Machine learning-derived asthma and allergy trajectories in children: a systematic review and meta-analysis

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Shareable abstract (@ERSpublications)
Trajectories of asthma and allergy are heterogeneous in children. However, relatively few longitudinal patterns are consistently identified in the literature, with actionable risk factors such as parental smoking. Improvement in methodology is warranted. https://bit.ly/3YnrN0s

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Abstract

Introduction Numerous studies have characterised trajectories of asthma and allergy in children using machine learning, but with different techniques and mixed findings. The present work aimed to summarise the evidence and critically appraise the methodology.

Methods 10 databases were searched. Screening, data extraction and quality assessment were performed in pairs. Trajectory characteristics were tabulated and visualised. Associated risk factor and outcome estimates were pooled using a random-effects meta-analysis.

Results 89 studies were included. Early-onset (infancy) persistent, mid-onset (~2–5 years) persistent, early-onset early-resolving (within ~2 years) and early-onset mid-resolving (by ~3–6 years) wheezing and eczema, respectively, were the most commonly identified disease trajectories. Intermediate/transient trajectories were rare. Male sex was associated with a higher risk of most wheezing trajectories and possibly with early-resolving eczema, while being slightly protective against mid-onset persistent eczema. Parental disease/genetic markers were associated with persistent trajectories of wheezing and eczema, respectively. Prenatal (and less so postnatal) tobacco smoke exposure was associated with most wheezing trajectories, as were lower respiratory tract infections in infancy (particularly with the early-onset resolving patterns). Most studies (69%) were of low methodological quality (particularly in modelling approaches and reporting). Few studies investigated allergic multimorbidity, allergic rhinitis and food allergy.

Conclusions Childhood asthma/wheezing and eczema can be characterised by a few relatively consistent trajectories, with some actionable risk factors such as pre-/postnatal smoke exposure. Improved computational methodology is warranted to better assess generalisability and elucidate the validity of intermediate/transient trajectories. Likewise, allergic multimorbidity and trajectories of allergic rhinitis and food allergy need to be further elucidated.

Introduction

Asthma and allergic diseases are among the most common diseases in childhood [1–3]. These conditions are associated with substantial morbidity and impose a societal burden through increased healthcare

utilisation, reduced academic performance, social life limitations and a reduced quality of life [4–7]. There is a wide range of clinical manifestations (phenotypes) of asthma and allergy, which can vary in terms of disease development (trajectories) [8–10]. Characterising trajectories is essential to identify risk factors, distinguish groups with similar outcomes/prognosis and optimise management. Machine learning (ML) is a promising and increasingly utilised tool for phenotyping longitudinal data, as it facilitates large-scale analysis in a data-driven and relatively hypothesis-free manner.

Many studies have used ML-based approaches to characterise the trajectories of asthma and allergy in children. Their findings, however, are mixed and fail to provide a clear picture, due to substantial variations in terms of follow-up time, assessment intervals, disease definitions and study populations. Furthermore, ML-based trajectory modelling depends on pre-processing, the nature of the input data and model settings. Given the diverse evidence on the topic, the aim of this work was three-fold, as follows: 1) summarise the identified trajectories of asthma and allergic disease in childhood, 2) critically assess computational methodologies, and 3) synthesise the subject characteristics and associated risk factors and outcomes of the identified trajectories. Ultimately, this work aims to provide a structured overview of the findings from recently published studies on the topic, thereby facilitating a detailed and systematic evaluation of their strengths, limitations, similarities, differences and patterns and highlighting opportunities for improvements in future studies.

Methods

This work was outlined in a protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42023441691) and has been published [11]. Reporting of the results was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [12] checklist (supplementary checklist 1) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [13] reporting guidelines (supplementary checklist 2). Deviations from the protocol are described in supplementary text 1.

Data sources and search strategy

The CAB Direct, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Embase, Google Scholar, PsycInfo, PubMed, Scopus, Web of Science, World Health Organization Global Index Medicus and WorldCat Dissertations and Theses databases were searched. The search queries consisted of three blocks, as follows: 1) asthma and allergy, 2) trajectory analysis, and 3) age. An initial search query was piloted in PubMed, during which additional search terms were identified. The resulting search query was modified for use in the other databases. A fourth block was added for databases with >1000 (arbitrary threshold to reduce screening load) results and appropriate filters for age (excluding adult-only studies). The search queries are presented in tables S1A–S1J. Non-English articles were translated using Google Translate. References in included studies (and relevant reviews) were screened as an additional source. Relevant articles under embargo, conference abstracts and abstracts without available full text were included but not assessed further (data extraction, quality assessment, narrative synthesis or meta-analysis). To provide an overview of the most up-to-date and methodologically refined approaches and outputs, we restricted the search to the past decade.

The eligibility criteria were as follows:

- *Study design*: observational studies with ⩾2 assessments of asthma or allergy with ⩾1 year between the first and last assessment.
- *Population*: representative samples of children (aged ⩽18 years at the last assessment; exception for studies with ⩾2 childhood assessments).
- *Objective*: identification/characterisation of trajectories of asthma, allergy (allergic rhinitis/rhinoconjunctivitis/conjunctivitis, atopic dermatitis or food allergy) or indirect measurement (*e.g.*, allergic sensitisation), regardless of assessment method, data source or definition.
- *Publication date*: past 10 years (2013–2023). Earlier original trajectory analyses were also eligible in cases of secondary analyses published within the past decade.

