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Research

# The Correlation between Allergic Diseases and Systemic Lupus Erythematosus

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## ABSTRACT

**Background:** The prevalence of autoimmune diseases and major chronic allergic diseases such as allergic rhinitis, asthma, and atopic dermatitis are increasing in line with the occurrence of climate change. Allergy and systemic lupus erythematosus (SLE) are sometimes being linked since both are immune diseases involving gene-environment interactions. The purpose of this research is to investigate the correlation between allergic diseases and SLE.
**Method:** This case-control study was performed on 39 SLE subjects from the Tittari Community and 39 non-SLE subjects aged 15-49 years old, from September until October 2021. All of them were females. The independent variable was allergic disease and the dependent variable was SLE. Participants' characteristics and allergy data were collected through answering the online Score for Allergic Rhinitis (SFAR) questionnaire, then the results were processed with bivariate and multivariate analyses.
**Results:** The correlation between allergic diseases and SLE was significant for atopic dermatitis but not for allergic rhinitis and asthma (p=0.018; p=0.352; p=0.151 respectively). The bivariate analysis revealed that the risk of SLE was 3.17 times higher in atopic dermatitis patients (OR=3.17; 95% CI=1.20-8.39; p=0.018). Furthermore, the multivariate analysis found that subjects with atopic dermatitis had the highest risk of SLE (OR= 3.18; 95% CI= 1.07-9.51; p=0.031).
**Conclusion:** Among allergic diseases, atopic dermatitis was found to be significantly correlated with SLE, where the risk of SLE was raised as the number of atopic dermatitis increased.

**Keywords:** systemic lupus erythematosus, allergic diseases, allergic rhinitis, asthma, atopic dermatitis

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## BACKGROUND

In the general population, allergic diseases are prevalent chronic conditions. Allergens trigger these diseases, and they usually present as recurrent, non-infectious inflammatory disorders. In systemic lupus erythematosus (SLE), a number of genetic and environmental trigger factors are known to play a role. Although genomic studies have focused on the links between SLE and genes, not all patients with defective alleles would develop SLE. Hyperreactivities to environ-

mental antigens and food allergens are linked to allergic diseases such as atopic dermatitis, allergic rhinitis, and asthma (Hsiao et al., 2014).

SLE is one of the most common systemic autoimmune diseases, with an estimated incidence rate of 5-10 new cases per 100.000 person-years. SLE is thought to be caused by immune dysregulation and a lack of self-tolerance. Genetic and non genetic factors such as female gender, ethnicity, family history, alcohol usage, and heavy smoking are all established predisposing factors for SLE (Wongtrakul et al., 2020).

A recent study stated that there is a complex interaction between climate change and the incidence of allergic diseases, as it is linked to inflammatory markers and allergen sensitization. Air pollution, including dust, and climatic factors (e.g. warmer temperatures and high CO2 levels) can be directly related to allergic diseases (Ziska, 2020). Global warming causes pollen season to last longer and begin earlier, as well as effects on allergen potency in allergic patients, all of which increase the likelihood of developing allergic-related respiratory diseases like asthma and allergic rhinitis, both in sensitized and symptomatic patients, by increasing the permeability of the respiratory epithelium (Chan et al., 2019). Aside from pollen distribution, climate change is associated with increased humidity and temperatures that are linked to the severity and prevalence of atopic dermatitis in several countries (Sogebi et al., 2016). Environmental changes such as climate factors, ultraviolet radiation, and seasonal distribution can work together to cause epigenetic changes in SLE resulting in immune dysregulation and loss of tolerance (Pan et al., 2019).

Both allergic diseases and SLE are characterized by inflammatory responses and share epidemiological similarities that suggest both conditions share a common etiology. Recent discoveries suggest that allergic diseases and autoimmune diseases like SLE may become risk factors for each other (Guo et al., 2017).

Immune dysregulation is a feature of autoimmune disorders and allergy diseases. It has been claimed that these conditions are essentially polarised with distinct mechanisms, with autoimmune disorders and allergic diseases principally mediated by T-helper (Th)1 and Th2 cellular immune responses, respectively. Both have a complicated aetiopathogenesis and develop as a result of a complex interplay between many genetic and environmental factors, as well as other unknown elements (Krishna et al., 2019).

