nachdem die Wirksamkeit der Akupunktur als Behandlung zur Verbesserung der Lebensqualität, Symptome und Medikationsbedarf bei Patienten mit allergischer Rhinitis gezeigt wurde, sollten zudem Kosten und Kosteneffektivität der Akupunktur untersucht werden. Dazu wurden in der Studie in 2.2.1 (randomisiert kontrollierte, dreiarmige, multizentrische Studie) die direkten und indirekten krankheitsspezifischen Kosten aus gesellschaftlicher Perspektive sowie die direkten krankheitsspezifischen Kosten aus Perspektive der Sozialversicherung für einen Zeitraum über 8 bzw. 16 Wochen bestimmt. Der Zeitraum von 16 Wochen wurde verwendet, da Teilnehmer der Kontrollgruppe 8 Wochen nach Studienbeginn ebenfalls die Möglichkeit hatten Akupunktur zu erhalten (sog. Wartelistenkontrolle) und daher gesundheitsökonomischen Analysen auch im Zeitraum der zweiten 8 Wochen szenariobasiert modelliert wurden.

Als Maß der Effektivität für die gesundheitsökonomische Analyse wurden qualitätsadjustierte Lebensjahre (quality-adjusted life-year, QALY) betrachtet, die aus den patientenberichteten Angaben zur allgemeinen, gesundheitsbezogenen Lebensqualität (SF-36) berechnet wurden. Als Maß der Kosteneffektivität wurde das inkrementelle Kosteneffektivitätsverhältnis (Incremental cost-effectiveness ratio, ICER) bestimmt. Dies ist definiert als die zusätzlichen Kosten für ein zusätzliches qualitätsadjustiertes Lebensjahr bei den Patienten mit Akupunktur im Vergleich zu den Patienten mit Scheinakupunktur bzw. nur Bedarfsmedikation. Von den initial 422 randomisierten Patienten standen für die Auswertung bei 364 Patienten vollständige Daten zu Kosten und Lebensqualität zu Verfügung.

Es ergaben sich höhere Kosten in der Akupunktur- und Scheinakupunkturgruppe als in Gruppe ohne Akupunktur. Diese Kosten wurden hauptsächlich durch die Intervention (Schein-/Akupunktur) verursacht. Zudem zeigten sich mehr qualitätsadjustierte Lebensjahre (QALYs) in der Akupunkturgruppe gegenüber der Gruppe ohne Akupunktur nach 8 Wochen. Je nach gesundheitsökonomischen Szenario und Zahlungsbereitschaft gilt die Akupunktur in dem beobachteten Zeitraum nicht als kosteneffektiv gegenüber nur Bedarfsmedikation, da die zur Beurteilung der Kosteneffektivität international üblichen Schwellenwerte der inkrementellen Kosteneffektivität teils deutlich überschritten wurden.

Reinhold T, Roll S, Willich SN, Ortiz M, Witt CM, Brinkhaus B. Cost-effectiveness for acupuncture in seasonal allergic rhinitis: economic results of the ACUSAR trial. Ann Allergy Asthma Immunol. 2013 Jul;111(1):56-63. https://doi.org/10.1016/j.anai.2013.04.008

3. Diskussion

Haustierhaltung und Geschlecht als Einflussfaktor für allergische Erkrankungen

Die Metaanalyse von individuellen, longitudinalen Rohdaten aus europäischen, bevölkerungsbasierten Geburtskohorten zeigte, dass die Haltung von Haustieren in den ersten Lebensjahren weder einen Risikofaktor noch einen protektiven Faktor für die Entstehung von Allergien darstellt. Aus primärpräventiver Sicht ist daher eine klare Empfehlung für oder gegen eine Haustierhaltung bei der Geburt eines Kindes nicht gegeben.

Die vorliegende Metaanalyse zum Einfluss von Haustierhaltung in Familien mit Säuglingen und Kleinkindern auf das kindliche Allergierisiko im Grundschulalter war bis dato die umfassendste und größte bevölkerungsbasierte Studie. Sie war auch aufgrund der vor der Analyse sorgfältig harmonisierten Rohdaten der beteiligten Geburtskohorten den Ergebnissen früherer Studien bzw. einer Metaanalyse von publizierten Effektschätzern aus sehr heterogenen Studien überlegen (Takkouche et al., 2008, Chen and Heinrich, 2009).