De-duplication, screening, and data extraction

De-duplication was manually performed in EndNote 21 (Clarivate Analytics, USA) using a semi-automated approach proposed by Bramer *et al*. [14]. The records were then transferred to Rayyan [15]. Screening was performed in two steps, as follows: 1) title/abstract/keyword screening and 2) full-text screening by two independent reviewers. After completion, the decisions were unblinded and differences discussed. A senior reviewer (B.I. Nwaru) arbitrated in edge cases. Data extraction was performed similarly, utilising a standardised Microsoft Excel (Microsoft Corp., USA) form (https://osf.io/tj4g8). Screening and data extraction were performed without the assistance of artificial intelligence (AI)-based

tools. Missing/incomplete data were requested from the corresponding author and then co-authors if no response was received within 1 week.

Quality assessment

Given the paucity of specified tools, to assess methodological quality a custom tool was developed based on reviews and reporting guidelines (*i.e.*, the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS)) [16] and the structure/rating system of the Effective Public Health Practice Project (EPHPP) [17]. Seven domains were evaluated, as follows: 1) selection bias, 2) data collection methods, 3) withdrawals and dropouts, 4) pre-processing, 5) trajectory modelling, 6) associated risk factors and outcomes, and 7) evaluation and reporting of results. Quality assessment was performed as the previous steps (*i.e.*, by two independent reviewers following by unblinding of ratings, discussion and arbitration where needed) without AI assistance. The robustness of the computational methodology was visually presented in further detail with a weighted score based on relevant items. Details on the quality assessment can be found at https://osf.io/ayf35 in the folder Documents/Screening, data extraction, and quality assessment/Quality assessment.

Data synthesis and statistical analysis

Extracted data were tabulated, plotted and narratively synthesised. Trajectories similar in terms of longitudinal disease pattern(s) (determined through consensus between B.I. Nwaru, D. Lisik, E. Goksör and G. Wennergren) were grouped and named. The definitions of "persistent", "transient", "early", "mid" and "late" in the provided names were based on the original trajectory names, but occasionally modified to better fit with other similar trajectories. Disease (measure) probability/prevalence over time was extracted using WebPlotDigitizer (https://automeris.io/). Comparable data on associated risk factors and outcomes were synthesised using a random-effects meta-analysis with robust variance estimation. This method can account for nonindependent effect sizes and varying weighting schemes [18]. In meta-analyses with only independent effect sizes or Satterthwaite degrees of freedom <4, random-effects meta-analysis with a restricted maximum-likelihood estimator was utilised. As some studies investigated large numbers of risk factors/outcomes, we implemented false discovery rate correction on the p-values. Depending on the input data, the effect measure was odds ratio (OR) or risk ratio. Heterogeneity was assessed through I^2 and τ^2 statistics and further evaluated with subgroup analysis by sex and asthma/allergy heredity. Static trajectory characteristics (*e.g.*, proportion of boys) were synthesised through a generalised linear mixed model with logit-transformed percentages, which is suitable for small samples and low/high proportions [19]. The corresponding 95% confidence interval was calculated through the Wilson score interval method without continuity correction. Sensitivity analysis was performed by excluding studies with a "weak" overall rating. Meta-analyses were presented as forest plots. All analyses were performed using the R statistical software (version 4.2.3; R Core Team).

Results

Screening and study characteristics

In total, 12 327 de-duplicated records were retrieved from the database searches. After the initial screening based on title/abstract/keywords, 183 records remained, which were assessed by full text (see table S2 for reasons for exclusion). Finally, 107 reports remained. Of these, three reports were secondary analyses of primary analyses (studies in which trajectory analyses were performed) published prior to 2013, which were also included, totalling 110 reports, of which 21 were conference abstracts (table S3) and 89 were full-text articles [20–108] based on 71 primary analyses (figure 1). A total of 47 reports were included in the 220 meta-analyses (details at https://osf.io/ayf35). Most studies were performed in high-income "Western" countries (figure S1) and were generally of low methodological quality (figures S2 and S3 and tables S4A and S4B), with little improvement over time (figure 2b). Trajectory modelling and reporting were the sections with the highest proportion of "weak" ratings. The number of assessments and length of follow-up varied widely but did not correlate clearly with the number of identified trajectories (figure S4).

Allergic multimorbidity

18 studies [21, 22, 25, 27–29, 38, 41, 42, 49, 50, 57, 69, 72, 73, 77, 80, 85] derived trajectories of two or more diseases or measures thereof (https://osf.io/xy58k). Most studies investigated unique sets of parameters over time and were not comparable. Two studies, however, assessed rhinitis, eczema, wheezing and nocturnal cough without concomitant cold/influenza (table S5). A trajectory was found in these studies of relatively persistent rhinitis and nocturnal cough (with somewhat prevalent wheezing and eczema). Meta-analyses did not reveal any significantly associated risk factor (table S5).

(Allergic) rhinitis and rhinoconjunctivitis

Only one study [60] derived trajectories of rhinitis (https://osf.io/xy58k).