Some research has recently revealed that people with allergic disorders are at a higher risk of acquiring autoimmune diseases, including SLE, albeit the degree of the claimed relationship differs greatly between studies (Hsiao et al., 2014; Lin et al., 2018; Wongtrakul et al., 2020). The objective of this study is to investigate if individuals with allergies have a higher risk of SLE than those who do not have allergies.

## SUBJECT AND METHOD

### 1. Study Design

This is a case-control study. The data collection process took two weeks, from September 22nd until October 7th, 2021. We shared an online Score for Allergic Rhinitis (SFAR) questionnaire with the members of the Tittari Community (as the case group), a community for SLE patients who have previously been diagnosed with SLE based on ACR 2019, and with people without SLE or other autoimmune diseases (as the control group). We used the SFAR questionnaire to investigate allergic diseases and the family history of allergy in the subjects.

**2. Population and Sample**

This study was performed on 39 SLE subjects from the Tittari Community and 39 non-SLE subjects. We exclude male populations as subjects to avoid bias in the incidence of allergy and SLE. From 43 SLE subjects and 47 non-SLE subjects, we selected those who had filled out the questionnaire completely, aged 15-49 years, and were females. After the exclusions, we included 39 SLE subjects and 39 non SLE subjects to be analysed in this study.

**3. Study Variables**

The dependent variable was SLE. The independent variable was allergic diseases.

**4. Operational Definition of Variables**

To asses the allergic diseases as the independent variable, we used the SFAR questionnaire to investigate allergic diseases and the family history of allergy in the subjects. The dependent variable was SLE patients who have been previously diagnosed with SLE based on ACR 2019, and people without SLE or other autoimmune diseases (as the control group).

**5. Study Instrument**

We used the SFAR questionnaire to investigate allergic diseases and the family history of allergy in the subjects. The SFAR score is an allergic rhinitis screening questionnaire developed by Annesi-Maesano et.al in 2002. In its original English questionnaire, there are 8 questions which are categorized into several groups to asses nasal symptoms, occurrence of rhino-conjungtivitis, period of the symptoms, trigger factors, perceived allergic status, self-allergic history, and family history of allergy (Lam et al., 2017). As the subjects were Indonesians, we utilized the Indonesian Modification of SFAR Questionnaire by Widuri & Fakhriani to get the optimal response. In this modification, the questions are developed into 13, and the minimum score to diagnose allergic rhinitis is 7 (Widuri and Fakhriani, 2021). We focused on the questions related to the diagnosis and symptoms of allergic rhinitis, asthma, atopic dermatitis, and subjects' family history of allergy, then analysed the relation of those parameters to the occurence of SLE (O'Neill et al., 2017).

**6. Statistical Analysis**

This part consists of dependent and independent variables under study. The demographic data between cases and controls was compared using chi-squared tests. We performed logistic regression analyses to identify risk factors independently associated with SLE. A two-tailed $p$ value of $<0.05$ was considered statistically significant. Pearson rank correlation was performed to show the correlation between allergic diseases and SLE. The non-parametric correlation test, spearman rank, was performed as an alternative if the normality test were below 0,05. We conducted all statistical analyses using SPSS Statistics version 25.

**7. Research Ethics**

The study was approved by the Research Ethics Committee of Dr. Moewardi General Hospital, Surakarta, Indonesia (No. 372/IV/HREC/2021).

## RESULTS

**1. Subjects Characteristics**

Table 1 shows the demographic features of subjects with SLE and non-SLE. In this study, 39 SLE patients and 39 non-SLE subjects who had met the inclusion and exclusion criteria were included. All the subjects in this study were females, aged 15-49 years old, and for SLE patients, they had been diagnosed with ACR 2019 previously by the Rheumatologist. The age group of 30 to 39-year-olds had the highest proportion of SLE patients (20.5%). SLE patients were more likely to have a family history of allergic diseases (OR = 1.57, 95% CI: 0.62 - 3.98).

