



Atopic Dermatitis Is Associated with Preeclampsia and Endometriosis

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TO THE EDITOR

NK cell function has been shown to be associated with atopic dermatitis (AD), with patients with AD usually having decreased circulating numbers of NK cells but increasing lesional skin numbers of NK cells (Kabashima and Weidinger, 2020; Mack et al., 2020; Möbus et al., 2021; Sun et al., 2021). An important regulator of NK cell function are *KIR* genes, which can have either inhibitory or activating effects on NK cells (Pende et al., 2019). In addition to having a potential role in the pathogenesis of AD, NK cells have also been implicated in the development of preeclampsia and endometriosis. Interactions between maternal uterine NK cells and the extravillous trophoblast, potentially mediated by KIR and HLA-C ligands interactions, can influence the development of preeclampsia and pregnancy outcomes (Hiby et al., 2004). KIR and HLA-C ligands have also been associated with the development of endometriosis (Chou et al., 2020). A recent study revealed that *KIR* gene variation is associated with AD (Margolis et al., 2021). Because NK cell function and *KIR* genes appear to be involved in the pathogenesis of AD, preeclampsia, and endometriosis, it is possible that there may be an association between these conditions.

To evaluate whether there is an association between AD with preeclampsia and endometriosis, a retrospective cohort study was performed using the Optum Clinformatics Data Mart (Optum) between January 2016 and July 2020, as well as using The Health Improvement Network (THIN) through February 2015. Patients

were identified in Optum through the presence of diagnostic codes for AD (L20x) and either asthma (J45x) or allergic rhinitis (J30x), and in THIN using a previously validated algorithm for this dataset (Abuabara et al., 2017).

To evaluate for a potential association with preeclampsia, in Optum, patients with AD were matched with up to five patients without AD, based on age and index date of pregnancy delivery. In THIN, patients with AD were matched with up to five patients without AD patients based on age, practice, and an encounter within ± 6 months of the latter of practice registration and diagnosis dates for the patient with AD. Logistic regression was used to examine for differences in the frequency of preeclampsia (O14x) during the first recorded pregnancy. In Optum, preeclampsia was defined as any encounter with a diagnosis code for preeclampsia within 180 days before or 90 days after the delivery date. In THIN, preeclampsia was defined by any diagnosis of preeclampsia within 180 days before or after the first pregnancy code.

To evaluate for a potential association with endometriosis, in Optum, patients with AD were matched 1:1 with patients who were diagnosed with a nevus or seborrheic keratosis, based on age and index date of diagnosis. In THIN, the same matching approach was used as described above. Logistic regression was used to examine for differences in the frequency of endometriosis (N80x). All analyses were restricted to female patients between the ages of 15 and 45 years at the time of the index date. Analyses in Optum

were additionally adjusted for follow-up time before and after the index date, and all individuals were required to have at least 1 year of continuous enrollment before and after the index date.

Analyses performed in Optum and THIN were synthesized using random effects meta-analysis. Statistical analyses were performed in Stata 15 (StataCorp, College Station, TX). This study was reported in adherence with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (von Elm et al., 2007).

Preeclampsia was more common in women with AD than controls in both the Optum (1.59% vs. 1.10%; adjusted odds ratio [aOR] = 1.27, 95% confidence interval [CI] 0.83–1.94) and THIN cohorts (0.74% vs. 0.67%; OR = 1.11, 95% CI = 1.03–1.19), although this association did not reach statistical significance in the Optum cohort (Table 1). In the meta-analysis, there was an association between AD and preeclampsia (OR = 1.11, 95% CI = 1.03–1.19). Endometriosis was more common in women with AD than controls in both the Optum (4.29% vs. 3.00%; aOR = 1.48, 95% CI = 1.24–1.78) and THIN cohorts (1.17% vs. 0.95%; OR = 1.24, 95% CI = 1.20–1.27) (Table 2). In the meta-analysis, there was an association between AD and endometriosis (OR = 1.32, 95% CI = 1.09–1.55).

