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DISSERTATION

Einfluss von Geschlecht und Pubertätsbeginn auf Asthma, Rhinitis und respiratorische Multimorbidität im Kindes- und Jugendalter

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INHALTSVERZEICHNIS

1 Zusammenfassung

1.1 Abstrakt (deutsch)

Einführung. Rhinitis und Asthma sind chronisch-entzündliche Atemwegserkrankungen mit weltweit häufigem Auftreten bereits im Kindes- und Jugendalter. Bei der Asthma-Prävalenz scheint eine männliche Dominanz in der Kindheit zu bestehen, die von einer weiblichen Dominanz in der Jugend und im Erwachsenenalter abgelöst wird. Die Datenlage zur Prävalenz von Rhinitis und von respiratorischer Multimorbidität (d.h. dem gleichzeitigen Auftreten von Rhinitis und Asthma) ist dagegen unzureichend. Die vorliegende Dissertation untersuchte geschlechtsspezifische Prävalenzen und Inzidenzen von Rhinitis, Asthma und respiratorischer Multimorbidität vor und nach Pubertätsbeginn. **Methoden.** In einer systematischen Übersichtsarbeit mit Metaanalyse (Publikation I) wurden 6.540 Publikationen zu Rhinitis-Prävalenzen vom Kindes- bis Erwachsenenalter gescreent; 67 Publikationen erfüllten die Kriterien zum Einschluß in die Metaanalyse. Des Weiteren wurden zwei Metaanalysen zur Bestimmung der geschlechtsspezifischen Prävalenzen (Publikation II) und Inzidenzen (Publikation III) von Rhinitis, Asthma und respiratorischer Multimorbidität in Abhängigkeit vom Pubertätsstatus durchgeführt. Primärdaten internationaler bevölkerungsbasierter Geburtskohortenstudien mit über 18.000 rekrutierten Kindern konnten harmonisiert und analysiert werden. Spezifisches Immunoglobulin-E (IgE) gegen Aeroallergene wurde im Serum bestimmt, um für IgE- versus nicht-IgE-assoziierte Rhinitis, Asthma und respiratorische Multimorbidität zu stratifizieren. **Ergebnisse.** Publikation I zeigte für die Rhinitis-Prävalenz im Kindesalter eine Dominanz der Jungen und bei Jugendlichen und Erwachsenen eine Dominanz der weiblichen Teilnehmer. Die Publikationen II (Prävalenz) und III (Inzidenz) zeigten eine männliche Dominanz für Rhinitis, Asthma und respiratorischer Multimorbidität vor Pubertätsbeginn. Für IgE-assoziierte Rhinitis-Inzidenz blieb die männliche Dominanz auch nach Pubertätsbeginn bestehen (female/male Harzard Ratio (HR) 0,66; 95% Konfidenzintervall 0,54-0,80), während sich für die nicht-IgE-assoziierte Rhinitis-Inzidenz eine Tendenz zu einer weiblichen Dominanz zeigte (1,20; 0,98-1,47). Nach Pubertätsbeginn deutete sich für die Inzidenz von IgE-assoziiertem Asthma (0,77; 0,53-1,11) und IgE-assoziierter respiratorischer Multimorbidität (0,74; 0,50-1,08) eine Tendenz zu einem ausgeglicheneren

Geschlechterverhältnis an. Dies war deutlicher für die Inzidenzen von nicht-IgE-assoziiertem Asthma (1,23; 0,75-2,00) und nicht-IgE-assoziierter respiratorischer Multimorbidität (0,96; 0,54-1,71). Die Ergebnisse für die Prävalenzen waren ähnlich. **Diskussion.** Die vorliegenden Analysen großer bevölkerungsbezogener Datensätze zeigten, dass der Pubertätsbeginn das geschlechtsspezifische Auftreten respiratorischer Erkrankungen, insbesondere der nicht-IgE-assoziierten, beeinflusste. Weibliche Teilnehmer hatten nach Pubertätsbeginn im Vergleich zu vor Pubertätsbeginn ein erhöhtes Risiko für Asthma, Rhinitis und respiratorische Multimorbidität. Diese Erkenntnisse sollten nicht nur in der Grundlagenforschung bei der Aufklärung der den Allergien zugrundeliegenden Mechanismen berücksichtigt werden, sondern auch Implikationen für die klinische Forschung und Praxis haben. Um eine mögliche Unterversorgung zu vermeiden, bedarf es einer erhöhten Aufmerksamkeit bezüglich neuauftretender Rhinitis, Asthma und respiratorischer Multimorbidität bei weiblichen Patienten ab Pubertätsbeginn, insbesondere bei negativen IgE-Status und Skin-Prick-Test.

1.2 Abstract (english)

Introduction. Rhinitis and asthma are common chronic inflammatory airway diseases, which can start as early as in childhood or adolescence. For asthma the prevalence shows a male predominance during childhood whereas it switches to a female predominance starting after puberty-onset; data for rhinitis and respiratory multimorbidity (i.e. the co-occurrence of rhinitis and asthma) are scarce. The current dissertation investigated the possible sex-switch of incidences and prevalences of rhinitis, asthma and respiratory multimorbidity before and after puberty-onset in large international population-based datasets. **Methods.** In a systematic review and meta-analysis (publication I) 6,540 publications were screened for data of sex-specific rhinitis prevalences throughout the lifespan; 67 publications fulfilled the inclusion criteria for the meta-analyses. Additionally, two meta-analyses included population-based birth cohort studies with over 18,000 recruited children to determine sex-specific prevalences (publication II) and incidences (publication III) of rhinitis, asthma and respiratory multimorbidity before and after puberty-onset. The participants' status of serum Immunoglobulin-E (IgE) was assessed to stratify for IgE-associated versus non-IgE-associated rhinitis, asthma and respiratory multimorbidity. **Results.** Publication I

showed a male predominance in childhood compared to a female predominance in adolescence and adulthood for the rhinitis prevalence. Similarly, publications II (prevalence) and III (incidence) based on European birth cohorts found a male predominance in rhinitis, asthma and respiratory multimorbidity before puberty-onset. For IgE-associated incident rhinitis a male predominance remained after puberty-onset (female/male Hazard Ratio (HR) 0.66; 95%Confidence-interval 0.54-0.80); whereas, for non-IgE-associated incident rhinitis there was a tendency towards a female predominance (1.20; 0.98-1.47). IgE-associated incident asthma (0.77; 0.53-1.11) and IgE-associated incident respiratory multimorbidity (0.74; 0.50-1.08) showed a slight tendency towards a more sex-balanced distribution after puberty-onset. For non-IgE-associated incident asthma (1.23; 0.75-2.00) and respiratory multimorbidity (0.96; 0.54-1.71) the tendency towards a sex balanced distribution seemed more pronounced. The results for the prevalences were similar. **Discussion.** Independent of age, puberty-onset was related to a sex-switch of prevalence and incidence distribution patterns of rhinitis, asthma and respiratory multimorbidity, especially for non-IgE-associated conditions. Females had an increased risk for asthma, rhinitis and respiratory multimorbidity after puberty-onset compared to before puberty-onset. These results should be considered in basic scientific research to investigate underlying mechanism of allergies and also lead to implications in clinical research and practice. Clinicians should be attentive to detect incident respiratory diseases in adolescent girls for a timely diagnosis and treatment, especially with a negative IgE-status and skin prick test to avoid possible insufficient medical care in this patient group.

2 Einführung

2.1 Klassifikationen von Rhinitis und Asthma

Rhinitis und Asthma sind häufig auftretende „chronisch-entzündliche Erkrankungen“ der oberen beziehungsweise unteren Atemwege (Buhl et al., 2017, S. 853; Licari et al., 2017). Prävalenzen variieren je nach Land und Region im Kindes- und Jugendalter von unter fünf bis über 20% (Björkstén et al., 2008; ISAAC Steering Committee, 1998). Rhinitis wird in der Regel in atopische (allergische, intrinsische) versus nicht-atopische (nicht-allergische, extrinsische) und in lokale allergische Rhinitis unterschieden (Small et al., 2018; Licari et al., 2017). Infektiöse Rhinitis sowie Klassifikationen nach

Symptomdauer und Symptomstärke wurden in der vorliegenden Arbeit nicht berücksichtigt. Bei Asthma kann ebenfalls zwischen atopischen (allergischen, intrinsischen) und nicht-atopischen (nicht-allergischen, extrinsischen) Formen unterschieden werden (Buhl et al., 2017). Die Bezeichnung ‚atopisch' oder ‚allergisch' beschreibt klassischerweise die Nachweisbarkeit von Immunoglobulin-E (IgE) Antikörpern im Serum und/oder einen positiven Skin Prick Test. Problematisch bei dieser Klassifikation ist, dass das Fehlen einer systemischen Reaktion eine allergische Reaktion nicht zwangsläufig ausschließt. Beispielsweise scheint es bei der lokalen allergischen Rhinitis ausschliesslich eine lokale Produktion von IgE-Antikörpern im betroffenen Gewebe zu geben, die ohne systemische Reaktion einhergeht und damit auch nicht durch Serum-IgE Level und Skin Prick Test festgestellt werden kann (Small et al., 2018; Licari et al., 2017).

In der Publikation I der Dissertation (Pinart et al., 2017) wurde noch die Nomenklatur ‚allergische Rhinitis' verwendet. Für die Publikationen II (Keller et al., 2018) und III (Hohmann et al., 2019) und für den Manteltext der Dissertation wurden die primären Endpunkte als ‚Rhinitis', ‚Asthma' und ‚respiratorische Multimorbidität' (definiert als gleichzeitiges Auftreten von Rhinitis und Asthma) bezeichnet und umfassten dabei allergische sowie nicht-allergische Subklassen. Die sekundären Endpunkte wurden nach dem IgE-Antikörper Status im Serum (kurz: IgE- versus nicht-IgE-assoziierte Erkrankungen) stratifiziert.

2.2 Rhinitis und Asthma als respiratorische Multimorbidität

Rhinitis und Asthma sind inflammatorische Atemwegserkrankungen, die eine pathologische Einheit zu bilden scheinen und auch als „United Airway Disease" oder ‚Combined Allergic Rhinitis and Asthma Syndrome (CARAS)' bezeichnet werden (Al-Ahmad, 2015). Häufig wird ein gemeinsames Auftreten der Erkrankungen beobachtet. Zwischen 50 bis 77% von Asthmapatienten berichten auch an einer allergischen Rhinitis erkrankt zu sein und zwischen 7 bis 22% der Rhinitispatienten berichten auch an Asthma erkrankt zu sein (Leynaert et al., 2004). Asthmapatienten mit allergischer Rhinitis haben schwerere Asthmasymptome sowie eine schlechtere Asthmakontrolle als Patienten, die ausschließlich an Asthma leiden (Porsbjerg et al., 2017). Die oberen und unteren Atemwege weisen anatomische Gemeinsamkeiten auf und auch einige der Krankheitsmechanismen von Rhinitis und Asthma sind ähnlich (Licari et al., 2017). Bei

Allergenexposition erfolgt in beiden Fällen eine Aktivierung des adaptiven Immunsystems und histologische Befunde beider Erkrankungen weisen makroskopische und histologische Ähnlichkeiten auf. Das Ansprechen beider Erkrankungen auf Allergenvermeidung, Hyposensibilisierung und Anti-IgE-Behandlung scheinen einen gemeinsamen Ansatz der Diagnostik und Therapie weiter zu rechtfertigen (Licari et al., 2017). In der vorliegenden Arbeit wird das gleichzeitige Auftreten von Rhinitis und Asthma im Weiteren als ‚respiratorische Multimorbidität' bezeichnet.

2.3 Der Einfluss von Geschlecht und Pubertätsbeginn

Im Kindesalter sind mehr Jungen als Mädchen von Asthma betroffen. Dieses Verhältnis gleicht sich im Jugend- bis ins Erwachsenenalter mindestens an (Almqvist et al., 2008; Postma, 2007). Es gibt Hinweise, dass auch allergische Rhinokonjunktivitis und respiratorische Multimorbidität in der Kindheit häufiger bei Jungen als bei Mädchen zu vorzufinden sind (Belgrave et al., 2014; Moyes et al., 2012). Für allergische Rhinokonjunktivitis zeigt sich, ähnlich wie bei Asthma, eine Zunahme der Erkrankungshäufigeit bei Mädchen im Jugendalter (Moyes et al., 2012). Zu Rhinitis und respiratorischer Multimorbidität gibt es kaum Längsschnittstudien. Bisherige Studienergebnisse lassen vermuten, dass die Verschiebung der geschlechtsspezifischen Erkrankungsprävalenzen um den Zeitpunkt des Pubertätsbeginns einsetzt (Fröhlich et al. 2017; Almqvist et al., 2008; Postma, 2007). Dies würde für die unterschiedlichen Erkrankungsprävalenzen von Jungen und Mädchen hormonelle Einflüsse als potentielle Mechanismen nahelegen.

3 Methodik

3.1 Methoden der Publikation I

Die systematische Übersichtsarbeit mit Metaanalyse ‚Sex-related Allergic Rhinitis Prevalence Switch from Childhood to Adulthood: A Systematic Review and Meta-Analysis' (Pinart et al., 2017, im Weiteren ‚Publikation I') wurde nach dem PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)-Leitfaden durchgeführt. Der primäre Endpunkt war die Prävalenz von Rhinitis, stratifiziert nach Alter und Geschlecht in populationsbasierten Querschnittsstudien (Pinart et al., 2017).

Die finale Literatursuche wurde am 3. Juni 2014 durchgeführt. Die systematische Suchstrategie in den medizinischen Datenbanken MEDLINE (mit dem Anbieter Pubmed) und EMBASE berücksichtigte Schlagwortregister (z.B. MeSH) und Fachbegriffe als Freitext. Ergänzend wurden Referenzen eingeschlossener Artikel per Handsuche nach zusätzlichen Publikationen durchsucht. Die Inhalte identifizierter Studienduplikate wurden als eine einzelne Publikation behandelt (Pinart et al., 2017).

