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Usage patterns of oral H1-antihistamines in 10 European countries: A study using MASK-air® and Google Trends real-world data

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ABSTRACT

Real-world data represent an increasingly important source of knowledge in health care. However, assessing their representativeness can be challenging. We compared (i) real-world data from a mobile app for allergic rhinitis (MASK-air®) on the usage of oral H1-antihistamines from 2016 to 2020 in 10 European countries with (ii) Google Trends data on the relative volume of searches for such antihistamines. For each country, we sorted 5 different oral H1-antihistamines by their frequency of use and volume of searches. We found perfect agreement on the order of antihistamine use in MASK-air® and in Google Trends searches in 4 countries (France, Germany, Sweden, and the United Kingdom). Different levels of agreement were observed in the remaining countries (kappa coefficient from −0.50 to 0.75). Oral H1-antihistamine data from Google Trends and MASK-air® were consistent with nationwide medication sales data from France, Germany, and the United Kingdom. These results suggest that MASK-air® data may be consistent with other sources of real-world data, although assessing the representativeness of their users may require further studies.

Keywords: Antihistamines, Allergic rhinitis, Infodemiology

TO THE EDITOR

Real-world data on allergic rhinitis (AR) can provide valuable information, notably regarding patients' symptoms and behaviours.[1,2] Important sources of real-world data on AR include mobile apps and activity of Internet users, frequently assessed by Google Trends (a tool which quantifies the relative volume of searches on a given topic/term in the Google Search engine for a given location and time period).[2] These sources, however, have important limitations.[3] For both mobile apps and Google Trends, the users' representativeness may be a matter of concern. In addition, Google Trends can be heavily influenced by media coverage,[4] as it assesses health information-seeking behaviour[5] (that is, the relative volume of searches is not only influenced by the real epidemiology of the diseases being assessed, but also by the attention they get in the media).[4]

Comparing data from these different sources, with a subsequent assessment of consistency of

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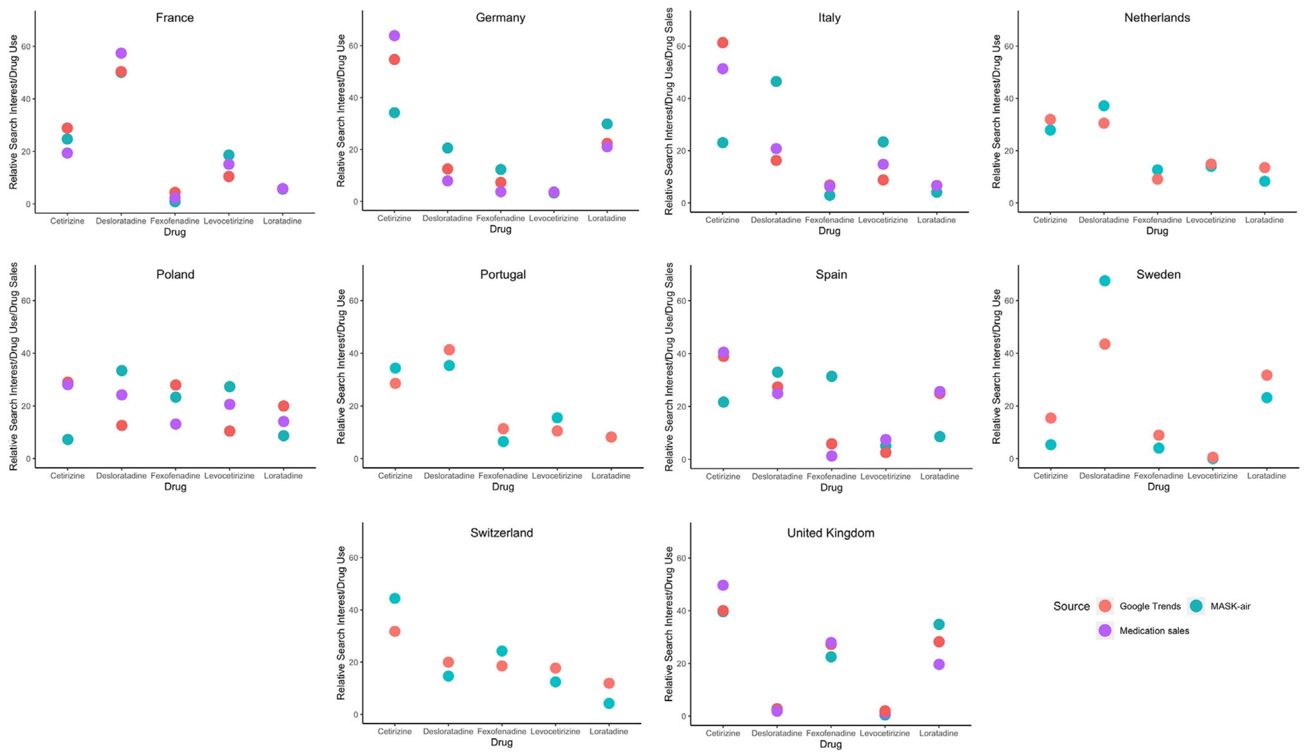