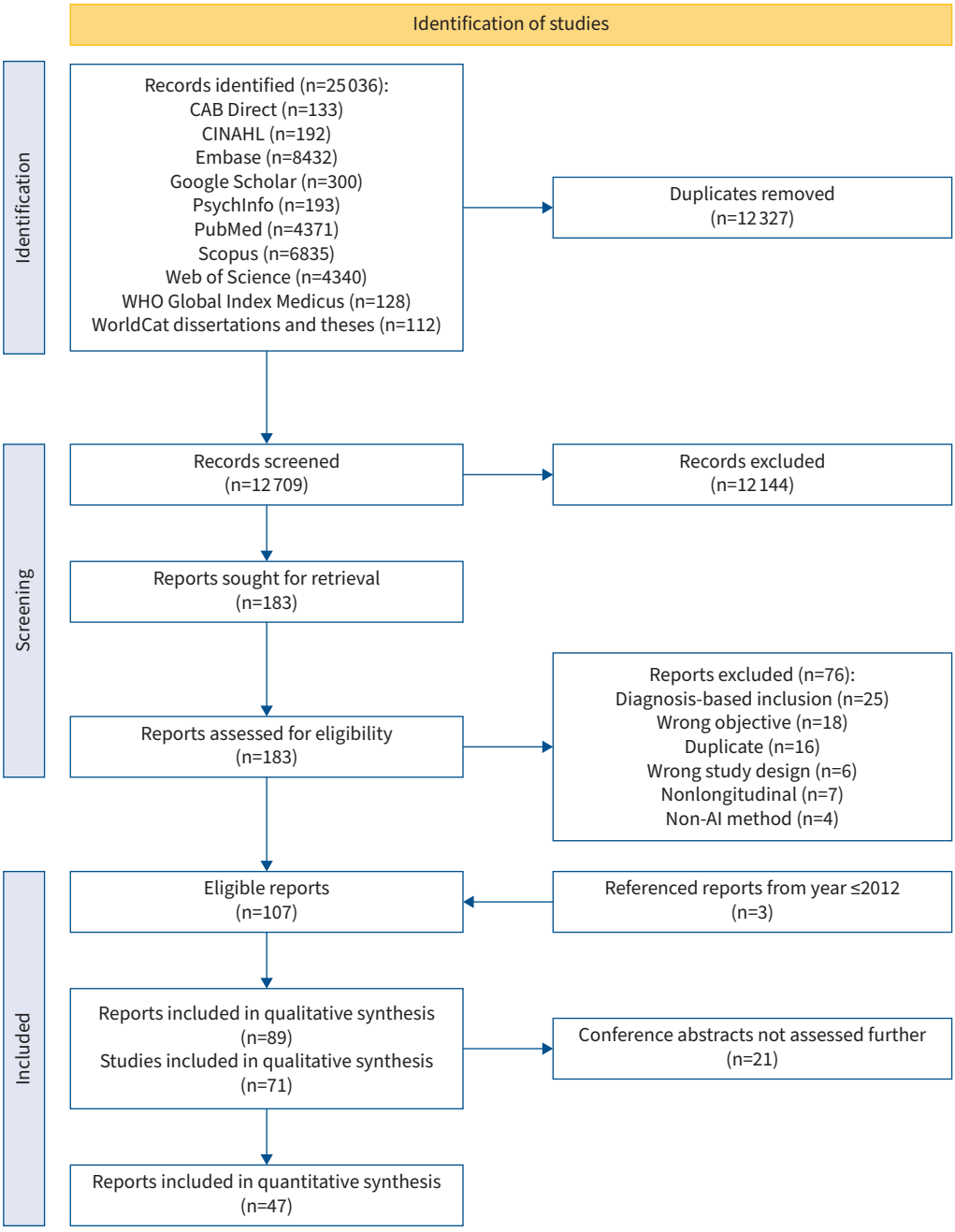

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. The "Referenced reports from year ⩽2012" represents the papers published in 2012 or earlier in which trajectories were derived and which were referenced in secondary analyses (published within the defined timeframe (2013–2023)) included in this work. AI: artificial intelligence; CINAHL: Cumulative Index to Nursing and Allied Health Literature; WHO: World Health Organization.

Allergic sensitisation

12 studies [21, 25, 35, 40, 42, 43, 47, 53, 54, 56, 76, 78] derived trajectories of allergic sensitisation (https://osf.io/xy58k). While the investigated allergens varied substantially, eight similar longitudinal patterns appeared in at least two studies (table S6). Six of these trajectories were characterised by aeroallergen sensitisation, commonly increasing with time. Of these, two were primarily targeted at mites, namely 1) *early-onset persistent mite-dominated sensitisation* and 2) *increasing mite-dominated sensitisation*, while one trajectory exhibited sensitisation to most investigated aeroallergens and the three remaining trajectories were defined by mite or grass/tree pollen sensitisation with varying sensitisation to other