Eine neue Studie aus dem Jahr 2018 zeigte eine Dosis-Wirkungsabhängigkeit zwischen Haustierhaltung (Hunde oder Katzen) und dem Auftreten von Asthma oder Allergien bei Kindern (Hesselmar et al., 2018). Der Anteil an Kindern mit Asthma oder Allergie sank mit steigender Anzahl an Haustieren. Dies scheint im Widerspruch zu den Ergebnissen der vorliegenden Metaanalyse zu stehen. Die neuere Studie zur Dosis-Wirkungsbeziehung ignorierte jedoch wichtige Confounder, u.a. elterliches Asthma und Allergien. Es ist bekannt, dass Eltern mit allergischen Erkrankungen seltener Haustiere haben (reverse causation) (Anyo et al., 2002). Da eine elterliche Allergie jedoch einer der wichtigsten Prädiktoren für die Entstehung einer Allergie des Kindes ist, ist davon auszugehen, dass diese Ergebnisse ohne Berücksichtigung der elterlichen Erkrankungen verzerrt waren und somit nicht die vorliegenden Ergebnisse in Frage stellen. Eine weitere aktuelle Studie an 3781 finnischen Kindern zeigte hingegen einen protektiven Effekt von Hunden als Haustier in Bezug auf Asthma, allergische Rhinitis und allergische Sensibilisierung, während Katzenhaltung protektiv in Bezug auf das atopisches Ekzem war (Ojwang et al., 2020). Bei der Studie handelt es sich zwar ebenfalls um eine Geburtskohortenstudie, jedoch zum Thema Typ I Diabetes. Erst im Alter der Kinder von 5 Jahren erfolgte die Einladung zur Teilnahme am zusätzlichen Studienteil zu Allergien. Dadurch ist die Auswahl der Kinder vermutlich weniger repräsentativ. Zudem wurden die Ergebnisse nur für mütterliche Asthma- bzw. Allergiestatus adjustiert (nicht für den Erkrankungsstatus beider Eltern). Dennoch können diese neueren Ergebnisse durchaus eine Ergänzung der vorliegenden Metaanalyse darstellen. Zum einen deutete sich auch in unserer Metaanalyse ein Trend hin zu einem protektiven Effekt durch

Hundebesitz an, der jedoch das konventionelle Level für statistische Signifikanz verfehlte. Zum anderen wurde in der vorliegenden Metaanalyse das atopische Ekzem (Dermatitis) nicht untersucht, da ihr Fokus auf den unterschiedlichen Formen der allergischen Atemwegserkrankungen lag und bei der Erhebung des atopischen Ekzems zu viel Heterogenität zwischen den einzelnen Geburtskohorten bestand. Zu dieser Fragestellung bzgl. der Entstehung des atopischen Ekzems stehen Metaanalysen noch aus.

Ergebnisse der Metaanalysen der Geburtskohorten zeigten zudem, dass es sowohl für die Inzidenz als auch für die Prävalenz eine Verschiebung des Geschlechterverhältnisses von höheren Erkrankungszahlen von Allergien bei Jungen im Vergleich zu Mädchen vor der Pubertät zu einem eher ausgeglichenen Verhältnis nach Pubertätsbeginn gibt. Dies zeigte sich bisher auch in andern Studien (Kurukulaaratchy et al., 2011, Yao et al., 2011, Engelkes et al., 2015). Studien, die zusätzlich einen längeren Beobachtungszeitraum abdecken, kamen zudem zum Schluss, dass es nicht nur eine Angleichung des Geschlechterverhältnisses gibt, sondern eine Reversion, so dass mehr Mädchen bzw. Frauen über Asthma und Rhinitis berichteten (Anderson et al., 1992, Almqvist et al., 2008).