Fig. 1 Panel representing agreement between the area under the curve (AUC) for Google Trends and MASK-air datasets for each country. Each point represents the relative AUC for Google Trends or MASK-air®

results, may help to understand the extent of such limitations. Therefore, as a case-study, we compared data from both Google Trends and a mobile app for AR (MASK-air®), in order to (i) assess oral H1-antihistamine (OAH) usage patterns in 10 different European countries and (ii) assess whether the OAHs most frequently reported in MASK-air® are the most frequently searched on Google Trends.

We retrieved MASK-air® data on the reported use of cetirizine, levocetirizine, fexofenadine, loratadine, and desloratadine for AR from January 1, 2016 to December 6, 2020. We selected these OAHs as they were the most frequently reported in MASK-air®. MASK-air® (www.mask-air.com) is a mobile app freely available in 28 countries and in which users are asked on a daily basis to report their AR symptoms and to enter their AR medications using a regularly updated list that contains all country-specific medications. MASK-air® follows the General Data Protection Regulation, all data are anonymised (including geolocation data) by means of k-anonymity, and users accept to have their data analysed for scientific purposes in the terms and conditions.

In addition, we searched Google Trends from January 1, 2016 to December 6, 2020 entering the following keywords as search topics: "Cetirizine", "Levocetirizine", "Fexofenadine", "Loratadine", and "Desloratadine". We retrieved MASK-air® and Google Trends data for the 10 European countries for which MASK-air® and Google Trends data were deemed of sufficient quantity and good quality, respectively (ie, France, Germany, Italy, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, and the United Kingdom).

MASK-air® daily medication data and Google Trends Relative Search Volume (RSV) data were aggregated on a monthly basis for each country (by averaging and summing respectively). They were then presented as a relative frequency (on a 0–100 scale, in function of the maximum value per country). To estimate the "popularity" of each OAH per country, we calculated the areas under the curve (AUC) (from the plots of (i) MASK-air®

OAH monthly reported use, and (ii) online searches on OAH per month) using the trapezoidal rule:[6]

$$\int_a^b f(x)dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

where *a* and *b* correspond to the first and last months of a given time interval.

With data from both MASK-air® and Google Trends searches, we sorted the yearly OAH data from the "most popular" (highest AUC) to the "least popular" (lowest AUC), for each country. The linearly weighted kappa coefficient for ordinal scales was used to assess the agreement on the "popularity order" of OAHs in Google Trends and MASK-air® data. Finally, because MASK-air® is solely meant to be used by patients with AR, and searches in Google Trends are not necessarily from patients with AR, we further calculated the AUC and agreement between MASK-air® and Google Trends data when considering only the pollen season months (March to June).[7] Our aim here was to minimise the impact of antihistamine searches for reasons other than AR.