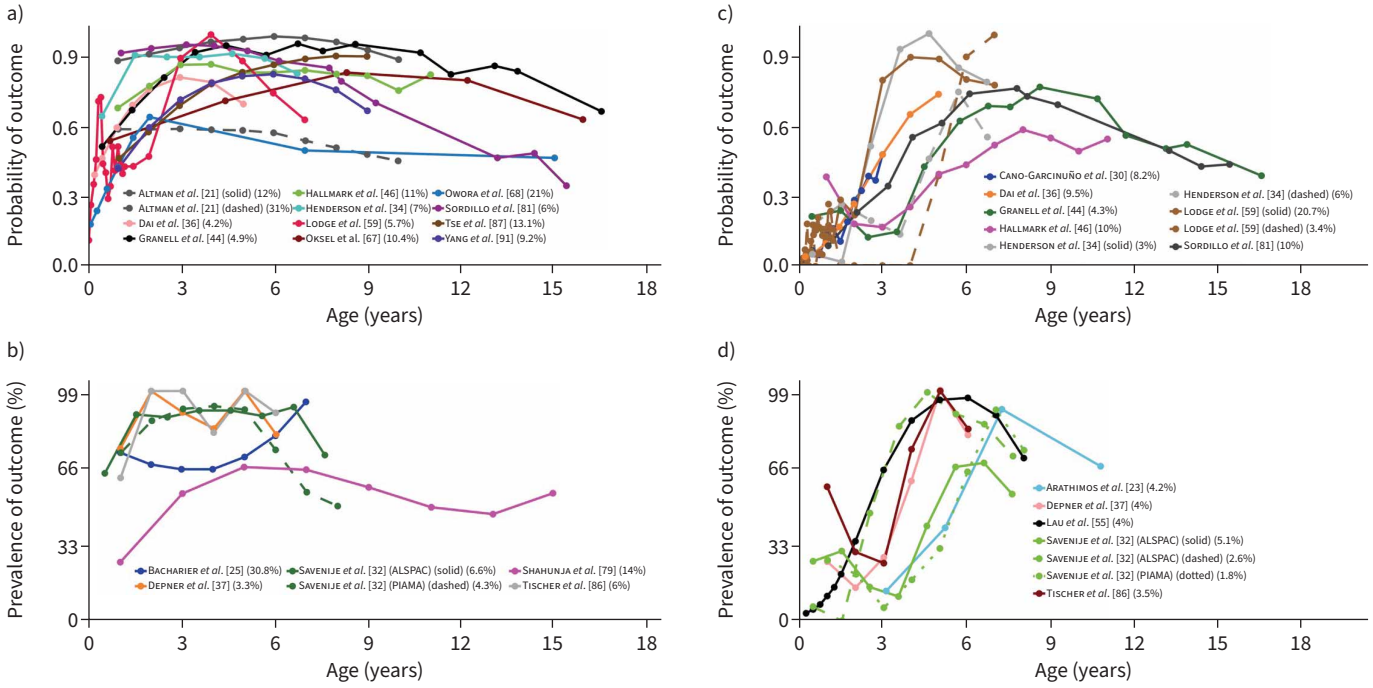

FIGURE 2 Early-onset and mid-onset persistent wheezing. Each line represents a trajectory from a study. When multiple trajectories are included from the same study, different line types (*e.g.* solid or dashed) distinguish between them. Line colour indicates the specific study source for each trajectory. Alongside each study, a percentage shows the proportion of the study's total sample represented by that trajectory. The points along each line denote the time-points at which an assessment of the trajectory-defining variable(s) was done. The *y*-axis denotes the prevalence/probability, while the *x*-axis indicates the subject age. a) Early-onset persistent wheezing in studies [21, 34, 36, 44, 46, 59, 67, 68, 81, 87, 91] which presented trajectories by probability. b) Early-onset persistent wheezing in studies [25, 32, 37, 79, 86] which presented trajectories by prevalence. c) Mid-onset persistent wheezing in studies [30, 34, 36, 44, 46, 59, 81] which presented trajectories by probability. d) Mid-onset persistent wheezing in studies [23, 32, 37, 55, 86] which presented trajectories by prevalence.

aeroallergens. Finally, one trajectory was dominated by sensitisation to grass pollen with a notable component of tree and peanut sensitisation and one trajectory was characterised by persistent sensitisation to egg and milk. In terms of related outcomes, meta-analyses suggested an association with (allergic) rhinitis at the end of follow-up (pooled OR 2.99 (95% CI 1.77–5.05) for *increasing mite-dominated sensitisation* and pooled OR 7.27 (95% CI 4.14–12.77) for *grass-dominated sensitisation with a notable component of late-onset tree and peanut sensitisation*). The aforementioned trajectory was also associated with asthma at the end of follow-up (pooled OR 3.63 (95% CI 1.93–6.81)).

Asthma, wheezing and cough without concomitant cold/influenza

34 studies [21, 23, 25, 26, 30, 32, 34, 36, 37, 39, 44–46, 51, 55, 58, 59, 62, 63, 66–68, 70, 75, 79, 81, 82, 84, 86–89, 91, 92] derived trajectories of asthma, wheezing and cough without concomitant cold/influenza (https://osf.io/xy58k). Most studies investigated wheezing (typically any wheezing in the past year), while nine studies investigated asthma through various definitions (*e.g.*, specific number of asthma-related clinic/hospital visits in the past year), among which one trajectory was reoccurring, namely *early-onset mid-resolving asthma-related healthcare utilisation* (table S7). Among the wheezing-based studies, six reoccurring trajectories were identified. Two of these were defined by persistent symptoms, namely 1) *early-onset persistent wheezing* and 2) *mid-onset persistent wheezing* (figure 2). Onset was seen at baseline/within first ~1 year and by 3–5 years, respectively. The most prominent risk factors for *early-onset persistent wheezing* were lower respiratory tract infections (LRTIs) in infancy (pooled OR 8.84 (95% CI 3.65–21.37)), parental asthma (pooled risk ratio 2.98 (95% CI 2.14–4.15)) and male sex (pooled risk ratio 1.72 (95% CI 1.55–1.92)). Similar findings were seen for *mid-onset persistent wheezing*, as follows: LRTI in infancy (pooled risk ratio 3.2 (95% CI 1.68–6.12)), parental asthma (pooled risk ratio 2.05 (95% CI 1.38–3.05)) and male sex (pooled risk ratio 1.53 (95% CI 1.33–1.75)). An allergic component appeared to be prevalent in these trajectories, as allergic sensitisation at age 6–12 years was associated with *early-onset persistent wheezing* (pooled OR 3.56 (95% CI 2.87–4.42)) and at age 6–8 years to *mid-onset persistent wheezing* (pooled OR 6.8 (95% CI 5.37–8.6)). Two trajectories were

characterised by resolving symptoms, namely 1) *early-onset early-resolving wheezing* and 2) *early-onset mid-resolving wheezing*, the former with remission by ~3 years and the latter with symptoms into early school years (figure 3). LRTI in infancy was the most prominently associated risk factor (pooled risk ratio 2.25 (95% CI 1.68–3.02) for *early-onset early-resolving wheezing* and pooled risk ratio 8.34 (95% CI 5.89–11.82) for *early-onset mid-resolving wheezing*). Daycare attendance also constituted a risk factor (pooled risk ratio 1.45 (95% CI 1.16–1.82) for *early-onset early-resolving wheezing* and pooled risk ratio 1.38 (95% CI 1.18–1.61) for *early-onset mid-resolving wheezing*). For *early-onset early-resolving wheezing*, however, the association was not significant in subjects with heredity for asthma/allergy (pooled risk ratio 1.29 (95% CI 0.9–1.86)). Finally, two wheezing trajectories were defined by a transient, relatively short episode of wheezing, namely 1) *mid-transient wheezing* and 2) *late-transient wheezing*. These trajectories were identified in fewer studies than the two persistent/resolving trajectories and generally constituted lower proportions of the sample.

