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Association of psoriasis with allergic multimorbidity of asthma, rhinitis, and eczema among adolescents: a cross-sectional study

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Abstract:	Background Associations between psoriasis and allergic diseases (asthma, rhinitis, and eczema) in children have been reported in a limited number of studies, and the association between psoriasis and multimorbidity (co-occurrence) of allergic diseases remains unclear. Hence, this study aimed to assess the association between psoriasis and the co-occurrence of asthma, rhinitis, and eczema in adolescents. Methods This school-based cross-sectional study enrolled adolescents (n=3,864) aged 11–14 years. Parents completed a questionnaire on doctor-diagnosed psoriasis as well as symptoms and clinical history of asthma, rhinitis, and eczema. Eight nonoverlapping groups comprising single and co-occurring current (past 12 months) asthma, rhinitis, and eczema were identified. A multinomial logistic regression model was used to estimate the adjusted odds ratios (aOR) and 95% confidence intervals (CI). Results In the analytical sample (n = 3,710; 1,641 male and 2,069 female participants), 3.5% reported doctor-diagnosed psoriasis, and 15.7%, 15.0%, and 10.3% had current asthma, rhinitis, and eczema symptoms, respectively. Doctor-diagnosed psoriasis was associated with “asthma only” (aOR = 2.11, 95% CI: 1.15–3.89), “eczema only” (6.65, 4.11–10.74), “asthma + eczema” (5.25, 2.36–11.65), “rhinitis + eczema” (3.60, 1.07–12.15), and “asthma + rhinitis + eczema” (7.38, 2.93–18.58). Doctor-diagnosed psoriasis was not statistically significantly associated with “rhinitis only” (1.42, 0.71-–2.84) and “asthma + rhinitis” (1.78, 0.69–4.56). Conclusion Our findings indicate that psoriasis is associated with the co-occurrence of allergic diseases among adolescents. However, further studies are required to investigate which biological mechanisms may be shared between psoriasis and allergic diseases.
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Response to Reviewers:	Point-by-point responses to reviewers' comments Manuscript Title: Association of psoriasis with allergic multimorbidity of asthma, rhinitis, and eczema among adolescents: a cross-sectional study Manuscript ID: AACI-D-23-00234 Note to the reviewers: We would like to thank the reviewers for their interest in our manuscript and the insightful, careful, and constructive comments and suggestions that improved our manuscript. Reviewer #1: GENERAL COMMENTS: This manuscript addresses a topic of broad for the readership of this journal. The manuscript is well written and gives an excellent introduction to the topic. However, I have one significant concern, as outlined below. Response: We thank the reviewer for the interest in our manuscript and for the critical and constructive comments that improved our manuscript. Please find below our responses to the comments. MAJOR COMPULSORY REVISIONS: The authors clearly describe the conflicting data in existing medical literature on the association between psoriasis and atopic disease, stating that "the association between psoriasis and allergic diseases has no consensus among studies..." [Line 75]. However, they ultimately conclude that their data reveal a clear association between these conditions. Response: We thank the reviewer for this comment. Most of the studies that have assessed the association between psoriasis and allergic diseases have reported positive associations, while only few studies have reported no or negative associations. Our conclusion is based on the observed results from our study, which showed that psoriasis was associated with allergic diseases. No single study can be certain, but we showed that in our sample there is an association between psoriasis and allergic diseases, and we have also indicated that future studies are needed to explain the underlying mechanisms of such associations. To clarify the issues, we have revised the statements we made in the introduction. The following was revised sentences were added to the introduction section: “The association between psoriasis and allergic diseases has been assessed in a limited number of studies. Majority of studies that have assessed the association between psoriasis and allergic diseases have reported positive associations and suggested that psoriasis and allergic diseases have a common pathogenesis [10-15], while few other reports found no or inverse association between psoriasis and allergic diseases [16, 17].”

The methods description (Lines 96-109) describes inclusion limited to physician-diagnosed psoriasis, with no indication whether self-reported psoriasis was also included (the inferred assumption is that it was not). However, in stark contrast, each of the atopic conditions included both physician- and self-reported disease. Physician subspecialists who manage atopic diseases understand how frequently patients referred to their clinics will come with a physician diagnosis that is incorrect, especially with respect to asthma. Even more frequent are patients who self-report asthma based on factors such as incorrectly perceived "wheezing" or who have been prescribed asthma treatment in the past--two criteria that were used for inclusion in the present study. Therefore, even if the data in the current study was limited to inclusion of physician-diagnosed of asthma, it may grossly overestimate the true prevalence of this condition in the study population, and further including self-reported asthma will only increase that overestimate.

Response:
We understand the importance of clear/valid case definitions and their implications on the study results. Nevertheless, in large population-based epidemiological studies, clinical diagnosis can be costly and requires substantial resources. Hence, self-reported criteria have been developed to overcome the need for clinical assessments by doctors for several diseases, including allergic diseases (International Study of Asthma and Allergies in Childhood [ISAAC; Reference: Asher et. Eur Respir J. 1995;8:483-91. DOI: 10.1183/09031936.95.08030483]). As we have described in the “Methods” section, “Ascertainment of study variables” subsection: “Ever doctor-diagnosed psoriasis” was determined by an affirmative response from the parent/guardian to the following question: “Has this child ever been diagnosed with psoriasis by a doctor?” This parent/guardian reported doctor-diagnosed psoriasis was used in our analysis. Hence, this definition only included individuals who reported that they have received a doctor diagnosis of psoriasis. Our inclusion of “doctor” diagnosed psoriasis was done to reduce the possibility of misclassification, as a prior study did show that the validity of self-reported psoriasis increases when asking if the condition was physician-diagnosed [Reference: Modalsli et. J Invest Dermatol. 2015;136:325–8. DOI: 10.1038/JID.2015.386].

To address this issues, we have added/modified the following to the discussion section:
“Although the reliability (Cohen’s kappa: 0.7558) [45] and validity (sensitivity: 56%; specificity: 99%; positive predictive value: 78%; negative predictive value: 96%) [46] of self-reported psoriasis diagnoses are reportedly high, misclassification of the disease status cannot be eliminated, which can bias the estimated measures of association. Our assessment focused on doctor-diagnosed psoriasis reported by parent/guardian. A prior study showed that the inclusion of “self-reported doctor-diagnosed psoriasis” compared to only “self-reported psoriasis” yielded increased validity [46].”

With regard to the ascertainment of asthma, we defined current asthma using ISAAC methodology as follows: an affirmative response to the items “history of physician-diagnosed asthma” and “wheezing in the past 12 months” and/or “asthma treatment in the past 12 months.” Hence, our asthma definition required a self-reported physician-diagnosed asthma plus having had wheezing episodes in the past 12 months and/or have used asthma treatment in the past 12 months. This approach included history of receiving a diagnosis plus having an asthma symptom (wheezing) and/or have used asthma medications in the past 12 months. We agree with the review that there is no perfect method to define asthma in large population-based studies, and misclassification is inevitable. However, we have used the standardized ISAAC questionnaire to define asthma [Lai et al. Thorax. 2009;64(6):476-83. DOI: 10.1136/thx.2008.106609]. Prior studies have investigated the validity of the ISAAC questionnaire against multiple asthma surrogates. For instance, among children aged 13-14 year, the ISAAC questionnaire had sensitivity value of 0.85 (95% CI: 0.73-0.93) and specificity value of 0.81 (95% CI: 0.76-0.86) against physician diagnosis of asthma [Jenkins et al. Int J Epidemiol. 1996;25(3):609-16. DOI: 10.1093/ije/25.3.609]. Similarly, a study demonstrated that the Finnish ISAAC questionnaire to be highly valid (sensitivity: 0.98 [95% CI: 0.92-0.99; specificity: 0.98 [95% CI: 0.97-0.98]) against anti-asthmatic medication reimbursement data of the Finnish Social Insurance Institution

[Nwaru et al. Clin Respir J. 2011;5(4):211-8. DOI: 10.1111/j.1752-699X.2010.00222.x]. Among children in the UK, using GP-recorded asthma as the gold standard, parental-reported ever doctor-diagnosed asthma had a sensitivity of 88.5% and a specificity of 95.7% [Cornish et al. BMJ Open. 2014;4(4):e005345. DOI: 10.1136/bmjopen-2014-005345]. Moreover, asthma defined in a similar manner to our “current asthma” variable was reported to be associated with lower lung function parameters [Arshad et al. Eur Respir J. 2020;55(3). pii: 1900477. DOI: 10.1183/13993003.00477-2019; Karmaus et al. Respir Res. 2019;20(1):98. DOI: 10.1186/s12931-019-1068-0]; hence, further validating the used definition in identifying participants with asthma. Moreover, compared to prior studies that used a comparable asthma definition, the estimated prevalence of current asthma (15.7%) in this report is similar to the prevalence estimate of current asthma (16.1%) in a preceding study among adolescents aged in 16-19 years in Kuwait [Alnajem et al. Respir Res. 2020 Nov 16;21(1):300. DOI: 10.1186/s12931-020-01569-9], and comparable to current asthma prevalence estimate among 18-year old Isle of Wight birth cohort participants (17.7%) [Soto-Ramirez et al. J Epidemiol. 2013;23(6):399-410. DOI: 10.2188/jea.je20120201].

