Exploring geographic differences in IgE response through network and manifold analyses

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Background: Component-resolved diagnostics allow detailed assessment of IgE sensitization to multiple allergenic molecules (component-specific IgEs, or c-sIgEs) and may be useful for asthma diagnosis. However, to effectively use component-resolved diagnostics across diverse settings, it is crucial to account for geographic differences.

Objective: We investigated spatial determinants of c-sIgE networks to facilitate development of diagnostic algorithms applicable globally.

Methods: We used multiplex component-resolved diagnostics array to measure c-sIgE to 112 proteins in an international collaboration of several studies: WASP (World Asthma Phenotypes; United Kingdom, New Zealand, Brazil, Ecuador, and Uganda), U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes; 7 European countries), and MAAS (Manchester Asthma and Allergy Study, a UK population-based birth cohort). Hierarchical clustering on low-dimensional representation of co-occurrence networks ascertained sensitization and c-sigE clusters across populations. Cross-country comparisons focused on a common subset of 18 c-sIgEs. We investigated sensitization networks across regions in relation to asthma severity.

Results: Sensitization profiles shared similarities across regions. For 18 c-sIgEs shared across study populations, the response structure enabled differentiation between different geographic areas and study designs, revealing 3 clusters: (1) Uganda, Ecuador, and Brazil, (2) U-BIOPRED children and adults, and (3) New Zealand, United Kingdom, and MAAS. Spectral clustering identified differences between clusters. We observed constant, almost parallel shifts between severe and nonsevere asthma in each country.

Conclusions: Patterns of c-sIgE response reflect geographic location and study design. However, despite geographic differences in c-sIgE networks, there is a remarkably consistent shift between networks of subjects with nonsevere and severe asthma. (J Allergy Clin Immunol 2026;157:262-72.)

Key words: *Asthma, allergic sensitization, cluster, network analysis, component-resolved diagnostics, statistical network analysis, asthma diagnosis*

The well-established association between asthma and specific IgE (sIgE) antibody responses is widely acknowledged, as has been reviewed elsewhere.[1-3] However, the question of how much asthma is attributable to atopy[4] remains unresolved, even among sensitized patients with an asthma diagnosis.[5] For example, many individuals with allergic sensitization do not have any symptoms, and in some sensitized patients with asthma, sensitization and asthma diagnosis may co-occur by chance (because both conditions are relatively common),[6] rather than sensitization affecting the presence or severity of symptoms.[7]

Machine learning approaches have been used to disaggregate sensitization.[8,9] Longitudinal analyses that considered allergen type and size as well as time of onset and remission of the IgE response ascertained through standard tests (skin prick test and serum IgE to whole allergen extracts) identified 4 distinct sensitization clusters with markedly different association with asthma diagnosis and asthma severity.[8,9] However, for an individual to be assigned to a sensitization cluster requires modeling of longitudinal data collected over years, while what we need clinically are diagnostic tools to differentiate, at a single point during clinical consultation, whether sensitization is contributing to asthma diagnosis or the severity of asthma symptoms, or whether it has relatively limited clinical relevance.[5]

We can now assess sensitization in much greater detail using component-resolved diagnostics (CRD or molecular allergology[10]), which measures specific IgE (sIgE) to individual allergenic molecules/components (component-specific IgE, or c-sIgEs), rather

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Abbreviations used
Alpha-gal: Galactose-α-1,3-galactose
ALSPAC: Avon Longitudinal Study of Parents and Children
CRD: Component-resolved diagnostics
c-sIgE: Component-sIgE
HC: Hierarchical clustering
MAAS: Manchester Asthma and Allergy Study
sIgE: Specific IgE
U-BIOPRED: Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes
WASP: World Asthma Phenotypes

than the whole allergen extract. Single-plex CRD was followed by the development of multiplex assays in which c-sIgE to many molecules is measured simultaneously.[10] Several studies have shown that CRD may be more informative than standard skin prick test and sIgE to whole extracts in asthma.[11-16] However, the inherent complexity of CRD microarray data makes interpretation challenging, and it remains difficult to extract all relevant information and identify interactions among large numbers of c-sIgEs potentially involved in the biological response.

We propose that using CRD coupled with machine learning/artificial intelligence can create interpretational algorithms to diagnose asthma and ascertain its severity. One approach to analyze CRD microarrays is to use network analysis to assess interactions and connectivity patterns between c-sIgEs and relate these to asthma.[15,16] Studies using this approach showed that in contrast to food allergy, where sensitization to specific food proteins predicts clinical reactivity,[17] in asthma, the pattern of interaction between c-sIgEs, rather than IgE to any individual molecule, seems to better predict asthma diagnosis[15] and asthma severity (among sensitized patients with asthma).[16] However, when developing interpretational algorithms for the use of CRD in asthma, it is of key importance to identify which other variables should be considered. Specifically, one of the key questions is whether and how geographic factors should be considered when comparing data from different parts of the world. Previous studies have shown that sensitization profiles are heterogeneous between countries,[18,19] and racial/ancestry differences in allergic sensitization have also been described.[20] Given the intuitive understanding that differences in climate, environmental exposures, and genetics across regions may introduce variations in sensitization, incorporating spatial adjustments becomes essential. This is of crucial importance if we are to develop interpretation tools for CRD arrays that physicians may use in different countries and emphasizes the need for cross-country investigations and comparisons.

In this analysis, we aimed to investigate geographic differences in c-sIgE response obtained through multiplex arrays by using manifold and network analyses applied to data collected in structured research settings in multiple countries.

METHODS

Detailed description of study populations and methods is presented in Methods section in this article's Online Repository available at www.jacionline.org. Informed consent was obtained from all participants and/or their parents/carers.

