Elevated C-reactive protein levels in atopic dermatitis patients with sleep disturbance is associated with the development of cardiovascular comorbidities and increased mortality: a multi-center cohort study

Varsha Parthasarathy B.S.[1], Zachary Bordeaux B.S.[1], Junwen Deng B.A.[1], Matthew Taylor B.A.[1],Martin P. Alphonse, Ph.D.[1], Shawn G. Kwatra M.D.[1]

[1] Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD, USA;

Introduction

- Atopic dermatitis (AD) is an intensely itchy inflammatory skin disease associated with a significant decrease in quality of life.[1]
- The quality of life impact in AD impacts patients' lifestyles, social interaction, and daily activities.[1]
- There are many described comorbidities of AD: e.g. systemic (malignancy, atherosclerosis), autoimmune (vitiligo, alopecia areata), psychiatric (anxiety).[2] These are possibly secondary to significant inflammation found in AD.[3]
- Large cohort research on the association between AD and sleep-related comorbidities is lacking.

Objectives

- To identify the association between AD and sleep-related comorbidities
- To characterize the impact of sleep disorders in AD on inflammatory labs and adverse cardiovascular outcomes

Materials and Methods

- This retrospective cohort study was performed via TriNetX, a de-identified healthcare research network of medical records from 73 million patients.
- AD patients were identified as having ≥2 diagnosed instances of ICD-10 code L28 between 2015-Present (Oct. 2020). Controls were identified as presenting for general examining with no atopic dermatitis or pruritic conditions. They were age-, sex-, race-matched to AD.
- P-values were adjusted with Benjamini-Hochberg method.

References

1. Silverberg JI, Gelfand JM, Margolis DJ, et al. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. Ann Allergy Asthma Immunol. 2018;121(3):340-347.

2. Roh YS, Huang AH, Sutaria N, et al. Real-world comorbidities of atopic dermatitis in the U.S. adult ambulatory population [published online ahead of print, 2021 Nov 17]. J Am Acad Dermatol. 2021;S0190-9622(21)02838-3.

3. Wongvibulsin, S., Sutaria, N., Kannan, S. et al. Transcriptomic analysis of atopic dermatitis in African Americans is characterized by Th2/Th17-centered cutaneous immune activation. Sci Rep 11, 11175 (2021).

4. van Leeuwen WM, Lehto M, Karisola P, Lindholm H, Luukkonen R, Sallinen M, Härmä M, Porkka-Heiskanen T, Alenius H. Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. PLoS One. 2009;4(2):e4589.

Results

- From 2015-2021, there were 120,480 AD patients and matched controls, with mean age: 36.4±23.1 years; Gender: 61% female
- AD patients had higher relative risk of all examined sleep-related conditions compared to controls ($p<0.01$ for all) (**Figure 1**)
- Overall, AD patients had higher levels of C-reactive protein (CRP) ($p<0.001$)
- AD patients with sleep disorders had higher levels of CRP compared to AD patients without sleep disorders ($p<0.05$) (**Figure 2**)
- AD patients with sleep disorders had higher risk of adverse cardiovascular outcomes compared to AD patients without sleep disorders ($p<0.01$), and higher levels of mortality (Hazard Ratio 1.24, 95% Confidence Interval 1.13-1.36) (**Figure 3**).