**Table 1. Subjects Characteristics**

| | SLE n=39 | Control n=39 | p | OR | 95% CI |
|---|---|---|---|---|---|
| **Gender** | | | | | |
| Female | 39 (50) | 39 (50) | NA | NA | |
| **Age (years)** | | | | | |
| 10 – 19 | 1 (1.3) | 0 | | | |
| 20 – 29 | 13 (16.7) | 20 (25.6) | 0.347 | NA | |
| 30 – 39 | 16 (20.5) | 12 (15.4) | | | |
| 40 – 49 | 9 (11.5) | 7 (9) | | | |
| **Family History** | | | | | |
| Yes | 16 (20.5) | 12 (15.4) | 0.345 | 1.57 | 0.62 - 3.98 |
| No | 23 (29.5) | 27 (34.6) | | | |
| **Allergic Diseases** | | | | | |
| Allergic Rhinitis | | | | | |
| Yes | 17 (21.8) | 13 (16.7) | 0.352 | 1.55 | 0.62 - 3.87 |
| No | 22 (28.2) | 26 (33.3) | | | |
| Atopic Dermatitis | | | | | |
| Yes | 19 (24.4) | 9 (11.5) | 0.018 | 3.17 | 1.20 - 8.39 |
| No | 20 (25.6) | 30 (38.5) | | | |
| Asthma | | | | | |
| Yes | 10 (12.8) | 5 (6.4) | 0.151 | 2.35 | 0.72 - 7.65 |
| No | 29 (37.2) | 34 (43.6) | | | |
| **Clinical Manifestations** | | | | | |
| Mucocutaneous | 22 (56.4) | | | | |
| Musculoskeletal | 26 (66.7) | | | | |
| Serosal | 4 (10.2) | | | | |
| Neuropsychiatric | 13 (33.3) | | | | |
| Renal | 13 (33.3) | | | | |
| Cardiovascular | 6 (15.3) | | | | |
| Gastrointestinal | 2 (5.1) | | | | |
| Hematologic | 4 (10.2) | | | | |
| Others | 3 (7.7) | | | | |

