luciferase by three amino acid substitutions. *Biochem Biophys Res Commun*. 2014;445(1):157-162.
5. Gasser P, Tarchevskaya SS, Guntern P, et al. The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. *Nat Commun*. 2020;11(1):165.
6. Mukai K, Gaudenzio N, Gupta S, et al. Assessing basophil activation by using flow cytometry and mass cytometry in blood stored 24 hours before analysis. *J Allergy Clin Immunol*. 2017;139(3):889-899 e811.
7. Hamilton RG, Franklin Adkinson N Jr. In vitro assays for the diagnosis of IgE-mediated disorders. *J Allergy Clin Immunol*. 2004;114(2):213-225; quiz 226.
8. Tsai CT, Mukai K, Robinson PV, et al. Isotype-specific agglutination-PCR (ISAP): a sensitive and multiplex method for measuring allergen-specific IgE. *J Allergy Clin Immunol*. 2018;141(5):1901-1904 e1915.
9. Tomabechi Y, Hosoya T, Ehara H, Sekine SI, Shirouzu M, Inouye S. Crystal structure of nanoKAZ: The mutated 19 kDa component of Oplophorus luciferase catalyzing the bioluminescent reaction with coelenterazine. *Biochem Biophys Res Commun*. 2016;470(1):88-93.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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ADHD in school-age children is related to infant exposure to systemic H1-antihistamines

To the Editor,

Attention-deficit/hyperactivity disorder (ADHD) and atopic dermatitis (AD) are two highly prevalent diseases in childhood. Many systemic H1-antihistamines (AH), especially 1st-generation agents (AH1) with significant sedating potential, are frequently used to treat AD-related pruritus and AD-related sleeping problems in infants.[1] There is, however, no recommendation for systemic treatment with AH within the first year of life. In a small retrospective study of children with AD, we recently observed a significant association of history of antihistamine use and increased risk of ADHD symptoms.[2] The objective of the present study was to analyze whether AH exposure within the first 2 years of life represents an independent risk factor for the development of ADHD in children with AD. Moreover, we aimed to investigate whether children, who are exposed to AH, but who do not have AD, have an increased risk for ADHD diagnosis later in childhood.

We undertook a birth cohort study based on comprehensive administrative healthcare data provided by a large statutory health insurance from Germany, AOK PLUS, which has also been used in the study of allergies before.[3,4] For the presented birth cohort study, the study database consisted of all subjects born in the years 2005 to 2007 and followed until 2014 (ie, their 7th to 9th birthday) or end of insurance status. Primary outcome of interest was the diagnosis of ADHD. A child was classified as having ADHD if it received at least two ICD-10 diagnoses (ICD-10 Code F90) within the observation period. For subgroup analyses, the population of children with ADHD was further constrained in a second more specific definition to those who additionally either received specific medication (methylphenidate N06BA04 or atomoxetine N06BA09) or behavioral therapy (BT). The onset of the disease has been set to the first day of the quarter when the diagnosis was first recorded. The exposures of interest were AH prescriptions within the first 2 years of life (see Supporting information S4 for respective ATC codes). The following variables were considered as confounders: sex, AD with onset in the first 2 years of life, and pediatrician to children ratio in the ZIP code area. An individual was classified as having AD if the diagnostic code had been documented at least twice (ICD-10 Code L20 or L30) in outpatient care within four quarters. Children with a first diagnosis of AD after their first 2 years of life were excluded.

Using a nonrandomized factorial design, we compared four groups of children:

1. Control group: no diagnosis of AD up to the age of 7-9 years depending on year of birth and no prescriptions of AH within the first 2 years of life,
2. Prescription of AH without AD diagnosis within the first 2 years of life,
3. AD and no prescription of AH within the first 2 years of life, and
4. Both, diagnosis of AD and prescription of AH within the first 2 years of life.

We applied time-to-event analyses with nonparametric cumulative event curves and semiparametric Cox proportional hazard models stratified by antihistamine and AD status and controlled by sex and pediatrician to children ratio.