Stärken und potenzielle Limitationen

Die Stärke der hier verwendeten Metaanalysen, die auf individuellen Teilnehmerdaten (IPD) mehrerer europäischer Geburtskohorten basieren, lag insbesondere darin, dass Rohdaten der einzelnen Studien zu Verfügung standen. Im Gegensatz zu den klassischen Metaanalysen konnten hier alle Daten sowohl harmonisiert werden (d.h. Endpunkte und Einflussfaktoren konnten jeweils standardisiert definiert werden) als auch mit den gleichen statistischen Methoden ausgewertet werden. Dabei konnten insbesondere gleiche oder möglichst vergleichbare Adjustierungsvariablen verwendet werden. Insbesondere bei Beobachtungsstudien spielt eine adäquate, möglichst vollständige Adjustierung (durch die fehlende Möglichkeit zur Randomisierung) eine entscheidende Rolle. In klassischen Metaanalysen aus publizierten Studien werden hingegen Ergebnisse zusammengefasst, die evtl. auf unterschiedlich erhobenen Daten beruhen und zudem mit unterschiedlichen Auswertungsmethoden berechnet wurden. Dadurch ist eine methodische Vergleichbarkeit der einzelnen Studienergebnisse oft nicht gegeben ist (Tierney et al., 2015).

Eine weitere Stärke der hier dargestellten Metaanalysen mit individuellen Teilnehmerdaten ist die große Fallzahl von über 19.000 Teilnehmern. Im Vergleich zu Einzelstudien ist hierdurch eine hohe statistische Power gegeben, die zu präzisen Ergebnissen führt. Ebenfalls war es dadurch möglich, Subgruppen (z. Bsp. nach Haustiertyp oder nach elterlicher Erkrankung) valide zu beantworten.

Ein zusätzlicher Vorteil war die longitudinale Datenerhebung der Geburtskohorten über mehrere Jahre in verschiedenen europäischen Ländern. Damit können Änderungen im Auftreten der Erkrankungen über die Zeit auf individueller Ebene bestimmt werden. Ergebnisse dieser Analysen sind damit robuster als Ergebnisse, die auf einer Reihe von einzelnen Querschnittsstudien mit unterschiedlichen Studienteilnehmern beruhen.

Eine mögliche Limitation der Ergebnisse der Metaanalysen bestand in der generellen Schwierigkeit, die Ursache-Wirkungsbeziehung zwischen Haustierhaltung und Allergiestatus der Eltern zu erfassen. Die elterliche Erkrankung kann die Entscheidung für oder gegen die Haltung von Haustieren beeinflussen. Die Gründe für oder gegen eine Haustierhaltung in den Familien (insbesondere bezogen auf Allergien) wurden nicht erfasst. Um diese mögliche Verzerrung zu berücksichtigen, wurden unsere Analysen zumindest jedoch für das Vorliegen elterlicher Allergien adjustiert.

Die Daten der teilnehmenden Geburtskohorten basierten zudem auf unterschiedlich langen Follow-Up-Zeiträumen (6 bis 10 Jahre). Beim Vergleich der Ergebnisse der Kohorten mit kürzerem vs. längerem Follow-Up konnten jedoch keine relevanten Unterschiede gefunden werden; d.h. die Ergebnisse waren über die betrachteten Zeitpunkte homogen.

Bei den vorliegenden Metaanalysen, die auf individuellen Teilnehmerdaten basieren, konnte die Adjustierung für mögliche Confounder nicht in jeder Kohorte völlig identisch durchgeführt werden. Es standen nicht für alle Kohorten die gleiche Anzahl an Variablen zu Verfügung, da manche Kohorten mehr Variablen erhoben hatten als andere. Eine zusätzlich im Rahmen der Auswertung durchgeführte Sensitivitätsanalyse mit der minimalen Anzahl an Adjustierungsvariablen, die für alle Kohorten zu Verfügung stand, zeigte jedoch keine wesentliche Änderung der Ergebnisse.

Da in den meisten eingeschlossenen Geburtskohorten keine Angaben zur Anzahl an Haustieren vorlag, konnten bezüglich des Effekts der Haustierhaltung auf die Prävalenz von allergischen Erkrankungen keine Analysen zu Dosis-Wirkungsbeziehungen durchgeführt werden. Dies wäre jedoch, gerade in Beobachtungsstudien ein wichtiger Aspekt zur Kausalitätsbestimmung. Ebenfalls gab es keine vollständige Erfassung der gesamten Haustierexposition, z. Bsp. Exposition bei Großeltern, Freunden, etc. Damit ist es möglich, dass Teilnehmer fehlklassifiziert wurden.

