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MASK-air® direct patient data support the ARIA-MeDALL hypothesis on allergic phenotypes

To the Editor,

The concept of 'one-airway-one-disease', based on the links between upper and lower airway allergic diseases,[1] may be an oversimplification. The ARIA-MeDALL (Allergic Rhinitis and its Impact on Asthma-Mechanisms of the Development of ALLergy) hypothesis—based on genomic, epidemiologic and clinical findings—proposed that rhinitis alone (R) may be a distinct entity from rhinitis and asthma multimorbidity (A + R), with therapeutic relevance.[2] However, the ARIA-MeDALL hypothesis has not been tested using real-world data. The aim of this study was therefore to assess the differences in symptoms and medications between R and A + R using data from MASK-air®, a freely available mHealth app.

The methods of this study are fully described in the online supplement. Briefly, in a previous study, using k-means cluster analysis, we identified three groups of MASK-air® users: those having 'probable asthma', 'possible asthma' or 'no evidence of asthma' (R).[4] In this study, we assessed MASK-air® data (2015–2020) cross-sectionally and compared patients with 'probable asthma', 'possible asthma' and 'no evidence of asthma' on (i) their maximum and median reported visual analogue scale (VAS) values for global allergy symptoms, nasal, ocular and asthma symptoms as well as on the impact of allergy on work,[3] (ii) the combined symptom-medication score (allergy-CSMS[5]) and (iii) the medication component of the allergy-CSMS. We performed a sensitivity analysis in a sample of patients with physician-diagnosed current asthma, past asthma and no evidence of asthma. Finally, we longitudinally compared users of the three groups on the frequency of complete weeks displaying well-controlled, partly-controlled, variably-controlled or uncontrolled rhinitis.

We analysed the data of 3797 patients from 25 countries (256,839 days) (Table S1 online, Figure S1 online). A total of 1733 patients provided complete weeks of MASK-air® data (14,409 weeks).

Patients with 'probable asthma' or 'possible asthma' displayed meaningfully higher VAS values and allergy-CSMS than those with 'no evidence of asthma' (Table 1). The differences were moderate–high for VAS eye, asthma and work as well as for allergy-CSMS. There were meaningful differences when rhinitis treatments were compared in the three groups: patients with 'probable asthma' reported more allergy medications than those with 'possible asthma' or 'no evidence of asthma'. Robust results were obtained in the subanalysis of 282 patients enrolled by physicians (Tables S2 and S3 online).

We compared allergy-CSMS levels in each country with data from >100 patients (Table 2). For maximum allergy-CSMS levels, moderate or large meaningful differences were observed for all countries when comparing 'probable asthma' versus 'no evidence of asthma'. Small meaningful differences were found for most countries when comparing 'probable asthma' and 'possible asthma'.

The percentage of weeks with controlled rhinitis ranged from 62.8% ('possible asthma') to 80.0% ('no evidence of asthma'), while the percentage of weeks with partly-controlled or uncontrolled rhinitis ranged from 12.6% ('no evidence of asthma') to 27.9% ('possible asthma') (Table S4 online).

In this study, using real-world data from an mHealth app, we observed that, by comparison to R, patients with 'probable asthma' display higher allergy-CSMS levels, higher VAS levels of nasal or ocular symptoms, an increased use of rhinitis medication and a higher frequency of weeks with partly-controlled or uncontrolled rhinitis. The CSMS results were individually found in different countries, suggesting the generalisability of the finding. Although some of the differences were not associated with high effect sizes and there may have been user-/day-related selection biases or some information biases (e.g. on asthma classification), these results overall support the existence of meaningful differences in rhinitis control when considering patients with A + R versus R. Overall, although not excluding other hypotheses, this study is in line with the ARIA-MeDALL hypothesis. Clinically, this study supports the assessment of the possibility of asthma in patients with more severe rhinitis.

[†]See Appendix 1 for all members of the ARIA Group.

TABLE 1 Characteristics of assessed participants.