In 4 countries (France, Germany, Sweden, and the United Kingdom), the order of OAH "popularity", as assessed by the AUC in MASK-air® and Google Trends, was exactly the same (Fig. 1 and Table 1). In 2 additional countries (Portugal and Switzerland), the OAH with the greatest AUC was the same for both Google Trends and MASK-air® data. In the Netherlands, OAH usage in MASK-air® and Google Trends was similar (the average difference between MASK-air® and Google Trends data was 4.1%), in spite of poor agreement (Fig. 1 and Table 1). Agreement was poorer for Italy, Poland, and Spain. The average difference between Google Trends and MASK-air® data ranged from 2.7% (United Kingdom) to 17.9% (Italy) (Table 1). The calculated kappa coefficient for agreement between MASK-air® and Google Trends data was 0.575 (0.511–0.694 in the leave-one-out sensitivity analysis) (Supplemental Table 1). Restricting our analysis to data from the pollen season yielded a kappa coefficient of 0.600 (0.556–0.722 in the leave-one-out sensitivity analysis) (Supplemental Tables 2 and 3).

Except for Portugal, similar seasonal patterns were observed for variations in MASK-air®-reported OAH use and in Google Trends RSV, as seen by an increase in RSV in Google Trends and an increase in OAH use in MASK-air® during the pollen season (Supplemental Figure 1).

In an ancillary analysis, we compared our results with nationwide medication sales data obtained from the IQVIA PharMetrics® Plus database.[8] We only had access to the 2016–2018 data from the 6 European countries with the highest sales for AR medication (France, Germany, Italy, Poland, Spain, and the United Kingdom) (Supplemental Table 4). Importantly, this list of countries includes the 3 countries for which we had found a poorer agreement between Google Trends and MASK-air® data. We found our data (from both Google Trends and MASK-air®) to be consistent with the sales data from France, Germany, and the United Kingdom (with the same order of OAH "popularity" being observed for MASK-air®, Google Trends and sales). For the other countries, the sales data were consistent with Google Trends data, but less consistent with MASK-air® data, except for Poland, in which both Google Trends and MASK-air® data differed from the sales data (Fig. 1 and Supplemental Table 4).

Real-world data are emerging as new sources of clinical evidence,[9] which can provide insight into patient experiences, treatments, and outcomes in real-world scenarios.[10] Google Trends and mobile apps are 2 important sources of real-world data. There has been a growth in the publication trends of infodemiology studies, such as those based on Google Trends data, since their inception in 2002.[11] Likewise, data obtained from mHealth solutions have increasingly been playing a role in the allergy field.[12] The 2020 update of the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for AR now incorporate real-world evidence from MASK-air®.[13] This reinforces the need for assessing and comparing different sources of real-world data. In spite of this, to the best of our knowledge, this is the first study to compare online search interest and

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	MASK-air® user data (AUC (%))				
	Cetirizine	Levocetirizine	Desloratadine	Loratadine	Fexofenadine
France	236.8 (24.7)	178.3 (18.6)	480.1 (50.2)	53.9 (5.6)	8.0 (0.8)
Germany	434.9 (34.2)	40.6 (3.2)	261.6 (20.6)	379.7 (29.8)	156.3 (12.3)
Italy	187.8 (23.1)	190.1 (23.4)	377.7 (46.4)	33.6 (4.1)	24.2 (3.0)
Netherlands	335.3 (27.9)	168.2 (14.0)	447.1 (37.2)	100.0 (8.3)	152.6 (12.7)
Poland	130.1 (7.3)	488.4 (27.3)	597.1 (33.4)	155.3 (8.7)	417.0 (23.3)
Portugal	373.7 (34.4)	168.8 (15.5)	384.3 (35.4)	89.7 (8.3)	70.6 (6.5)
Spain	467.9 (21.7)	110.5 (5.1)	711.6 (33.0)	186.0 (8.6)	677.7 (31.5)
Sweden	26.9 (5.3)	0	342.5 (67.5)	117.5 (23.2)	20.4 (4.0)
Switzerland	380.0 (44.4)	106.7 (12.5)	125.6 (14.7)	36.2 (4.2)	207.6 (24.3)
UK	389.8 (39.6)	3.6 (0.4)	26.8 (2.7)	342.4 (34.8)	220.9 (22.5)

Table 1. Area under the curve (AUC) for each OAH, per country. *a.* Average percentage difference between MASK-air® and Google Trends data

mHealth data on medication usage with nationwide medication sales. Our study found an overall reasonable agreement between Google Trends and MASK-air® data on OAH "popularity", as supported by the calculated kappa coefficient[14] and the average difference between MASK-air® and Google Trends data (Fig. 1 and Table 1). More importantly, for several countries, we found the data from MASK-air® to be consistent with both Google Trends data and data from nationwide medication sales.