Study populations, setting, and participants

The World Asthma Phenotypes (WASP) study[21,22] is a case–control study across 5 centers in the United Kingdom, New Zealand, Brazil, Ecuador, and Uganda. In each center, 200 asthma patients and 50 non-asthma controls were recruited. In 4 centers, most participants were aged 8-20 years, and in Bristol (Avon Longitudinal Study of Parents and Children, or ALSPAC), United Kingdom, the participants were aged 25-27 years. Ethics approval was obtained from the London School of Hygiene and Tropical Medicine ethics committee (approval 9776) and the participating study centers. For Bristol, ethical approval was obtained from the ALSPAC ethics and law committee and the local research ethics committees.

The Manchester Asthma and Allergy Study (MAAS)[23] is a population-based birth cohort in Manchester, United Kingdom. In this analysis, we used data collected at age 11 years. The study was approved by the research ethics committee and was registered as ISRCTN72673620.

Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED)[24,25] is a European multicenter observational study. The adult cohort was recruited from 16 centers in 11 countries and the pediatric cohort from 7 centers in 5 countries.[26] The study was approved by the ethics committee for each center and is registered at ClinicalTrials.gov (NCT01976767, NCT01982162). Adult groups included severe and mild-to-moderate nonsmoking patients with asthma, and smokers and ex-smokers with severe asthma.[24] The pediatric groups in this analysis included severe and mild-to-moderate school-age asthma.[26] A glossary of terms related to data analysis is provided in the Online Repository available at www.jacionline.org.

Measurement of c-sIgE antibodies

Blood samples were collected from participants who provided informed consent. c-sIgEs to 112 allergen components were measured with ImmunoCAP ISAC (Thermo Fisher Scientific, Uppsala, Sweden). Levels of c-sIgEs were reported in ISAC-standardized units, or ISU (following manufacturer guidelines) and were considered positive if c-sIgE was ≥0.30 ISU. Data were discretized and annotated as described previously.[13]

Sensitization patterns in different geographic areas

We first explored sensitization patterns among participants (sensitization clusters) and patterns of c-sIgE coexpression (component clusters) to ascertain whether previously identified sensitization and component clusters[15,16] are generalizable across geographic areas.

Filtering procedures. Initial filtering steps were applied within each dataset. Nonsensitized individuals (those with no positive c-sIgE) were excluded. Among sensitized patients, only c-sIgEs positive in at least 2% of observations were retained.[13-16] This step allowed examination of cohort-specific sensitization profiles.

Sensitization clusters. To investigate structural variations in sensitization patterns among participants across different countries, we first applied hierarchical clustering (HC) via Ward linkage,[27] in combination with the Jaccard distance, on the binary responses to c-sIgE (positive/negative) for each country separately. The cross-country analysis of sensitization clusters was conducted by maintaining a fixed number of 4 clusters, allowing for a comparative examination of the observed patterns and groupings.

Component clusters and their connectivity patterns. We ascertained component clusters using HC, which organizes data into a treelike structure known as a dendrogram. This reveals the hierarchy and similarities between clusters without requiring a predefined number of clusters. We used an agglomerative approach with the Ward linkage method, which minimizes within-cluster variance because it merges the most similar clusters step by step, highlighting different patterns of connectivity and biological properties among c-sIgEs.

Comparative analysis of sensitization across countries with common c-sIgE set

Uniform filtering was applied across all datasets. After nonsensitized subjects were excluded, we retained the c-sIgEs that were positive in at least 1% of the overall population in all studies to ensure a consistent set of nodes across networks. This approach facilitates the assessment of similarities across countries on the basis of a subset of globally prevalent c-sIgEs.

We constructed co-occurrence networks among the common c-sIgEs for each country separately. The networks were then projected into a low-dimensional Euclidean space[28] (see Figs E1 and E2 in the Online Repository available at www.jacionline.org), which emphasizes the similarities among countries based on entire connectivity structure. The selection of the number of dimensions for the Euclidean space was carried out using elbow criteria, ensuring an optimal representation capturing the inherent variability in c-sIgE sensitization patterns across countries. To group countries according to their c-sIgE connectivity structures, we applied HC using as input the acquired Euclidean coordinates, using the Euclidean distance and the Ward method for cluster aggregation.

We then focused on characterizing the identified clusters. This involved computing the mean network for each cluster, maintaining consistency with the methodology applied throughout the analysis. To identify c-sIgE groups that most distinctly characterized each specific study group, we used spectral clustering, as described in the Methods section of the Online Repository available at www.jacionline.org. The number of eigenvectors utilized in the spectral clustering process was carefully chosen using the elbow rule, enhancing the precision of cluster identification by focusing on the most informative eigenvectors.

In the final analysis, we compared sensitization networks between patients with mild-to-moderate and severe asthma across different countries. To ensure comparable definitions of asthma severity, which are outlined in the Online Repository available at www.jacionline.org, we used data from MAAS and WASP and excluded U-BIOPRED. We constructed the graphs and applied the same methodology as described above.

RESULTS

Characteristics of study populations

WASP. c-sIgEs were available for 824 participants, of whom 781 had positive response to at least one c-sIgE (635 asthma cases). The breakdown for each country is shown in Table E1 in the Online Repository available at www.jacionline.org.

MAAS. CRD data were obtained for 461 (56.1%) of 822 participants who attended clinical follow-up at age 11 years. Demographic data of these 461 participants have been described in detail previously (see Table E2 in the Online Repository available at www.jacionline.org).[15] There were no significant differences in demographic characteristics or outcomes between cohort members with and without CRD,[11] and 94 (20.4%) had current asthma. Of those with CRD, 221 (47.9%) had positive c-sIgE to at least one of the components,[11] 74 of whom had current asthma.