Atopic dermatitis and eczema

11 studies [20, 24, 48, 61, 64, 65, 71, 74, 83, 90, 93] derived trajectories of atopic dermatitis/eczema (https://osf.io/xy58k). Most commonly, disease was defined by parental/self-report of itchy rash (in age-typical locations) in the past year. Seven longitudinal patterns were identified in at least two studies (table S8). Two of these were persistent, namely 1) *early-onset persistent eczema* and 2) *mid-onset (persistent) eczema*, with onset in infancy in the former and by ~3 years in the latter (figure 4). The most prominent risk factor for *early-onset persistent eczema* was parental allergy (pooled OR 2.6 (95% CI 1.22–5.55)). Male sex was associated with lower risk for *mid-onset (persistent) eczema* (pooled OR 0.62 (95% CI 0.45–0.87)), but the association was nonsignificant for *early-onset persistent eczema* (pooled OR 0.86 (95% CI 0.63–1.17)). Both trajectories were associated with an increased risk of atopic disease and related outcomes, *e.g.*, allergic sensitisation, pooled OR 3.87 (95% CI 1.83–8.17) for *early-onset persistent eczema* (at 6–10 years) and pooled OR 1.87 (95% CI 1.25–2.82) for *mid-onset (persistent) eczema* (at 6–8 years). The five remaining patterns indicated remission, three of which had early onset, as follows:

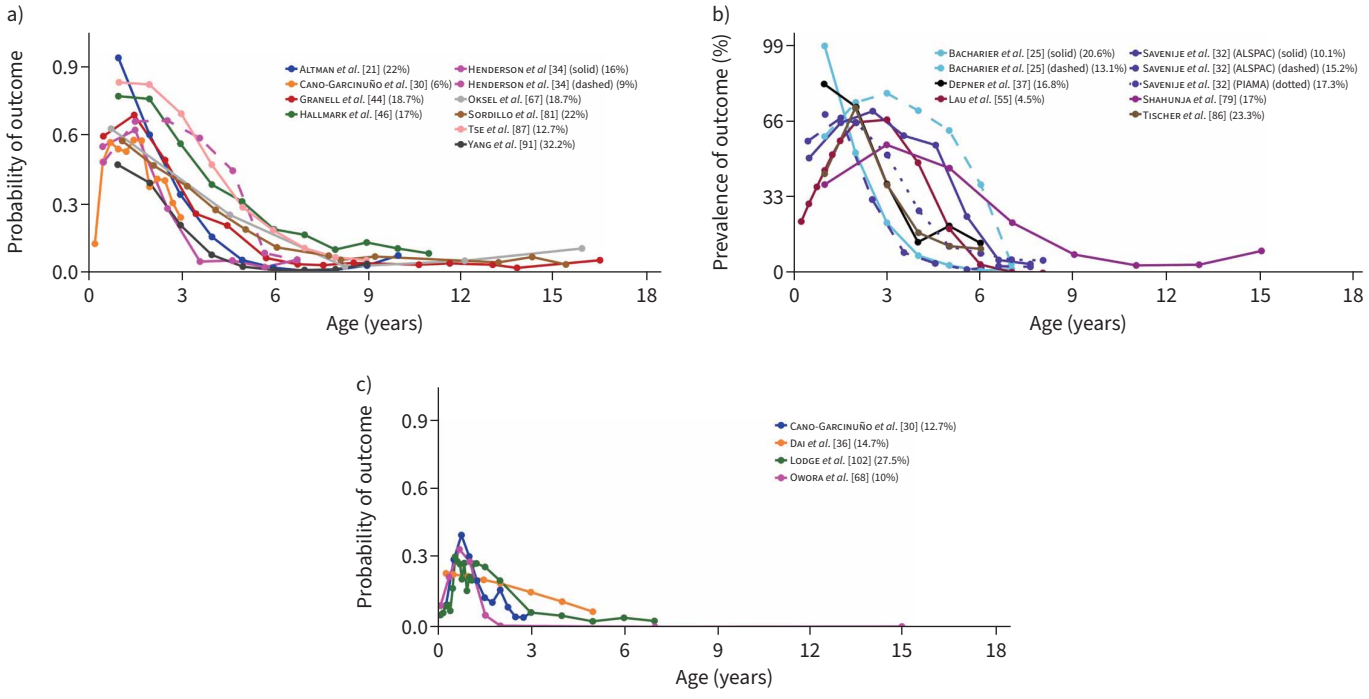

FIGURE 3 Early-onset mid-resolving and early-onset early-resolving wheezing. Each line represents a trajectory from a study. When multiple trajectories are included from the same study, different line types (*e.g.* solid, dotted or dashed) distinguish between them. Line colour indicates the specific study source for each trajectory. Alongside each study, a percentage shows the proportion of the study's total sample represented by that trajectory. The points along each line denote the time-points at which an assessment of the trajectory-defining variable(s) was done. The *y*-axis denotes the prevalence/probability, while the *x*-axis indicates the subject age. a) Early-onset mid-resolving wheezing in studies [21, 30, 34, 44, 46, 67, 81, 87, 91] which presented trajectories by probability. b) Early-onset mid-resolving wheezing in studies [25, 32, 37, 55, 79, 86] which presented trajectories by prevalence. c) Early-onset early-resolving wheezing in studies [30, 36, 59, 68] which presented trajectories by probability.