This study has some limitations. It is possible that MASK-air® medication usage is underreported. However, this information bias is probably non-differential regarding drug, country and season. Also, while MASK-air® data refer exclusively to patients with AR, data regarding antihistamines in Google Trends include those from searches performed for any reason, not only AR. To account for this, we performed an additional analysis where we restricted Google Trends and MASK-air® data on antihistamines to the pollen season. We found similar results, with a slight increase in agreement (kappa coefficient increased from 0.575 to 0.600). Importantly, the kappa coefficient considers only the relative "popularity" of each OAH, disregarding the closeness of data between MASK-air® and Google Trends. Therefore, our conclusions are jointly based on (i) the calculated kappa coefficient for agreement between ordinal scales; (ii) the average difference between different sources of real-world data; and (iii) the visual assessment of Fig. 1. Furthermore, we did not have access to nationwide sales data for the whole studied period and for four of the countries for which Google Trends and MASK-air® data had shown a moderate agreement. Additionally, we assessed only the top 5 reported OAHs in MASK-air®, which do not include the more recent generation OAHs, such as bilastine, mizolastine, ebastine and rupatadine. RWD on these OAHs, particularly data from Google Trends, is of poorer quality, and more studies assessing the data on the use of these more recent generation OAHs in AR are needed.

In conclusion, although we found some across-country differences in the agreement between Google Trends and MASK-air® data, in most countries, the order of OAH searches on Google Trends was close or equal to that in which they were reported in MASK-air®. Our results suggest that, regarding medication use, data from MASK-air® users are consistent with other sources of real-world data regarding medication use, although assessing the representativeness of mobile app users may require further observational studies. These findings underline the validity of MASK-air® in allergy research as, unlike other sources of real-world data such as Google Trends and nationwide medication sales, they

Google Trends Relative Search Volume (AUC (%))					Average % difference[a]	Kappa coefficient
Cetirizine	Levocetirizine	Desloratadine	Loratadine	Fexofenadine		
435.7 (28.9)	157.7 (10.5)	760.2 (50.5)	87.3 (5.8)	65.7 (4.4)	3.3	1.00
517.5 (54.7)	33.0 (3.5)	118.2 (12.5)	211.5 (22.3)	66.6 (7.0)	8.3	1.00
592.3 (61.2)	85.5 (8.8)	157.8 (16.3)	65.2 (6.7)	66.5 (6.9)	17.9	0.25
576.1 (32.0)	268.4 (14.9)	550.0 (30.5)	243.8 (13.5)	163.8 (9.1)	4.1	0.50
676.4 (29.1)	243.9 (10.5)	293.7 (12.6)	466.0 (20.0)	652.0 (28.0)	15.1	−0.50
586.9 (28.6)	217.3 (10.5)	852.9 (41.3)	169.1 (8.2)	235.0 (11.4)	4.4	0.50
652.6 (39.0)	43.6 (2.6)	458.6 (27.4)	419.9 (25.0)	98.8 (5.9)	13.5	0.25
224.2 (15.4)	7.7 (0.5)	632.4 (43.5)	460.7 (31.7)	129.6 (8.9)	9.6	1.00
512.4 (31.8)	286.0 (17.7)	322.1 (20.0)	192.5 (11.9)	299.4 (18.6)	7.3	0.75
557.6 (40.0)	26.8 (1.9)	37.1 (2.7)	392.7 (28.2)	378.8 (27.2)	2.7	1.00

Table 1. Area under the curve (AUC) for each OAH, per country. *a.* Average percentage difference between MASK-air® and Google Trends data

allow us to look at individual co-medication patterns and combinations with individual exposure and severity of disease.

Abbreviations
AR, Allergic Rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; AUC, Area Under the Curve; OAH, Oral H1-antihistamines; RSV, Relative Search Volume.