To address this issues, we have added the following to the discussion section: “Nonetheless, we have used the standardized ISAAC questionnaire to ascertain allergic diseases, which has been shown to have good validity [21]. For instance, a prior study showed that the ISAAC criteria for ascertaining asthma symptoms as compared to physician diagnosis of asthma had a sensitivity of 85% and specificity of 81% [47]. Similarly, among children in the UK, using GP-recorded asthma as the gold standard, parental-reported ever doctor-diagnosed asthma had a sensitivity of 88.5% and a specificity of 95.7% [48]. Moreover, prior studies that defined asthma in a similar manner to our “current asthma” variable showed that their defined asthma to be associated with reduced lung function parameters [24, 49]. Compared to prior studies that defined asthma in a similar manner to our study, the estimated prevalence of current asthma (15.7%) in this report is similar to the prevalence estimate of current asthma (16.1%) in a preceding study conducted among adolescents aged in 16-19 years in Kuwait [50], and comparable to current asthma prevalence estimate among 18-year old Isle of Wight birth cohort participants (17.7%) in the UK [51]. Such observations further support the used asthma definition.”

In the discussion section (Lines 203-218), the authors attempt to address this weakness of the current study of having included self-reported disease, but ultimately do not address why only physician-diagnosed psoriasis was included, while both physician- and self-reported atopic diseases were included. The authors ultimately conclude that this does not represent a significant weakness because their data is similar to the results of reference 20 [Joel et al.]. However, it is not explained why this particular reference carries more importance that the large number of other similarly conducted studies that conclude the opposite.

Response:
As we have described in our response to the previous comment, the information analyzed in this study relied on parental/guardian reported prior diagnosis by physician and signs and symptoms of the conditions. For psoriasis, ever doctor-diagnosed psoriasis was determined by an affirmative response from the parent/guardian to the following question: “Has this child ever been diagnosed with psoriasis by a doctor?” This parent/guardian reported doctor-diagnosed psoriasis was used in our analysis. For allergic diseases (asthma, rhinitis, and eczema), we have used both parent/guardian-reported physician diagnosis plus signs/symptoms of the disease. We have provided detailed description of the definitions in the methods section of the paper and provided references. We have indicated in the discussion section that misclassification of the diseases cannot be eliminated and might influence the measures of associations. We used reference 20 as an example, but did not stress that this reference carries more importance. We understand the review’s concern and have removed the sentence that makes a comparison with reference #20 from the revised manuscript. Our intention was to indicate that the magnitude and direction of the effect measures in our study are similar to prior studies. Hence, we speculate that information bias, if any, has minimal effects on our results.

	The following was added/modified to the discussion section: “Furthermore, given that the magnitude and direction of the estimated measures of association (ORs) in our study is are similar to that in previous studies [10, 13-15, 26], we speculate that the effect of misclassification, if any, should be minimal on our results.” It would be helpful to know whether the findings of this study would differ if the data included were limited to only physician-diagnosed asthma and other atopic conditions. Response: Current asthma, current rhinitis, current eczema variables that we have analyzed were defined by using reported physician diagnosis plus signs/symptoms of the respective conditions. As described in our prior point of response, our “current asthma” definition required a self-reported physician-diagnosed asthma plus having had wheezing episodes in the past 12 months and/or have used asthma treatment in the past 12 months. This approach included history of receiving a diagnosis plus having an asthma symptom (wheezing) and/or have used asthma medications in the past 12 months. Current eczema was defined as “ever doctor-diagnosed eczema” and/or “having ever had a recurrent itchy rash for at least 6 months” plus “having an itchy rash at any time in the past 12 months that affected the folds of the elbows or the areas behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes.” This definition follows the well-established criteria by Hanifin and Rajka [Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1980; 92: 44-7]. Moreover, to minimize misclassifying current rhinitis, we have used the following definition: “ever doctor-diagnosed rhinitis” and “having problems with a sneezing, runny, or blocked nose in the absence of a cold or flu in the past 12 months.” Hence, the used definitions of allergic diseases should provide improved classification than solely relaying on self-reported physician diagnosis. MINOR ESSENTIAL REVISIONS: none identified DISCRETIONARY REVISIONS: Lines 146-147: It is reported that exposure to secondhand smoke and cats during infancy were associated with an increased prevalence of physician-diagnosed psoriasis in this study. The readership of this journal is primarily specialists in atopic diseases. Please consider adding discussion either in the introduction or discussion section about what environmental factors have previously been associated with an increased risk of psoriasis and compare this with the same environmental factors' impact on the development of atopic diseases. Response: We thank the reviewer for this suggestion. We have added a paragraph to the discussion section on the common risk factors that have been reported for psoriasis and allergic diseases. The following was added to the discussion section: “Moreover, in terms of risk factors, genetic predisposition is the major contributor to the development of psoriasis, with few environmental and behavioral/lifestyle factors being implicated in the etiology of psoriasis [31, 32]. Alcohol use, smoking, and obesity have been shown to be risk factors for psoriasis [33-35]. To investigate possible causal effects of the identified risk factors, Mendelian Randomization studies have reported potential causal effects of smoking and obesity on psoriasis, but not alcohol consumption [36-38]. Similarly, smoking and obesity have been shown to be risk factors for the development of allergic diseases [39-41]. Moreover, breastfeeding has been shown to be associated with allergic diseases [42, 43], and more recently few studies have reported the association between breastfeeding and psoriasis [20, 44]. Collectively, the aforementioned factors have been speculated to alter immune development and responses, hence altering the risk of immune mediated diseases such as psoriasis and allergic diseases.”

Reviewer #2:

This was an interesting cross-sectional study of school aged children looking at associations between psoriasis and various atopic conditions.
The main limitation was this was parent self report, not data acquired from a chart review to confirm these actual diagnoses. How did the authors account for this limitation?

Response:
We thank the reviewer for the interest in our manuscript and for the critical and constructive comment that improved our manuscript.

We agree with the reviewer, self-reporting of conditions might lead to misclassification. Nonetheless, we have applied rigorous definitions that have been previously used in epidemiological studies. The definitions that we used relayed on physician diagnosis plus signs/symptoms of the conditions. For instance, our “current asthma” definition required a self-reported physician-diagnosed asthma plus having had wheezing episodes in the past 12 months and/or have used asthma treatment in the past 12 months. This approach included history of receiving a diagnosis plus having an asthma symptom (wheezing) and/or have used asthma medications in the past 12 months. We have used the standardized ISAAC questionnaire to define asthma [Lai et al. Thorax. 2009;64(6):476-83. DOI: 10.1136/thx.2008.106609]. Prior studies have investigated the validity of the ISAAC questionnaire against multiple asthma surrogates. For instance, among children aged 13-14 year, the ISAAC questionnaire had sensitivity value of 0.85 (95% CI: 0.73-0.93) and specificity value of 0.81 (95% CI: 0.76-0.86) against physician diagnosis of asthma [Jenkins et al. Int J Epidemiol. 1996;25(3):609-16. DOI: 10.1093/ije/25.3.609]. Similarly, a study demonstrated that the Finnish ISAAC questionnaire to be highly valid (sensitivity: 0.98 [95% CI: 0.92-0.99; specificity: 0.98 [95% CI: 0.97-0.98]) against anti-asthmatic medication reimbursement data of the Finnish Social Insurance Institution [Nwaru et al. Clin Respir J. 2011;5(4):211-8. DOI: 10.1111/j.1752-699X.2010.00222.x]. Among children in the UK, using GP-recorded asthma as the gold standard, parental-reported ever doctor-diagnosed asthma had a sensitivity of 88.5% and a specificity of 95.7% [Cornish et al. BMJ Open. 2014;4(4):e005345. DOI: 10.1136/bmjopen-2014-005345]. Moreover, asthma defined in a similar manner to our “current asthma” variable was reported to be associated with lower lung function parameters [Arshad et al. Eur Respir J. 2020;55(3). pii: 1900477. DOI: 10.1183/13993003.00477-2019; Karmaus et al. Respir Res. 2019;20(1):98. DOI: 10.1186/s12931-019-1068-0]; hence, further validating the used definition in identifying participants with asthma. Moreover, compared to prior studies that used a comparable asthma definition, the estimated prevalence of current asthma (15.7%) in this report is similar to the prevalence estimate of current asthma (16.1%) in a prior study among adolescents aged in 16-19 years in Kuwait [Alnajem et al. Respir Res. 2020 Nov 16;21(1):300. DOI: 10.1186/s12931-020-01569-9], and comparable to current asthma prevalence estimate among 18-year old Isle of Wight birth cohort participants (17.7%) [Soto-Ramirez et al. J Epidemiol. 2013;23(6):399-410. DOI: 10.2188/jea.je20120201]. Such observations further validate the used asthma definition