U-BIOPRED. CRD was available for 761 subjects; 520 (68.33%) of 761 were adults, and 241 (31.67%) of 761 were children. The proportion of those with at least one positive c-sIgE was 256 (49.23%) of 520 in adults and 140 (58.09%) of 241 in children. The characteristics of participants with c-sIgE data in U-BIOPRED have been described in detail previously.[16]

Clustering structures across diverse geographic areas

Table E3, in the Online Repository available at www.jacionline.org, shows the sample sizes for each data source and the number of c-sIgEs selected for the initial clustering analysis after the filtration procedure.

Sensitization clusters. Fig 1 shows the results of HC of subjects on the basis of binary sensitization for each dataset. This analysis showed that despite the variation in the prevalence of sensitization to specific allergens across different geographic areas, the sensitization profiles shared some similarities. Specifically, the clustering structures in Bristol and New Zealand (WASP), MAAS, and U-BIOPRED revealed 4 sensitization clusters:[15] (1) lower-grade sensitization, (2) multiple sensitization, (3) predominantly house dust mite sensitization, and (4) predominantly grass/tree sensitization.

A different structure was observed in Ecuador and Uganda, where, with a 4-clustering solution, a unique cluster formed of participants sensitized predominantly to galactose-α-1,3-galactose (alpha-gal) emerged.

Component clusters. Fig E3, in the Online Repository available at www.jacionline.org, shows the results of HC applied to c-sIgEs across countries. Although differences among countries emerged because of the variation in roots of exposures, the emerging clusters were broadly reflective of the underlying similarities between allergenic protein structural homogeneity and sources that were shared across countries.[15]

Comparative analysis across countries with common c-sIgE set

The filtration procedure resulted in a set of 18 common c-sIgEs (see Fig E4 in the Online Repository available at www.jacionline.org). Table E4, also available in the Online Repository, shows the proportion of positive responses to these 18 c-sIgEs across different populations.

Network analyses using these 18 c-sIgEs identified sensitization network patterns that share identical sets of nodes. The structure of sensitization networks is displayed in Fig 2. While discerning similarities and differences among networks by observation is challenging, it appears that several specific countries share similar structures. For instance, c-sIgEs to allergens such as Der f 1, Phl p 1, and Fel d 1 consistently appear as central nodes in the networks from the United Kingdom and New Zealand. Moreover, the general structure of the networks shows that certain allergens are frequently co-occurring, forming similar groups across different regions.

To further investigate these similarities, the networks were embedded in a Euclidean subspace to display graph similarities (Fig E2).[28] The Euclidean power metric was used for this purpose,

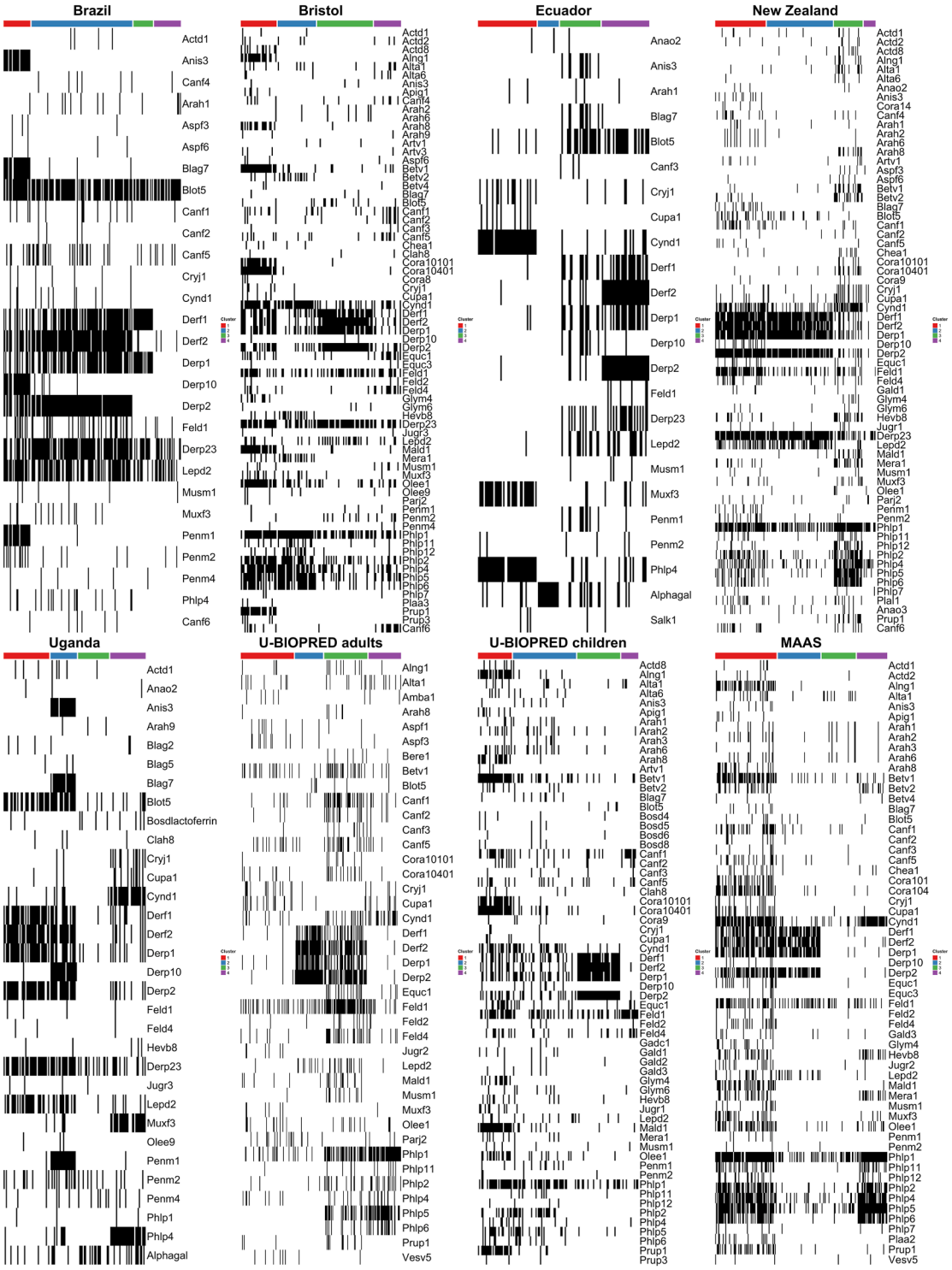

FIG 1. Patterns of IgE responses to allergen components for individual participants across all study populations. Rows represent c-sIgEs; columns, study participants; and colors, sensitization clusters' membership. Squares are colored if participant has positive response (<0.30 to particular sIgE).

with 3 principal components selected. These 3 principal components explained 78% of the total variability in the datasets (Fig 3).