AD is a common persistent dermatologic illness that often begins in early childhood. Classically, other allergic illnesses have been associated with AD such as asthma, food allergies, and seasonal allergies. In this cohort study, using two administrative databases, we identify an association of AD with preeclampsia and endometriosis. The effect estimates were small but similar in both datasets, revealing the generalizability of this finding. The findings of our work and others support that nonallergic illnesses are also associated

Abbreviations: AD, atopic dermatitis; CI, confidence interval; Optum, Optum Clinformatics Data Mart; THIN, The Health Improvement Network

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Table 1. Association of Atopic Dermatitis with Preeclampsia

	Atopic Dermatitis	Without Atopic Dermatitis
Optum		
N	1,821	7,946
Continuous enrollment prior to index, d, mean (SD)	1,240 (1,082)	1,097 (985)
Continuous enrollment after index, d, mean (SD)	630 (304)	553 (288)
Preeclampsia, n (%)	29 (1.59)	88 (1.10)
OR preeclampsia (95% CI), adj ¹	1.27 (0.83–1.94)	<i>P</i> = 0.276
THIN		
N	142,773	515,542
Preeclampsia, n (%)	1,067 (0.74)	3,482 (0.67)
OR preeclampsia (95% CI)	1.10 (1.03–1.19)	<i>P</i> = 0.004

Abbreviations: adj, adjusted; CI, confidence interval; d, days; Optum, Optum Clinformatics Data Mart; THIN, The Health Improvement Network
¹Adjusted for follow-up time

Table 2. Association of Atopic Dermatitis with Endometriosis

	Atopic Dermatitis	Without Atopic Dermatitis
Optum		
N	18,342	18,342
Continuous enrollment prior to index, d, mean (SD)	1,639 (1,317)	1,170 (793)
Continuous enrollment after index, d, mean (SD)	709 (253)	747 (271)
Endometriosis, n (%)	304 (4.3)	213 (3.0)
OR endometriosis preeclampsia (95% CI), adj ¹	1.48 (1.24–1.78)	<i>P</i> < 0.001
THIN		
N	567,557	2,295,873
Endometriosis, n (%)	6,725 (1.17)	21,995 (0.95)
OR endometriosis (95% CI)	1.23 (1.08–1.40)	<i>P</i> = 0.002

Abbreviations: adj, adjusted; CI, confidence interval; d, days; Optum, Optum Clinformatics Data Mart; THIN, The Health Improvement Network
¹Adjusted for follow-up time

with AD (Sinaii et al., 2002; Stockholm et al., 2017). Furthermore, the associations with preeclampsia and endometriosis are potentially related to genetic variation in *KIR* genes and NK cell function, revealing additional immunologic pathways that may be associated with AD (Margolis et al., 2021; Nakimuli et al., 2015).

This study has several strengths, including replicating the findings in two independent datasets from two different countries (United States and United Kingdom). This study is limited in that the Optum cohort was relatively small, limiting power to detect differences in our analysis of preeclampsia. Although we have attempted to mitigate this risk using matched cohorts, there is the potential for unmeasured confounding

related to degree of interaction with the healthcare system, race and ethnicity, obesity, and smoking; these variables are all poorly measured in our cohorts, making adjustment unreliable. In addition, because we do not have associated genetic data, we are unable to assess whether *KIR* gene function may be a key factor in these observed associations. Future studies are needed to replicate our findings further and to examine for potential biologic mediators of these observed associations, including potential interactions with ancestry.

Data availability statement

Data are not available from the authors because this dataset is restricted.

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AUTHOR CONTRIBUTIONS

Conceptualization: DJM; Data Curation: JSB, DBS; Formal Analysis: JSB, DBS; Funding Acquisition: DJM; Investigation: JSB, DBS, DJM; Methodology: JSB, DBS, DJM; Project Administration: DJM; Resources: DJM; Software: JSB, DBS; Supervision: DJM; Validation: JSB, DBS; Visualization: JSB, DBS, DJM; Writing - Original Draft Preparation: JSB; Writing - Review and Editing: JSB, DBS, DJM

CONFLICT OF INTEREST

The authors state no conflict of interest.

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