Moreover, current eczema was defined as “ever doctor-diagnosed eczema” and/or “having ever had a recurrent itchy rash for at least 6 months” plus “having an itchy rash at any time in the past 12 months that affected the folds of the elbows or the areas behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes.” This definition follows the well-established criteria by Hanifin and Rajka [Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1980; 92: 44-7]. Moreover, to minimize misclassifying current rhinitis, we have used the following definition: “ever doctor-diagnosed rhinitis” and “having problems with a sneezing, runny, or blocked nose in the absence of a cold or flu in the past 12 months.” Hence, the used definitions of allergic diseases should provide improved classification than solely relaying on self-reported physician diagnosis.

To address this issues, we have added the following to the discussion section: “Nonetheless, we have used the standardized ISAAC questionnaire to ascertain

	allergic diseases, which has been shown to have good validity [21]. For instance, a prior study showed that the ISAAC criteria for ascertaining asthma symptoms as compared to physician diagnosis of asthma had a sensitivity of 85% and specificity of 81% [47]. Similarly, among children in the UK, using GP-recorded asthma as the gold standard, parental-reported ever doctor-diagnosed asthma had a sensitivity of 88.5% and a specificity of 95.7% [48]. Moreover, prior studies that defined asthma in a similar manner to our “current asthma” variable showed that their defined asthma to be associated with reduced lung function parameters [24, 49]. Compared to prior studies that defined asthma in a similar manner to our study, the estimated prevalence of current asthma (15.7%) in this report is similar to the prevalence estimate of current asthma (16.1%) in a preceding study conducted among adolescents aged in 16-19 years in Kuwait [50], and comparable to current asthma prevalence estimate among 18-year old Isle of Wight birth cohort participants (17.7%) in the UK [51]. Such observations further support the used asthma definition.” As we have described in the “Methods” section, “Ascertainment of study variables” subsection: “Ever doctor-diagnosed psoriasis” was determined by an affirmative response from the parent/guardian to the following question: “Has this child ever been diagnosed with psoriasis by a doctor?” This parent/guardian reported doctor-diagnosed psoriasis was used in our analysis. Hence, this definition only included individuals who reported that they have received a doctor diagnosis of psoriasis. Our inclusion of “doctor” diagnosed psoriasis was done to reduce the possibility of misclassification, as a prior study have shown that the validity of self-reported psoriasis increases when asking if the condition was physician-diagnosed [Reference: Modalsli et. J Invest Dermatol. 2015;136:325–8. DOI: 10.1038/JID.2015.386]. In addition, we have previously shown that the majority of individuals who reported a doctor-diagnosed psoriasis in our study sample have reported the involvement of typical psoriasis anatomical sites (scalp [47.6%], and extensor surfaces of the knees [50%] and elbows [38.1%]) which further supports the validity of our definition of psoriasis. To address this issues, we have added/modified the following to the discussion section: “Although the reliability (Cohen’s kappa: 0.7558) [45] and validity (sensitivity: 56%; specificity: 99%; positive predictive value: 78%; negative predictive value: 96%) [46] of self-reported psoriasis diagnoses are reportedly high, misclassification of the disease status cannot be eliminated, which can bias the estimated measures of association. Our assessment focused on doctor-diagnosed psoriasis reported by parent/guardian. A prior study showed that the inclusion of “self-reported doctor-diagnosed psoriasis” compared to only “self-reported psoriasis” yielded increased validity [46]. Moreover, we have previously shown that the majority of individuals who reported a doctor-diagnosed psoriasis in our study sample have reported the involvement of typical psoriasis anatomical sites (scalp [47.6%], and extensor surfaces of the knees [50%] and elbows [38.1%]) [20], which further supports the validity of our definition of psoriasis. ”
Additional Information:	
Question	**Response**
Is this study a clinical trial?<hr>A clinical trial is defined by the World Health Organisation as 'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'.	No

Association of psoriasis with allergic multimorbidity of asthma, rhinitis, and eczema among adolescents: a cross-sectional study

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Abstract

Background: Associations between psoriasis and allergic diseases (asthma, rhinitis, and eczema) in children have been reported in a limited number of studies, and the association between psoriasis and multimorbidity (co-occurrence) of allergic diseases remains unclear. Hence, this study aimed to assess the association between psoriasis and the co-occurrence of asthma, rhinitis, and eczema in adolescents.

Methods: This school-based cross-sectional study enrolled adolescents (n=3,864) aged 11–14 years. Parents completed a questionnaire on doctor-diagnosed psoriasis as well as symptoms and clinical history of asthma, rhinitis, and eczema. Eight nonoverlapping groups comprising single and co-occurring current (past 12 months) asthma, rhinitis, and eczema were identified. A multinomial logistic regression model was used to estimate the adjusted odds ratios (aOR) and 95% confidence intervals (CI).

Results: In the analytical sample (n = 3,710; 1,641 male and 2,069 female participants), 3.5% reported doctor-diagnosed psoriasis, and 15.7%, 15.0%, and 10.3% had current asthma, rhinitis, and eczema symptoms, respectively. Doctor-diagnosed psoriasis was associated with “asthma only” (aOR = 2.11, 95% CI: 1.15–3.89), “eczema only” (6.65, 4.11–10.74), “asthma + eczema” (5.25, 2.36–11.65), “rhinitis + eczema” (3.60, 1.07–12.15), and “asthma + rhinitis + eczema” (7.38, 2.93–18.58). Doctor-diagnosed psoriasis was not statistically significantly associated with “rhinitis only” (1.42, 0.71––2.84) and “asthma + rhinitis” (1.78, 0.69–4.56).

Conclusion: Our findings indicate that psoriasis is associated with the co-occurrence of allergic diseases among adolescents. However, further studies are required to investigate which biological mechanisms may be shared between psoriasis and allergic diseases.

Key words: psoriasis, eczema, asthma, rhinitis, multimorbidity, adolescents.

Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disease that affects over 60 million people worldwide, with varying prevalence estimates across regions [1]. The systemic impact of psoriasis-related inflammation causes long-term damage to multiple tissues and organs [2]. Patients with psoriasis may present different comorbidities, including psoriatic arthritis, metabolic syndrome (obesity, hypertension, type 2 diabetes, and dyslipidemia), cardiovascular disease (stroke and myocardial infarction), chronic obstructive pulmonary disease, chronic kidney disease, and inflammatory bowel disease [1, 2]. In addition, mental disorders, including depression and anxiety, have been reported as common comorbidities in patients with psoriasis [1, 2]. Hence, psoriasis impairs the physical and psychosocial well-being of affected individuals.