Auswahl der Publikationen und Datenextraktion. Einschlusskriterien für die identifizierten Publikationen waren: 1) Studienpopulation ist die Allgemeinbevölkerung einschließlich aller Altersgruppen, 2) originäre Forschungsergebnisse, 3) Studiendesign sind Kohortenstudien (querschnittliche Ergebnisse werden berichtet) und Querschnittsstudien, 4) Publikation enthält Ergebnisse zur Prävalenz und/oder Inzidenz von Rhinitis stratifiziert nach Alter und Geschlecht (Pinart et al., 2017).

Die Auswahl der Publikationen erfolgte in zwei Schritten. Zwei unabhängige Reviewer überprüfen die Titel und Zusammenfassungen der Publikationen nach den oben genannten Einschlusskriterien und alle eingeschlossenen und ‚unklaren' Publikationen wurden als Volltexte bestellt. In einem zweiten Schritt überprüften zwei unabhängige Reviewer jeden Volltext nach den oben genannten Einschlusskriterien und der finale Ein- oder Ausschluss der Publikation wurde bestimmt. In beiden Schritten wurden Unstimmigkeiten der Gutachter diskutiert und gegebenenfalls durch das Hinzuziehen eines dritten Reviewers im Konsensusverfahren gelöst (Pinart et al., 2017).

Die Datenextraktion der Volltexte wurde jeweils von zwei unabhängigen Gutachtern zu prädefinierten Informationen (beispielsweise zu Studienort und -region, Studiendesign, primären Endpunkten) durchgeführt. Unstimmigkeiten in der Datenextraktion zwischen den Reviewern wurden durch Diskussion und, wenn notwendig, durch den Einbezug eines dritten Reviewers gelöst. Fehlende oder nicht eindeutige Informationen zu Endpunkten wurden, wenn möglich, von den Autoren der Publikation erfragt (Pinart et al., 2017).

Statistische Analysen. Für die statistischen Analysen wurden die Softwarepakete R Version 3.1.2 (R Foundation for Statistical Computing) und STATA 12.0 (Stata Corporation, College Station, TX, USA) genutzt. Metaanalysen wurden mit dem Random Effekt-Modell mit Inverser-Varianz-Methode durchgeführt, um eine erwartete

Heterogenität zwischen den Studien zu berücksichtigen. Zur Erfassung der geschlechts- und altersspezifischen Verteilung der Rhinitis-Prävalenzen wurden jeweils für das Kindes- (bis zehn Jahre), Jugend- (zehn bis 18 Jahre) und Erwachsenenalter (älter als 18 Jahre) gepoolte Schätzer für das male/female ratio (MFR) mit 95%-Konfidenzintervallen (95%KI) berechnet. I^2 wurde als Maß für die Studienheterogenität verwendet. Um Einflussfaktoren für die Heterogenität zwischen den Studien zu untersuchen, wurde eine Meta-Regressionsanalyse mit den Moderatorvariablen Studienzeitraum (vor 2000 versus nach 2000), Studienregion (Kontinent) und Wohnsitz (urban versus gemischt urban/ländlich) verwendet (Pinart et al., 2017).

3.2 Methoden der Publikationen II und III

Die analysierten Daten der Publikationen ‚The sex-shift in single disease and multimorbid asthma and rhinitis during puberty – a study by MeDALL' (Keller et al., 2018, im Weiteren ‚Publikation II) und ‚Sex-specific incidence of asthma, rhinitis and respiratory multimorbidity before and after puberty onset: individual participant meta-analyses of five birth cohorts collaborating in MeDALL' (Hohmann et al., 2019, im Weiteren ‚Publikation III') waren größtenteils deckungsgleich. Die Daten der Publikationen II und III entstammten den gleichen Geburtskohortenstudien aus dem von der Europäischen Union geförderten Projekt ‚Mechanisms of the Development of Allergy' (MeDALL) und es gab einen gemeinsamen Prozess der Datengewinnung. Die folgenden Unterkapitel beschreiben somit, sofern nicht anders angegeben, das methodische Vorgehen für beide Publikationen.

Harmonisierung der Daten und Ergebungsinstrumente. Im EU-Projekt MeDALL wurden für 14 europäische Geburtskohortenstudien drei harmonisierte Hauptfragebögen entwickelt und in die Landessprachen übersetzt: i) Elternfragebogen für Eltern mit Kindern von 4-9 Jahren, ii) Elternfragebogen für Eltern mit Jugendlichen von 14-18 Jahren und iii) Fragebogen für Jugendliche von 14-18 Jahren. Außerdem wurden harmonisierte Standard Operating Procedures (SOPs) für die Messungen von Größe, Gewicht, Dermatitis-Erfassung, FeNO- und Spirometrie-Messungen, DNA-Extrahierung und Gewinnung von Serum-Proben erstellt (Hohmann et al., 2014). Daten früherer Erhebungszeitpunkte der teilnehmenden Geburtskohorten wurden retrospektiv harmonisiert und, zusammen mit den Daten des gemeinsamen Follow-Ups, in einer zentralen Datenbank gespeichert (Hohmann et al., 2014).

Auswahl der Geburtskohorten. Die Einschlusskriterien für die Auswahl der Geburtskohorten für die Analysen der Publikationen II und III waren: „i) mindestens eine Erhebung von Daten zu Rhinitis und Asthma von der Geburt bis zehn Jahren, ii) mindestens eine Erhebung von Daten zu Rhinitis und Asthma im Alter von elf bis 18 Jahren, iii) mindestens eine Erhebung von spezifischem Serum-IgE gegen Aeroallergene, iv) mindestens eine Erhebung von Daten zur Pubertätsentwicklung im Alter von zehn Jahren oder älter“ (Keller et al., 2018, Übersetzung durch den Autor). Für die Publikation III gab es das zusätzliche Einschlusskriterium vi) „maximaler Zeitraum von 5 Jahren zwischen konsekutiven Erhebungsdaten von jeweils Asthma und Rhinitis“ (Hohmann et al., 2019, Übersetzung durch den Autor).

Primäre und sekundäre Endpunkte. Die jeweils drei primären Endpunkte waren geschlechtsspezifische Prävalenzen (Publikation I) und geschlechtsspezifische Inzidenzen (Publikation II) von Rhinitis, Asthma und respiratorischer Multimorbidität. Für die Auswertung der sechs sekundären Endpunkte wurden die geschlechtsspezifischen Prävalenzen (Publikation II) und Inzidenzen (Publikation III) jeweils stratifiziert nach IgE- versus nicht-IgE-assoziiertem Asthma, IgE- versus nicht-IgE-assoziierter Rhinitis und IgE- versus nicht-IgE-assoziierter respiratorischer Multimorbidität (Hohmann et al. 2019; Keller et al. 2018).

1) Rhinitis wurde definiert als eine positive Antwort auf die Frage (originäre ISAAC-Frage, entnommen aus den englisch-sprachigen MeDALL-Fragebögen, Hohmann et al., 2014): *“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?”* (Hohmann et al. 2019; Keller et al. 2018).

2) Asthma wurde definiert als eine positive Antwort auf mindestens zwei der drei folgenden Fragen (entnommen aus den englisch-sprachigen MeDALL-Fragebögen, Hohmann et al., 2014): i) *“Has your child (/Have you) ever been diagnosed by a doctor as having asthma?”,* ii) *“Has your child (/Have you) had wheezing or whistling in your chest at any time in the last 12 months?” (yes/no)* und iii) *“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?”* (Hohmann et al. 2019; Keller et al. 2018).

3) Respiratorische Multimorbidität wurde definiert als das zeitgleiche Auftreten von Asthma und Rhinitis, ebenfalls bezogen auf die letzten 12 Monate vor der Erhebung (Hohmann et al., 2019; Keller et al., 2018).

Inzidenz wurde definiert als ein erstmaliger positiver Status der jeweiligen Erkrankung zum aktuellen Erhebungszeitpunkt. Ein negativer Status der Inzidenz wurde bestimmt als ein negativer Status der jeweiligen Erkrankung zum aktuellen sowie auch zu allen vorherigen Erhebungszeitpunkten (Hohmann et al., 2019).

Bestimmung des Pubertätsbeginns. Der Pubertätsstatus wurde von den Geburtskohorten mit der ‚Pubertal Development Scale' (PDS) oder mit an diesem Erhebungsinstrument angelehnten Fragen erhoben. Für die Jungen wurden die Fragebogen-Items ‚Entwicklung der Schambehaarung', ‚Einsetzen des Stimmbruchs' und ‚Entwicklung der Bartbehaarung', für die Mädchen die Items „Entwicklung der Schambehaarung', ‚Einsetzen der Menstruation" und ‚Brustentwicklung' verwendet (Hohmann et al., 2019; Keller et al., 2018). Jedes Item wurde auf einer Drei- oder Vier-Punkt Likert-Skala beantwortet (Carskadon und Acebo, 1993). Aus der Addition der Werte resultierten fünf Pubertätsstadien, die für die Analysen der Publikationen II und III zu einer dichotomen Variable zusammengefasst wurden: ‚nein' (Pubertätsstadien 'präpubertär' und 'frühe Pubertätsphase') versus ‚ja' (Pubertätsstadien 'mittlere Pubertätsphase', 'späte Pubertätsphase'' und 'Pubertät abgeschlossen') (Hohmann et al., 2019; Keller et al., 2018).

Confoundervariablen (Störgrößen). In den Metaanalysen der Publikationen II und III wurde für die möglichen Confounder i) ‚Alter der Teilnehmer', ii) ‚elterlicher Allergiestatus' (positiv wenn mindestens ein Elternteil eine positive Rhinitis- und/oder Asthma-Anamnese berichtet), iii) ‚Rauchen der Mutter in der Schwangerschaft' (ja/nein) und iv) ‚Geburtskohorte' kontrolliert (Hohmann et al., 2019; Keller et al., 2018).

Statistische Analysen. Für die Analysen der Publikationen II und III wurden SAS, Version 9.4 (SAS Institute, Cary, NC, USA) und R, Version 3.1.2 (R Foundation for Statistical Computing) verwendet. Bei fehlenden Werten erfolgte ein listenweiser Fallausschluss. Berechnete p-Werte wurden in beiden Publikationen nicht konfirmativ interpretiert, alle statistischen Analysen waren explorativ und es wurde nicht für multiples Testen adjustiert (Hohmann et al., 2019; Keller et al., 2018).

Statistische Analysen der Publikation II. Die individuellen Rohdaten von sechs Geburtskohorten wurden gepoolt und in einer einstufigen Individual Participant Data (IPD)-Metaanalyse ausgewertet. Dazu wurden adjustierte female/male Odds Ratios (OR) und 95%-Konfidenzintervalle (KI) mittels verallgemeinerten Schätzgleichungen (Generalized estimating equations, GEE) mit den Faktoren Geschlecht, Pubertät, und dem Interaktionsterm ‚Geschlecht*Pubertät' sowie einer Kohorten-Identifikationsvariable für alle primären und sekundären Endpunkte berechnet. Pro Endpunkt wurden zwei ORs berechnet; ein OR zur Darstellung der geschlechtsspezifischen Chance vor Pubertätsbeginn zu erkranken versus ein OR zur Darstellung der geschlechtsspezifischen Chance nach Pubertätsbeginn zu erkranken.

Statistische Analysen der Publikation III. Daten von fünf Geburtskohorten wurden in einer einstufigen IPD-Metaanalyse gepoolt und ausgewertet. Adjustierte female/male Hazard Ratios (HR) und 95%-Konfidenzintervalle (KI) wurden mit Proportional Hazard-Modellen mit dem Interaktionsterm ‚Geschlecht*Pubertät' für alle primären und sekundären Endpunkte berechnet. Die Variable ‚Pubertät' wurde als zeitabhängige Kovariate in das Modell eingeschlossen. Pro Endpunkt wurden zwei HRs berechnet; eins zur Darstellung des geschlechtsspezifischen Hazards der jeweiligen Erkrankung vor Pubertätsbeginn und eins zur Darstellung des geschlechtsspezifisches Hazards nach Pubertätsbeginn. Um Kohortencluster zu berücksichtigen wurde eine Kohorten-Identifikationsvariable als Kovariate in die Analyse mitaufgenommen. Teilnehmerdaten wurden zum aktuellen Erhebungszeitpunkt zensiert, wenn bereits zu einem früheren Erhebungszeitpunkt ein positiver Status der Inzidenz bestimmt wurde (Hohmann et al., 2019).

4 Ergebnisse

4.1 Hauptergebnisse der Publikation I

Die elektronische Suche plus Handsuche ergaben 6.540 geeignete Publikationen. Das Screenen der Titel und Zusammenfassungen sowie der Volltexte reduzierte die Anzahl auf 86 geeignete Publikationen. 35 Publikationen stammten aus Asien, 28 aus Europa, 16 aus Amerika, fünf aus Afrika und zwei der Publikationen stammten aus Ozeanien.

Geeignet für den Einschluss in die Metaanalyse waren 67 Publikationen (Pinart et al., 2017).

Für die Metaanalyse zur geschlechtsspezifischen Prävalenz von Rhinitis bei Kindern bis 10 Jahren konnten Daten aus 35 Publikationen mit insgesamt 133.885 Jungen und 135.152 Mädchen verwendet werden: der gepoolte Schätzer des Male/Female Ratios (MFR) war 1,21 (95%KI 1,17-1,25). Für die Metaanalyse für die geschlechtsspezifische Prävalenz von Rhinitis von Jugendlichen von 11 bis 18 Jahren wurden Daten aus 36 Publikationen mit insgesamt 137.443 männlichen und 142.939 weiblichen Teilnehmern verwendet (MFR 0,90; 95%KI 0,85-0,95). Für Erwachsene (älter als 18 Jahre) wurden Daten aus sieben Publikationen mit insgesamt 20.398 männlichen und 23.690 weiblichen Teilnehmern verwendet (MFR 0,96; 95%KI 0,83-1,10). Der gepoolte Schätzer der jugendlichen und erwachsenen Teilnehmer war MFR 0,91 (95%KI 0,86-0,95) (Pinart et al., 2017).