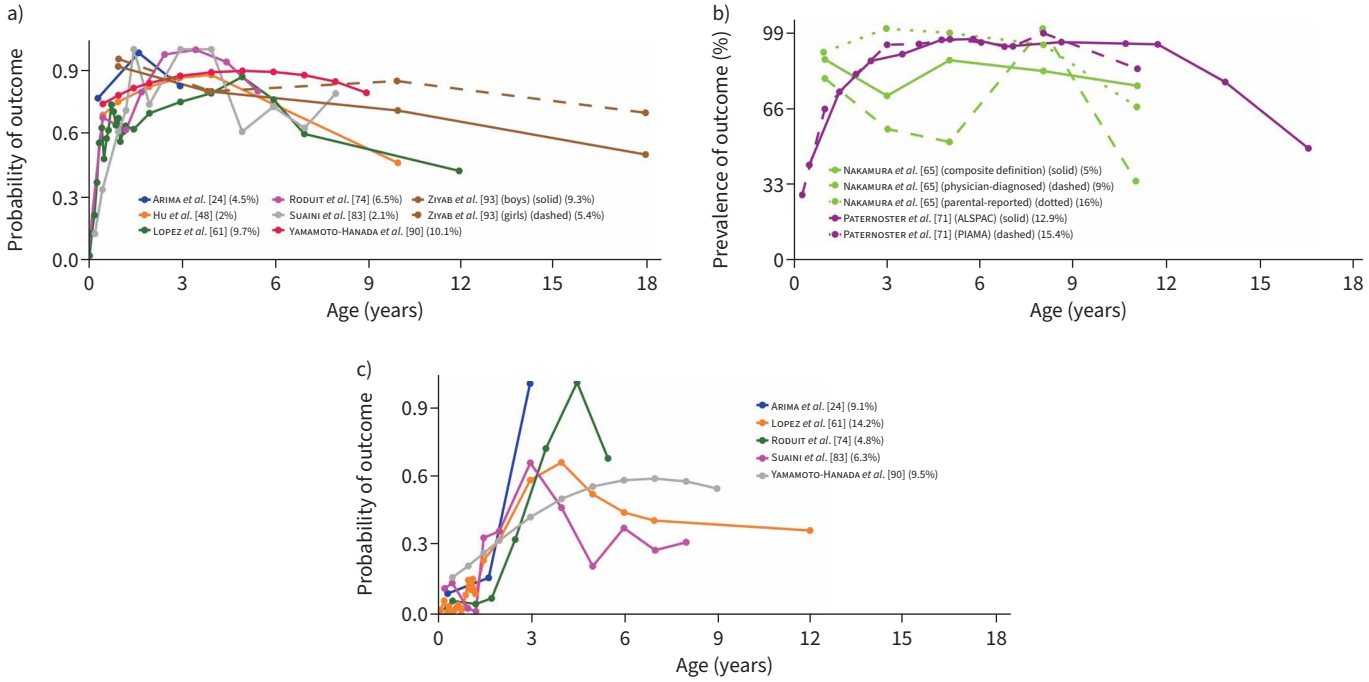

FIGURE 4 Early-onset and mid-onset persistent eczema. Each line represents a trajectory from a study. When multiple trajectories are included from the same study, different line types (*e.g.* solid or dashed) distinguish between them. Line colour indicates the specific study source for each trajectory. Alongside each study, a percentage shows the proportion of the study's total sample represented by that trajectory. The points along each line denote the time-points at which an assessment of the trajectory-defining variable(s) was done. The *y*-axis denotes the prevalence/probability, while the *x*-axis indicates the subject age. a) Early-onset persistent eczema in studies [24, 48, 61, 74, 83, 90, 93] which presented trajectories by probability. b) Early-onset persistent eczema in studies [65, 71] which presented trajectories by prevalence. c) Mid-onset persistent eczema in studies [24, 61, 74, 83, 90] which presented trajectories by probability.

1) *early-onset early-resolving eczema*, 2) *early-onset mid-resolving eczema* and 3) *early transient eczema.* In *early-onset early-resolving eczema*, remission was seen within ∼18 months, whereas *early-onset mid-resolving eczema* was commonly present until early school years (figure 5). Male sex was borderline associated with *early-onset mid-resolving eczema* (pooled OR 1.27 (95% CI 1.0–1.62); in sensitivity analysis this associated was weakened). *Early transient eczema* was characterised by a longitudinal pattern similar to *early-onset mid-resolving eczema*, albeit with somewhat later onset. Finally, two studies identified *mid-onset late-resolving eczema* and *late-onset late-resolving eczema*, respectively.

Computational methodology

No clear trends were seen in methodology across the past 10 years. The most common (utilised in ∼50% of studies) modelling approach was latent class analysis. Other naïve techniques (not explicitly modelling by time/age), *e.g.*, longitudinal k-means and partitional clustering algorithms, were also common. Few studies assessed modelling stability/overfitting or reported sufficient information for assessments of internal homogeneity and model performance in comparison to other possible solutions. Practically none of the studies provided analysis code (https://osf.io/ny8qu).

Discussion

In this work, characteristics and associated risk factors/outcomes of asthma and allergy trajectories in children were synthesised. Although most studies defined asthma and allergic disease similarly (parental/self-reported disease/symptoms in the past year), substantial heterogeneity was seen in methodology, *e.g.*, modelling approaches, missing data management, subject age, number of assessments and assessment intervals. Nevertheless, most studies of wheezing and eczema identified several similar trajectories. These trajectories were associated with multiple risk factors, *e.g.*, sex, parental asthma/allergy and early-life exposure, as well as several outcomes, including allergic sensitisation and allergy/asthma at the end of follow-up. Subgroup and sensitivity analyses mostly revealed comparable albeit occasionally slightly weaker associations.