	Probable asthma (A1) [*N* = 1256]	Possible asthma (A2) [*N* = 1118]	No evidence of asthma (NoA) [*N* = 1423]	Effect sizes		
				A1 vs. NoA	A2 vs. NoA	A1 vs. A2
Reported days—*N* (average days per user)	97,261 (77.4)	71,831 (64.3)	87,747 (61.7)	-	-	-
Females—*N* (%)	799 (63.6)	590 (52.8)	753 (52.9)	0.22	0	0.22
Age—mean (SD)	41.3 (13.3)	39.8 (15.1)	34.8 (13.1)			
Self-reported asthma—*N* (%)	1212 (96.5)	341 (30.5)	0	2.77	1.17	1.60
Asthma medication reporting[a]—*N* (%)	937 (74.6)	54 (4.8)	6 (0.4)	1.96	0.32	1.64
0 days	319 (25.4)	1064 (95.2)	1417 (99.6)	1.96	0.32	1.64
1 day	86 (6.8)	54 (4.8)	6 (0.4)	0.40	0.32	0.09
2 days	132 (10.5)	0	0	0.66	0	0.66
3 or more days	719 (57.2)	0	0	1.72	0	1.72
Total days reporting asthma medication—*N* (%)	49,986 (51.4)	4280 (6.0)	1377 (1.6)	1.35	0.24	1.10
SABA	5927 (6.0)	43 (0.1)	4 (0.01)	0.48	0.04	0.43
LABA + ICS	31,378 (32.3)	31 (0.04)	1 (0.001)	1.21	0.04	1.17
ICS	10,404 (10.7)	21 (0.03)	2 (0.002)	0.67	0.03	0.63
OCS	1650 (1.7)	185 (0.3)	124 (0.1)	0.20	0.05	0.15
LAMA	1987 (2.0)	0	0	0.28	0	0.28
Omalizumab	198 (0.2)	0	0	0.09	0	0.09
Rhinitis medication reporting—*N* (%)	939 (74.8)	746 (66.7)	916 (64.4)	0.23	0.05	0.18
Total days reporting rhinitis medication—*N* (%)	50,140 (51.6)	30,006 (41.8)	33,821 (38.5)	0.26	0.07	0.20
Oral antihistamines monotherapy	10,229 (10.5)	9146 (12.7)	11,026 (12.6)	0.07	0	0.07
Intranasal steroids monotherapy	6479 (6.7)	4142 (5.8)	4610 (5.3)	0.06	0.02	0.04
Azelastine-fluticasone monotherapy	3183 (3.3)	2353 (3.3)	3704 (4.2)	0.05	0.05	0
Oral antihistamines + intranasal steroids	10,669 (11.0)	4426 (6.2)	5356 (6.1)	0.18	0	0.17
Azelastine-fluticasone + other rhinitis medication	5121 (5.3)	2480 (3.5)	1616 (1.8)	0.20	0.11	0.09
Conjunctivitis – *N* (%)	940 (74.8)	819 (73.3)	1046 (73.5)	0.03	0.01	0.03
VAS global allergy symptoms—median (IQR)						
Maximum values[b]	72 (33)	72 (39)	61 (43)	0.38[c]	0.37[c]	0
Median values[b]	18 (31)	17 (29)	11 (22)	0.41	0.36	0.05
VAS nose—median (IQR)						
Maximum values[b]	75 (24)	76 (41)	66 (45)	0.30	0.34	0.04
Median values[b]	18 (33)	18 (30)	11 (22)	0.40	0.40	0
VAS eye—median (IQR)						
Maximum values[b]	61 (48)	62 (49)	42 (51)	0.52	0.57	0.03
Median values[b]	9 (25)	8 (23)	2 (11)	0.76	0.62	0.08
VAS asthma – median (IQR)						
Maximum values[b]	65 (37)	42 (40)	4 (8)	2.85	1.86	0.79
Median values[b]	13 (27)	3 (11)	0 (0)	1.13	0.95	0.84
VAS work—median (IQR)						
Maximum values[b]	46 (46)	45 (47)	28 (43)	0.64[c]	0.58[c]	0.03
Median values[b]	16 (28)	13 (25)	6 (17)	0.71	0.53	0.18
Allergy-CSMS—median (IQR)						
Maximum values[b]	53.4 (26.3)	49.6 (30.9)	35.4 (27.1)	0.88[c]	0.67	0.18
Median values[b]	17.8 (23.6)	13.6 (19.5)	7.8 (12.5)	0.84	0.54	0.30
Allergy medication score[d]—median (IQR)						
Maximum values (all patients)[b]	0.7 (0.4)	0.4 (0.4)	0.4 (0.4)	0.58	0.08	0.49
Median values (all patients)[b]	0.4 (0.7)	0 (0.4)	0 (0.4)	1.26	0	1.26