4.2 Hauptergebnisse der Publikation II

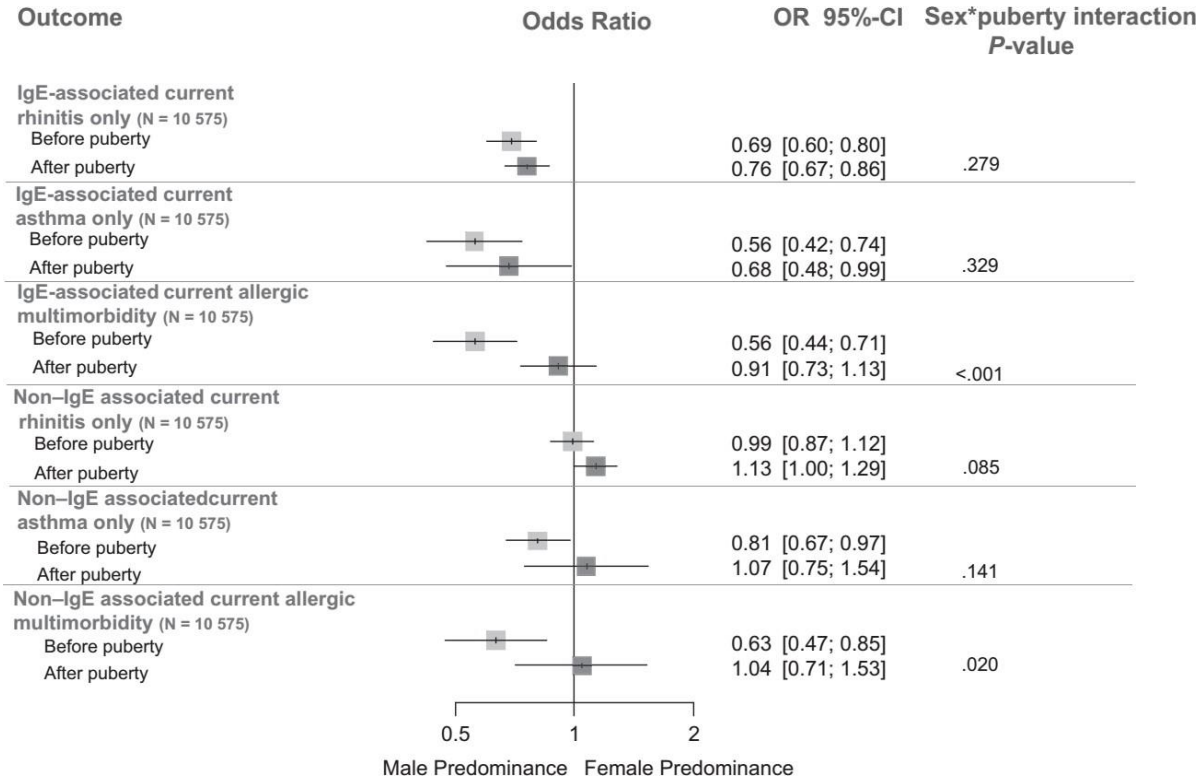
Sechs Geburtskohorten aus vier europäischen Ländern (Dänemark, Deutschland, Niederlande, Schweden) mit insgesamt 19.013 Teilnehmern (51% männlich) mit einem Follow-Up von 4 bis maximal 20 Jahren wurden in die Analysen eingeschlossen.

Primäre Endpunkte. Vor Pubertätsbeginn hatten Mädchen im Vergleich zu Jungen eine niedrigere Chance für die Erkrankung an Rhinitis (female/male OR 0,79; 95%-KI 0,73-0,86) und Asthma (0,71; 0,63-0,81); nach Pubertätsbeginn blieb diese Tendenz für Rhinitis bestehen (0,86; 0,79-0,94). Für Asthma war das OR nach Pubertätsbeginn 0,81; 95%-KI 0,64-1,02. Für die Prävalenz der respiratorischen Multimorbidität gab es unter den primären Endpunkten für Mädchen im Vergleich zu Jungen die niedrigste Chance zu Pubertätsbeginn zu erkranken (0,55; 0,46-0,64); nach Pubertätsbeginn glich sich das Geschlechterverhältnis in der Tendenz an (0,89; 0,74-1,07; Keller et al., 2018).

Sekundäre Endpunkte. Für alle IgE-assoziierten Endpunkte zeigte sich für Mädchen im Vergleich zu den Jungen eine niedrigere Chance vor Pubertätsbeginn zu erkranken; für IgE-assoziierte-Rhinitis (0,76; 0,60-0,80) und IgE-assoziiertes Asthma (0,68; 0,48-0,99) blieb dies auch nach Pubertätsbeginn bestehen (siehe Abbildung 1). Für respiratorische Multimorbidität war das Geschlechterverhältnis nach Pubertätsbeginn eher ausgeglichen (0,91; 0,73-1,13).

Für die Prävalenz von nicht-IgE-assoziierter Rhinitis war das Geschlechterverhältnis vor Pubertätsbeginn eher ausgeglichen während es nach Pubertätsbeginn eine Tendenz zu einer Dominanz der Mädchen gab (0,99; 0,87-1,12 versus 1,13; 1,00-1,29). Für nicht-IgE-assoziiertes Asthma bestand nur eine leichte (0,81; 0,67-0,97), für nicht-IgE-assoziierte respiratorische Multimorbidität (0,63; 0,47-0,85) eine deutliche erniedrigte Chance der Mädchen im Vergleich zu den Jungen vor Pubertätsbeginn zu erkranken; nach Pubertätsbeginn war das Geschlechterverhältnis eher ausgeglichen (Asthma 1,07; 0,75-1,54; respiratorische Multimorbidität 1,04; 0.71-1.53; siehe Abbildung 1) (Keller et al., 2018).

Abbildung 1. Ergebnisse der einstufigen Metaanalyse. Odds Ratios (OR) und 95%-Konfidenzintervalle (CI) für geschlechtsspezifische Prävalenzen der sekundären Endpunkte vor und nach Pubertätsbeginn (Legende vom Autor übersetzt und Abbildung übernommen aus Keller et al., 2018).



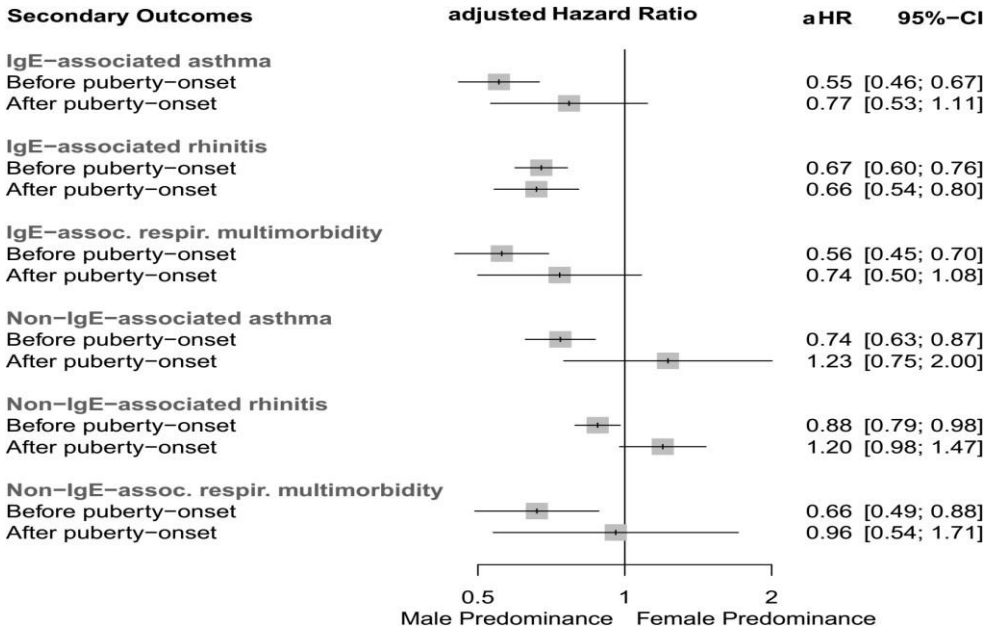
4.3 Hauptergebnisse der Publikation III

Fünf Geburtskohorten aus drei europäischen Ländern (Deutschland, Niederlande, Schweden) mit insgesamt 18.451 Teilnehmern (51% männlich) mit einem Follow-Up von 4 bis maximal 20 Jahren wurden in die Analysen eingeschlossen.

Primäre Endpunkte. Vor Pubertätsbeginn hatten Mädchen ein niedrigeres Risiko für die Inzidenz von Rhinitis (female/male HR 0,73;95%-KI 0,69-0,78), Asthma (0,67; 0,61-0,74) und respiratorischer Multimorbidität (0,58; 0,51-0,66). Nach Pubertätsbeginn glich sich das Risiko für die Inzidenz der drei primären Endpunkte für Jungen und Mädchen tendenziell an (Rhinitis 0,90; 0,79-1,02; Asthma 0,84; 0,64-1,10; respiratorische Multimorbidität 0,84; 0,63-1,13) (Hohmann et al., 2019).

Sekundäre Endpunkte. Es zeigte sich ein niedrigeres Risiko für Mädchen im Vergleich zu Jungen für alle IgE-assoziierten Endpunkte vor Pubertätsbeginn (siehe Abbildung 2). Für IgE-assoziierte Rhinitis blieb das niedrigere Risiko für Mädchen auch nach Pubertätsbeginn bestehen (0,66; 0,54-0,80); für die Inzidenz von IgE-assoziiertem Asthma (0,77; 0,53-1,11) und IgE-assoziierter respiratorischer Multimorbidität (0,74; 0,50-1,08) gab es eine leichte Tendenz zu einem ausbalancierteren Geschlechterverhältnis. Für die nicht-IgE-assoziierte Inzidenz von Rhinitis zeigte sich ein nur wenig erniedrigtes Risiko für Mädchen im Vergleich zu Jungen (0,88; 0,79-0,98) vor und ein tendenziell erhöhtes Risiko für Mädchen nach Pubertätsbeginn (1,20; 0,98-1,47). Für die Inzidenzen von nicht-IgE-assoziiertem Asthma (0,74; 0,63-0,87) und respiratorischer Multimorbidität (0,66; 0,49-0,88) bestand ein niedrigeres Risiko für Mädchen im Vergleich zu Jungen vor Pubertätsbeginn. Nach Pubertätsbeginn war das Geschlechterverhältnis für die Risiken der Inzidenzen von nicht-IgE-assoziiertem Asthma (1,23; 0,75-2,00) und respiratorischer Multimorbidität (0,96; 0,54-1,71) ausgeglichen (Hohmann et al., 2019).

Abbildung 2. Adjustierte Hazard Ratios (aHR) and 95%-Konfidence Intervalle (KI) für das Risiko der Inzidenz von IgE- und nicht-IgE-assoziiertem Rhinitis (n= 10.331), Asthma (n= 10.320) und respiratorischer Multimorbidität (n=10.304) für Jungen versus Mädchen vor und nach Pubertätsbeginn (Legende vom Autor übersetzt und Abbildung übernommen aus Hohmann et al., 2019).



5 Diskussion

Rhinitis. Der systematische Review mit Metaanalyse (Publikation I, Pinart et al., 2017) zur Prävalenz von Rhinitis fand eine Dominanz der Jungen im Kindesalter und eine Dominanz der weiblichen Teilnehmer bei Jugendlichen und Erwachsenen. Eine Unterscheidung zwischen IgE- und nicht-IgE-assoziierter Rhinitis konnte aufgrund unzureichender Datenlage nicht getroffen werden. Ein Bedarf longitudinaler Studien mit Erfassung des Pubertäts- und IgE-Status für Rhinitis und respiratorische Multimorbidität wurde aufgezeigt (Pinart et al., 2017). Die Metaanalysen der Primärdaten (Publikationen II und III) reagierten auf diesen Forschungsbedarf. Ihre Ergebnisse zeigten eine männliche Dominanz für die Prävalenz und Inzidenz von IgE-assoziierter Rhinitis vor und nach Pubertätsbeginn. Für die Prävalenz und Inzidenz nicht-IgE-assoziierter Rhinitis bestand vor Pubertätsbeginn in den Tendenzen ein eher ausbalanciertes Geschlechterverhältnis; nach Pubertätsbeginn die Tendenz einer weiblichen Dominanz (Keller et al., 2018; Hohmann et al., 2019). Dies bestätigte die Ergebnisse einer britischen longitudinalen Kohortenstudie die bei 18-jährigen für IgE-assoziierte Rhinitis eine männliche Dominanz hingegen für nicht-IgE-assoziierte Rhinitis eine weibliche Dominanz aufzeigte (Kurukulaaratchy et al., 2011).

Asthma. Publikationen II (Keller et al., 2018) und III (Hohmann et al. 2019) zeigten eine männliche Dominanz vor Pubertätsbeginn für die Inzidenz und Prävalenz von IgE- und nicht-IgE assoziierten Asthma. Nach Pubertätsbeginn blieb für IgE-assoziiertes Asthma die männliche Dominanz für die Prävalenz bestehen; auch für die Inzidenz gab es nur tendenziell ein ausbalanciertes Geschlechterverhältnis. Für nicht-IgE-assoziiertes Asthma gab es für die Prävalenz und Inzidenz nach Pubertätsbeginn ein deutlich ausbalanciertes Geschlechterverhältnis. In der Literatur ist eine stärkere Assoziation von Asthmaerkrankungen mit dem weiblichen Geschlecht im Jugend- und Erwachsenenalter im Vergleich zum Kindesalter bekannt (Almqvist et al., 2008; Postma, 2007). Eine niederländische Kohortenstudie fand unter Nutzung medizinischer Registerdaten eine männliche Dominanz der Asthmaprävalenz vor und eine Umkehr des Geschlechterverhältnisses bis zum Alter von 18 Jahren (Engelkes et al., 2015). Die Publikationen II (Keller et al., 2018) und III (Hohmann et al., 2019) fanden tendenziell eher einen Geschlechterausgleich ab Pubertätsbeginn. Allerdings waren die meisten Teilnehmer der Publikationen II und II (14 bis 16 Jahre) im Vergleich zu der holländischen Studie von Engelkes et al. (2015) (bis zu 18 Jahre) beim letzten Follow-Up jünger und ein potentieller kumulativer Einfluss eines längeren Zeitraums postpubertärer Hormonexposition konnte in den Publikationen II und III noch nicht beobachtet werden. Eine weitere Studie berichtete ein ausgeglichenes Geschlechterverhältnis von Asthmainzidenzen im Alter von 11 Jahren und tendenziell höhere Asthmainzidenzen im Alter von 16 Jahren bei weiblichen versus männlichen Studienteilnehmern; dabei war der Pubertätsstatus nicht mit den Asthmainzidenzen assoziiert (Vink et al., 2010). Im Gegensatz zu Publikationen II (Keller et al., 2018) und III (Hohmann et al. 2019) unterschied die Studie von Vink et al., (2010) nicht zwischen vor versus nach Pubertätsbeginn, sondern zwischen frühen, mittleren und späten Pubertätsstadien was vermutlich auch dem höheren Alter der Teilnehmer von Vink et al. (2010) bei Studienbeginn von bereits 11 Jahren geschuldet war.