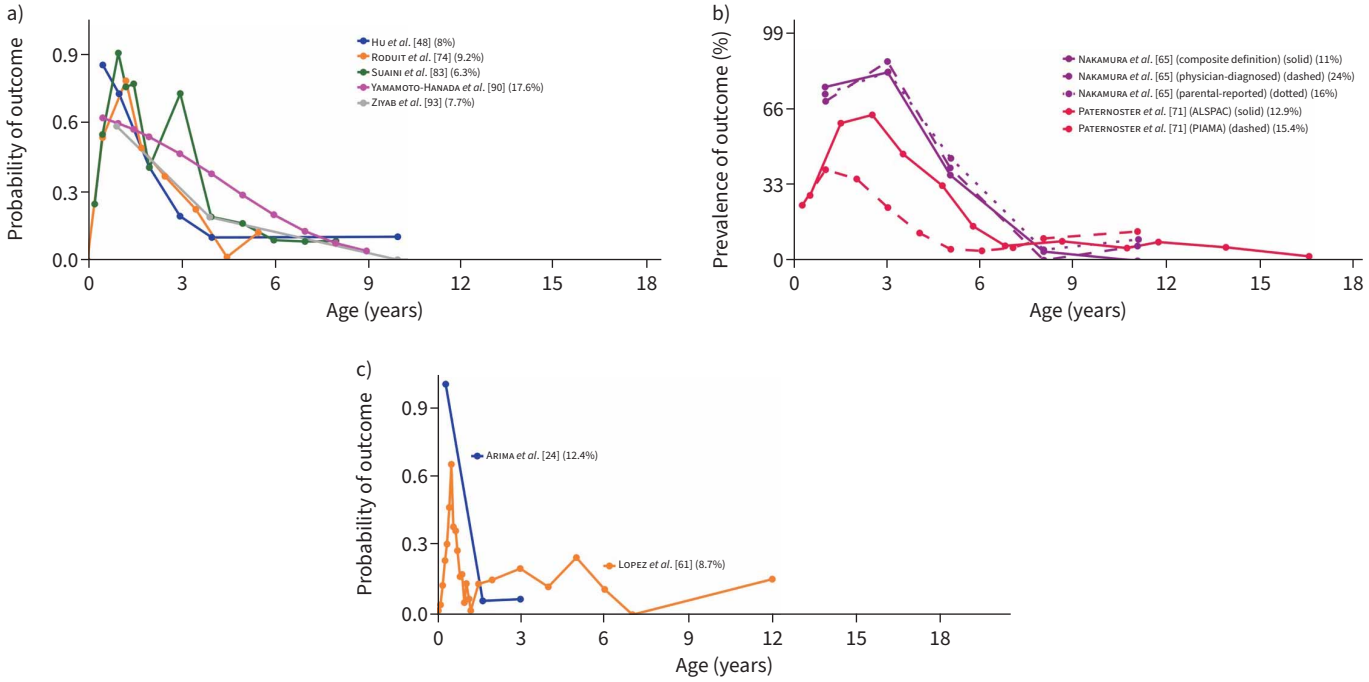

FIGURE 5 Early-onset mid-resolving and early-onset early-resolving eczema. Each line represents a trajectory from a study. When multiple trajectories are included from the same study, different line types (*e.g.* solid or dashed) distinguish between them. Line colour indicates the specific study source for each trajectory. Alongside each study, a percentage shows the proportion of the study's total sample represented by that trajectory. The points along each line denote the time-points at which an assessment of the trajectory-defining variable(s) was done. The *y*-axis denotes the prevalence/probability, while the *x*-axis indicates the subject age. a) Early-onset mid-resolving eczema in studies [48, 74, 83, 90, 93] which presented trajectories by probability. b) Early-onset mid-resolving eczema in studies [65, 71] which presented trajectories by prevalence. c) Early-onset early-resolving eczema in studies [24, 61] which presented trajectories by probability.

The comprehensive search strategy and intricate methodology assessment and trajectory characterisation provide a rich overview of the literature. Furthermore, the 220 meta-analyses contribute clinical context and an indication of the pathophysiological mechanisms involved. However, this work has some limitations. Relevant articles may have been published following the database searches. Nevertheless, we believe, given the publication rate in recent years (figure 2b), that the findings from more recent papers would likely not differ substantially from our data, while older findings are of reasonably similar or weaker methodological quality. Meta-analyses typically included few studies, which limits precision and interpretability, particularly given the between-study heterogeneity, notable classification uncertainty [67] and insufficient follow-up time. This also hampered sensitivity/subgroup analysis and rendered publication bias assessment impractical. Longitudinal studies are costly and most included studies were performed in high-income countries, restricting generalisability. While we developed the quality assessment tool based on multiple guidelines and recommendations of experts in the field (https://osf.io/kc3wt), it is possible that factors of importance have been overlooked and the rating system was ultimately subjectively constructed. Finally, the definition and naming of the trajectories are subjective and some trajectories could theoretically be categorised to other groups.