Although the pathophysiology of psoriasis remains unclear, cross-talk between innate and adaptive immune systems underlies the inflammatory infiltrate observed in psoriasis [3]. Activated myeloid dendritic cells release interleukin-12 (IL-12) and IL-23, which induce the proliferation of T-helper type 1 (Th1), Th17, and Th22 cells that subsequently produce pro-inflammatory cytokines (e.g., IL-17, IL-122, interferon gamma [IFN-γ], and tumor necrosis factor-alpha [TNF-α]) that characterize psoriasis, with the IL-23/Th17 pathway being the most predominant [2]. In contrast, allergic diseases, such as asthma, rhinitis, and eczema (atopic dermatitis), mainly involve skewed Th2-cells response to foreign bodies (allergens), which can lead to over-expression of IL-4 and IL-13, and subsequently increased production of immunoglobulin E, thereby causing an allergic reaction [4]. Although up-regulation of Th1 cells has been hypothesized to correlate with down-regulation of Th2 cells and vice versa, this paradigm has been challenged as the coexistence of autoimmune diseases caused by Th1

immune responses and allergic diseases caused by Th2 immune responses is not rare [5, 6]. Furthermore, genetic studies on allergic and autoimmune diseases have demonstrated considerable commonality in susceptibility loci [7], especially between eczema and psoriasis as inflammatory diseases of the skin [8], while others have reported opposing genetic susceptibility at the same loci [9].

The association between psoriasis and allergic diseases has been assessed in a limited number of studies. Majority of the studies that have assessed the association between psoriasis and allergic diseases have reported positive associations~~no consensus among studies: while a few observational epidemiologic studies have supported this association~~ and suggested that psoriasis and allergic diseases ~~they~~ have a common pathogenesis [10-15], while few ~~other~~ reports found no or inverse association between psoriasis and allergic diseases [16, 17]. Given that the multimorbidity (co-occurrence) of allergic disease is not rare [18], the association between psoriasis and multimorbidity of allergic diseases requires further investigations. Hence, we aimed to evaluate the association of psoriasis with asthma, rhinitis, and eczema both as single and co-occurring conditions in adolescents.

Methods

Study design, setting, and population

This school-based cross-sectional study enrolled adolescents (n = 3,864) aged 11–14 years resident in Kuwait. As previously described [19], a representative sample of middle school students attending public schools was obtained using stratified two-stage cluster sampling. The study questionnaire was sent home with the adolescents for parental/guardian completion and return. Ethical approval for the current study was obtained from the Standing Committee for the Coordination of Health and Medical Research, Ministry of Health, Kuwait (No. 2016/451). Written informed consent was obtained from the parents or legal guardians of the adolescents participating in this study, which was conducted following the principles and guidelines of the Declaration of Helsinki for medical research involving human participants.

Ascertainment of study variables

Ever doctor-diagnosed psoriasis was determined by an affirmative response from the parent/guardian to the following question: "Has this child ever been diagnosed with psoriasis by a doctor?" [20]. The International Study of Asthma and Allergies in Childhood (ISAAC) methodology was applied to ascertain allergic diseases [21]. Current (past 12 months) eczema was defined as "ever doctor-diagnosed eczema" and/or "having ever had a recurrent itchy rash for at least 6 months" plus "having an itchy rash at any time in the past 12 months that affected the folds of the elbows or the areas behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes" [22, 23]. Current asthma was defined by an affirmative response to the items "history of physician-diagnosed asthma" and "wheezing in the past 12 months" and/or "asthma treatment in the past 12 months" [19, 24]. Current rhinitis was defined as "ever

doctor-diagnosed rhinitis" and "having problems with a sneezing, runny, or blocked nose in the absence of a cold or flu in the past 12 months" [25]. Combinations of current asthma, rhinitis, and eczema resulted in eight nonoverlapping groups of single and coexisting allergic diseases: "no allergic disease," "asthma only," "rhinitis only," "eczema only," "asthma + rhinitis," "asthma + eczema," "rhinitis + eczema," and "asthma + rhinitis + eczema" groups.

Covariates

The parent/guardian reported the mode of participant birth (vaginal or cesarean section) and whether the participant was ever directly fed at the breast during infancy. Household exposure to secondhand smoke was assessed by asking whether any household member smoked cigarettes or tobacco-related products inside the home. To ascertain exposure to household cats and dogs during infancy, two separate questions were asked: "Did you have a cat/dog in your home during the first year of this child life?"

Statistical analysis

Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). The statistical significance level was set at $\alpha = 0.05$. Descriptive analyses were performed to calculate frequencies and proportions of categorical variables. Chi-square (χ^2) test was used to assess associations between categorical variables. The association between psoriasis status (exposure variable) and allergic diseases (outcome variable) was assessed using: i) binary logistic regression when evaluating the association with each allergic disease (non-mutually exclusive), and ii) multinomial logistic regression when evaluating the association with the single/co-occurring allergic disease(s) [mutually exclusive; nominal outcome variable, with the "no

allergic disease" category set as the reference]. Adjusted odds ratios (aOR) and their 95% confidence intervals (CI) were estimated. In addition to age and sex, individual characteristics that demonstrated possible association (p-value < 0.2) with psoriasis were included in the multivariable models as potential confounders.

Results

A total of 5,228 schoolchildren (2,483 male and 2,745 female adolescents) were invited to participate, of whom 3,864 (1,695 male and 2,169 female adolescents) agreed to participate (response proportion: 73.9%). The analytical sample (n = 3,710; restricted to participants with complete information on ever doctor-diagnosed psoriasis, current asthma, rhinitis, and eczema) and the total study sample (n = 3,864) were similar regarding the studied characteristics (Table 1). Of the total analytical sample, 3.5% of the adolescents reported having doctor-diagnosed psoriasis. The prevalence of current (past 12 months) asthma, rhinitis, and eczema were estimated to be 15.7%, 15.0, and 10.3%, respectively (Table 1).

Table 2 shows the prevalence of ever doctor-diagnosed psoriasis according to individual characteristics. The prevalence of psoriasis was similar in male and female participants (3.4% vs. 3.7%, p = 0.598). The prevalence of ever doctor-diagnosed psoriasis was higher among adolescents who were exposed to secondhand smoke in their households than among those who were not exposed (4.3% vs. 2.9%, p = 0.019). Similarly, having cats during infancy was associated with an increased prevalence of ever doctor-diagnosed psoriasis (7.6% vs. 3.3%, p < 0.001). Breastfed during infancy was associated with a lower prevalence of ever doctor-diagnosed psoriasis compared with those who were never breastfed (3.1% vs. 4.8%, p = 0.014).

Associations between ever doctor-diagnosed psoriasis and non-mutually exclusive occurrence of current asthma, rhinitis, and eczema are shown in Table 3. Ever doctor-diagnosed psoriasis was associated with increased prevalence of current asthma (aOR = 1.93, 95% CI: 1.28–2.91) and

current eczema (aOR = 5.36, 95% CI: 3.68–7.82), but not current rhinitis (aOR = 1.31, 95% CI: 0.83–2.07; Table 3).

Associations between ever doctor-diagnosed psoriasis and single and co-occurring allergic diseases are shown in Table 4. The prevalence of “asthma only” (aOR = 2.11, 95% CI: 1.15–3.89) and “eczema only” (aOR = 6.65, 95% CI: 4.11–10.74), but not the prevalence of “rhinitis only” (aOR = 1.42, 95% CI: 0.71–2.84), was increased in children with ever doctor-diagnosed psoriasis compared to those without prior diagnosis of psoriasis. Moreover, ever doctor-diagnosed psoriasis was associated with the co-occurrence of “asthma + eczema” (aOR = 5.25, 95% CI: 2.36–11.65), “rhinitis + eczema” (aOR = 3.60, 95% CI: 1.07–12.15), and “asthma + rhinitis + eczema” (aOR = 7.38, 95% CI: 2.93–18.58; Table 4).

Discussion

In this study, we demonstrated that doctor-diagnosed psoriasis was associated with an increased prevalence of current asthma and eczema, but not with rhinitis. Moreover, when assessing the mutually exclusive occurrence (nonoverlapping groups) of allergic diseases, psoriasis was associated with "asthma only" and "eczema only," and the co-occurrence of "asthma + eczema," "rhinitis + eczema," and "asthma + rhinitis + eczema". These findings suggest that the association between psoriasis and asthma is not dependent on the coexistence of other allergic diseases (i.e., eczema and rhinitis). Moreover, we demonstrated that psoriasis increased the odds of co-occurring allergic diseases.