Wie in jeder Studie, insbesondere jedoch bei Geburtskohorten zu spezifischen Erkrankungen, muss ein möglicher Selektionsbias durch die Selbstselektion der Teilnehmer berücksichtig werden (participation bias). So werden Eltern vermutlich eher an einer Studie teilnehmen, wenn sie selbst oder der Familienkreis von der zu untersuchenden Erkrankung betroffen sind. Für Studien zur reinen Prävalenz oder Inzidenz ist dies ein bedeutender Fehlerfaktor. Als Konsequenz des participation bias wird die

Prävalenz bzw. die Inzidenz überschätzt, da die genetische Disposition bei vielen Erkrankungen ein bedeutender Einflussfaktor ist. Bei Studien, die jedoch Zusammenhänge zwischen Risikofaktoren und Erkrankung untersuchen, sollte dieser Selektionsbias die Ergebnisse nicht verzerren; dies gilt insbesondere für die vorliegenden Geburtskohorten, in der die spezifische Untersuchung von Haustierhaltung zum Zeitpunkt des Einschlusses in die Studien nicht Teil der damaligen Forschungsfrage und damit Teilnehmerinformation war. Zusätzlich konnte in der Analyse der Kohorten für den Faktor „elterliche Erkrankung“ adjustiert werden. Dennoch ist unklar, wie repräsentativ die Studienergebnisse für die Allgemeinbevölkerung der jeweiligen Länder ist, da die der Mehrzahl der Geburtskohorten in Großstädten durchgeführt wurde (Keil et al., 2006).

Eine weitere Einschränkung ergibt sich durch die Art der Erhebung von Daten zum Erkrankungsstatus, die in den vorliegenden Studien per Fragebogen der Eltern erhoben wurden. Es wurden zwar die international häufig eingesetzten, standardisierten und validierten ISAAC-Fragen (ISAAC: International Study of Asthma and Allergies in Childhood) verwendet (Asher et al., 1995), dennoch sind Abweichungen der Selbstangaben der Eltern zu einer standardisierten Erhebung durch Ärzte möglich.

Ein Nachteil des longitudinalen Designs ist das Vorliegen fehlender Werte aufgrund von Drop-out. Bei einem unsystematischem Drop-out besteht das Problem lediglich in einer Verringerung der Fallzahl und damit der Reduktion der Power für die Analysen. Dies ist für die vorliegenden Metaanalysen aufgrund der hohen Fallzahl mit über 19.000 Teilnehmern jedoch kaum problematisch. Handelt es sich jedoch um einen systematischen Drop-out, könnte dies, je nach Muster und Ursache der fehlenden Werte, die Ergebnisse verzerren. Dies gilt generell für jede longitudinale Studie und ist in der Regel kaum quantifizierbar, da die Teilnehmer die Studienteilnahme jederzeit und ohne Angabe von Gründen beenden können.

Eine weitere Limitation der vorliegenden Auswertungen ist, dass nicht alle Daten der einzelnen Studien in gleichen, jährlichen Abständen verfügbar waren. Diese Heterogenität im Studiendesign ist ein häufig anzutreffendes Phänomen bei Metaanalysen. Durch die Verwendung der Rohdaten, konnten die unterschiedlichen Zeitpunkte der Datenerhebung pro Studie jedoch bei den Analysen zur Inzidenz und Prävalenz von allergischen Erkrankungen adäquat berücksichtigt werden.

Für die Untersuchungen zum Einfluss des Pubertätsstatus lagen für einen kleinen Teil der Kohorten die Daten nur bis zum Alter der Teilnehmer von 14 Jahren vor. Das bedeutet, dass zum Ende der Datenerhebung die Pubertät noch nicht für alle Teilnehmer abgeschlossen war. Langzeitdaten, die deutlich über die Pubertät hinausgehen, lagen noch nicht vor. Dies kann in nachfolgenden Analysen der nächsten Jahre weiter ausgewertet werden.