Es scheint, dass vor allem der Pubertätsbeginn den Entwicklungsstart geschlechtsspezifischer Unterschiede markieren könnte. In der Literatur finden sich Nachweise für das höhere Risiko für erwachsene Frauen an nicht-IgE versus an IgE-assoziiertem Asthma zu erkranken (Hansen et al., 2015). Es wurde vorgeschlagen, nicht-IgE-assoziiertes Asthma als einen klinisch distinkten Phänotyp mit spezifischen Charakteristiken wie höherem Erkrankungsalter, weiblichem Geschlecht und einer

stärkeren Symptomatik von IgE-assoziiertem Asthma abzugrenzen (Pillai et al., 2011). Die vorliegenden Ergebnisse unterstützen diese Aussage tendenziell für Asthma und legen ebenfalls eine ähnliche Unterscheidung klinischer Phänotypen für Rhinitis und respiratorische Multimorbidität nahe.

Respiratorische Multimorbidität. Die Publikationen II und III zeigten für die Prävalenz und Inzidenz von IgE- sowie nicht-IgE-assoziierter respiratorischer Multimorbidität eine männliche Dominanz vor Pubertätsbeginn und eine (tendenzielle) Ausbalancierung des Geschlechterverhältnisses nach Pubertätsbeginn. Wie bereits für Rhinitis und Asthma, war die Verschiebung des Geschlechterverhältnisses deutlicher bei der nicht-IgE-assoziierten respiratorischen Multimorbidität. Eine systematische Übersichtsarbeit von Querschnittsstudien unter der Schirmherrschaft des Projektes MeDALL berichtete für respiratorische Multimorbidität eine männliche Dominanz in der Kindheit, in der Jugendzeit eine weibliche Dominanz und im Erwachsenenalter keine geschlechtsspezifischen Unterschiede (Fröhlich et al., 2017). Tendenziell spiegelt dies die Ergebnisse der primären Endpunkte der Publikationen II (Keller et al. 2018) und III (Hohmann et al., 2019) wider. Die Ergebnisse für die weibliche Dominanz in der Jugendzeit für die Prävalenz respiratorischer Multimorbidität basierten bei Fröhlich et al. (2017) auf nur zwei Querschnittsstudien. In beiden Studien wurde der Pubertätsstatus nicht berücksichtigt und auch die Erfassungen von Rhinitis und Asthma weichen von denen in Publikationen II und III ab (Luna et al., 2011; Brito et al., 2009). Dementsprechend ist die Vergleichbarkeit der Ergebnisse begrenzt, sodass nicht notwendigerweise ein Widerspruch zu Publikationen II und III bestehen muss. Eine Unterscheidung zwischen IgE- und nicht-IgE-assoziierter respiratorischer Multimorbidität wurde in bisherigen Studien zur Untersuchung von geschlechtsspezifischen Prävalenzen und Inzidenzen nicht getroffen.

Mögliche Mechanismen. Der Pubertätsbeginn als Zeitpunkt für eine Verschiebung des Geschlechterverhältnisses für die Prävalenzen und Inzidenzen von Asthma, Rhinitis und respiratorischer Multimorbidität legt unter anderem die Vermutung über einen Zusammenhang mit Sexualhormonen nahe. Mädchen mit einer frühen Menarche haben im Vergleich zu Mädchen mit einer späten Menarche höhere Estrogen-Konzentrationen und ein erhöhtes Risiko für Asthma (Postma, 2007) und Rhinitis (Wei et al., 2015). Schwangerschaft, die unter anderem mit steigenden Konzentrationen von Östrogen und

Progesteron assoziiert ist, scheint mit erhöhten Rhinitis-Inzidenzen einherzugehen (Caparroz et al., 2016). Auch andere natürliche Gründe die mit einem Anstieg der Östrogenkonzentration einhergehen (z.B. während des Monatszyklus, in der Schwangerschaft oder bei Adipositas), scheinen mit einem Anstieg von Asthma-Prävalenzen und die natürliche Abnahme von Östrogenkonzentrationen (z.B. in den Wechseljahren) scheinen mit einer Abnahme von Asthma-Prävalenzen assoziiert zu sein (Townsend et al., 2012; Carey et al., 2007; Postma, 2007). Sexualhormon-Rezeptoren werden unter anderem im Lungengewebe exprimiert und gelten als mögliche prä- und postnatale Einflussfaktoren einer geschlechtsspezifischen Lungenentwicklung (Townsend et al., 2012; Carey et al., 2007; Postma, 2007). Auch geschlechtsspezifische Profile der Immunantwort könnten zur Aufklärung der Geschlechterdifferenz von Asthmaprävalenzen beitragen. Weibliche Sexualhormone sind involviert in einer verstärkten Typ-2 Immunantwort, der Produktion von Interleukinen und eosinophiler Degranulation und Adhäsion, während Androgene suppressiv auf die genannten Mechanismen zu wirken scheinen. Frauen scheinen im Vergleich zu Männern eine stärkere Assoziation von der Konzentration eosinophiler Granulozyten mit Asthmasymptomen zu haben und sind bei gleicher Konzentration gegenüber dem Einfluss einer Eosinophilie vulnerabler (Townsend et al., 2012; Carey et al., 2007). Weitere Erklärungen für geschlechtsspezifische Risiken für Asthma könnten auch eine geschlechtsspezifische Suszeptibilität gegenüber Umweltexpositionen oder Lebensstilfaktoren sein (Almqvist et al., 2008; Postma, 2007). Insgesamt sind Studien zum Hormoneinfluss auf Rhinitis und respiratorische Multimorbidität selten. Im Sinne der „United Airway Disease“ wäre zu vermuten, dass manche Pathomechanismen für Rhinitis und Asthma vergleichbar sind und eventuell auch als Erklärungsmodelle für respiratorische Multimorbidität dienen könnten.

Stärken und Limitationen

Publikation I (Pinart et al., 2017) ist der erste systematische Review zur Überprüfung einer Verschiebung des Geschlechterverhältnisses der Rhinitis-Prävalenzen von der Kindheit bis ins Erwachsenenalter. Es wurden nur Ergebnisse aus Querschnittstudien zusammengefasst; dies lässt keine direkten Rückschlüsse auf den longitudinalen Verlauf einer Erkrankung zu. Auch konnte aufgrund unzureichender Datenlage nicht zwischen IgE- und nicht-IgE-assoziierter Rhinitis unterschieden werden. Dies könnte

heterogene Ergebnisse der eingeschlossenen Studien erklären; drei Publikationen berichteten eine männliche, 12 eine weibliche Dominanz der Rhinitis-Prävalenz bei Jugendlichen (Pinart et al. 2017).

Publikationen II (Keller et al., 2018) **und III** (Hohmann et al., 2019) sind die ersten harmonisierten multizentrischen Auswertungen longitudinaler Primärdaten, die eine Verschiebung der Geschlechtsverhältnisse bei Pubertätsbeginn von Prävalenzen und Inzidenzen von Rhinitis und respiratorischer Multimorbidität untersuchen. Wie in allen längsschnittlichen Studien könnten Drop-outs zu reduzierten Teilnehmerzahlen in späteren Follow-Ups oder, wenn sie systematisch auftreten, auch zu Verzerrungen der Ergebnisse führen. Für letzteres zeigten sich in den Analysen der Publikationen II und III jedoch keine Hinweise. Für die Unterscheidung zwischen IgE- versus nicht-IgE-assoziierten Prävalenzen und Inzidenzen wurde spezifisches Serum-IgE für übliche Aeroallergene verwendet. Es besteht die Möglichkeit, dass nicht alle für die Teilnehmer relevanten spezifischen IgEs erfasst wurden. Dies würde zu einer Unterschätzung IgE-assoziierter Erkrankungen führen. Die Erhebung von Rhinitis beruhte auf einer Selbstauskunft. Die Frage wurde aus den validierten ISAAC Fragebögen übernommen, dennoch ist eine Überschätzung von Rhinitis-Fällen im Vergleich zu einer Erhebung mittels Arzt-Diagnose nicht auszuschließen. Die Definition von Asthma-Fällen erfolgte in den Publikationen II und III aus einer Kombination der Selbstauskünfte zu ‚Current Wheeze', einer ärztlichen Asthma-Diagnose und der Nutzung von Asthma-Medikamenten in den letzten 12 Monaten. Weibliches Geschlecht könnte ab dem Jugendalter mit einer Unterdiagnostizierung und Unterversorgung von Asthma assoziiert sein (Almqvist et al., 2008). Daher ist bei der oben genannten Asthma-Definition nicht auszuschließen, dass die wahren Prävalenzen und Inzidenzen der weiblichen Jugendlichen höher und damit auch die wahre Verschiebung der Geschlechterverhältnisse nach dem Pubertätsbeginn grösser waren als in der vorliegenden Arbeit berichtet. Die Geburtskohorten erlaubten meist eine Datenauswertung bis ins frühe Jugendalter: PIAMA und DARC bis 14 Jahre, GINI-Plus und LISA bis 15 und BAMSE bis 16 Jahre. Nur die MAS-Kohorte hatte zum Zeitpunkt der Auswertung die aktuellste Datenerhebung im frühen Erwachsenenalter (20 Jahre) durchgeführt. Auch wenn viele der Teilnehmer zum jeweils letzten Erhebungszeitpunkt Anzeichen des Pubertätsbeginns angaben, lässt die Datenlage keine Untersuchung der

Auswirkung einer langfristigen postpubertären Hormonexposition auf die Prävalenz- und Inzidenzentwicklungen der Erkrankungen zu (Hohmann et al., 2019).

Schlussfolgerung und Implikationen. Der Pubertätsbeginn war, unabhängig vom Alter der Teilnehmer, ein wichtiger Einflussfaktor für das geschlechtsspezifische Risiko für das Auftreten insbesondere nicht-IgE-assoziierter respiratorischer Erkrankungen. Die Verschiebung der geschlechtsspezifischen Risiken der Prävalenzen (Publikation II, Keller et al.,2018) konnten partiell mit den erhöhten Risiken für Neuerkrankungen, also den Inzidenzen (Publikation III, Hohmann et al. 2019) erklärt werden. Frühere Studien berichten erhöhte IgE-Konzentrationen bei präpubertären Jungen im Vergleich zu Mädchen; ab Pubertätsbeginn fallen diese bei Mädchen weiter ab. Im Verlauf des Erwachsenenalters bleiben höhere IgE-Konzentrationen bei Männern im Vergleich zu Frauen bestehen (Townsend et al., 2012). Frauen haben demnach niedrigere IgE-Werte im Serum sowie eine verstärkte Immunantwort, die sie anfälliger für Autoimmun- und allergische Erkrankungen macht (Townsend et al., 2012). Diese Kombination legt nahe, dass andere Mechanismen des Immunsystems, wie beispielsweise eine lokale IgE-Expression, für die Ausbildung einer allergischen Erkrankung relevant sein könnten. Es scheint sowohl bei Asthma wie auch bei Rhinitis unter Umständen eine lokale IgE-Expression im Bronchialepithel beziehungsweise in der Nasenschleimhaut zu geben, die nicht als spezifisches IgE im Serum oder durch Skin Prick Tests nachweisbar ist (Krzych-Fałta et al., 2018; Small et al., 2018; Licari et al., 2017).

Kliniker sollten Symptomen von neu-auftretender Rhinitis, Asthma und respiratorischer Multimorbidität bei weiblichen Patienten ab Pubertätsbeginn, insbesondere bei negativen IgE- und Skin-Prick Tests, eine erhöhte Aufmerksamkeit widmen. Langfristig sollte dadurch eine potenzielle Unterversorgung dieser Patientengruppe vermieden werden.

Weiterführende Fragestellungen. Da sich die Prävalenz einer Erkrankung aus der Inzidenz und Remission zusammensetzt, liefern die Inzidenz-Ergebnisse der Publikation III eine partielle Erklärung der Prävalenzen aus Publikation II; Ergebnisse zu Remissionen stehen aus. Zudem wäre ein Follow-Up der Teilnehmer der Geburtskohorten im Erwachsenenalter wünschenswert, um einen potenziell kumulativen Effekt von mehreren Jahren postpubertärer Hormonexposition untersuchen zu können. Geht man von einem Dosis-Wirkungseffekt aus, wäre es möglich eine

deutlichere Geschlechterverschiebung der Erkrankungsprävalenzen vorzufinden. Mit Hinblick auf die Geschlechterverschiebung insbesondere bei nicht-IgE-assoziierten Erkrankungen, sollten geschlechtsspezifische Unterschiede auch bezüglich einer lokalen IgE-Expression gezielt untersucht werden.