In agreement with our findings, previous studies have found associations between psoriasis and asthma [10-14, 26]. Moreover, the association observed between psoriasis and eczema is supported by previous reports, as summarized in a meta-analysis [27]. To the best of our knowledge, only two prior studies have investigated such associations among children and reported increased odds of asthma [13, 15] and eczema [15] in relation to psoriasis. Although we observed an increased odds of rhinitis in relation to psoriasis (aOR = 1.31, 95% CI: 0.83–2.07), this association was not statistically significant, contradicting previous findings that observed increased risk of rhinitis related to psoriasis in children [13, 15]. Our analysis adds to the literature by investigating associations between psoriasis and the coexistence of asthma, rhinitis, and eczema. This investigation showed that psoriasis was associated with increased odds of single and co-occurrence of allergic diseases, with the odds of the co-occurrence of "asthma, rhinitis, and eczema" being noticeably increased. Hence, our findings suggest that psoriasis and allergic diseases are not mutually exclusive and may share certain biological mechanisms.

Classically, psoriasis and allergic diseases are considered Th1- and Th2-driven diseases, respectively. Nonetheless, the role of the IL-23/Th17 pathway leading to IL-17 secretion has emerged as dominant in the pathophysiology of psoriasis [1, 2]. Moreover, a recent study has shown that a group of patients with asthma had high IL-17 levels and demonstrated psoriasis-like immunophenotypic features [28]. A study using murine models has shown that psoriatic inflammation enhanced airway inflammation through the IL-23/Th17 axis.[29] Similarly, IL-17 reportedly contributes to the immune dysregulation observed in patients with eczema [30]. Therefore, Th17-cell activation leading to IL-17 production could be a common link between psoriasis and allergic diseases. In addition, a genome-wide association study demonstrated overlapping loci between eczema, asthma, and psoriasis, further indicating a shared genetic background [8].

Moreover, in terms of risk factors, genetic predisposition is the major contributor to the development of psoriasis, with few environmental and behavioral/lifestyle factors being implicated in the etiology of psoriasis [31, 32]. Alcohol use, smoking, and obesity have been shown to be risk factors for psoriasis [33-35]. To investigate possible causal effects of the identified risk factors, Mendelian Randomization studies have reported potential causal effects of smoking and obesity on psoriasis, but not alcohol consumption [36-38]. Similarly, smoking and obesity have been shown to be risk factors for the development of allergic diseases [39-41]. Moreover, breastfeeding has been shown to be associated with allergic diseases [42, 43], and more recently few studies have reported the association between breastfeeding and psoriasis [20, 44]. Collectively, the aforementioned factors have been speculated to alter immune development

and responses, hence altering the risk of immune mediated diseases such as psoriasis and allergic diseases.

The population-based design (capturing the spectrum of diseases) and large sample size are the strengths of our study. Although the reliability (Cohen's kappa: 0.7558) [45] and validity (sensitivity: 56%; specificity: 99%; positive predictive value: 78%; negative predictive value: 96%) [46] of self-reported psoriasis diagnoses are reportedly high, misclassification of the disease status cannot be eliminated, which can bias the estimated measures of association. Our assessment focused on doctor-diagnosed psoriasis reported by parent/guardian. A prior study showed that the inclusion of "self-reported doctor-diagnosed psoriasis" compared to only "self-reported psoriasis" yielded increased validity [46]. Moreover, ~~Previously,~~ we have previously shown that the majority of individuals who ~~self-~~reported a doctor-diagnosed psoriasis ~~diagnosis~~ in our study sample have reported the involvement of typical psoriasis anatomical sites (scalp [47.6%], and extensor surfaces of the knees [50%] and elbows [38.1%]) [20], which further supports the validity of our definition of psoriasis. Similarly, the misclassification of asthma, rhinitis, and eczema symptoms cannot be excluded. Nonetheless, we have used the standardized ISAAC questionnaire to ascertain allergic diseases, which has been shown to have good validity [21]. For instance, a prior study showed that the ISAAC criteria for ascertaining asthma symptoms as compared to physician diagnosis of asthma had a sensitivity of 85% and specificity of 81% [47]. Similarly, among children in the UK, using GP-recorded asthma as the gold standard, parental-reported ever doctor-diagnosed asthma had a sensitivity of 88.5% and a specificity of 95.7% [48]. Moreover, prior studies that defined asthma in a similar manner to our "current asthma" variable showed that their defined asthma to be associated with reduced lung

function parameters [24, 49]. Compared to prior studies that defined asthma in a similar manner to our study, the estimated prevalence of current asthma (15.7%) in this report is similar to the prevalence estimate of current asthma (16.1%) in a preceding study conducted among adolescents aged in 16-19 years in Kuwait [50], and comparable to current asthma prevalence estimate among 18-year old Isle of Wight birth cohort participants (17.7%) in the UK [51]. Such observations further support the used asthma definition. Furthermore, given that the magnitude and direction of the estimated measures of association (ORs) in our study ~~is~~ are similar to that in previous studies [10, 13-15, 26]~~.~~, we speculate that ~~For instance, Joel et al. have reported an association between psoriasis and asthma (aOR = 2.22, 95% CI: 2.08–2.37), which has a similar magnitude to our estimate (aOR = 1.93, 95% CI: 1.28–2.91)~~ the effect of misclassification, if any, should be minimal ~~in~~ on our results. It is essential to also indicate that our reported cross-sectional (concurrent) associations do not implicate any causal associations.

Conclusions

This study demonstrated associations between psoriasis and the single- and co-occurrence of allergic diseases in a sample of adolescents, and these findings add new knowledge into the limited literature in this area. Such associations further suggest that the coexistence of psoriasis and allergic diseases is not rare, and the paradigm of their nonoverlapping existence requires reexamination. Further studies are needed to investigate the biological mechanisms and genetic polymorphisms shared by psoriasis and allergic diseases that may result in their coexistence. The elucidation of these mechanisms may improve the clinical management of patients with coexisting psoriasis and allergic diseases.

List of abbreviations

IL: interleukin

Th: T-helper type cells

IFN-γ: interferon gamma

TNF-α: tumor necrosis factor-alpha

aOR: adjusted odds ratio

CI: confidence interval

Declarations

Ethics approval and consent to participate

Ethical approval for the current study was obtained from the Standing Committee for the Coordination of Health and Medical Research, Ministry of Health, Kuwait (No. 2016/451). Written informed consent was obtained from the parents or legal guardians of the adolescents participating in this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AHZ conceived, designed, and planned the study, obtained funding, supervised the research conduct, analyzed and interpreted the data, and drafted the manuscript. YA, DZ, MA, JWH, and WK contributed to the study conception, design and planning, contributed to data interpretation, and critically revised the manuscript. All authors critically revised the manuscript for important intellectual content. The manuscript has been read and approved by all authors.

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Table 1. Characteristics of the total study sample and the analytical study sample

Variables	Total study sample (n = 3864)	Analytical study sample* (n = 3710)
Sex, n (%)		
Male	1695 (43.9)	1641 (44.2)
Female	2169 (56.1)	2069 (55.8)
Age (years), n (%)		
≤ 11	1065 (27.6)	1026 (27.6)
12	1170 (30.3)	1125 (30.3)
13	964 (24.9)	919 (24.8)
≥ 14	665 (17.2)	640 (17.3)
BMI-for-age groups, n (%)		
Thinness (< -2 SD)	219 (5.8)	209 (5.8)
Normal (-2 to 1 SD)	1517 (40.1)	1457 (40.1)
Overweight (> 1 to 2 SD)	961 (25.3)	921 (25.3)
Obese (> 2 SD)	1089 (28.8)	1048 (28.8)
Missing, n	78	75
Mode of birth, n (%)		
Vaginal	3106 (81.8)	2998 (81.7)
Cesarean section	692 (18.2)	673 (18.3)
Missing, n	66	39
Breastfeeding ever, n (%)		
Yes	2894 (76.3)	2796 (76.3)
Missing, n	72	45
Secondhand smoke exposure, n (%)		
Yes	1755 (45.8)	1694 (45.8)
Missing, n	28	8
Cat exposure in infancy, n (%)		
Yes	232 (6.1)	224 (6.1)
Missing, n	35	15
Dog exposure in infancy, n (%)		
Yes	85 (2.2)	84 (2.3)
Missing, n	32	10
Ever doctor-diagnosed psoriasis		
Yes	136 (3.6)	131 (3.5)
Missing, n	58	0
Current eczema, n (%)		
Yes	388 (10.2)	381 (10.3)
Missing, n	73	0
Current asthma, n (%)		
Yes	600 (15.7)	581 (15.7)
Missing, n	35	0
Current rhinitis, n (%)		
Yes	566 (15.1)	558 (15.0)
Missing, n	105	0

BMI: body mass index; SD: standard deviation.