Bei der vorliegenden Metaanalyse, die nur publizierte Ergebnisse von Einzelstudien zur geschlechtsspezifischen Prävalenz erfasste und zusammenfügte, kann grundsätzlich ein möglicher Publikationsbias nicht ausgeschlossen werden. Nicht für jede durchgeführte Studie bzw. Analyse werden die Ergebnisse veröffentlicht (Thornton and Lee, 2000, Dickersin and Min, 1993). Zudem werden nicht alle Ergebnisse einer Studie berichtet (selective (non-)reporting bias) (Boutron et al., 2019, Page et al., 2019, Chan et al., 2004). Wenn die Veröffentlichung der Ergebnisse vom Ergebnis selbst abhängen, muss von einem Bias ausgegangen werden. Dies zeigt sich insbesondere bei Wirksamkeitsstudien, wenn Ergebnisse, die nicht den gewünschten Effekt zeigen, nicht veröffentlich werden. Da in die vorliegende Metaanalyse jedoch nur bevölkerungsbezogene Beobachtungsstudien eingeschlossen wurden, die in der Regel auf großen Fallzahlen basieren und weniger interessensbasiert sind, ist die selektive Nicht-Veröffentlichung von bedeutenden Studien – und damit das Vorliegen eines Publikationsbias – eher unwahrscheinlich.

Aus der Public-Health Perspektive muss zudem die große Heterogenität bisheriger Studienergebnisse zur Frage des Einflusses von Haustierhaltung auf allergische Erkrankungen berücksichtig werden. Da es nicht möglich ist, zu dieser Forschungsfrage randomisiert kontrollierte, doppelblinde Interventionsstudien durchzuführen, ist die Verfügbarkeit von valider Evidenz limitiert. Sämtliche Studienergebnisse basieren auf Beobachtungsstudien mit entsprechendem Risiko für Bias. Zusammenfassen scheint sich jedoch ableiten zu lassen, dass Haustierhaltung in den frühen Lebensjahren keinen relevanten Risikofaktor für allergische Erkrankungen bei Kindern im Schulalter darstellt. Zukünftige Studien sollten (zumindest als Sensitivitätsanalysen) möglichst gleichartige Auswertungs- und Adjustierungsmethoden verwenden und sich Dosis-Wirkungsbeziehungen widmen; Metaanalysen sollten mit individuellen Teilnehmerdaten, anstatt mit publizierten Ergebnissen, durchgeführt werden, um eine vergleichbare Methodik zu ermöglichen. Im Zeitalter der zunehmenden Verbreitung der Open-data-Bewegung kann dies zukünftig einfacher realisierbar werden.

Wirksamkeit und Kosten von Akupunktur bei der Behandlung von allergischer Rhinitis

In der dreiarmigen randomisiert kontrollierten Studie mit 422 Patienten mit saisonaler allergischer Rhinitis zeigte sich eine Verbesserung der Rhinitis-bezogenen und allgemeinen Lebensqualität und der Symptome sowie eine Verringerung der Bedarfsmedikation in der Akupunkturgruppe gegenüber der Scheinakupunkturgruppe und der Gruppe ohne Akupunktur nach 8 Wochen. Krankheitsspezifische Kosten waren in der Akupunktur- und Scheinakupunkturgruppe höher als in der Gruppe ohne Akupunktur; diese Mehrkosten waren hauptsächlich durch die Intervention verursacht.

Bisher haben nur wenige Studien die Wirksamkeit der Akupunktur bei allergischer Rhinitis untersucht. Insbesondere hatte dabei keine Studie die gemeinsame Betrachtung von krankheitsspezifischer Lebensqualität und der Verwendung von Bedarfsmedikation als co-primäre Endpunkte untersucht. Ohne die systematische Einbeziehung der Bedarfsmedikation sind Ergebnisse, die Unterschiede bzw. keine Unterschiede in den Behandlungsgruppen zeigen, jedoch nur eingeschränkt interpretierbar.