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7 Eidesstattliche Versicherung

„Ich, Cynthia Hohmann, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Einfluss von Geschlecht und Pubertätsbeginn auf Asthma, Rhinitis und respiratorische Multimorbidität im Kindes- und Jugendalter selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. 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.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

8 Anteilserklärung an den erfolgten Publikationen

Cynthia Hohmann hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Pinart M, Keller T, Reich A, Fröhlich M, Cabieses B, Hohmann C, Postma DS, Bousquet J, Antó JM, Keil T (2017). Sex-Related Allergic Rhinitis Prevalence Switch from Childhood to Adulthood: A Systematic Review and Meta-Analysis. *Int Arch Allergy Immunol*. 2017;172(4):224-235.
Beitrag im Einzelnen:

- Mitarbeit an der Konzipierung der elektronischen Suchstrategie
- Mitarbeit bei der Erstellung der Excel-Tabellen als Hilfsmittel für die Bewertung der identifizierten Studien wie die Ein- und Ausschlußtabellen und die Datenextraktionstabellen
- Mitarbeit beim Screening der Titel und Abstracts zum Studieneinschluss und Studienausschluss
- Mitarbeit beim Reviewen der ausgewählten Volltexte
- Mitarbeit beim Extrahieren der Daten der Volltexte
- Mitarbeit an der Konzeption und Erstellung der Publikation, insbesondere Diskussion und Interpretation der Ergebnisse, kritisches Lesen und Kommentieren aller Versionen des Manuskriptes und Zustimmung zur Publikation

Publikation 2: 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. (2018). The sex-shift in single disease and multimorbid asthma and rhinitis during puberty - a study by MeDALL. *Allergy*, 73(3):602-614. Impact Factor: 6,7
Beitrag im Einzelnen:

- Mitarbeit bei der Harmonisierung der vorhandenen Daten der teilnehmenden europäischen Geburtskohorten (Teilnahme an 2 Workshops mit aktiver Diskussionsteilnahme und Versendung der Berliner Daten an die zentrale Datenbank)
- Federführend bei der Harmonisierung der neu-erhobenen Daten der Geburtskohorten

- Koordination der Kommunikation aller an der Studie beteiligter internationaler Mitarbeiter
- Organisation mehrerer Arbeitstreffen (Frankfurt, Berlin, Rom, Turin, München, Barcelona), inklusive der Vorarbeit wie Zusammenstellung, Reorganisation und Übersetzungen der vorhandenen Variablen, Erstellung der konkreten Arbeitsmaterialien für die Arbeitstreffen, Nachbereitung der Arbeitstreffen
- Federführend bei der Zusammenstellung, Übersetzung, Gestaltung und Online-Programmierung der finalen Fragebögen
- Federführend bei der Zusammenstellung, Organisation der Übersetzungen und Gestaltung der Standard Operative Procedures für die körperlichen Untersuchungen
- Mitarbeit am initialen Datenanalyseplan
- Mitarbeit an der Konzeption und Erstellung der Publikation, insbesondere Diskussion und Interpretation der Ergebnisse, kritisches Lesen und Kommentieren aller Versionen des Manuskriptes und Zustimmung zur Publikation

Publikation 3: Hohmann C, Keller T, Gehring U, Wijga A, Standl M, Kull I, Anna Bergstrom A, Lehmann I, von Berg A, Heinrich J, Lau S, Wahn U, Maier D, Anto J, Bousquet J, Smit H, Keil T, Roll S. (2019). 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. *BMJ Open Resp Res*, 6:e000460. Impact Factor: -

Beitrag im Einzelnen:

- Mitarbeit bei der Harmonisierung der vorhandenen Daten der teilnehmenden europäischen Geburtskohorten (Teilnahme an 2 Workshops mit aktiver Diskussionsteilnahme und Versendung der Berliner Daten an die zentrale Datenbank)
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- Federführend bei der Zusammenstellung, Übersetzung, Gestaltung und Online-Programmierung der finalen Fragebögen
- Federführend bei der Zusammenstellung, Organisation der Übersetzungen und Gestaltung der Standard Operative Procedures für die körperlichen Untersuchungen

- Mitarbeit am initialen Datenanalyseplan
- Eigenständige Literaturrecherche und Auswahl der relevanten Literatur
- Federführend bei der Erstellung der Tabellen
- Federführend bei der Konzeption und Erstellung der Publikation, inklusive aller Tabellen (Hauptartikel und Supplement)
- Anpassung der Graphiken

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Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

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Unterschrift des Doktoranden/der Doktorandin

9 Originalpublikationen

Publikation I. Pinart M, Keller T, Reich A, Fröhlich M, Cabieses B, Hohmann C, Postma DS, Bousquet J, Antó JM, Keil T. (2017) Sex-Related Allergic Rhinitis Prevalence Switch from Childhood to Adulthood: A Systematic Review and Meta-Analysis. *Int Arch Allergy Immunol*,172(4):224-235. S. Karger AG, Basel. Impact Factor: 2,9.
Link: https://www.karger.com/Article/Abstract/464324

Publikation II. 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. (2018). The sex-shift in single disease and multimorbid asthma and rhinitis during puberty - a study by MeDALL. *Allergy*, 73(3):602-614. Impact Factor: 6,7.
Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5836860/pdf/ALL-73-602.pdf

Publikation III. Hohmann C, Keller T, Gehring U, Wijga A, Standl M, Kull I, Bergstrom A, Lehmann I, von Berg A, Heinrich J, Lau S, Wahn U, Maier D, Anto J, Bousquet J, Smit H, Keil T, Roll S. (2019). 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. *BMJ Open Resp Res*, 6:e000460. Impact Factor: 1,3.
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Sex-Related Allergic Rhinitis Prevalence Switch from Childhood to Adulthood: A Systematic Review and Meta-Analysis

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Keywords

Allergic rhinitis · Meta-analysis · Prevalence · Sex differences · Systematic review

Abstract

Background: A sex-related switch in the prevalence of asthma from childhood (male predominance) to adulthood (female predominance) has been described, but for allergic rhinitis this remains unclear. We aimed to examine sex- and age-group-specific differences in allergic rhinitis prevalence by systematically evaluating studies from across the globe. ***Methods:*** A systematic search of MEDLINE and Embase for population-based cross-sectional studies was performed regardless of the language of publication. The search was restricted to the present millennium (2000 to June 2014). Study quality was defined by the sampling method, response rate, sample size, and data collection method. To assess sex differences in the prevalence of self- or parent-reported symptoms of rhinitis, calculated pooled estimates of the male-female ratio (MFR) were obtained using random-effects model meta-analyses due to heterogeneity. A meta-regression analysis was also performed. ***Results:*** Out of 6,539 publications identified, 67 cross-sectional population-based studies (291,726 males and 301,781 females) were included in our meta-analysis. In children (<11 years of age) significantly more boys than girls had rhinitis symptoms (MFR 1.21, 95% CI 1.17–1.25), whereas in adolescents (11 to <18 years of age) males were significantly less often affected than females (MFR 0.90, 95% CI 0.85–0.95). No sex-specific prevalence difference was observed in adults (MFR 0.96, 95% CI 0.83–1.17). These findings were consistent in all continents except in Asia, where the male predominance remained beyond childhood. ***Conclusions:*** The male predominance of rhinitis prevalence in child-

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hood changed towards a female predominance in adolescence across the globe, except in Asia. Longitudinal studies are needed to confirm these cross-sectional data and examine possible determinants and underlying mechanisms.

Introduction

The prevalence of asthma and rhinitis has increased over the past decades, reaching epidemic proportions in Western and developing countries [1]. Sex differences in the prevalence of asthma, eczema, and food allergy are observed in clinical and epidemiological studies [2]. In childhood, the asthma prevalence is higher in boys than in girls, whereas after puberty there is a female predominance of asthma persisting throughout adulthood [3, 4]. Conversely, allergic sensitization seems to remain more prevalent among male adults [5, 6]. However, little is known about the predominating sex in the prevalence of rhinitis in the pre- and postpubertal phases. During adolescence, by comparison to boys, the prevalence of rhinitis is higher in girls in Saudi Arabia and Brazil [7, 8] and lower in Iran [9] and Kuwait [10].

There are no systematic reviews on sex-specific differences in the prevalence of self- or parent-reported symptoms of rhinitis summarizing studies from childhood to adulthood. As with asthma, there may be a sex-related prevalence switch of rhinitis symptoms between boys and girls after puberty that persists throughout adulthood [3, 11].

The primary objective of this systematic review with meta-analyses of cross-sectional studies was to examine sex differences in the prevalence of self- or parent-reported rhinitis symptoms from childhood through adolescence into adulthood. Secondary objectives were to describe possible regional and temporal differences in the prevalence of rhinitis assessed in population-based cross-sectional studies.

Methods

Data Sources, Search Strategy, and Selection Criteria

This systematic review was reported in accordance with the recommendations set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12]. The protocol can be accessed at PROSPERO (www.crd.york.ac.uk/PROSPERO/, registration No. CRD42016036105). A systematic search was conducted using computerized bibliographic databases such as MEDLINE through the PubMed webpage and Embase, and the search was restricted to studies published in the first 14 years of the present millennium (2000 – 2014). Our search retrieved all relevant studies regardless of the language of publication. MeSH terms were chosen according to the database (minimal variations) and a selection of string terms to increase the capture of relevant papers (online suppl. search strategies; for all online suppl. material, see www.karger.com/doi/10.1159/000464324). The EndNote X7® (Thomson Reuters) bibliographic database was used to manage the results of our literature searches.

Inclusion and Exclusion Criteria

Study selection was based on an a priori set of inclusion and exclusion criteria. Broad inclusion criteria were used to take advantage of all available knowledge on the assessment of potential gender differences in the prevalence and/or incidence of rhinitis among the general population.

The inclusion criteria were the following: (1) studies that recruited participants of both sexes from the general population of all age groups, (2) reported prevalence and/or incidence of the disease stratified by sex and age if the population under study included children and adults, and/or that described risk factors explained by sex, (3) longitudinal or cross-sectional studies.

Studies that: (1) were not original (i.e., reviews, guidelines, etc.), (2) did not report prevalence and/or incidence estimates stratified by sex and age if the population under study included children and adults, (3) whose participants were selected by their occupation, (4) recruited only male or female participants, and (5) those studies that recruited patients from institutes such as allergy outpatient clinics, were excluded. The following study designs were excluded: ecological studies, case reports, case series, case-control studies, experimental studies, intervention studies, and clinical studies.

In the present systematic review, only the results of cross-sectional studies assessing the prevalence of self-reported or parent-reported symptoms of current rhinitis, defined as the presence of rhinitis symptoms in the last 12 months were reported.

Study Selection, Data Extraction and Quality Assessment

Study selection was performed following a 2-step process. First, 2 independent reviewers (M.P. and C.H.) conducted title scans in a parallel fashion. We rated each citation as: "include," "exclude," or "unclear." Second, the same independent reviewers screened the abstracts of those records rated as "include" or "unclear." Disagreements encountered in both steps were resolved through referral to a third reviewer (T.K. or M.F.).

Prior to data extraction, 2 reviewers (M.P. and M.F.) independently reviewed full texts of all selected publications rated as "include" or "unclear." M.P. designed the data extraction form. The predesigned data extraction form with 5 studies selected from the pool of included studies was piloted and M.F., A.R., and T. Keller identified issues that served to improve the form. At least 2 reviewers (T. Keller, C.H., B.C., A.R., M.F., and M.P.) abstracted data from the selected full texts independently with disagreements through referral to a third reviewer (T.K.). We contacted the authors of several studies [13 – 17] by e-mail for further information regarding the measurements stratified by sex. Only the studies whose authors provided a response within 2 weeks were included in the meta-analyses.

Data were extracted on the following information using SoSci-Survey (https://www.soscisurvey.de/): country, study design, description of the process of recruitment of participants, age of participants, sample size and residency, response rate, observation period, definition of disease and measurement, method of data

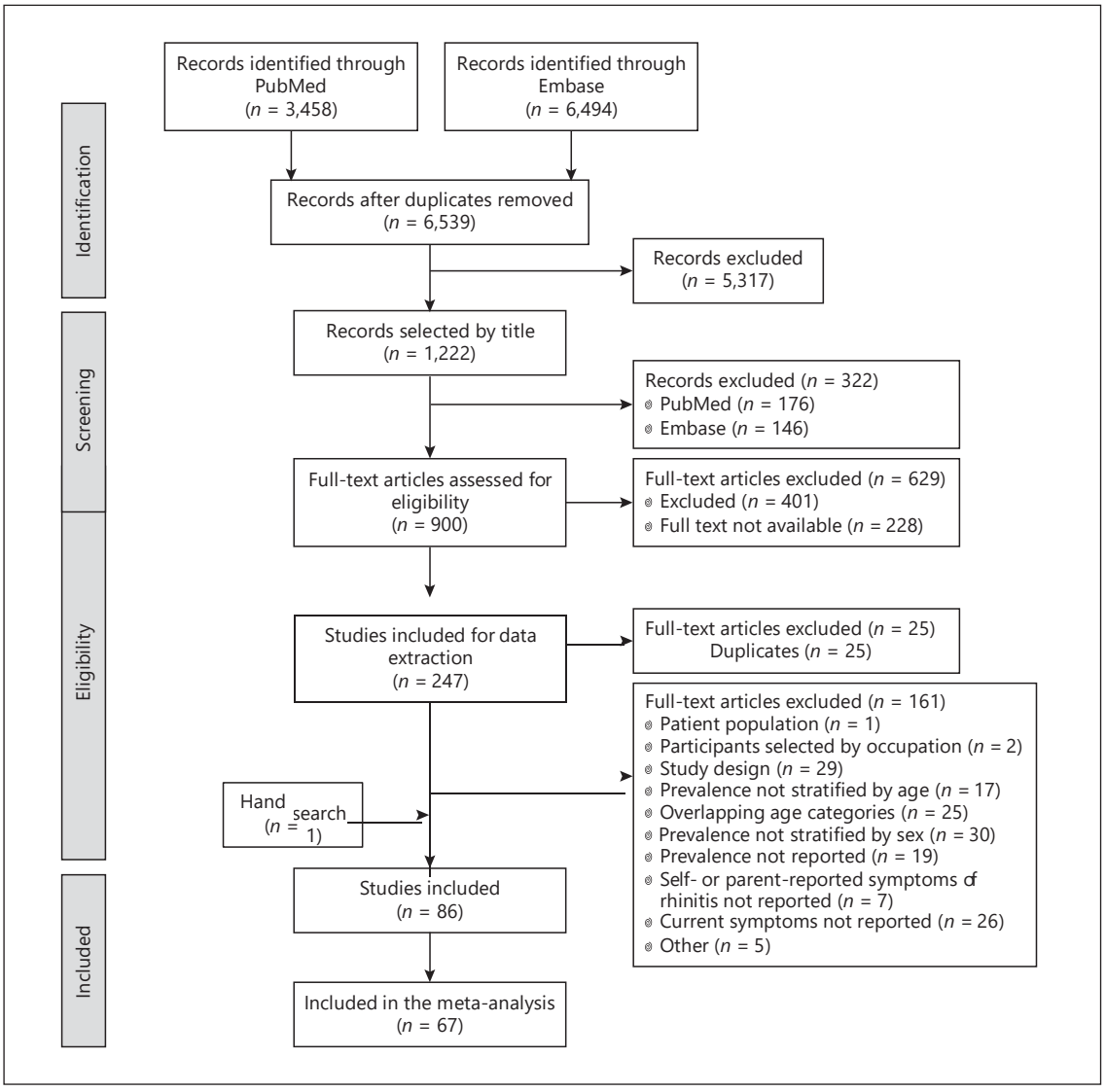

Fig. 1. PRISMA flow chart for the literature search.

collection, prevalence and incidence of rhinitis stratified by sex as well as sex-specific information on risk factors for rhinitis.