* Refers to the sample of participants with complete information on psoriasis status, current eczema status, current, asthma status, and current rhinitis status.

Table 2. Prevalence of ever-doctor diagnosed psoriasis according to individual characteristics

Variables	n	Ever doctor-diagnosed psoriasis, % (n)	P-value*
Sex			
Male	1641	3.4 (55)	0.598
Female	2069	3.7 (76)	
Age (years)			
≤ 11	1026	3.7 (38)	0.245
12	1125	2.7 (30)	
13	919	4.2 (39)	
≥ 14	640	3.8 (24)	
BMI-for-age groups			
Thinness (< -2 SD)	209	6.2 (13)	0.145
Normal (-2 to 1 SD)	1457	3.4 (50)	
Overweight (> 1 to 2 SD)	921	3.9 (36)	
Obese (> 2 SD)	1048	3.1 (32)	
Mode of birth			
Vaginal	2998	3.6 (107)	0.848
Cesarean section	673	3.4 (23)	
Breastfeeding ever			
Yes	2796	3.1 (86)	0.014
No	869	4.8 (42)	
Secondhand smoke exposure			
Yes	1694	4.3 (73)	0.019
No	2008	2.9 (58)	
Cat exposure in infancy			
Yes	224	7.6 (17)	<0.001
No	3471	3.3 (114)	
Dog exposure in infancy			
Yes	84	6.0 (5)	0.226
No	3616	3.5 (126)	

BMI: body mass index; SD: standard deviation.

* Calculated using chi-square (χ^2) test.

Table 3. Adjusted associations between ever doctor-diagnosed psoriasis and allergic diseases

	Ever doctor-diagnosed psoriasis			
	Yes (n = 131)	No (n = 3579)		
Allergic disease	**% (n)**	**% (n)**	**aOR‡ (95% CI)**	**P-value**
Asthma	26.0 (34)	15.3 (547)	1.93 (1.28-2.91)	0.002
Rhinitis	18.3 (24)	14.9 (534)	1.31 (0.83-2.07)	0.253
Eczema	36.6 (48)	9.3 (333)	5.36 (3.68-7.82)	<0.001

aOR: Adjusted odds ratio; CI: Confidence interval.

‡ Adjusted for sex, age, BMI-for-age groups, breastfeeding, secondhand smoke exposure, and cat exposure in infancy.

Table 4. Adjusted associations between ever doctor-diagnosed psoriasis and single and co-occurring allergic diseases

		Ever doctor-diagnosed psoriasis			
	Total (n = 3710)	**Yes (n = 131)**	**No (n = 3579)**		
Allergic disease	**% (n)**	**% (n)**	**% (n)**	**aOR‡ (95% CI)**	**P-value**
None	68.1 (2526)	40.5 (53)	69.1 (2473)	1.00 (Reference)	–
Asthma only	8.9 (328)	11.5 (15)	8.8 (313)	2.11 (1.15-3.89)	0.016
Rhinitis only	9.0 (334)	7.6 (10)	9.1 (324)	1.42 (0.71-2.84)	0.316
Eczema only	6.1 (227)	23.7 (31)	5.5 (196)	6.65 (4.11-10.74)	<0.001
Asthma + Rhinitis	3.8 (141)	3.8 (5)	3.8 (136)	1.78 (0.69-4.56)	0.232
Asthma + Eczema	1.9 (71)	6.1 (8)	1.8 (63)	5.25 (2.36-11.65)	<0.001
Rhinitis + Eczema	1.1 (42)	2.3 (3)	1.1 (39)	3.60 (1.07-12.15)	0.039
Asthma + Rhinitis + Eczema	1.1 (41)	4.6 (6)	1.0 (35)	7.38 (2.93-18.58)	<0.001

aOR: Adjusted odds ratio; CI: Confidence interval.

‡ Adjusted for sex, age, BMI-for-age groups, breastfeeding, secondhand smoke exposure, and cat exposure in infancy.

Point-by-point responses to reviewers' comments

Manuscript Title: Association of psoriasis with allergic multimorbidity of asthma, rhinitis, and eczema among adolescents: a cross-sectional study

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Note to the reviewers: We would like to thank the reviewers for their interest in our manuscript and the insightful, careful, and constructive comments and suggestions that improved our manuscript.

Reviewer #1: GENERAL COMMENTS:

This manuscript addresses a topic of broad for the readership of this journal. The manuscript is well written and gives an excellent introduction to the topic. However, I have one significant concern, as outlined below.

Response:

We thank the reviewer for the interest in our manuscript and for the critical and constructive comments that improved our manuscript. Please find below our responses to the comments.

MAJOR COMPULSORY REVISIONS:

The authors clearly describe the conflicting data in existing medical literature on the association between psoriasis and atopic disease, stating that "the association between psoriasis and allergic diseases has no consensus among studies..." [Line 75]. However, they ultimately conclude that their data reveal a clear association between these conditions.

Response:

We thank the reviewer for this comment. Most of the studies that have assessed the association between psoriasis and allergic diseases have reported positive associations, while only few studies have reported no or negative associations. Our conclusion is based on the observed results from our study, which showed that psoriasis was associated with allergic diseases. No

single study can be certain, but we showed that in our sample there is an association between psoriasis and allergic diseases, and we have also indicated that future studies are needed to explain the underlying mechanisms of such associations. To clarify the issues, we have revised the statements we made in the introduction.

The following was revised sentences were added to the introduction section:

"The association between psoriasis and allergic diseases has been assessed in a limited number of studies. Majority of studies that have assessed the association between psoriasis and allergic diseases have reported positive associations and suggested that psoriasis and allergic diseases have a common pathogenesis [10-15], while few other reports found no or inverse association between psoriasis and allergic diseases [16, 17]."

The methods description (Lines 96-109) describes inclusion limited to physician-diagnosed psoriasis, with no indication whether self-reported psoriasis was also included (the inferred assumption is that it was not). However, in stark contrast, each of the atopic conditions included both physician- and self-reported disease. Physician subspecialists who manage atopic diseases understand how frequently patients referred to their clinics will come with a physician diagnosis that is incorrect, especially with respect to asthma. Even more frequent are patients who self-report asthma based on factors such as incorrectly perceived "wheezing" or who have been prescribed asthma treatment in the past--two criteria that were used for inclusion in the present study. Therefore, even if the data in the current study was limited to inclusion of physician-diagnosed of asthma, it may grossly overestimate the true prevalence of this condition in the study population, and further including self-reported asthma will only increase that overestimate.

Response:

We understand the importance of clear/valid case definitions and their implications on the study results. Nevertheless, in large population-based epidemiological studies, clinical diagnosis can be costly and requires substantial resources. Hence, self-reported criteria have been developed to

overcome the need for clinical assessments by doctors for several diseases, including allergic diseases (International Study of Asthma and Allergies in Childhood [ISAAC; Reference: Asher et. Eur Respir J. 1995;8:483-91. DOI: 10.1183/09031936.95.08030483]). As we have described in the "Methods" section, "Ascertainment of study variables" subsection: "*Ever doctor-diagnosed psoriasis" was determined by an affirmative response from the parent/guardian to the following question: "Has this child ever been diagnosed with psoriasis by a doctor?*" This parent/guardian reported doctor-diagnosed psoriasis was used in our analysis. Hence, this definition only included individuals who reported that they have received a doctor diagnosis of psoriasis. Our inclusion of "doctor" diagnosed psoriasis was done to reduce the possibility of misclassification, as a prior study did show that the validity of self-reported psoriasis increases when asking if the condition was physician-diagnosed [Reference: Modalsli et. J Invest Dermatol. 2015;136:325–8. DOI: 10.1038/JID.2015.386].