HC revealed that even for the 18 shared components, the structure of response allowed for clear differentiation between different areas and type of studies (Fig 4). From the hierarchical tree, distinct patterns emerged, revealing the identification of 3 separate clusters. Cluster 1 included Uganda, Ecuador, and Brazil (WASP), cluster 2 U-BIOPRED children and U-BIOPRED

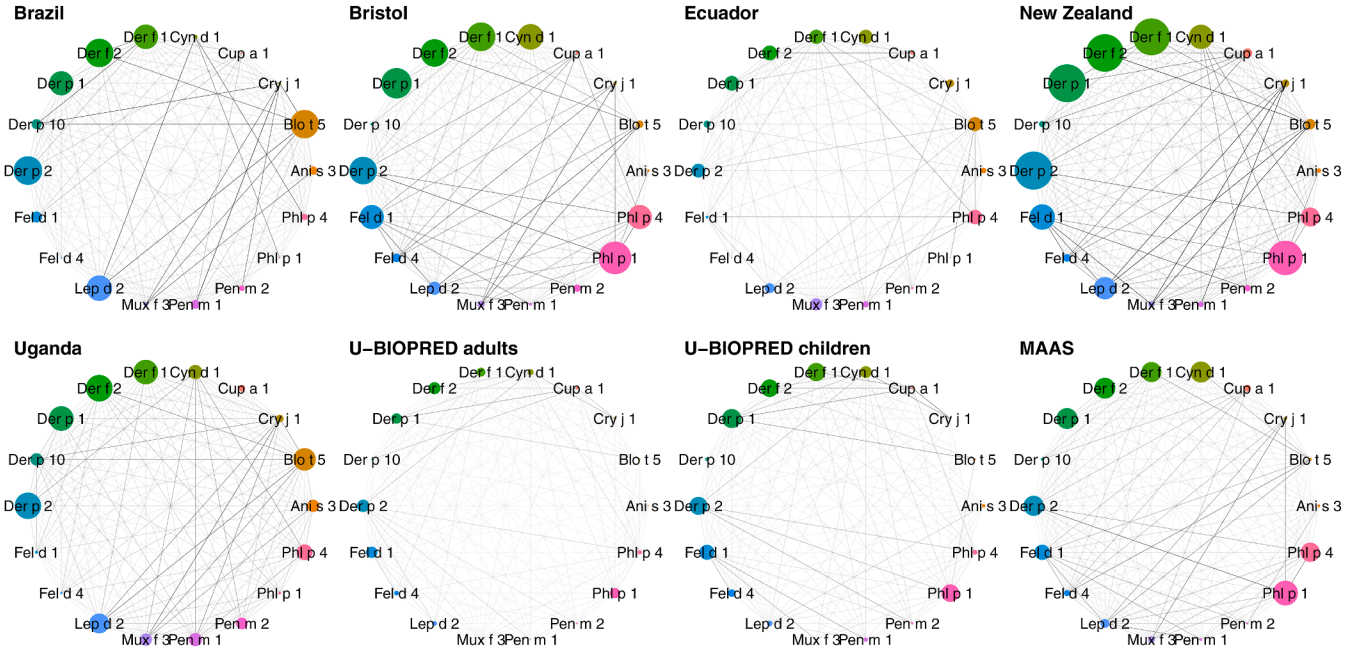

FIG 2. Sensitization network patterns across different countries. Node size is proportional to prevalence of given sensitization (strength); shade of edge is proportional to intensity of relationship between pairs of IgEs measured through co-occurrence, with darker edge indicating stronger observed co-occurrence.

adults, and cluster 3 New Zealand and Bristol (WASP) and MAAS. Further analysis of clusters 2 and 3 demonstrated that although these were identified as distinct entities, their proximity suggests close similarity. This suggests the existence of within-group similarities in both geographic location and country income differences (cluster 1 vs clusters 2 and 3) and study design (study of patients with asthma vs case–control/birth cohort studies, cluster 2 vs cluster 3).

Fig 5 shows the mean sensitization network for each of the 3 identified clusters. The networks depicted can be considered as centroids or prototypes for each derived cluster, summarizing the differences between them. Notably, while the cluster formed by MAAS, New Zealand, and Bristol shares a similar connectivity pattern with the U-BIOPRED cluster, the first group exhibits higher prevalences of sensitization co-occurrences. In contrast, the mean network for cluster 1 (Brazil, Ecuador, and Uganda) is characterized by a higher prevalence of c-sIgE to Blo t 5 and lower levels to Phl p 1, among other differences.

We then performed spectral clustering to identify the c-sIgEs driving the distinctions between the 3 retrieved groups. These are shown in Fig 6. Clusters 2 and 3 shared similar c-sIgE components. However, it is noticeable that 5 c-sIgEs groups characterized cluster 1, further highlighting the differences between these 3 clusters.