Study quality assessment was determined by 4 criteria: sampling method, response rate, sample size, and data collection method to investigate sources of heterogeneity between studies, if present. The maximum score was 5 points. Studies that scored 0 – 2 were labelled "low quality," 3 – 4 were "moderate quality," and a score of 5 indicated "high quality."

Quantitative Data Synthesis

To assess sex differences in the prevalence of rhinitis before and after puberty we measured calculated pooled estimates of the male-female ratio (MFR), together with associated 95% confidence intervals (95% CI), using random-effects model meta-analyses with the inverse variance method due to the expected heterogeneity of the studies. I^2 was calculated to quantify inconsistency across studies. To investigate the source of potential heterogeneity we performed meta-regression analyses regarding the study period (conducted until 2000 vs. after 2000), region (continent), and residency (urban vs. mixed rural/urban background) as moderator variables. Statistical analyses were done using R and the STATA 12.0 software package (Stata Corporation, College Station, TX, USA).

Results

Characteristics of Included Studies

After the removal of duplicates, 6,539 hits were retrieved, of which 1,222 studies were identified after title screening. A total of 250 studies were eligible for data

extraction, of which 85 were included. One study suggested by the reviewer fit the inclusion criteria, giving a total of 86 cross-sectional studies (online suppl. references), of which 67 were included in the meta-analysis (Fig. 1). Studies were mainly of moderate to high quality. A detailed summary of the 86 studies and their quality rating score can be found in online supplementary Tables S1 – S4.

The studies were conducted mainly in Asia (35) and Europe (28), followed by the Americas (16), Africa (5), and Oceania (2). The majority of the studies recruited children from an urban background. Fourteen studies assessed both children (aged around 6 – 7 years) and adolescents (aged around 13 – 14 years), and provided the prevalence stratified by age [9,18 – 30].

The prevalence of rhinitis was questionnaire based, mainly using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire for children and adolescents ($n = 71$) [31], followed by the European Community Respiratory Health Survey (ECRHS) in adults ($n = 6$) [32]. A total of 46 studies examined sex differences in the prevalence of rhinitis in children aged <11 years, 43 in children aged 11 – 18 years, and 12 studies in adults (Table 1).

Pooled estimates were based on 88 MFRs from 67 studies that provided the necessary information to derive the MFR, including 291,726 males and 301,781 females (Fig. 2, 3).

Table 1. Characteristics of studies included in the systematic review

Study characteristics	Cross-sectional studies, *n*
Total	86
Study period[1]	
1991 – 2000	23
2001 – 2014	61
Unknown	14
Region	
Africa	5
Asia	35
Europe	28
Americas	16
North/Central	8
South	8
Oceania	2
Sample size analyzed	
<1,000	10
1,001 – 5,000	34
5,001 – 10,000	23
10,001 – 100,000	18
>100,000	1
Age category[1]	
0 – 10 years	46
11 – <18 years	43
18+ years	12
Urbanicity	
Urban	45
Rural/urban[2]	30
Unclear/not reported	11
Method for assessing prevalence[1]	
ISAAC questionnaire	71
ECHRS questionnaire	6
Other questionnaire/s	9

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

[1] Total may exceed 86 as some studies reported the prevalence of rhinitis in several age categories.

[2] Subjects from 3 studies had a rural background only.

Prevalence of Rhinitis Symptoms during Childhood

The meta-analysis for childhood included 35 studies with data from 133,885 males and 135,152 females (Fig. 2). The pooled estimates for the MFR of the prevalence of self- or parent-reported symptoms of rhinitis in children before puberty (<11 years) was 1.21 (95% CI 1.17 – 1.25).

None of the included studies reported a female predominance, although 12 studies did not report sex differences. The largest studies conducted in Korea [23, 33], Japan [22], and Spain [34] analyzed 57,358 males and 60,506 females and showed sex differences with an MFR similar to the pooled estimate.

Prevalence of Rhinitis Symptoms during and Shortly after Puberty

The meta-analysis for the age group of 11 – 17 years included 36 studies with data from 137,443 males and 142,939 females (Fig. 3). The pooled estimate for the MFR of the prevalence of rhinitis symptoms in adolescents aged 11 – 17 years was 0.90 (95% CI 0.85 – 0.95).

Three studies conducted in Korea [23], Iran [9], and Kuwait [10] showed a clear male predominance during and shortly after puberty, whereas 15 studies found a strong female predominance during and shortly after puberty. Three studies analyzed sex differences in the prevalence of rhinitis in 2 different time periods: New Zealand [28] (1993 and 2003), [35] (1995 and 2002), and Brazil [36] (2007 and 2010). They found a female predominance, which was similar in both study periods.

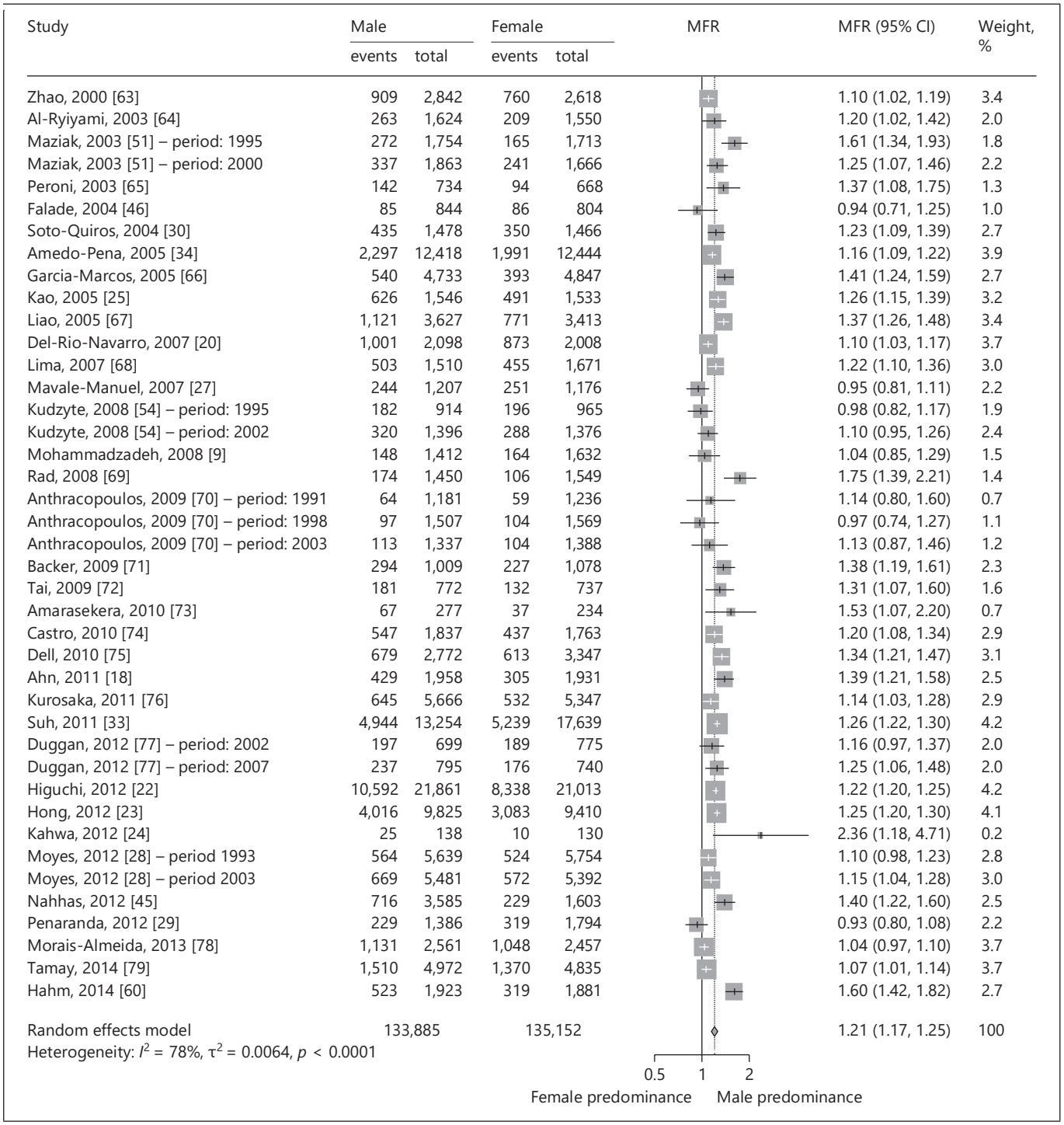

Fig. 2. Forest plot estimating the difference in prevalence of rhinitis between boys and girls aged <11 years (before puberty). The term "events" corresponds to the number of children with current rhinitis.

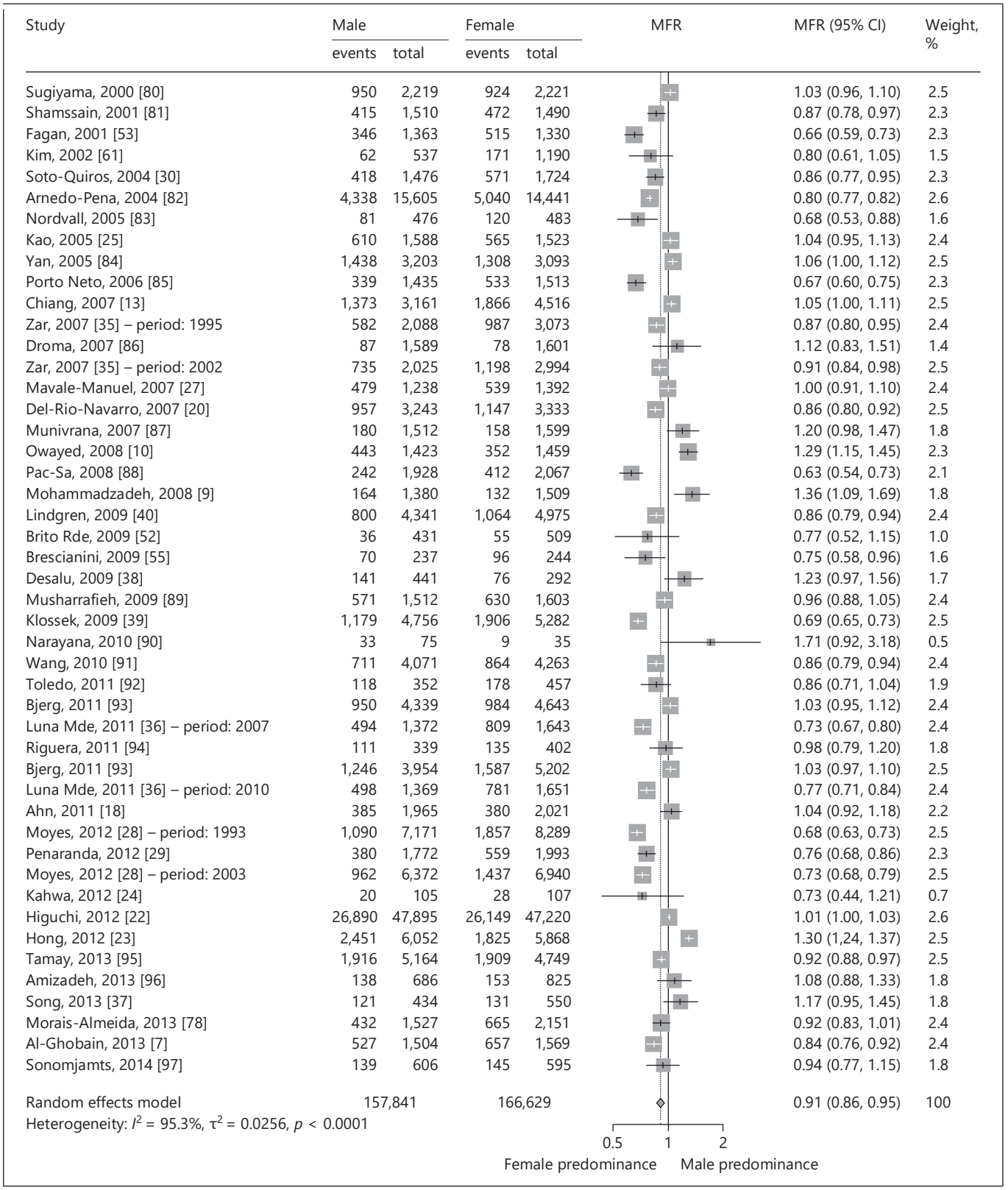

Fig. 3. Forest plot estimating the difference in prevalence of rhinitis between males and females during and after puberty (aged 11 to <18 years) and throughout adulthood (18+ years). The term "events" corresponds to the number of children with current rhinitis.