The whole study cohort consisted of 41 484 children. Details on the study population are provided in Table 1. From the 41 484 children included in the present study, a high proportion of 13.4% (n = 5540) were exposed to AH within the first 2 years of life, 10.2% (n = 4234) receiving 1st-generation AH (AH1) (primarily dimetindene). Children without AD, but infant exposure to AH1, had a 35% increased risk for ADHD (HR 1.35; 95%-CI 1.25-1.47, *P*-value < .001) (Table 2). This effect was also significant for the specific secondary case definition (HR 1.23; 95%-CI 1.05-1.45, *P*-value < .010). Compared to children

Abbreviations: AD, atopic dermatitis; ADHD, attention-deficit/hyperactivity disorder; AH, H1-antihistamines; AH1, 1st-generation H1-antihistamines; AR, allergic rhinitis; BBB, blood-brain barrier; OTC, over-the-counter.

TABLE 1 Baseline characteristics of the study population with focus of 1st-generation H1-antihistamines (AH1)

	Total	No AH1	AH1[a] (<2 y of age)
Population	41 484	37 235	4249
Male sex (Percentage)	21 630 (52.1%)	19 253 (51.7%)	2377 (55.9%)
ADHD	3003 (7.3%)	2592 (7.0%)	411 (9.7%)
ADHD + Med/BT	811 (2.0%)	715 (1.9%)	96 (2.3%)
AD (<2 y)	11 330 (27.3%)	9257 (27.3%)	2073 (48.8%)

[a] Mainly dimetindene, 15 children that received clemastine, but without dimetindene.

TABLE 2 Results of regression analyses with focus of 1st-generation H1-antihistamines (AH1)

	ADHD		ADHD with specific medication or behavioral therapy	
Variable	HR with 95% CI	*P*-value	HR with 95% CI	*P*-value
Sex (reference Girls)	2.46 (2.27-2.67)	<.001	4.11 (3.44-4.90)	<.001
No AD and No AH1	1 (reference)			
No AD and AH1	1.35 (1.25-1.47)	<.001	1.23 (1.05-1.45)	.010
AD and No AH1	1.41 (1.22-1.64)	<.001	1.12 (0.83-1.52)	.454
AD and AH1	1.47 (1.28-1.70)	<.001	1.21 (0.91-1.62)	.194
Pediatrician to children ratio within 15 km	1.07 (0.99-1.15)	.069	1.11 (0.96-1.27)	.159

without AD and without AH1 exposure in infancy, children with AD and AH1 exposure in infancy had a 47% increased risk for later ADHD (HR 1.47; 95% CI 1.28-1.70, *P*-value < .001), see Table 2 and Figure S3B. Second-generation AH such as cetirizine (n = 1.194, 2.9%) and desloratadine (n = 550, 1.3%) were less often prescribed than AH1. See Tables S1 and S2 and Figure S3A for the effect of AH on ADHD.

This large birth cohort study provides important new evidence that early life exposure to AH, especially AH1, may be an independent risk factor for ADHD development. This effect may be mediated by disturbance of the REM sleep and its secondary effects on brain maturation.[5,6] Especially for neonates and infants where REM sleep is very common, reduction of REM sleep by antihistamines that pass the BBB may increase the risk for later ADHD development.[7] This is especially critical if children treated with antihistamines suffer from other atopic diseases such as allergic rhinitis or atopic eczema as indicated by the highest risk for ADHD in children with AD and AH1 exposure in our cohort. The identified relationship between early antihistamine exposure and increased risk for ADHD development may also be explained by a protopathic bias. Sleep disorders and related antihistamine consumption may represent signs of an underlying yet undiagnosed ADHD disease.[8,9] Note that, in 23.6% of the analyzed cases, expositions to antihistamines were unclear as none of the approved indications for antihistamines have been documented in outpatient care. In addition, most of the antihistamines (ie, dimetindene and cetirizine) are OTC medicines in Germany. Nevertheless, we assume that parents do not proactively buy and use antihistamines for very young children for the first time. Despite these limitations, we conclude that exposure to antihistamines may be an independent risk factor for ADHD development with REM sleep disturbance being a potential pathophysiological pathway. This needs to be considered by physicians and parents when the use of AH, especially AH1 in very small children, is intended. Due to the high proportion of children receiving antihistamines early in their life, this finding is of high public health relevance. The use of antihistamines early in life should be considered with caution, and parents should be advised by the physician/pharmacy.