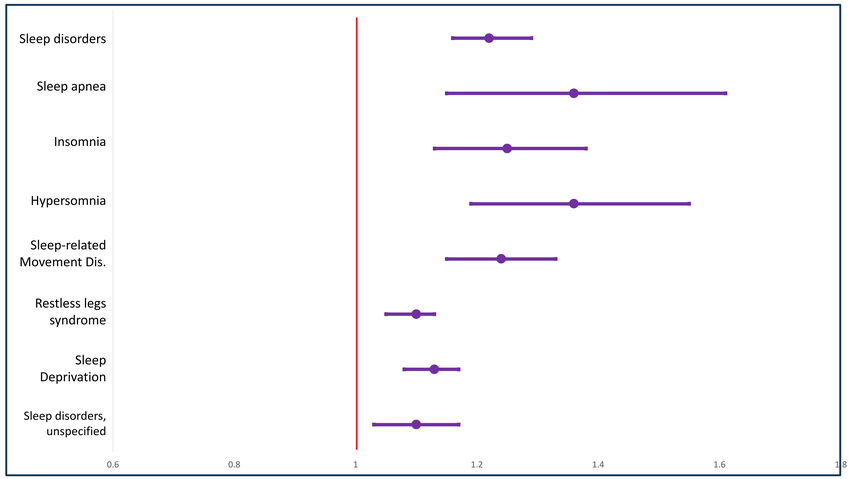

Figure 1. Relative risk of sleep disorders in AD vs. control patients

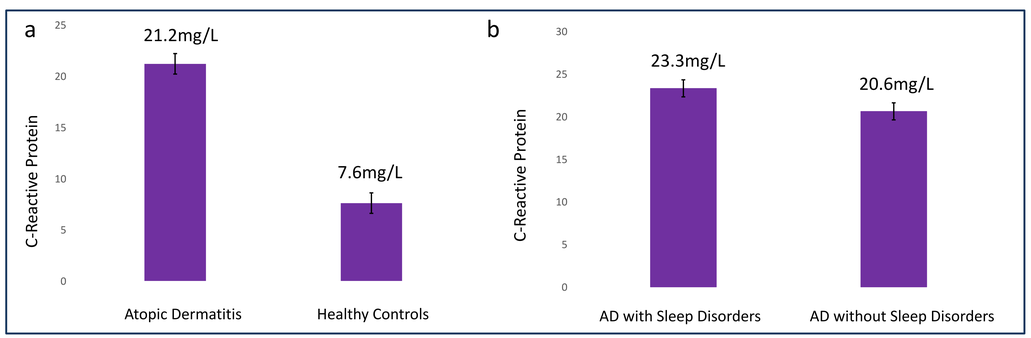

Figure 2. (a) C-reactive protein (CRP) levels between AD and controls, (b) CRP levels between AD with and without sleep disorders

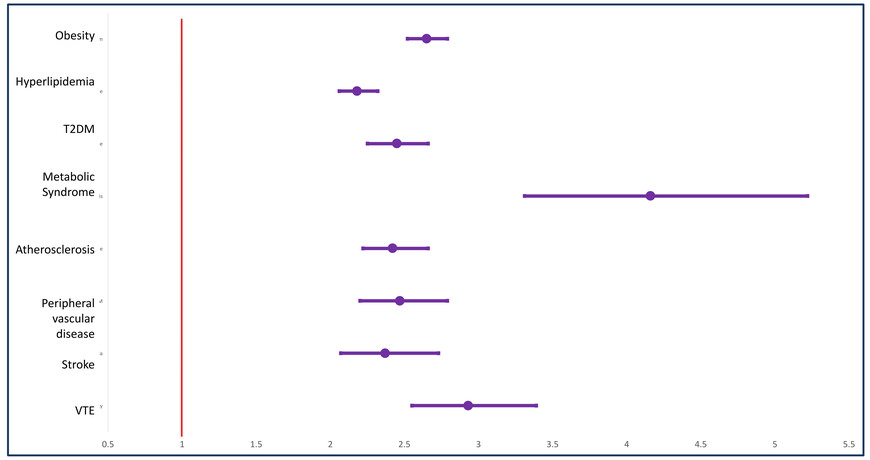

Figure 3. Relative risk of adverse cardiovascular outcomes in AD with sleep disorders vs. AD without sleep disorders (*T2DM Type 2 Diabetes Mellitus, VTE Venous Thromboembolism*)

Discussion and Conclusions

- Atopic dermatitis is associated with an increased risk of developing sleep-related disorders.
- AD patients with sleep disorders had higher levels of CRP, supportive of high inflammation in AD.[3]
- Poor sleep quality is known to increase systemic inflammatory markers such as IL-6, IL-17, and CRP.[4]
- AD patients with sleep disorders also had higher risk of developing adverse cardiovascular outcomes; CRP is a known mediator of inflammation associated with cardiovascular complications.[4]
- **Clinicians should consider the potential risk for sleep disorders and cardiac comorbidities secondary to inflammation in patients diagnosed with AD**.