Sensitization networks in severe versus nonsevere asthma across different geographic areas

Fig 7, *A,* shows sensitization networks among patients with nonsevere and severe asthma projected into 2-dimensional Euclidean space. We observed almost parallel and consistent shifts between the two groups in each country, suggesting that there is a constant direction characterizing the distinction between sensitized patients with severe versus nonsevere asthma across different geographic areas. Fig 7, *B,* depicts network measure of node-specific strength to highlight the difference in the connectivity network structures across the 18 c-sIgEs between patients with and without severe asthma.

DISCUSSION

We leveraged data collected from various studies across the world to investigate the impact of geographic location, study design, and asthma severity on c-sIgE responses. When we clustered study participants, c-sIgE sensitization profiles shared some similarities across different geographic areas and could be categorized into distinct clusters on the bases of unique patterns of sensitization to different molecules. These clusters were similar to those we previously described in European populations and qualitatively labeled as multiple sensitization, lower-grade sensitization, predominantly house dust mite sensitization, and predominantly pollen sensitization.[15] However, the individual c-sIgEs contributing to this structure differed between European countries/New Zealand and African and South American centers (Fig 1). Furthermore, in Ecuador and Uganda, a unique cluster was identified formed of participants only sensitized to alpha-gal.

To identify the structural and biological foundations of the underlying architecture in c-sIgE responses, we also subjected c-sIgEs to statistical grouping to determine component clusters. The identified clusters were reflective of the similarities in structural homogeneity between allergenic proteins and their sources. Some of these were shared across countries, but again, individual c-sIgEs contributing to this structure differed, with considerably smaller numbers of c-sIgEs in each component cluster in studies from Africa and South America (Fig E3).

Even in comparative analysis across countries using a common set of 18 c-sIgE with a positive response in at least 1% of the overall population, the structure of response differentiated between different geographic areas (and country income) and the

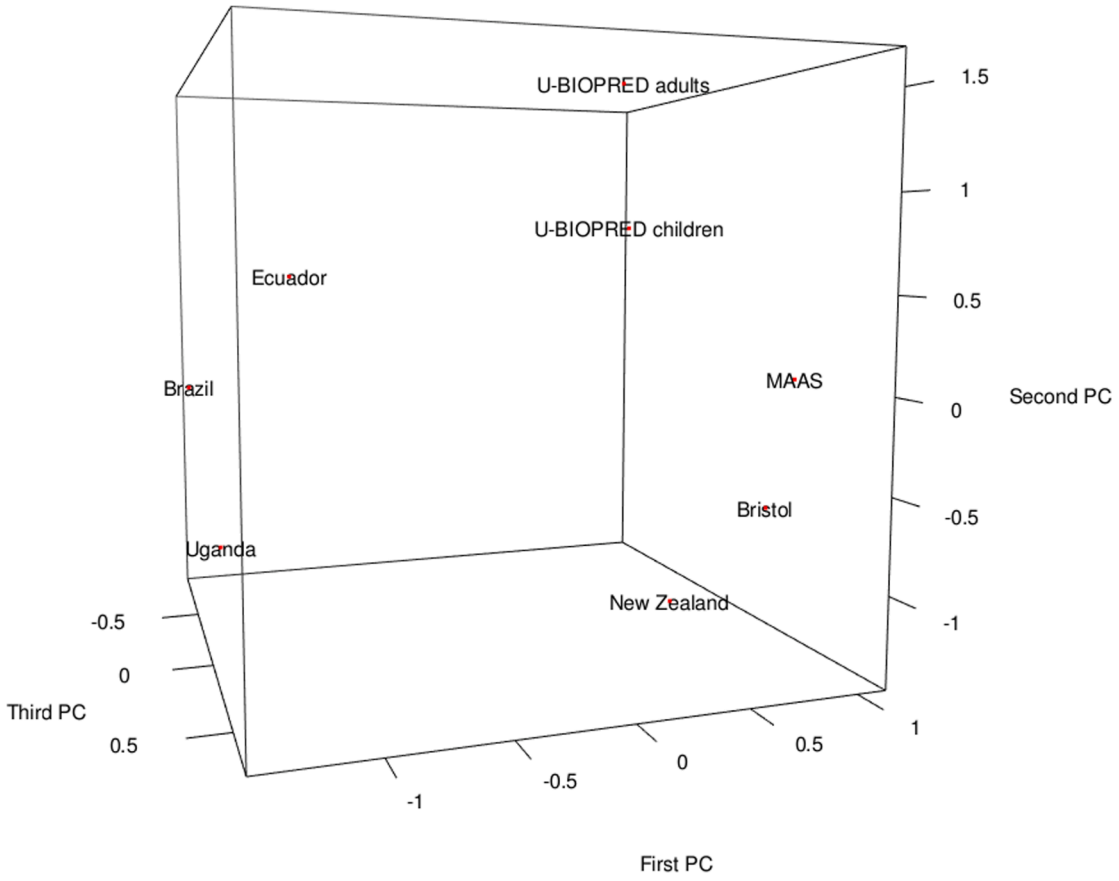

FIG 3. Euclidean space embedding to compare sensitization networks. Each point represents Euclidean projection of entire network for geographic location considering common set of 18 c-sIgEs.

type and design of studies. Three separate clusters emerged, with cluster 1 including low- and middle-income countries (Uganda, Ecuador, and Brazil), cluster 2 comprising exclusively U-BIOPRED participants, and cluster 3 including New Zealand and United Kingdom (Bristol [WASP] and MAAS). However, although clusters 2 and 3 were distinct, their proximity suggested close similarity. These within-group similarities and between-group differences are likely a reflection of a geographic location/country income and the study design (low- and middle-income countries vs high-income countries, population-based studies vs studies in patients with asthma only). Despite geographic (and likely genetic) similarities between those grouped in clusters 2 and 3, differences in participant selection in studies of different design potentially underlie the distinction between these two clusters.

Notably, despite clear geographic differences, we observed almost parallel and constant shifts between c-sIgE networks of patients with and without severe asthma across all countries. This suggests that despite geographic location and country income, there are consistent patterns of sensitization that may differentiate sensitized patients with and without severe asthma.