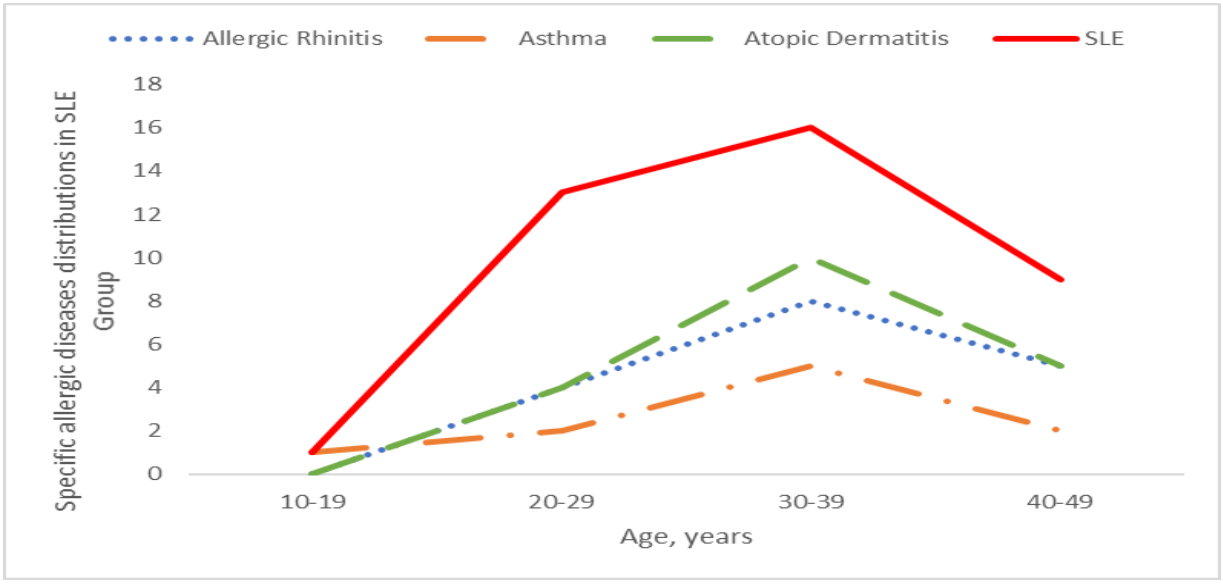


**Figure 1. Proportional distributions of allergic diseases and SLE based on age groups**

**Table 2. The Correlation of Allergic Diseases and SLE based on Age Group**

| Age group | Variables | Category | Cases n(%) | Controls n(%) | p | OR | 95% CI |
|---|---|---|---|---|---|---|---|
| **10 - 19** | Allergic Rhinitis | Yes | 0 | 0 | NA | NA | |
| | | No | 1 (100) | 0 | | | |
| | Asthma | Yes | 1 (100) | 0 | | | |
| | | No | 0 | 0 | | | |
| | Atopic Dermatitis | Yes | 0 | 0 | | | |
| | | No | 1 (100) | 0 | | | |
| **20 - 29** | Allergic Rhinitis | Yes | 4 (12.1) | 5 (15.2) | 0.704 | 1.33 | 0.28 - 6.30 |
| | | No | 9 (27.3) | 15 (45.5) | | | |
| | Asthma | Yes | 2 (6.1) | 2 (6.1) | 0.643 | 1.64 | 0.20 - 13.34 |
| | | No | 11 (33.3) | 18 (54.5) | | | |
| | Atopic Dermatitis | Yes | 4 (12.1) | 4 (12.1) | 0.479 | 1.78 | 0.36 - 8.88 |
| | | No | 9 (48.5) | 16 (27.3) | | | |
| **30 - 39** | Allergic Rhinitis | Yes | 8 (28.6) | 5 (17.9) | 0.658 | 1.40 | 0.31 - 6.33 |
| | | No | 8 (28.6) | 7 (25) | | | |
| | Asthma | Yes | 5 (17.9) | 1 (3.6) | 0.144 | 5.00 | 0.50 - 50.07 |
| | | No | 11 (39.3) | 11 (39.3) | | | |
| | Atopic Dermatitis | Yes | 10 (35.7) | 5 (17.9) | 0.265 | 2.33 | 0.51 - 10.78 |
| | | No | 6 (21.4) | 7 (25) | | | |
| **40 - 49** | Allergic Rhinitis | Yes | 5 (31.3) | 3 (18.8) | 0.608 | 1.67 | 0.23 - 12.22 |
| | | No | 4 (25) | 4 (25) | | | |
| | Asthma | Yes | 2 (12.5) | 2 (12.5) | 0.766 | 0.71 | 0.074 - 6.92 |
| | | No | 7 (43.8) | 5 (31.3) | | | |
| | Atopic Dermatitis | Yes | 5 (31.3) | 0 | 0.012 | NA | |
| | | No | 4 (25) | 7 (43.8) | | | |

Figure 2 shows the odds ratios of the logistic regression analysis. Allergic dermatitis is shown to be the only one to develop SLE, with a risk of becoming SLE that is increased 3.18 times than the other individuals.

SLE is influenced by the combination of genetic and environmental factors. Because this disease has various manifestations and the symptoms might change over time, it is critical to identify those who may develop a distinct SLE phenotype (Lin et al., 2018). Previous skin involvement and a range of skin lesions, including urticaria, are common in SLE patients. During the course of the disease, mucocutaneous symptoms were documented in up to 70% of the patients (Lin et al., 2018). Prior research has suggested that the presence of allergic diseases such as allergic rhinitis, atopic dermatitis, and asthma may be associated with the development of SLE in the future.

In this study, we found the highest proportion of SLE was in the age group of 30 to 39-years-old, followed by the age group of 20 to 29-years-old. Likewise, the allergic diseases (allergic rhinitis, atopic dermatitis, and asthma) also had the highest proportion in the age group of 30-39 years old. This finding supports the theory that SLE affects women in their second or third decade of life due to the increased susceptibility of females of reproductive age and gives them a one-in-ten probability of dying before the age of 40 (Margery-Muir et al., 2017; O'Neill et al., 2017).