To address this issues, we have added/modified the following to the discussion section:
"Although the reliability (Cohen's kappa: 0.7558) [45] and validity (sensitivity: 56%; specificity: 99%; positive predictive value: 78%; negative predictive value: 96%) [46] of self-reported psoriasis diagnoses are reportedly high, misclassification of the disease status cannot be eliminated, which can bias the estimated measures of association. Our assessment focused on doctor-diagnosed psoriasis reported by parent/guardian. A prior study showed that the inclusion of "self-reported doctor-diagnosed psoriasis" compared to only "self-reported psoriasis" yielded increased validity [46]."

With regard to the ascertainment of asthma, we defined current asthma using ISAAC methodology as follows: an affirmative response to the items "history of physician-diagnosed asthma" and "wheezing in the past 12 months" and/or "asthma treatment in the past 12 months." Hence, our asthma definition required a self-reported physician-diagnosed asthma plus having had wheezing episodes in the past 12 months and/or have used asthma treatment in the past 12 months. This approach included history of receiving a diagnosis plus having an asthma symptom (wheezing) and/or have used asthma medications in the past 12 months. We agree with the review that there is no perfect method to define asthma in large population-based studies, and

misclassification is inevitable. However, we have used the standardized ISAAC questionnaire to define asthma [Lai et al. Thorax. 2009;64(6):476-83. DOI: 10.1136/thx.2008.106609]. Prior studies have investigated the validity of the ISAAC questionnaire against multiple asthma surrogates. For instance, among children aged 13-14 year, the ISAAC questionnaire had sensitivity value of 0.85 (95% CI: 0.73-0.93) and specificity value of 0.81 (95% CI: 0.76-0.86) against physician diagnosis of asthma [Jenkins et al. Int J Epidemiol. 1996;25(3):609-16. DOI: 10.1093/ije/25.3.609]. Similarly, a study demonstrated that the Finnish ISAAC questionnaire to be highly valid (sensitivity: 0.98 [95% CI: 0.92-0.99; specificity: 0.98 [95% CI: 0.97-0.98]) against anti-asthmatic medication reimbursement data of the Finnish Social Insurance Institution [Nwaru et al. Clin Respir J. 2011;5(4):211-8. DOI: 10.1111/j.1752-699X.2010.00222.x]. Among children in the UK, using GP-recorded asthma as the gold standard, parental-reported ever doctor-diagnosed asthma had a sensitivity of 88.5% and a specificity of 95.7% [Cornish et al. BMJ Open. 2014;4(4):e005345. DOI: 10.1136/bmjopen-2014-005345]. Moreover, asthma defined in a similar manner to our "current asthma" variable was reported to be associated with lower lung function parameters [Arshad et al. Eur Respir J. 2020;55(3). pii: 1900477. DOI: 10.1183/13993003.00477-2019; Karmaus et al. Respir Res. 2019;20(1):98. DOI: 10.1186/s12931-019-1068-0]; hence, further validating the used definition in identifying participants with asthma. Moreover, compared to prior studies that used a comparable asthma definition, the estimated prevalence of current asthma (15.7%) in this report is similar to the prevalence estimate of current asthma (16.1%) in a preceding study among adolescents aged in 16-19 years in Kuwait [Alnajem et al. Respir Res. 2020 Nov 16;21(1):300. DOI: 10.1186/s12931-020-01569-9], and comparable to current asthma prevalence estimate among 18-year old Isle of Wight birth cohort participants (17.7%) [Soto-Ramirez et al. J Epidemiol. 2013;23(6):399-410. DOI: 10.2188/jea.je20120201].

<u>To address this issues, we have added the following to the discussion section:</u>

"Nonetheless, we have used the standardized ISAAC questionnaire to ascertain allergic diseases, which has been shown to have good validity [21]. For instance, a prior study showed that the ISAAC criteria for ascertaining asthma symptoms as compared to physician diagnosis of asthma had a sensitivity of 85% and specificity of 81% [47]. Similarly, among children in the UK, using GP-recorded asthma as the gold standard, parental-reported ever doctor-diagnosed asthma had a

sensitivity of 88.5% and a specificity of 95.7% [48]. Moreover, prior studies that defined asthma in a similar manner to our "current asthma" variable showed that their defined asthma to be associated with reduced lung function parameters [24, 49]. Compared to prior studies that defined asthma in a similar manner to our study, the estimated prevalence of current asthma (15.7%) in this report is similar to the prevalence estimate of current asthma (16.1%) in a preceding study conducted among adolescents aged in 16-19 years in Kuwait [50], and comparable to current asthma prevalence estimate among 18-year old Isle of Wight birth cohort participants (17.7%) in the UK [51]. Such observations further support the used asthma definition."

In the discussion section (Lines 203-218), the authors attempt to address this weakness of the current study of having included self-reported disease, but ultimately do not address why only physician-diagnosed psoriasis was included, while both physician- and self-reported atopic diseases were included. The authors ultimately conclude that this does not represent a significant weakness because their data is similar to the results of reference 20 [Joel et al.]. However, it is not explained why this particular reference carries more importance that the large number of other similarly conducted studies that conclude the opposite.

Response:

As we have described in our response to the previous comment, the information analyzed in this study relied on parental/guardian reported prior diagnosis by physician and signs and symptoms of the conditions. For psoriasis, ever doctor-diagnosed psoriasis was determined by an affirmative response from the parent/guardian to the following question: "Has this child ever been diagnosed with psoriasis by a doctor?" This parent/guardian reported doctor-diagnosed psoriasis was used in our analysis. For allergic diseases (asthma, rhinitis, and eczema), we have used both parent/guardian-reported physician diagnosis plus signs/symptoms of the disease. We have provided detailed description of the definitions in the methods section of the paper and provided references. We have indicated in the discussion section that misclassification of the

diseases cannot be eliminated and might influence the measures of associations. We used reference 20 as an example, but did not stress that this reference carries more importance. We understand the review's concern and have removed the sentence that makes a comparison with reference #20 from the revised manuscript. Our intention was to indicate that the magnitude and direction of the effect measures in our study are similar to prior studies. Hence, we speculate that information bias, if any, has minimal effects on our results.

The following was added/modified to the discussion section:

"Furthermore, given that the magnitude and direction of the estimated measures of association (ORs) in our study is are similar to that in previous studies [10, 13-15, 26], we speculate that the effect of misclassification, if any, should be minimal on our results."

It would be helpful to know whether the findings of this study would differ if the data included were limited to only physician-diagnosed asthma and other atopic conditions.

Response:

Current asthma, current rhinitis, current eczema variables that we have analyzed were defined by using reported physician diagnosis plus signs/symptoms of the respective conditions. As described in our prior point of response, our "current asthma" definition required a self-reported physician-diagnosed asthma plus having had wheezing episodes in the past 12 months and/or have used asthma treatment in the past 12 months. This approach included history of receiving a diagnosis plus having an asthma symptom (wheezing) and/or have used asthma medications in the past 12 months. Current eczema was defined as "ever doctor-diagnosed eczema" and/or "having ever had a recurrent itchy rash for at least 6 months" plus "having an itchy rash at any time in the past 12 months that affected the folds of the elbows or the areas behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes." This definition follows the well-established criteria by Hanifin and Rajka [Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1980; 92: 44-7]. Moreover, to minimize misclassifying current rhinitis, we have used the following definition: "ever doctor-diagnosed rhinitis" and "having problems with a sneezing, runny, or blocked nose in the absence of a cold

or flu in the past 12 months." Hence, the used definitions of allergic diseases should provide improved classification than solely relaying on self-reported physician diagnosis.

MINOR ESSENTIAL REVISIONS: none identified

DISCRETIONARY REVISIONS:

Lines 146-147: It is reported that exposure to secondhand smoke and cats during infancy were associated with an increased prevalence of physician-diagnosed psoriasis in this study. The readership of this journal is primarily specialists in atopic diseases. Please consider adding discussion either in the introduction or discussion section about what environmental factors have previously been associated with an increased risk of psoriasis and compare this with the same environmental factors' impact on the development of atopic diseases.

Response:

We thank the reviewer for this suggestion. We have added a paragraph to the discussion section on the common risk factors that have been reported for psoriasis and allergic diseases.