One limitation of our study is that some potentially important allergens were not included in the array we used. For example, there are relatively few fungal components, which may be important,[29] and the array did not include Der p 23 and Der p 37, which have been associated with asthma.[30,31] We cannot exclude the possibility that our analyses would provide different solutions if additional components were available, but it is unlikely that this would affect the underlying structures we describe. Another limitation is the sparseness of data. We restricted the comparison across countries to 18 c-sIgEs, as this was necessary to leverage on shared c-sIgEs information.

We used slightly different versions of the CRD microarray in different studies. For analysis in WASP, we used the updated version of the CRD microarray, which contains c-sIgE to alpha-gal. In MAAS and U-BIOPRED, we used the original test. However, comparison of the underlying structure of connectivity between c-sIgE in Bristol and Manchester revealed identical clusters as well as the same differences in networks of connectivity among those with and without asthma. Thus, for the principal aims of this study—investigation of spatial determinants of c-sIgE networks to facilitate the development of diagnostic algorithms applicable globally—subtle differences in individual components on the array are unlikely to affect the results.

We acknowledge that patients with asthma are likely to be receiving different treatments depending on their geographic area. Nonetheless, we observed almost parallel and constant shifts between individuals with and without severe asthma in each country.

It is plausible that some subtypes of sensitization are benign (ie, not associated with asthma symptoms) and some are pathologic.[32] However, we lack the tools to determine in individual sensitized patients whether sensitization is related to their asthma or just an incidental finding.[5] Traditional diagnostic tests, such as skin

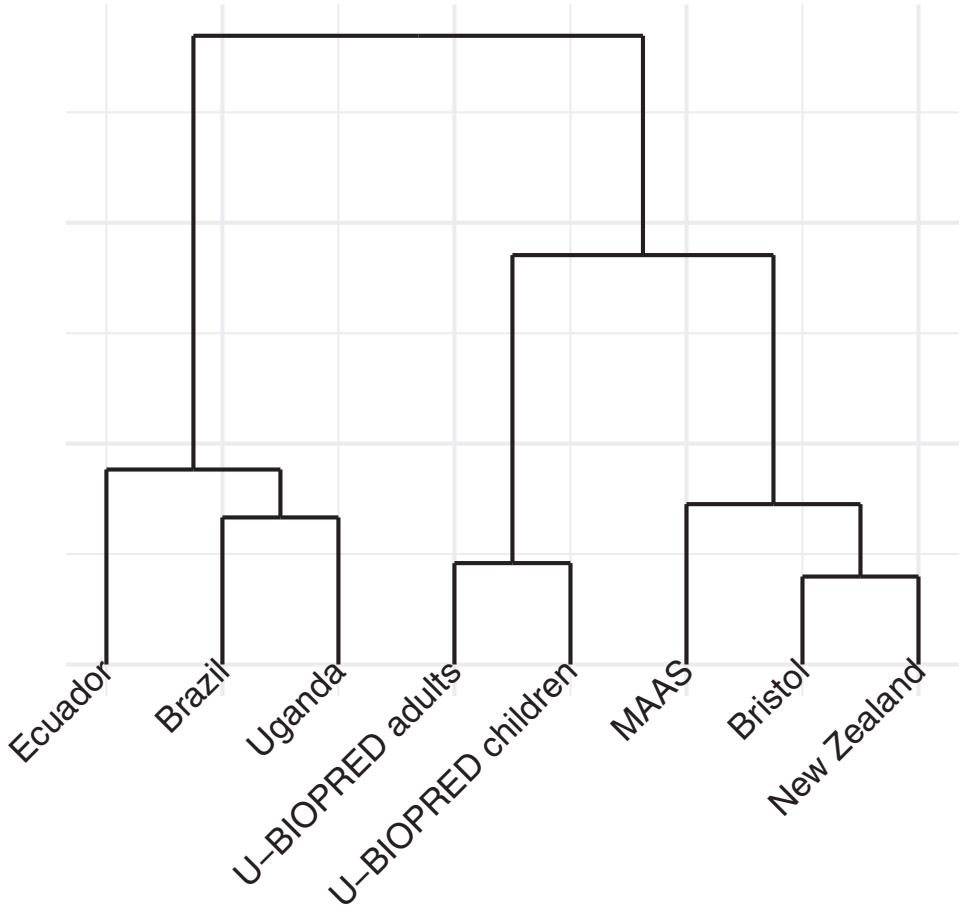

FIG 4. Hierarchical clustering of sensitization network based on retrieved Euclidean coordinates. Geographic locations are subsequently merged along dendrogram according to their similarities. Euclidean distance and Ward method have been applied.

prick tests and sIgE to whole allergen extracts, fall short in definitively establishing this.[1] Quantification of sensitization increases diagnostic accuracy,[33] but the problem of a significant number of false-positive test results remains,[34] and it is difficult to use the size of response clinically as a predictor of asthma diagnosis and severity because of a major overlap.[33-35] Molecular allergology may provide solutions to address this gap. Our early studies identified 3 patterns of c-sIgE response measured by a commercial CRD array in mid childhood, with a strong association between asthma and sensitization to a cluster of components of plant, animal, and fungal origin.[11] In further studies, we demonstrated an association between different longitudinal trajectories of c-sIgE responses and asthma diagnosis.[12] However, while it is possible to determine the latent structure within the CRD multiplex array data using machine learning techniques, translating this into clinically useful tools for diagnosing or monitoring asthma in clinical practice is challenging. An important step toward the development of such tools is identifying which variables should be considered (such as age and geographic location). We recently investigated the dynamics of temporal development of multiple c-sIgEs and networks from early childhood to adolescence to show that although c-sIgEs networks change significantly over time, consistent differences in networks between subjects with and without asthma are observed across ages.[36] Therefore, while age will have to be considered in CRD interpretation algorithms for asthma diagnosis, the temporal differences should not affect our current analysis on the spatial determinants of c-sIgE networks. Importantly, if interpretation tools/algorithms for CRD microarrays that are applicable globally and that can help physicians diagnose asthma (or ascertain its severity) are to be developed and implemented, both age and geographic location will have to be included and considered for accurate interpretation.