**Table 3. Multivariate Analysis**

| Variables | Category | Cases n(%) | Controls n(%) | p | OR | 95%CI |
|---|---|---|---|---|---|---|
| **Age group** | 10-19 y.o | 1 (1.3) | 0 | 0.310 | 1.38 | 0.74 - 2.58 |
| | 20-29 y.o | 13 (16.7) | 20 (25.6) | | | |
| | 30-39 y.o | 16 (20.5) | 12 (15.4) | | | |
| | 40-49 y.o | 9 (11.5) | 7 (9) | | | |
| **Family history** | Yes | 16 (20.5) | 12 (15.4) | 0.326 | 1.73 | 0.59 - 5.05 |
| | No | 23 (29.5) | 27 (34.6) | | | |
| **Allergic Rhinitis** | Yes | 17 (21.8) | 13 (16.7) | 0.326 | 0.54 | 0.15-1.90 |
| | No | 22 (28.2) | 26 (33.3) | | | |
| **Atopic Dermatitis** | Yes | 19 (24.4) | 9 (11.5) | 0.031 | 3.18 | 1.07-9.41 |
| | No | 20 (25.6) | 30 (38.5) | | | |
| **Asthma** | Yes | 10 (12.8) | 5 (6.4) | 0.167 | 2.66 | 0.65-10.92 |
| | No | 29 (37.2) | 34 (43.6) | | | |

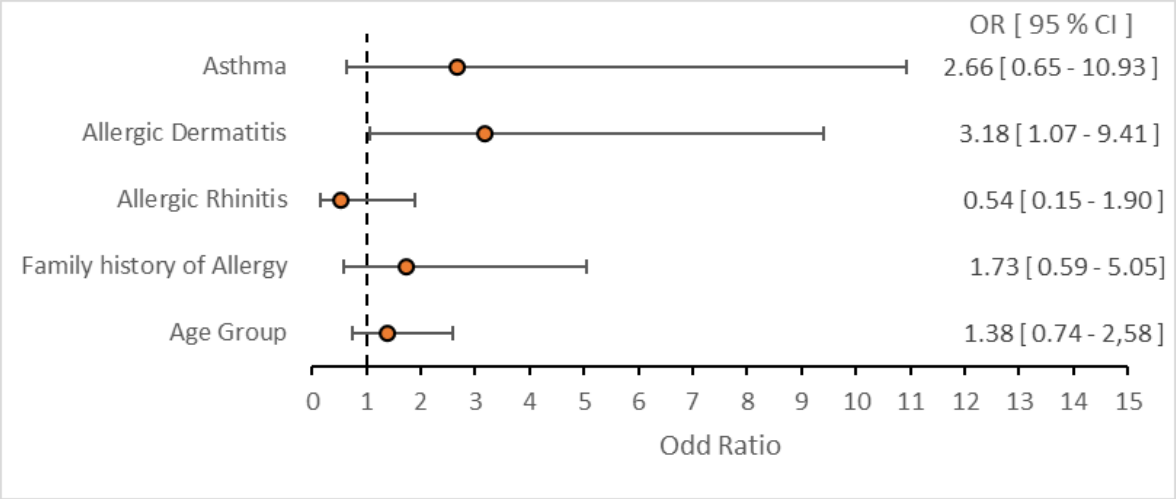


**Figure 2. Forest Plot of logistic regression odd ratios**

## DISCUSSION

Allergic disease comorbidities and a family history of allergic diseases were more common in SLE patients than in controls and were linked to an increased risk of SLE. Systemic Lupus Erythematosus patients exhibited more atopic disease comorbidities than controls, including allergic rhinitis, allergic conjunctivitis, atopic dermatitis, and asthma, according to Hsiao YP et al (Hsiao et al., 2014). The majority of SLE patients had musculoskeletal symptoms (66.7%), which was consistent with prior research. Arthritis and athralgias have been seen in as many as 95% of SLE patients. The clinical signs of SLE can be confused for another type of inflammatory arthritis, that leads to delaying diagnosis by months or years (Khan et al., 2017).

Our study results showed that there was a relationship between atopic dermatitis and SLE. Both atopic dermatitis and SLE patients show an increase in Th2 cytokines like IL-5, IL-13 and Th17 cytokines like IL-17 and IL-22, while there is a decrease in IL-2 as the main cytokines of Th1. SLE patients with active disease were found to have an increased level of IgE, identical to people

with allergic diseases. As a result, it is probable that enhanced Th2 activity and IgE production seen in allergic diseases could lead to the development of SLE later in life (Ponvilawan et al., 2021).