TABLE 1 (Continued)

	Probable asthma (A1) [N = 1256]	Possible asthma (A2) [N = 1118]	No evidence of asthma (NoA) [N = 1423]	Effect sizes		
				A1 vs. NoA	A2 vs. NoA	A1 vs. A2
Maximum values (treated patients)[b]	0.8 (0.4)	0.6 (0.4)	0.5 (0.4)	1.34	0.79	0.55
Median values (treated patients)[b]	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)	0.09	0	0.09

Abbreviations: CSMS, combined symptom-medication score; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroid (some may have been used for rhinitis as well); SABA, short-acting beta-agonist; SD, standard-deviation; VAS, visual analogue scale.

[a]Considering SABA, ICS, ICS + LABA, LAMA, biologics (only omalizumab use was reported) and other reported asthma medications with a lower frequency of use (e.g. short-acting muscarinic antagonists).

[b]Values obtained among the maximum or median values per patient.

[c]Difference equal to or higher than the minimal important difference (11 points for VAS global and VAS work; 15 points for the CSMS).

[d]Medication component of the allergy-CSMS without conversion into a scale of 0–100 (scale range: 0–1.5); treated patients concern those receiving at least 1 day of rhinitis treatment.

Note: Effect size: Small (0.20–0.49), moderate (0.50–0.79), high (≥0.80) standardised difference.

TABLE 2 Allergy combined symptom-medication score (CSMS) levels in patients from different countries with probable, possible and no evidence of asthma.

	Probable asthma (A1)	Possible asthma (A2)	No evidence of asthma (NoA)	Effect sizes		
				A1 vs. NoA	A2 vs. NoA	A1 vs. A2
Maximum CSMS values—median (IQR)						
Brazil	59.8 (22.3)	59.5 (27.8)	37.6 (33.9)	1.07[a]	1.01[a]	0.02
France	60.0 (20.5)	55.1 (22.8)	45.8 (17.9)	1.07	0.60	0.29
Germany	59.0 (30.1)	47.1 (26.7)	29.9 (22.6)	1.53[a]	0.89[a]	0.59
Greece	47.4 (20.0)	54.0 (24.6)	35.2 (16.3)	0.84	1.13[a]	0.39
Italy	52.6 (23.2)	47.3 (25.5)	38.1 (25.0)	0.80	0.49	0.29
Lithuania	43.7 (24.2)	41.4 (33.0)	33.4 (25.2)	0.55	0.37	0.09
Mexico	51.7 (25.0)	45.2 (33.2)	37.8 (25.7)	0.74	0.33	0.29
Netherlands	65.1 (16.5)	55.1 (20.8)	49.4 (21.5)	1.03[a]	0.35	0.66
Poland	48.2 (40.3)	55.2 (32.4)	30.0 (27.3)	0.72[a]	1.23[a]	0.27
Portugal	49.6 (24.6)	45.7 (26.3)	40.2 (21.5)	0.51	0.28	0.20
Spain	58.9 (26.6)	54.8 (24.5)	41.7 (35.8)	0.75[a]	0.60	0.22
Turkey	50.7 (31.5)	47.7 (26.0)	36.7 (39.6)	0.57	0.50	0.14
Median CSMS values—median (IQR)						
Brazil	14.8 (16.6)	24.7 (28.3)	10.1 (14.4)	0.46	0.81	0.55
France	22.4 (30.9)	14.1 (22.0)	11.7 (17.3)	0.62	0.19	0.46
Germany	22.8 (21.8)	13.0 (20.3)	7.1 (10.0)	1.21[a]	0.49	0.60
Greece	19.1 (15.7)	21.9 (15.5)	10.3 (12.6)	0.82	1.04	0.23
Italy	18.6 (24.4)	10.9 (14.4)	6.6 (12.8)	0.91	0.54	0.58
Lithuania	10.9 (15.4)	8.9 (12.2)	6.1 (8.6)	0.54	0.35	0.20
Mexico	14.9 (20.2)	11.9 (18.2)	8.6 (10.7)	0.65	0.32	0.25
Netherlands	30.3 (37.0)	17.2 (24.4)	13.3 (18.2)	0.76[a]	0.25	0.53
Poland	13.5 (21.8)	17.8 (24.2)	7.3 (9.5)	0.61	0.84	0.29
Portugal	16.4 (23.5)	10.1 (18.9)	10.3 (16.0)	0.45	0.02	0.48
Spain	18.8 (27.2)	17.6 (27.6)	7.3 (13.0)	0.95	0.76	0.07
Turkey	17.8 (24.1)	16.6 (14.7)	4.5 (7.8)	1.04	1.49	0.08

[a]Difference equal to or higher than the minimal important difference (15 points).