In the current study, we observed similar clustering structures for Bristol (MAAS), New Zealand (WASP), and U-BIOPRED, reflecting the 4 sensitization clusters previously described.[15] In Uganda and Ecuador, a distinct structure was noted where a unique cluster of participants, sensitized solely to alpha-gal, appeared within the 4-cluster solution. These differences likely reflect differences in specific allergen exposure, other environmental exposures, and susceptibility and ancestry of different populations. Previous studies have indicated that sensitization patterns vary across different countries,[18,19] and ancestral differences in allergic sensitization have also been documented.[20,37] However, the findings of the current study demonstrate that despite geographic differences, the comparison between severe and nonsevere asthma based on c-sIgEs responses reveals a constant pattern across the globe.

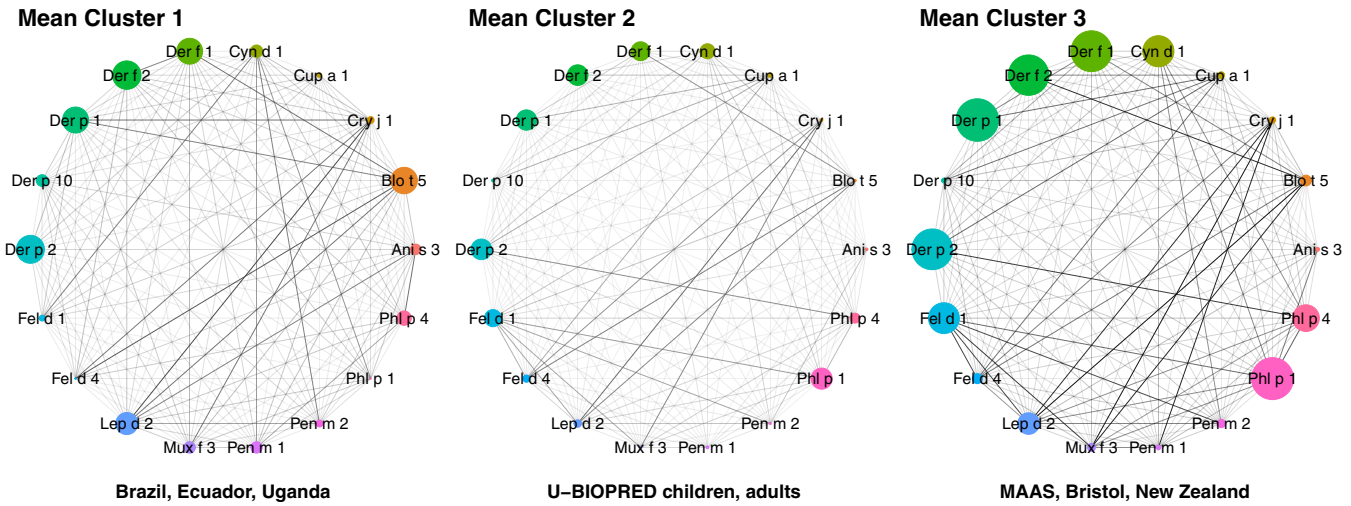

FIG 5. Comparative mean sensitization network for 3 country clusters. Node size is proportional to prevalence of given sensitization (strength); shade of edge is proportional to intensity of relationship between pairs of IgEs measured through co-occurrence, with darker edge indicating stronger observed co-occurrence.

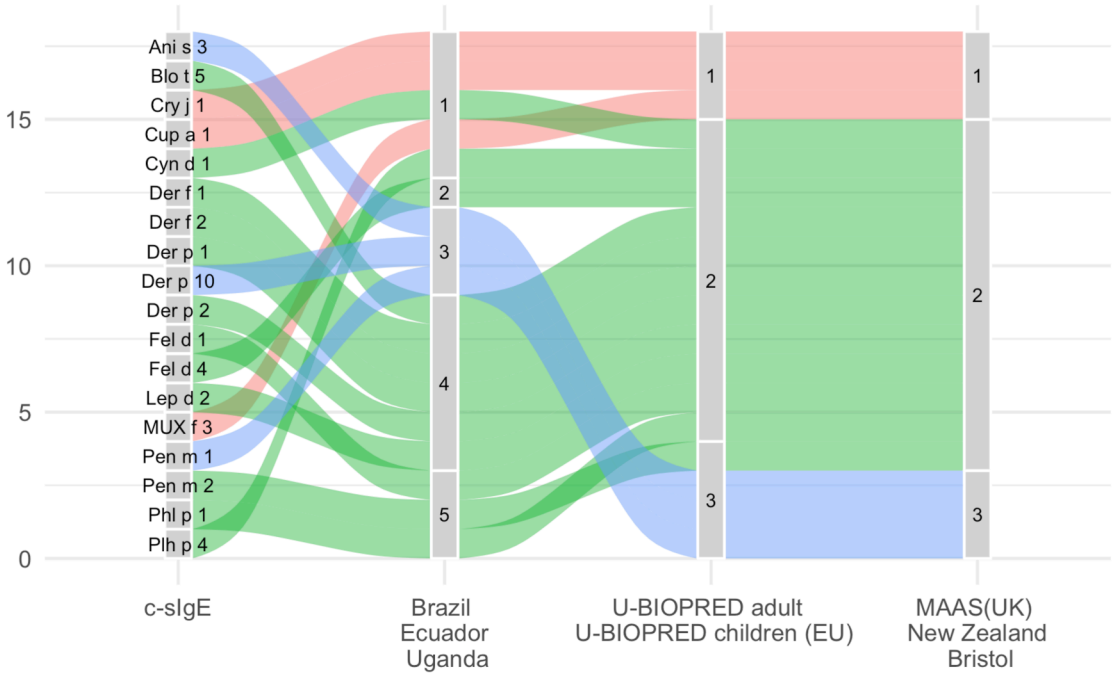

FIG 6. Partition of c-sIgEs characterizing retrieved clusters.