The wheezing patterns that were commonly found in the included studies correspond with clinically recognisable phenotypes. The association with male sex is in accordance with studies reporting that asthma is more prevalent in boys until puberty, after which a switch between boys and girls is seen. Likewise, physiological differences in early childhood, *e.g.*, smaller airway diameter in relation to lung volume in boys compared to girls, as well as (epi)genetic differences [109] may explain the higher prevalence of asthmatic symptoms in boys during this age [110], reflecting the findings in our meta-analyses. As most of the included studies did not follow subjects beyond puberty onset, male sex was associated with a higher risk of most trajectories. LRTI in infancy was strongly associated with both persistent and resolving wheezing trajectories, reflecting that respiratory viral infections are related to not only transient viral wheezing, but also wheezing associated with eczema/allergic sensitisation, so-called "true asthma". However, LRTI and other factors related to respiratory (cross)infections, *e.g.*, older siblings and daycare

attendance, were more strongly associated with resolving wheezing trajectories, likely reflecting the infection-related wheezing seen in early childhood. Although daycare attendance was significantly associated with an increased risk of wheezing trajectories, as found in a previous related meta-analysis [111], our meta-analyses did not replicate significant protective associations for breastfeeding. The *mid-transient wheezing* trajectory was identified in four studies but was rare in the study populations. It is possible, given the likeness to the *early-onset early-resolving wheezing* trajectory, that the former group constitutes a subgroup of the latter, albeit with more persistent and pronounced symptoms.

For eczema, the commonly identified trajectories also reflect clinically recognisable phenotypes. Male sex being associated with borderline higher risk of *early-onset mid-resolving eczema* and slightly lower risk of *mid-onset (persistent) eczema* is consistent with previous reviews and likely reflects sex-related mechanisms similar to those in asthma, but switching earlier on [112]. *Early transient eczema* was identified and differentiated from *early-onset early-resolving eczema* and *early-onset mid-resolving eczema* in three studies. As these trajectories are relatively similar, with the onset in *early-transient wheezing* only months later than the two aforementioned trajectories, it is possible that this subgroup constitutes those with eczema triggered by certain factors with a later exposure window. The other transient trajectories (*mid-onset late-resolving eczema* and *late-onset late-resolving eczema*) were rare and whether these constitute generalisable/clinically meaningful entities is unclear.

The allergic sensitisation trajectories are difficult to interpret/generalise, given the varying assessment methods and allergens assessed, as well as the central role of allergen prevalence and exposure to sensitisation, by means of *e.g.*, follow-up length and geographical region [113].

Follow-up time, number of assessments and intervals in-between have been reported to substantially influence the discoverability of smaller classes [114]. Our findings, however, mostly indicate a pattern between studies investigating single diseases *versus* allergic multimorbidity, with larger number of trajectories found in the latter. This is in line with simulation studies suggesting that higher number of indicators enables discovery of larger number of classes [115]. The transient trajectories were relatively uncommon and varied widely in longitudinal patterns, but may represent clinically relevant subgroups. To discern the validity of such subgroups, more robust modelling approaches are needed. External validation, relatively rare in studies published thus far, is pivotal to ascertain overall generalisability of disease trajectories. Translating these findings to clinical practice will require even more, not least characterisation of subjects at different stages and use of prediction models to further our understanding of parameters prospectively indicative of development of specific disease trajectories. On a related note, reporting of computational choices and outputs in general and of modelling metrics and classification uncertainty in particular needs to be more detailed for evaluation and comparison of results between studies. At present, well-established frameworks and guidelines for unsupervised trajectory analyses are lacking, although recent checklists such as GRoLTS contribute a well-needed foundation [16]. Finally, while it is clear that asthma and allergic diseases are intricately related (supported by the strong association between identified trajectories and allergic comorbidity), more longitudinal phenotyping studies of allergic rhinitis and food allergy and studies encompassing multiple diseases/measures are warranted to comprehensively elucidate the frequency and characteristics of longitudinal patterns of asthma and allergy.

In conclusion, our findings indicate the presence of relatively few reproducible trajectories of wheezing and eczema in children. These trajectories were clinically recognisable with multiple associated (actionable) risk factors. Suboptimal modelling and reporting limited critical assessment and comparability. More studies are needed to characterise food allergy and allergic rhinitis.

Questions for future research

- Assessment of the robustness and clinical validity of intermediate and late childhood-onset trajectories of asthma and allergic disease.
- Investigation of longitudinal patterns of allergic rhinitis and food allergy in children.
- Exploration of trajectories of asthma or allergy based on severity, *e.g.* healthcare utilisation and perceived symptoms.

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Author contributions: D. Lisik supported the study conceptualisation, drafted and revised the search queries and data extraction/quality assessment forms, performed the searches, performed screening, performed data extraction and quality assessment, performed the meta-analyses, interpreted the findings, and drafted and revised the manuscript. S.S. Özuygur Ermis performed screening, performed data extraction and quality assessment, and revised the manuscript. G.P. Milani supported the study conceptualisation, revised the search queries and data extraction/quality assessment forms, performed data extraction and quality assessment, and revised the manuscript. E. Goksör interpreted the findings and revised the manuscript. R. Basna supported the study conceptualisation, revised the search queries and data extraction/quality assessment forms, and revised the manuscript. G. Wennergren interpreted the findings and revised the manuscript. H. Kankaanranta interpreted the findings and revised the manuscript. B.I. Nwaru conceived the study idea, supported the study conceptualisation, revised the search queries and data extraction/quality assessment forms, interpreted the findings, and revised the manuscript. The remaining authors (G.C.I. Spolidoro, S. Ercan, M. Salisu, F. Odetola, D.G. Ghiglioni and D. Pylov) performed data extraction and quality assessment, and revised the manuscript.

Conflict of interest: H. Kankaanranta reports personal fees for lectures and consulting from AstraZeneca, Boehringer-Ingelheim, Chiesi Pharma, GSK, MSD, Novartis, Orion Pharma, and Sanofi Genzyme outside the current work. The remaining authors report that they have no conflict of interest.

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