The following was added to the discussion section:

"Moreover, in terms of risk factors, genetic predisposition is the major contributor to the development of psoriasis, with few environmental and behavioral/lifestyle factors being implicated in the etiology of psoriasis [31, 32]. Alcohol use, smoking, and obesity have been shown to be risk factors for psoriasis [33-35]. To investigate possible causal effects of the identified risk factors, Mendelian Randomization studies have reported potential causal effects of smoking and obesity on psoriasis, but not alcohol consumption [36-38]. Similarly, smoking and obesity have been shown to be risk factors for the development of allergic diseases [39-41]. Moreover, breastfeeding has been shown to be associated with allergic diseases [42, 43], and more recently few studies have reported the association between breastfeeding and psoriasis [20, 44]. Collectively, the aforementioned factors have been speculated to alter immune development and responses, hence altering the risk of immune mediated diseases such as psoriasis and allergic diseases."

Reviewer #2:

This was an interesting cross-sectional study of school aged children looking at associations between psoriasis and various atopic conditions.

The main limitation was this was parent self report, not data acquired from a chart review to confirm these actual diagnoses. How did the authors account for this limitation?

Response:

We thank the reviewer for the interest in our manuscript and for the critical and constructive comment that improved our manuscript.

We agree with the reviewer, self-reporting of conditions might lead to misclassification. Nonetheless, we have applied rigorous definitions that have been previously used in epidemiological studies. The definitions that we used relayed on physician diagnosis plus signs/symptoms of the conditions. For instance, our "current asthma" definition required a self-reported physician-diagnosed asthma plus having had wheezing episodes in the past 12 months and/or have used asthma treatment in the past 12 months. This approach included history of receiving a diagnosis plus having an asthma symptom (wheezing) and/or have used asthma medications in the past 12 months. We have used the standardized ISAAC questionnaire to define asthma [Lai et al. Thorax. 2009;64(6):476-83. DOI: 10.1136/thx.2008.106609]. Prior studies have investigated the validity of the ISAAC questionnaire against multiple asthma surrogates. For instance, among children aged 13-14 year, the ISAAC questionnaire had sensitivity value of 0.85 (95% CI: 0.73-0.93) and specificity value of 0.81 (95% CI: 0.76-0.86) against physician diagnosis of asthma [Jenkins et al. Int J Epidemiol. 1996;25(3):609-16. DOI: 10.1093/ije/25.3.609]. Similarly, a study demonstrated that the Finnish ISAAC questionnaire to be highly valid (sensitivity: 0.98 [95% CI: 0.92-0.99; specificity: 0.98 [95% CI: 0.97-0.98]) against anti-asthmatic medication reimbursement data of the Finnish Social Insurance Institution [Nwaru et al. Clin Respir J. 2011;5(4):211-8. DOI: 10.1111/j.1752-699X.2010.00222.x]. Among children in the UK, using GP-recorded asthma as the gold standard, parental-reported ever doctor-diagnosed asthma had a sensitivity of 88.5% and a specificity of 95.7% [Cornish et al. BMJ Open. 2014;4(4):e005345. DOI: 10.1136/bmjopen-2014-005345]. Moreover, asthma defined in a similar manner to our "current asthma" variable was reported to be associated with lower lung function parameters [Arshad et al. Eur Respir J. 2020;55(3). pii: 1900477. DOI:

10.1183/13993003.00477-2019; Karmaus et al. Respir Res. 2019;20(1):98. DOI: 10.1186/s12931-019-1068-0]; hence, further validating the used definition in identifying participants with asthma. Moreover, compared to prior studies that used a comparable asthma definition, the estimated prevalence of current asthma (15.7%) in this report is similar to the prevalence estimate of current asthma (16.1%) in a prior study among adolescents aged in 16-19 years in Kuwait [Alnajem et al. Respir Res. 2020 Nov 16;21(1):300. DOI: 10.1186/s12931-020-01569-9], and comparable to current asthma prevalence estimate among 18-year old Isle of Wight birth cohort participants (17.7%) [Soto-Ramirez et al. J Epidemiol. 2013;23(6):399-410. DOI: 10.2188/jea.je20120201]. Such observations further validate the used asthma definition

Moreover, current eczema was defined as "ever doctor-diagnosed eczema" and/or "having ever had a recurrent itchy rash for at least 6 months" plus "having an itchy rash at any time in the past 12 months that affected the folds of the elbows or the areas behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes." This definition follows the well-established criteria by Hanifin and Rajka [Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1980; 92: 44-7]. Moreover, to minimize misclassifying current rhinitis, we have used the following definition: "ever doctor-diagnosed rhinitis" and "having problems with a sneezing, runny, or blocked nose in the absence of a cold or flu in the past 12 months." Hence, the used definitions of allergic diseases should provide improved classification than solely relaying on self-reported physician diagnosis.

To address this issues, we have added the following to the discussion section:

"Nonetheless, we have used the standardized ISAAC questionnaire to ascertain allergic diseases, which has been shown to have good validity [21]. For instance, a prior study showed that the ISAAC criteria for ascertaining asthma symptoms as compared to physician diagnosis of asthma had a sensitivity of 85% and specificity of 81% [47]. Similarly, among children in the UK, using GP-recorded asthma as the gold standard, parental-reported ever doctor-diagnosed asthma had a sensitivity of 88.5% and a specificity of 95.7% [48]. Moreover, prior studies that defined asthma in a similar manner to our "current asthma" variable showed that their defined asthma to be associated with reduced lung function parameters [24, 49]. Compared to prior studies that defined asthma in a similar manner to our study, the estimated prevalence of current asthma

(15.7%) in this report is similar to the prevalence estimate of current asthma (16.1%) in a preceding study conducted among adolescents aged in 16-19 years in Kuwait [50], and comparable to current asthma prevalence estimate among 18-year old Isle of Wight birth cohort participants (17.7%) in the UK [51]. Such observations further support the used asthma definition."

As we have described in the "Methods" section, "Ascertainment of study variables" subsection: "Ever doctor-diagnosed psoriasis" was determined by an affirmative response from the parent/guardian to the following question: "Has this child ever been diagnosed with psoriasis by a doctor?" This parent/guardian reported doctor-diagnosed psoriasis was used in our analysis. Hence, this definition only included individuals who reported that they have received a doctor diagnosis of psoriasis. Our inclusion of "doctor" diagnosed psoriasis was done to reduce the possibility of misclassification, as a prior study have shown that the validity of self-reported psoriasis increases when asking if the condition was physician-diagnosed [Reference: Modalsli et. J Invest Dermatol. 2015;136:325–8. DOI: 10.1038/JID.2015.386]. In addition, we have previously shown that the majority of individuals who reported a doctor-diagnosed psoriasis in our study sample have reported the involvement of typical psoriasis anatomical sites (scalp [47.6%], and extensor surfaces of the knees [50%] and elbows [38.1%]) which further supports the validity of our definition of psoriasis.

<u>To address this issues, we have added/modified the following to the discussion section:</u>
"Although the reliability (Cohen's kappa: 0.7558) [45] and validity (sensitivity: 56%; specificity: 99%; positive predictive value: 78%; negative predictive value: 96%) [46] of self-reported psoriasis diagnoses are reportedly high, misclassification of the disease status cannot be eliminated, which can bias the estimated measures of association. Our assessment focused on doctor-diagnosed psoriasis reported by parent/guardian. A prior study showed that the inclusion of "self-reported doctor-diagnosed psoriasis" compared to only "self-reported psoriasis" yielded increased validity [46]. Moreover, we have previously shown that the majority of individuals who reported a doctor-diagnosed psoriasis in our study sample have reported the involvement of typical psoriasis anatomical sites (scalp [47.6%], and extensor surfaces of the knees [50%] and elbows [38.1%]) [20], which further supports the validity of our definition of psoriasis. "

Tuesday, March 26, 2024

Dear Professor Harold Kim,
Editor-in-Chief
Allergy, Asthma & Clinical Immunology

RE:

Manuscript No.: AACI-D-23-00234

Manuscript title: Association of psoriasis with allergic multimorbidity of asthma, rhinitis, and eczema among adolescents: a cross-sectional

Thank you for your e-mail of February 28, 2024. We are pleased that you are interested in our manuscript for possible publication in *Allergy, Asthma & Clinical Immunology*. We also thank the reviewers for their interest, critical, and insightful comments, which improved our manuscript.

We have addressed the comments raised by the reviewers and have carefully revised the manuscript. We hope that it is now suitable for publication in your esteemed journal. I am sending the revised manuscript with tracked changes (marked) and the point-by-point responses to reviewers' comments.

We thank you in advance for your consideration and look forward to hearing from you again.

Yours sincerely,
Ali H. Ziyab