KEYWORDS

atopic dermatitis, histamine, pediatrics

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CONFLICTS OF INTEREST

SF, FT, and MR report no conflicts of interest. SA reports personal fees outside the submitted work and has been investigator, advisor, or lecturer for Novartis, LEO Pharma, Lilly, Sanofi-Aventis, and AbbVie. Unrelated to this study, JS received institutional grants for investigator-initiated research from Sanofi-Aventis, Pfizer, Novartis, and ALK-Abelló and acted as a consultant for Sanofi-Aventis and Novartis.

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REFERENCES

1. Simons FER. H1-antihistamines in Children. *Clin Allergy Immunol*. 2002;17:437-464
2. Schmitt J, Buske-Kirschbaum A, Tesch F, et al. Increased attention-deficit/hyperactivity symptoms in atopic dermatitis are associated with history of antihistamine use. *Allergy*. 2018;73(3):615-626.
3. Schmitt J, Romanos M, Schmitt NM, Meurer M, Kirch W. Atopic eczema and attention-deficit/hyperactivity disorder in a population-based sample of children and adolescents. *JAMA*. 2009;301(7):724.
4. Schmitt J, Schmitt NM, Kirch W, Meurer M. Early exposure to antibiotics and infections and the incidence of atopic eczema: a population-based cohort study. *Pediatr Allergy Immunol*. 2010;21(2p1):292-300.
5. Church MK, Maurer M, Simons FER, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. *Allergy*. 2010;65(4):459-466.
6. Schnatschmidt M, Schlarb A. Sleep and mental disorders in childhood and adolescence. *Z Kinder Jugendpsychiatr Psychother*. 2018;46(5):368-381.
7. Díaz-Román A, Buela-Casal G. Shorter REM latency in children with attention-deficit/hyperactivity disorder. *Psychiatry Res*. 2019;278:188-193.
8. Gregory AM, Eley TC, O'Connor TG, Plomin R. Etiologies of associations between childhood sleep and behavioral problems in a large twin sample. *J Am Acad Child Adolesc Psychiatry*. 2004;43:744-751.
9. Horwitz RI, Feinstein AR. The problem of protopathic bias in case-control studies. *AmJ Med*. 1980;68:255-258.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Validation of the MASK-air app for assessment of allergic rhinitis

To The Editor,

Recently, a mobile app (Allergy Diary, now MASK-air® freely available on Google Play and the Apple app store) was used to collect data on patients with allergic rhinitis (AR),[1,2] evidencing the usefulness of this tool for assessing patient behavior in AR. Among other features, the app includes visual analog scale (VAS) measures for general, nasal, ocular, and asthma symptoms and daily medication intake.

The present prospective study aims to validate this app for the control of AR, comparing it to a written questionnaire.

Participating patients with AR (Supplementary material S1, Table S1, Figure S1) were randomly assigned to one of the two groups: (1) AR patients who were invited to use the Spanish version of the MASK-air® app at the baseline visit (app group); and (2) AR patients who were not invited to use the app were asked to use paper-based questionnaires. (non-App as control group). All patients included had a reflective total nasal symptom score (rTNSS) ≥8 at baseline. Patients assigned to the app group had to use the application daily to record their symptoms; patients assigned to the non-app group had to complete a written questionnaire with same items on days 1, 3, 7, 14, 21, and 28, and a final visit one week later to deliver the questionnaire to the researcher.

The usefulness of the app for rhinitis control was evaluated at baseline and at the end of the study (1 month) using the RCAT (Rhinitis Control Assessment Test) questionnaire validated in Spanish as primary objective.[3] Other AR outcomes evaluated were treatment adherence as measured by the Morisky-Green-Levine questionnaire,[4] reflective total nasal symptom score (rTNSS), ocular symptom score (rTOSS), the modified ARIA severity classification,[5,6] a quality-of-life questionnaire (ESPRINT-15),[7] and daily visual analog