Skin involvement and a range of skin lesions, including urticaria, are common in SLE patients. During the course of the disease, mucocutaneous symptoms were documented in up to 70% of the patients (Lin et al., 2018). Experimentally elicited IgE autoantibodies and/or IgG autoantibodies were thought to cause eczematous lesions in atopic dermatitis, according to the proposed mechanism. In about 25% of severe AD patients, IgE autoantibodies against proteins from keratinocytes and endothelial cells were found in about 25% of patients. In 14 investigations comprising 2644 participants, the prevalence of "autoreactivity" in atopic dermatitis patients ranged from 23% to 91%t. As a result, two significant observations support the concept that "autoreacttivity" plays a role in atopic dermatitis which are Autologous (human components) elicits immediate hypersensitive reactions in atopic dermatitis. Approximately 20-30% of atopic dermatitis patients have ANA, ranging in titer between 1:40 and 1:1280. It was suggested that the ANA (+) in atopic dermatitis patients should be carefully followed up in the long term to monitor the development of SLE manifestations if other autoantibodies are positive. However, the role of autoantibodies contributing to atopic diseases requires further investigation (Hsiao et al., 2014).

According to a recent study, the pathophysiology of atopic dermatitis and SLE is similar, with both diseases being associated with inflammation and autoimmune disease. Confino-Cohen et al found that individuals with atopic dermatitis had a higher risk of SLE, and the high incidence of autoantibodies suggested a pathogenic mechanism that could be autoimmune in nature (Confino-Cohen et al., 2012). Our findings imply that, even in the absence of SLE-specific serologic markers, atopic dermatitis may be an early symptom of SLE. These findings have significance for clinicians treating atopic dermatitis in order to detect probable SLE early.

Similar to our study, several observational studies have found a relationship between allergic rhinitis and various autoimmune diseases, in addition to SLE. When case-control and cohort studies with acceptable quality and minimal risk of bias were included in a recent meta-analysis, it was found that allergic rhinitis may increase the risk of rheumatoid arthritis. According to population-based cohort studies, similar findings were seen in Sjögren's syndrome and psoriasis (Krishna et al., 2019; Wongtrakul et al., 2020). Clinical studies have found a greater level of IgE during the active phase of SLE. As a result, it is probable that enhanced Th2 activity and IgE production seen in allergic rhinitis patients could lead to the development of SLE later in life (Wongtrakul et al., 2020).

In this study the subjects with asthma also had the risk of SLE especially in the age group of 20-29 years old and 30-39 years old. Asthma and SLE may have immune-pathogenic mechanisms that are similar. Hyperresponsiveness to exogenous antigens has been identified as an immunological feature of both asthma and SLE, according to studies. In both asthma and SLE patients, elevated levels of TH2 class cytokines, including as IL-4, IL-5, and IL-13, have been found. Furthermore, people with SLE have been found to have higher levels of total IgE, which is commonly related with asthma and allergic diseases(Charoenngam et al., 2020).

Immune dysregulation and elevated inflammatory mediators are involved in the pathophysiology of both allergy and auto-

immune disorders. In various allergic diseases, IgE is a well-known essential mediator. IgE may have a role in the etiology of autoimmunity by stimulating both type 1 (Th1) and type 2 (Th2) helper T cells and contributing to persistent inflammation and autoantibody generation, according to recent research (Wongtrakul et al., 2020).

A strong link between allergic diseases and the risk of SLE has been found in several studies. Our findings back up the theory that atopic dermatitis is one of the comorbid diseases associated with SLE. Furthermore, our findings suggest that some autoimmune or autoinflammatory disorders may have a close relationship with SLE, as previous research has suggested (Lin et al., 2018). Even after accounting for these comorbidities, a history of atopic dermatitis was found to be related to a greater risk of SLE.

Among allergic diseases, atopic dermatitis was found to be significantly correlated with SLE. Clinically diagnosed atopic dermatitis has been linked to an increased incidence of SLE and may be the first sign of SLE in female patients. For early detection of SLE, clinicians should evaluate or follow up on female patients with atopic dermatitis. For a better knowledge of the pathogenesis of both allergic diseases and SLE, more research is needed. We suggest to measure the disease activity of SLE as there will be a stronger correlation between allergic disease and active status of SLE and also to perform skin prick test and spirometry to diagnose rhinitis allergy and asthma more accurately.

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**CONFLICT OF INTEREST**

There is no conflict of interest.

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