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Availability of data and materials
The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions
Rafael José Vieira: statistical analysis, writing of original draft, editing (equal).
Bernardo Sousa-Pinto: conceptualisation, statistical analysis, reviewing (equal).
Josep M. Anto: conceptualisation, reviewing (equal).
Aziz Sheikh: conceptualisation, reviewing (equal).
Ludger Klimek: conceptualisation, reviewing (equal).
Torsten Zuberbier: conceptualisation, reviewing (equal).
João Almeida Fonseca: conceptualisation, reviewing (equal).
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Authors consent for publication
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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2022.100660.

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REFERENCES

1. Sousa-Pinto B, Halonen JI, Antó A, et al. Prediction of asthma hospitalizations for the common cold using Google trends: infodemiology study. *J Med Internet Res*. 2021;23(7), e27044. https://doi.org/10.2196/27044.
2. Kang MG, Song WJ, Choi S, et al. Google unveils a glimpse of allergic rhinitis in the real world. *Allergy*. 2015;70(1):124–128. https://doi.org/10.1111/all.12528.
3. Bousquet J, Ansotegui IJ, Anto JM, et al. Mobile technology in allergic rhinitis: evolution in management or revolution in health and care? *J Allergy Clin Immunol Pract*. 2019;7(8):2511–2523. https://doi.org/10.1016/j.jaip.2019.07.044.
4. Sousa-Pinto B, Anto A, Czarlewski W, Anto JM, Fonseca JA, Bousquet J. Assessment of the impact of media coverage on COVID-19-related Google trends data: infodemiology study. *J Med Internet Res*. 2020;22(8), e19611. https://doi.org/10.2196/19611.
5. Barbosa MT, Morais-Almeida M, Sousa CS, Bousquet J. The "big five" lung diseases in COVID-19 pandemic – a Google trends analysis. *Pulmonology*. 2021;27(1):71–72. https://doi.org/10.1016/j.pulmoe.2020.06.00.
6. Tallarida RJ, Rodney BM. Area under a curve: trapezoidal and Simpson's rules. In: *Manual of Pharmacologic Calculations*. New York, NY: Springer; 1987:77–81.
7. Bédard A, Basagaña X, Anto JM, et al. Treatment of allergic rhinitis during and outside the pollen season using mobile technology. A MASK study. *Clin Transl Allergy*. 2020;10(1):62. https://doi.org/10.1186/s13601-020-00342-x.
8. Bousquet J, Schroder-Bernhardi D, Bachert C, et al. Heterogeneity of the pharmacologic treatment of allergic rhinitis in Europe based on MIDAS and OTCims platforms. *Clin Exp Allergy*. 2021;51(8):1033–1045. https://doi.org/10.1111/cea.13884.
9. Rudrapatna VA, Butte AJ. Opportunities and challenges in using real-world data for health care. *J Clin Invest*. 2020;130(2):565–574. https://doi.org/10.1172/JCI129197.
10. Booth CM, Karim S, Mackillop WJ. Real-world data: towards achieving the achievable in cancer care. *Nat Rev Clin Oncol*. 2019;16(5):312–325. https://doi.org/10.1038/s41571-019-0167-7.
11. Zeraatkar K, Ahmadi M. Trends of infodemiology studies: a scoping review. *Health Inf Libr J*. 2018;35(2):91–120. https://doi.org/10.1111/hir.12216.
12. Bousquet J, Chavannes NH, Guldemond N, Haahtela T, Hellings PW, Sheikh A. Realising the potential of mHealth to improve asthma and allergy care: how to shape the future. *Eur Respir J*. 2017;49(5), 1700447. https://doi.org/10.1183/13993003.00447-2017.
13. Bousquet J, Schünemann HJ, Togias A, et al. Allergic rhinitis and its impact on asthma working group. Next-generation allergic rhinitis and its impact on asthma (ARIA) guidelines for allergic rhinitis based on grading of recommendations assessment, development and evaluation (GRADE) and real-world evidence. *J Allergy Clin Immunol*. 2020;145(1):70–80. https://doi.org/10.1016/j.jaci.2019.06.049. e3.
14. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159–174.