Note: Effect size: Small (0.20–0.49), moderate (0.50–0.79), high (≥0.80) standardised differences.

Abbreviation: IQR, interquartile range.

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AUTHOR CONTRIBUTIONS

JB was responsible for the study design, data analysis and manuscript writing (original draft). BSP and RJV were responsible for data analysis and manuscript writing (original draft). The remaining authors were responsible for data collection and for critical revision and editing of the manuscript.

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CONFLICT OF INTEREST STATEMENT

JB reports personal fees from Cipla, Menarini, Mylan, Novartis, Purina, Sanofi-Aventis, Teva, Uriach, other from KYomed-Innov, other from MASK-air-SAS, outside the submitted work. JB owns shares in MASK-air® SAS and KYomed-Innov. VK reports other from Norameda, other from BerlinCHemie Menarini, outside the submitted work. DLL reports personal fees from ALK, Allakos, Amstrong, Astrazeneca national and global, Chiesi, DBV Technologies, Grunenthal, GSK national and global, Mylan/Viatris, Menarini, MSD, Novartis, Pfizer, Sanofi, Siegfried, UCB, Carnot, grants from Abbvie, Lilly, Sanofi, Astrazeneca, Lilly, Pfizer, Novartis, Circassia, UCB, GSK, Purina institute, outside the submitted work. FR reports personal fees from Novartis, personal fees and nonfinancial support from Sanofi, personal fees from AstraZeneca, personal fees from GSK, personal fees from Medinfar, personal fees from Azentis, from SPAIC, outside the submitted work. LTB reports personal fees from LETI, personal fees from Vitoria Laboratories, personal fees from Novartis, outside the submitted work. TZ reports grants and personal fees from Novartis, grants and personal fees from Henkel, personal fees from Bayer, personal fees from FAES, personal fees from Astra Zeneca, personal fees from AbbVie, personal fees from ALK, personal fees from Almirall, personal fees from Astellas, personal fees from Bayer, personal fees from Bencard, personal fees from Berlin Chemie, personal fees from FAES, personal fees from Hal, personal fees from Leti, personal fees from Mesa, personal fees from Menarini, personal fees from Merck, personal fees from MSD, personal fees from Novartis, personal fees from Pfizer, personal fees from Sanofi, personal fees from Stallergenes, personal fees from Takeda, personal fees from Teva, personal fees from UCB, personal fees from Henkel, personal fees from Kryolan, personal fees from L'Oreal, outside the submitted work; and Organizational affiliations: Commitee member: WHO-Initiative 'Allergic Rhinitis and Its Impact on Asthma' (ARIA); Member of the Board: German Society for Allergy and Clinical Immunology (DGAKI); Head: European Centre for Allergy Research Foundation (ECARF); President: Global Allergy and Asthma European Network (GA2LEN); Member: Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO). The other authors have no COI to disclose, outside the submitted work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

APPENDIX 1

ARIA Group

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Eosinophilic allergic rhinitis is strongly associated with the CD45RB^{lo} subset of CD161^{+} Th2 cells that secretes IL-2, IL-3, IL-4, IL-5, IL-9, and IL-13

To the Editor,

Allergic airway diseases such as allergic rhinitis (AR) affects more than 400 million individuals worldwide and afflicts substantial health and economic morbidity.[1] AR is strongly associated with a Type 2 response, characterized by the cytokines IL-5, IL-4, and IL-13. However, the key drivers behind AR immunopathogenesis remains to be elucidated. This study aims to identify critical pathogenic cell populations associated with AR using the Singapore System Immunology Cohort (SSIC)[2] and a clinician-diagnosed pediatric cohort with active AR manifestation (Table S1). In both cohorts, the