Generell ist bei Studien zu Akupunktur die Verblindung bzgl. der Intervention problematisch. Während bei Patienten (insbesondere bei Akupunktur-naiven Patienten) zumindest in den Gruppen der Akupunktur und Scheinakupunktur eine Verblindung möglich ist, sind Studienärzte grundsätzlich nicht verblindbar. Und auch bei einer Scheinakupunktur ist eine sichere Verblindung auf Patientenseite nicht immer gewährleistet, insbesondere, wenn Studienteilnehmer bereits zuvor Akupunktur erhalten haben. Damit sind Verzerrungen der Ergebnisse grundsätzlich nicht auszuschließen. Zusätzlich ist eine Scheinakupunktur kein echtes Plazebo, da durch die Penetration der Haut durch die Nadel physiologische Effekt unvermeidbar sind. Da der genaue Wirkmechanismus der Akupunktur sowohl bei allergischen Erkrankungen, als auch bei anderen Erkrankungen bisher nicht belegt ist, ist unklar, ob und in wie weit auch eine penetrierende Scheinakupunktur bereits physiologische Effekte hat.

Durch den saisonalen Charakter der Erkrankung sind Langzeiteffekte von Behandlungen generell schwer zu beurteilen. Nach Abschluss der Pollensaison sind die allergischen Symptome verschwunden, unabhängig davon ob und welche spezifische Behandlung durchgeführt wurde. Eine Langzeitevaluation von Endpunkten ist daher nur eingeschränkt möglich. Dies betrifft auch die Kosten und Kosteneffektivität, die in dieser Studie nur über einen Zeitraum von bis zu 16 Wochen analysiert wurden.

Zusätzlich ist bei multizentrischen Studien eine ungleiche Pollenexposition durch regionale Unterschiede wahrscheinlich. Manche Patienten mit saisonaler allergischer Rhinitis können daher regional stärker belastet sein als andere, was sich auf die Symptomatik und insbesondere auch auf die Rhinitis-bezogene Lebensqualität und die Einnahme der Begleitmedikation auswirken kann. Da die Randomisierung jedoch für den Faktor Zentrum stratifiziert wurde und die Studie über eine relativ hohe Fallzahl von insgesamt 422 Patienten verfügt, sollten sich solche regionalen Unterschiede ausgleichen.

Bei der Untersuchung von Kosten und Kosteneffektivität sind die Ergebnisse, im Gegensatz zur Untersuchung der Wirksamkeit, von variabel anzunehmenden Kostenschätzungen der Akupunktur abhängig. Eine Erhöhung oder Senkung der Interventionskosten z. Bsp. durch Änderungen der Gebührenordnung, hätte demnach eine direkte Auswirkung auf die Ergebnisse zur Kosteneffektivität einer Intervention. Insbesondere in dem Fall, dass das Ergebnis einer Interventionsstudie dazu führt,

dass eine Therapie als eine reguläre Leistung gesetzlicher Krankenkassen berücksichtigt wird, geht dies häufig mit Veränderungen der Interventionskostenhöhe einher. Dies beeinflusst direkt die kostenseitigen Ergebnisse einer Kosteneffektivitätsstudie. Zudem können geänderte Interventionskosten auch auf der Effektseite einen Einfluss haben. So ist es denkbar, dass eine geringere ärztliche Vergütung für die Durchführung einer Akupunktur das Behandlungsergebnis beeinflusst (z.B. geringere Motivation des Arztes). Ergebnisse von Kosteneffektivitätsstudien müssen demnach immer in ihrem jeweiligen Kontext bewertet werden.

Limitationen ergeben sich auch durch die Art der Kostenbewertung. Im Falle der ACUSAR Studie wurde der Ressourcenverbrauch der Studienpatienten mit einem Patientenfragebogen erfasst. Die hier dokumentierten Ressourcen (z.B. Zahl von Arztkontakten) wurde im Rahmen der Studienauswertung anschließend mit einheitlichen Standardkosten monetär bewertet. Dieser Ansatz reflektiert naturgemäß nicht die tatsächlich aufgetretenen Kosten und birgt das Risiko einer systematischen Über- oder Unterschätzung. Aus diesem Grund wird in aktuelleren gesundheitsökonomischen Studien zunehmend auch die Zusammenarbeit mit Kostenträgern angestrebt (z.B. Krankenkassen, Krankenhauscontrolling), die im Rahmen eines solchen Studienvorhabens deutlich detailliertere Kosteninformationen zur Verfügung stellen könnten. Im Falle der ACUSAR Studie war dies nicht möglich, da die Patienten der Studie in zahlreichen unterschiedlichen Krankenkassen versichert waren, was einen im Rahmen dieser Studie nicht-finanzierbaren administrativen Aufwand (z.B. für Datenlieferverträge, Datenschutz) erzeugt hätte.