Prevalence of Rhinitis Symptoms throughout Adulthood

The meta-analysis for adulthood included 7 studies with data from 20,398 males and 23,690 females (Fig. 3). The pooled estimate for the MFR of the prevalence of symptoms of rhinitis in adults (aged 18 years and older) was 0.96 (95% CI 0.83 – 1.10). When the estimates including both pubertal and adult subjects were pooled, the MFR was 0.91 (95% CI 0.86 – 0.95), indicating a persistence in the female predominance.

None of the studies reported a male predominance in the prevalence of rhinitis during adulthood, although 2 studies conducted in Korea [37] (with 984 subjects aged ≥65 years) and Nigeria [38] (733 subjects aged 18 – 45 years) showed a borderline male predominance. In contrast, 2 European studies conducted in France [39] (10,038 subjects aged 18 – 65 years) and Sweden [40] (9,316 subjects aged 18 – 77 years) supported the persistence of a female predominance in the prevalence of rhinitis during adulthood. The 2 European studies were the only ones that also included middle-aged adults (aged 48 – 55 years). The other studies either included only elderly subjects, aged ≥65 years, or younger adults, aged 18 – 45 years.

Possible Influencing Factors for the Sex-Related Rhinitis Prevalence Switch

To explore the source of heterogeneity we performed meta-regression analyses with study period (until 2,000 vs. after 2,000), region (Asia vs. rest of the world), and residency (urban vs. rural/urban) as moderator variables. Only during puberty/adolescence and in adulthood, the region showed an effect as a moderator variable influencing the MFR ($p < 0.001$). Meta-regression analyses showed a sex-related rhinitis prevalence switch in studies conducted in non-Asian countries compared to those conducted in Asian countries. Only in the latter, a continuous male predominance from childhood to adulthood was observed.

Regional and Temporal Differences in the Prevalence of Rhinitis between Males and Females

As secondary outcomes, regional differences in the prevalence of rhinitis among males and females were explored (online suppl. Fig. S1, S2). Before puberty, all continents with the exception of the 2 African studies showed an MFR favoring a male predominance. During puberty and throughout adulthood, European, American, and studies conducted in Oceania supported a sex-related switch in rhinitis prevalence towards a female predominance. Studies conducted in Africa showed a borderline female predominance, whereas Asian studies showed a borderline male predominance.

Temporal differences (before and after the year 2000) in the prevalence of rhinitis among males and females were also assessed (online suppl. Fig. S3, S4). Before puberty, both study periods supported the male predominance in the prevalence of rhinitis. Similarly, both study periods supported the sex-related switch towards a female predominance in the prevalence of rhinitis during puberty and throughout adulthood.

Discussion

Main Findings

This systematic review with meta-analyses confirmed the hypothesis that, as in asthma, there is a sex-switch in the prevalence of rhinitis, which occurs during puberty. We found a male predominance in childhood that shifted towards a slight female predominance at around puberty. However, this did not seem to persist into adulthood, where we saw a rather balanced prevalence between the sexes. We covered studies that recruited children 30 years apart (from 1990 to 2010), but when the pooled estimates were stratified by study period before and after the millennium, our findings did not change. When we stratified the results according to region, the sex-related prevalence switch during puberty was confirmed in studies conducted in Europe, the Americas, Oceania and, of borderline significance, in Africa, but not in the meta-analysis with only Asian studies. These also showed an overall male predominance of rhinitis prevalence in adults.

Strengths and Limitations

We used broad inclusion criteria to take advantage of the available knowledge on the assessment of potential sex differences in the prevalence of rhinitis among the general population. We searched the PubMed and Embase databases, which cover most of the available medical literature. Although we did not restrict our search to specific languages, we may have missed studies if they were published in journals not included in the 2 major databases.

We deliberately limited the search to the present millennium (from 2000 to 2014) since prevalence of allergic diseases and rhinitis may have changed during the last decades. Our pooled estimates relied heavily upon data from studies conducted mainly in Europe and Asia, suggesting that the generalizability of our findings may be affected by the study setting. Even studies conducted in

Asia do not cover the whole continent. Studies conducted in Africa and Oceania were underrepresented, accounting for only 8% of the studies.

We found considerable inconsistency in our main as well as in the subgroup analyses by age, region, and study period, as indicated by the Higgins' I^2 tests. Therefore, caution must be exercised when interpreting the summary measures of the meta-analyses. We explored potential sources of heterogeneity using meta-regression models including several covariates such as study period, region (continent), and residency, and found that "continent" explained some of the inconsistency across the studies. However, neither study period nor having an urban or rural background seemed to influence the sex-switch found during puberty. Furthermore, because the prevalence of allergens varies among Asian countries, such as Korea and Japan, caution must be exercised when interpreting the results from the Asian continent. However, no sex differences have been observed in the prevalence of allergic rhinitis among Korean and Japanese subjects (from childhood to adulthood; online suppl. Fig. S1, S2). AR can be classified as seasonal, perennial or occupational according to the exposed allergens. However, the difficulties in differentiating between seasonal and perennial symptoms have been acknowledged [41]. Cedar pollen is the most prevalent allergen in Japan, and subjects sensitized to cedar pollen are also sensitized to a myriad of other allergens, such as house dust mite, which is very common in all Asian countries. Bearing in mind the limitations of classifying rhinitis according to the type of allergens [41], the Allergic Rhinitis and Its Impact on Asthma (ARIA) initiative has proposed a new classification, "intermittent" or "persistent" rhinitis, based on the duration and severity of symptoms [41, 42]. This classification has been considered in guidelines by many countries, including Korea and Japan [41, 43], to make AR more comparable with Western countries.

In the present systematic review, we specifically included prevalence studies, i.e. cross-sectional investigations that do not allow a longitudinal assessment of a direct shift in the prevalence or incidence between boys and girls. Furthermore, we assessed the prevalence of self-reported and parent-reported symptoms of current rhinitis, defined as the presence of typical symptoms of rhinitis in the last 12 months. This is a widely used method in population studies since rhinitis definitions based on doctors' diagnoses would exclude some milder and moderate allergic rhinitis symptoms and is prone to sex-related bias since in many societies ill women are more likely to seek medical advice than men. The validation of questionnaire-based assessments of allergic rhinitis questions showed in a large Japanese study, for example, a very good diagnostic accuracy of simple questions regarding objective clinical measurements such as serum-specific IgE and tests for nasal eosinophilia [44]. However, we cannot rule out a possible overestimation in the prevalence of rhinitis when using validated questionnaires, such as the ISAAC [31] or ECRHS [32]. On the other hand, we are not aware of any indication that a possible overestimation of the prevalence differs between men and women, thus we assume that this would not affect the MFRs that we evaluated.

Response rates were not provided by sex, with the exception of 2 studies in which participation was similar between the sexes in 1 study (86 vs. 85%) [45], and slightly higher in males in the other (87 vs. 77%) [46]. In our meta-analysis by age group we focused on current rhinitis, defined as symptoms in the last 12 months to include possible seasonal rhinitis.

There was no differentiation between allergic and nonallergic rhinitis and it is possible that the sex switch differs between these diseases. In our review, very few studies examined sensitization to allergens to distinguish between allergic and nonallergic rhinitis by means of IgE or skin prick test. However, they were insufficient to statistically explore the effect of sensitization in males and females across the different age categories.

Comparison with Other Allergic Diseases

We have found several nonsystematic reviews on sex differences in asthma development [3, 5, 11] and other allergy-related diseases [47]. In the case of eczema, an insignificant sex difference or male predominance in preschool children was observed, whereas a female predominance was observed in adulthood [47]. In the case of asthma, a change in sex predominance favoring females has been observed with the transition from childhood to adulthood [3, 5]. Because asthma and rhinitis coexist more often than expected [48], we hypothesized that rhinitis may also undergo similar sex reversal during puberty [49]. Our results support this hypothesis, though they failed to show a female predominance in adulthood, likely due to the limited studies found in adults.

Possible Mechanisms Explaining Sex Differences

Cross-sectional population-based studies do not allow conclusions to be drawn on determinants (longitudinal studies needed) or mechanisms (e.g., experimental studies), but they may be used to generate hypotheses for possible explanations of the sex differences in the prevalence

of rhinitis. The potential determinants reported in the studies were related to anatomical differences, differences in the immune response profile [11, 50, 51], and physiological changes during puberty, such as endogenous [7, 18, 28, 52] or exogenous sexual hormones (birth control pills) [53]. Very few studies assessed the allergic sensitization status of children and adolescents with rhinitis. Other determinants reported were different patterns of vulnerability to lifestyle factors [51, 54] and in the perception of symptoms [55], as well as the use of cosmetics [7]. There is a genetic difference between boys and girls in the susceptibility to environmental exposures, such as gas cooking, smoking, ozone, pets, house dust mites or pollens [5]. Sex-specific differences in environmental exposures such as lifestyles and job patterns cannot be neglected [56]. Because of the complexity of allergy-related diseases, causes and associated factors explaining this phenomenon remain elusive. Although only few genetic studies have been stratified by sex, it seems that there are some asthma-related [3, 57] and allergic rhinitis-related [58] polymorphisms in females.

Implications for Research

Further research is needed to understand the sex-related switch occurring during puberty and fill the gaps in our knowledge. Longitudinal studies are required to confirm these cross-sectional results. Studies should also examine determinants and possible mechanisms for this sex-related rhinitis prevalence switch during puberty, considering allergic sensitization [50, 59 – 61]. Most of the studies have mainly investigated the prevalence of rhinitis in children, and limited literature has been found in adults likely due to the underestimation of its prevalence and medical significance [37]. Rhinitis in elderly adults is becoming common and studies should also consider this age group. In the present review, the number of studies in adults was scarce, mixing subjects aged between 18 and 65 years and beyond. Further studies in adults are required, particularly segregating premenopausal, menopausal, and post-menopausal females, given that hormonal changes occur during menopause. These should aim to elucidate the influence of sex hormones upon the prevalence of rhinitis using a standardized methodology and preferably also measuring sex hormones in the blood.

Our findings on regional differences are of great interest and may be due to ethnicity or environmental exposure. Research is needed assessing the diversity of rhinitis across the globe. Because rhinitis can have a perennial and a seasonal nature, differences between the northern and the southern hemisphere are expected. A review assessing the prevalence of rhinitis in regions of the world suggested that the prevalence of rhinitis in Europe and the USA was more uniform compared to the greater diversity in the prevalence of rhinitis found in the rest of the world [62]. Our results contradict this study, as we found high heterogeneity both within and between European and American studies, although MFRs were similar.

Conclusions

Our global meta-analysis showed sex-related differences in rhinitis prevalence with a switch at around puberty from a male predominance to a female predominance. The male predominance from childhood seemed to persist in adolescence only in Asia. For the prevalence of rhinitis in adulthood, our systematic evaluation found no predominance in either males or females, although the number of studies was low. In the future, it will be mandatory to perform longitudinal studies differentiating between allergic and nonallergic rhinitis, in which the follow-up is continued into adulthood.

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Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

M.P. and T.K. conceived and designed the experiments. M.P., C.H., M.F., A.R., T. Keller, and B.C. performed the experiments. Data analysis and/or interpretation of the systematic review were conducted by M.P., M.F., A.R., and T. Keller. M.P., T. Keller, A.R., M.F., B.C., C.H., D.S.P., J.B., J.M.A., and T.K. contributed to the writing of the paper.

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ORIGINAL ARTICLE

Epidemiology and Genetics

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.

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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.

KEY WORDS
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) ≥ 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 ≥ 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).

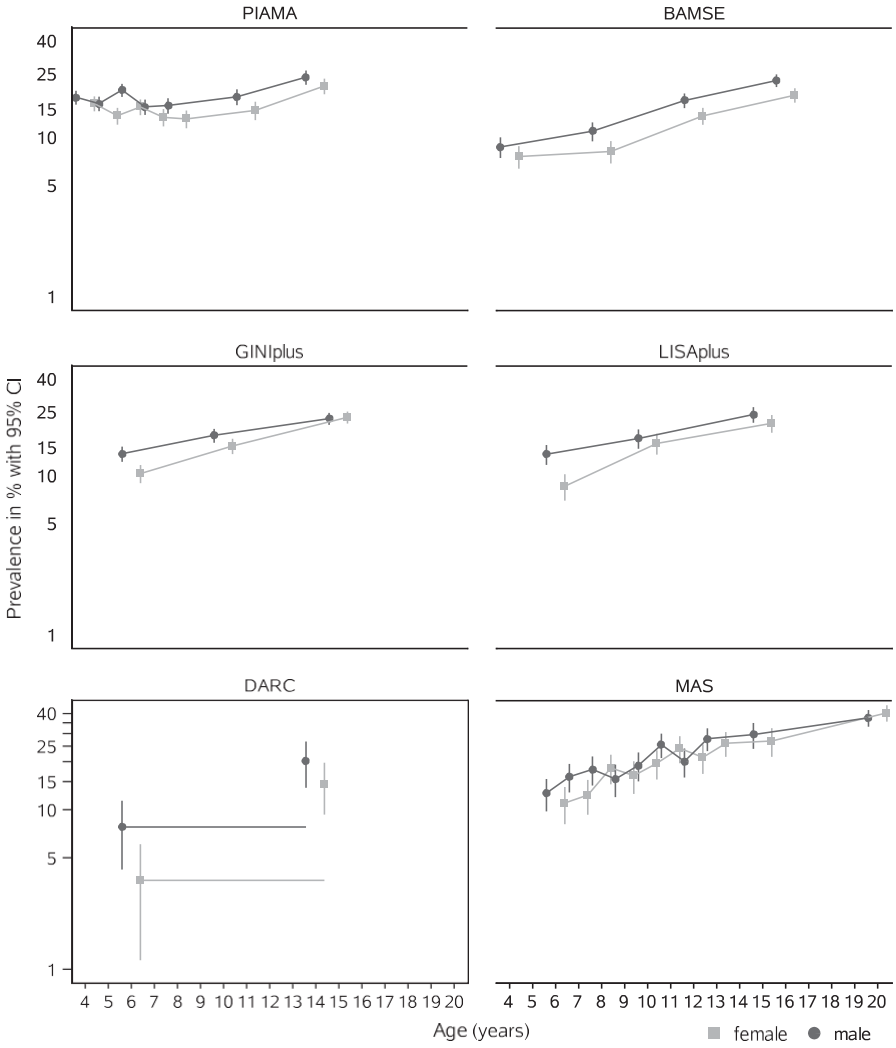
3.7 | IgE- and non-IgE associated outcomes

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.