Although investigation of individual c-sIgEs was not within the scope of this study, several interesting observations warrant further study. For example, as expected, the prevalence of c-sIgE to Phl p 1 was higher than of IgE to Cyn d 1 in the United Kingdom and other high-income countries, but much lower in low- and middle-income countries (Uganda, Ecuador, and Brazil). In these 3 locations, c-sIgE to MUXF3 was highly prevalent. Furthermore, in contrast to studies in high-income countries, the prevalence of c-sIgE to Phl p 4 was much higher compared to Phl p 1. A possible explanation may be that some of the components (eg, Cyn d 1 and Phl p 4) are native rather than recombinant molecules and carry cross-reactive carbohydrate determinants (CCD) on their surface. Participants in Ecuador, Uganda, and Brazil may have a high c-sIgE to CCD, contributing to IgE reactivity to cross-reactive native molecules but not to recombinant Phl p 1.

In conclusion, we demonstrated that differences in CRD sensitization occur across countries, but we also identified similarities shared across different geographic areas. Our results suggest that if we are to develop interpretive algorithms based on CRD data, it is essential to account for spatial differences by considering various geographic locations. In addition, our results strongly suggest that it is possible (and, we suggest, necessary) to

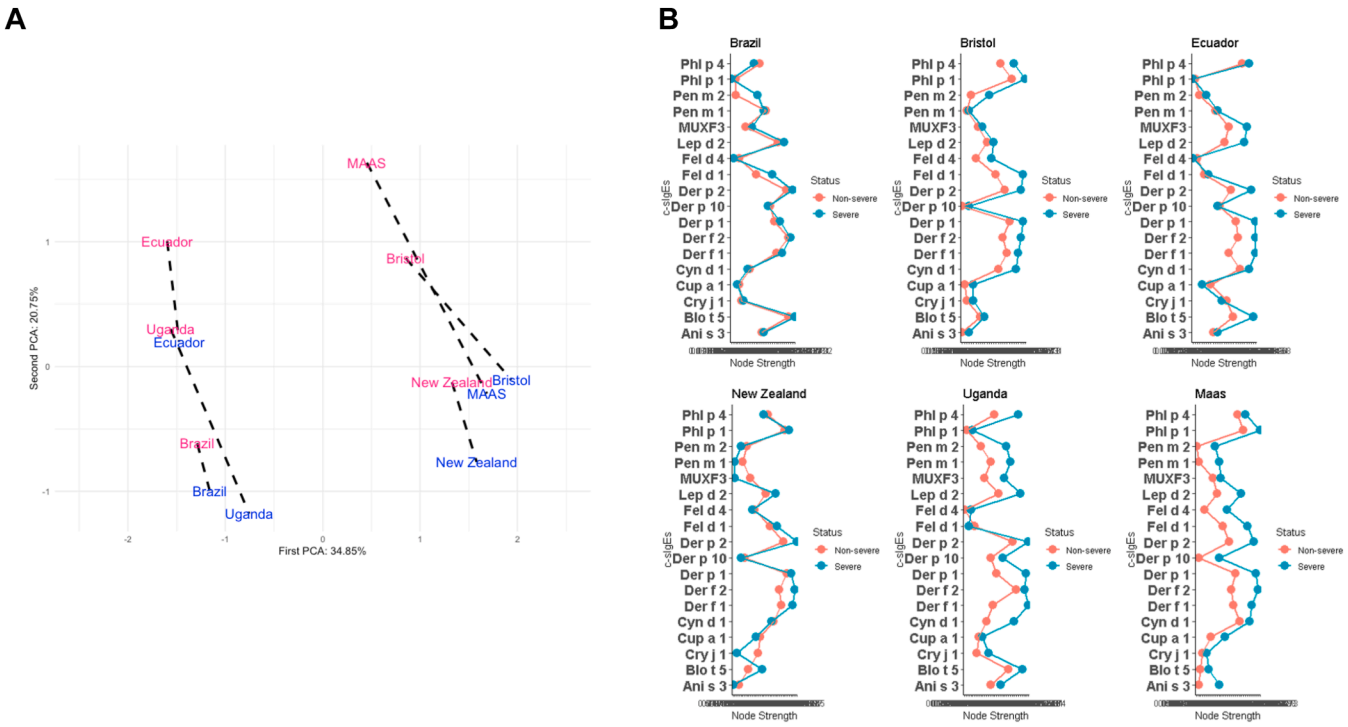

FIG 7. Network projected into Euclidean space for severe vs nonsevere asthma. **A,** Sensitization networks projected into 2-dimensional Euclidean space. First principal component (PC1) on is on x-axis and second principal component (PC2) on y-axis. Points colored *pink* represent nonsevere disease; *blue,* severe disease. **B,** Node-specific strength across retrieved graphs.

develop a universally interpretable predictive algorithm for asthma that is based on CRD data. Our study does not directly provide a patient-level predictive tool, but it lays the groundwork for developing asthma prediction algorithms for individual patients.

DISCLOSURE STATEMENT

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Key messages

- **The patterns of c-sIgE responses are reflective of geographic location and study design.**
- **Despite geographic differences in c-sIgE networks, there is a remarkably consistent shift between networks of subjects with mild-to-moderate and severe asthma.**
- **Geographic location must be considered when building diagnostic or predictive algorithms for asthma.**

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