Nur wenige Akupunkturstudien zu allergischer Rhinitis haben bisher Kosteneffektivitätsergebnisse berichtet. Trotz der Limitationen ist durch die relativ große Fallzahl und Randomisierung eine gute Abschätzung der wahren Kosteneffektivität möglich. Allerdings gilt diese nur für den beobachteten Zeitraum von 8 bzw. 16 Wochen, nicht für den beobachteten möglichen Langzeiteffekt der Akupunktur in darauffolgenden Jahr. Andererseits ist die externe Validität einer randomisiert kontrollierten Studie unklar; Daten der alltäglichen Routine bei Ärzten, die Akupunktur durchführen, können von in Studien erhobenen, experimentellen Bedingungen abweichen.

Zusammenfassend finden sich nach dieser Studie Hinweise für eine Wirksamkeit von Akupunktur bei Patienten mit saisonaler allergischer Rhinitis. Dieses Studienergebnis wird von anderen qualitativ hochwertigen Studien bestätigt (Choi et al., 2013, Xue et al., 2015), so dass eine Metanalyse folgerte, dass Akupunktur eine sichere und wirksame Therapie bei Allergischer Rhinitis sein kann (Feng et al., 2015). Inzwischen wurde Akupunktur auch in eine US-amerikanische HNO-Praxis Guideline aufgenommen (Seidman et al., 2015).

4. Zusammenfassung

Metaanalysen, die auf individuellen Teilnehmerdaten mehrerer großer, europäischer Geburtskohorten basierten, zeigten, dass die Haltung von Haustieren in der frühen Kindheit weder vor der Entstehung von Asthma oder allergischer Rhinitis im Schulalter schützt, noch einen Risikofaktor dafür darstellt. Die Stärke der Analysen bestand insbesondere darin, dass Rohdaten der einzelnen Studien zu Verfügung standen, sodass die Daten sowohl harmonisiert als auch mit den gleichen statistischen Methoden ausgewertet werden konnten.

Im Gegensatz zur Haustierhaltung scheint das Geschlecht eine Rolle bei der Entstehung von allergischen Erkrankungen Asthma und Allergische Rhinitis zu spielen. Dabei sind die Geschlechtsunterschiede je nach Alter unterschiedlich ausgeprägt. In jüngeren Jahren sind die Erkrankungen bei Jungen dominanter, während sich im Erwachsenenalter die Geschlechterunterschiede angleichen. Dies zeigt sich insbesondere bei Multimorbidität von Asthma und allergischer Rhinitis.

Als Behandlungsoption zeigte die Akupunktur in einer dreiarmigen, randomisiert kontrollierten Studie bei Patienten mit allergischer Rhinitis eine Verbesserung der krankheitsspezifischen Symptome und der Rhinitis-bezogenen und allgemeinen Lebensqualität im Vergleich zu einer Scheinakupunktur bzw. im Vergleich zur reinen Bedarfsmedikation nach 8 Wochen. Ebenso zeigte sich eine Reduktion der Einnahme der Begleitmedikation in der Akupunkturgruppe gegenüber den beiden Vergleichsgruppen. Zusätzlich wurden im nachfolgenden Jahr therapeutische Effekte in leicht abgeschwächter Form beobachtet. Die positiven klinischen Effekten gingen jedoch mit erhöhten behandlungs- und krankheitsbezogenen Kosten in der Akupunkturgruppe im Vergleich zur reinen Bedarfsmedikation einher. Das Verhältnis dieser zusätzlichen Kosten und der zusätzlich erzielten Effekte, würde jedoch, bei Zugrundelegung international üblicher Orientierungswerte zur gesellschaftlichen Zahlungsbereitschaft, nicht als kosteneffektiv eingestuft werden.

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,
- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

……. ……..

Datum Unterschrift

Dr. Stephanie Roll