TAB L E 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



FI GU RE 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

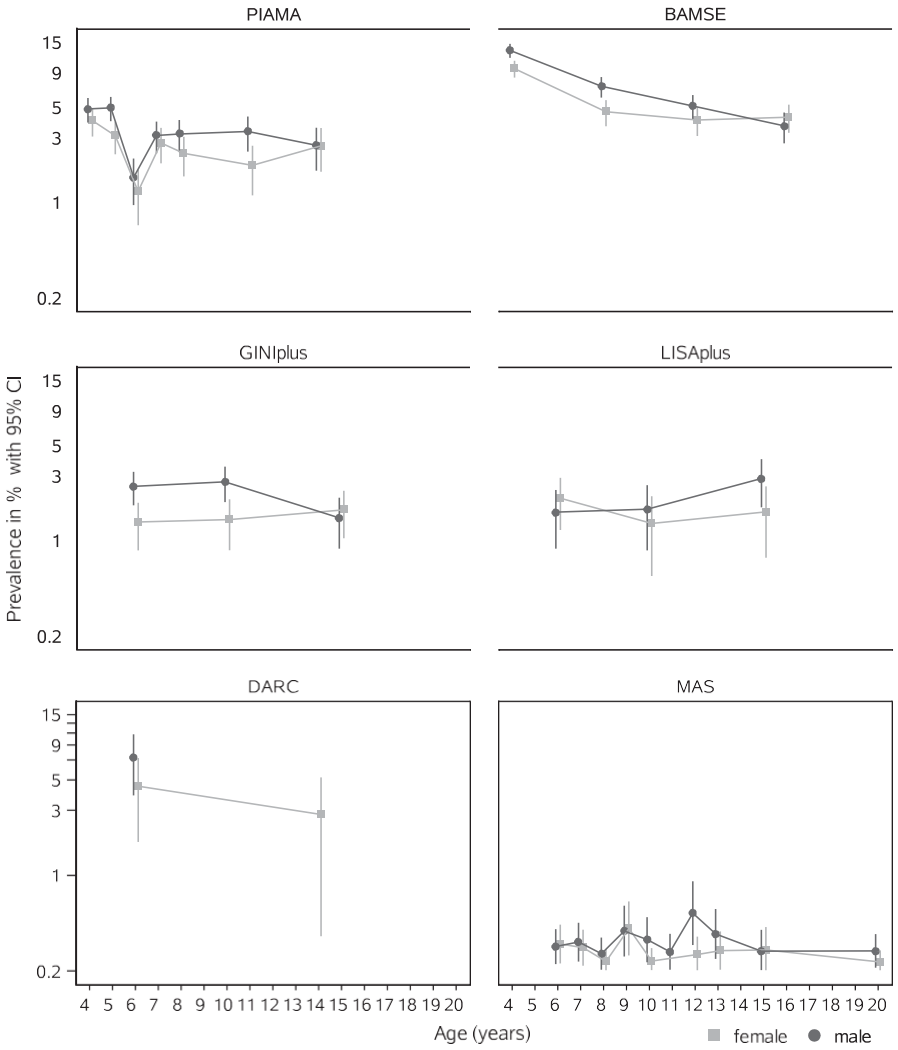
Including IgE against the common aero- and food allergens showed similar effect estimates for IgE- and non-IgE associated current rhinitis only, current asthma only and allergic multimorbidity compared to our primary definition of allergic sensitization status based only on common aero-allergens (Table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



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

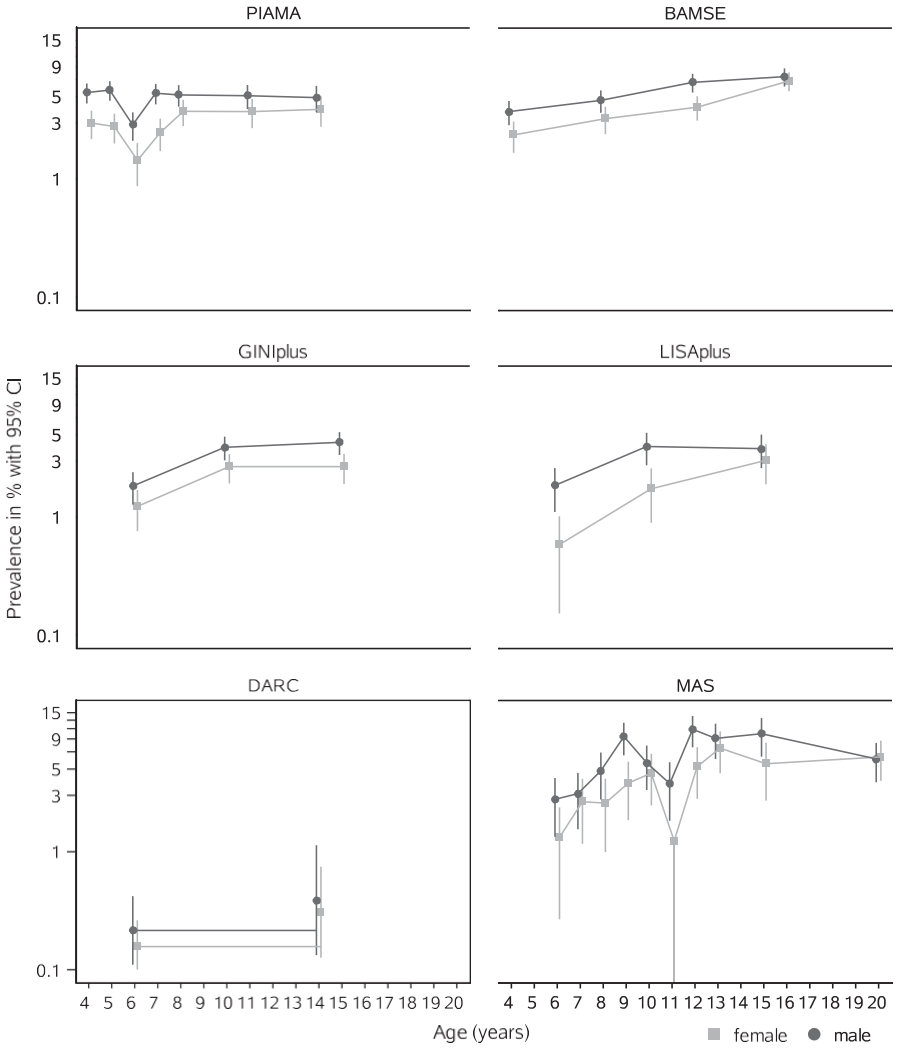
The non-IgE associated (single and multimorbid) phenotypes showed a slight female predominance after puberty onset, which was strongest for non-IgE associated rhinitis.

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



FI GU RE 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

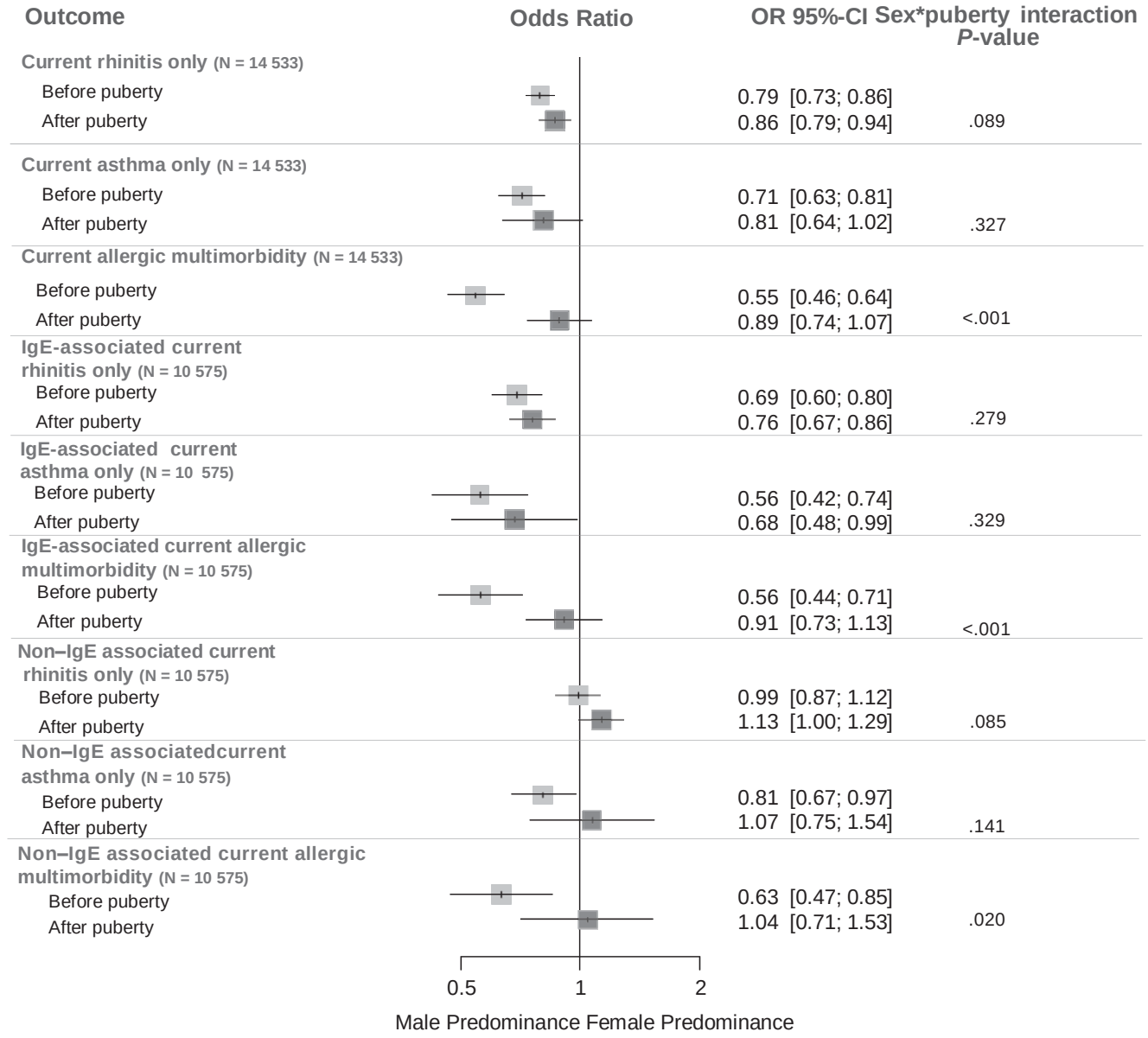


FIGURE 4 Odds Ratios from one-stage IPD meta-analysis of sex effect (female vs male) before and after puberty for all outcomes

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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SUPPOR TING INFORMATION

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

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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 were 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.

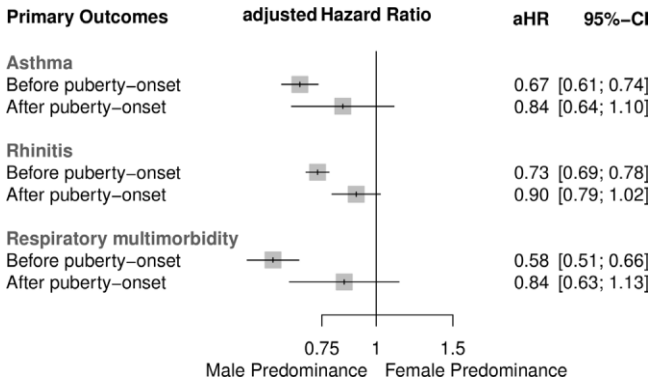

Figure 1 Adjusted HRs and 95% CIs for the risk of the incidence of asthma, rhinitis and respiratory multimorbidity for boys versus girls before and after puberty onset. The presented results are based on analyses of n=14 245, n=14 266 and n=14 233 participants, respectively. aHR, adjusted HR.

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).

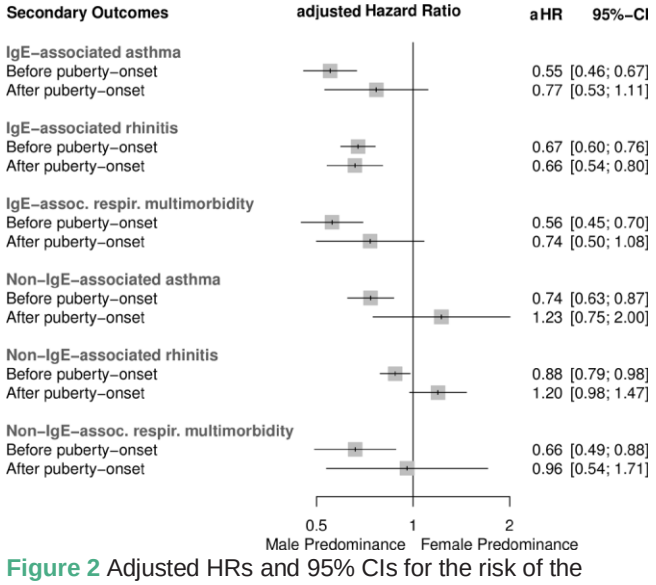

Figure 2 Adjusted HRs and 95% CIs for the risk of the incidence of IgE-associated and non-IgE-associated asthma, rhinitis and respiratory multimorbidity for boys versus girls before and after puberty onset. The presented results are based on analyses of n=10 320, n=10 331 and n=10 304 participants, respectively.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

Mein Lebenslauf wird aus datenschutzrechtlichen Gruenden in der elektronischen Version meiner Arbeit nicht veroeffentlicht.

11 Publikationsliste

Gesamt-Impact Factor: 156,2

1. Hohmann C, Keller T, Gehring U, Wijga A, Standl M, Kull I, Bergstrom A, Lehmann I, von Berg A, Heinrich J, Lau S, Wahn U, Maier D, Anto J, Bousquet J, Smit H, Keil T, Roll S. 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. *BMJ Open Resp Res*. 2019;6:e000460.
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