Tobacco smoke as a risk factor for allergic sensitization in adults: Conclusions of a systematic review and meta-analysis

To the Editor:

Allergic sensitization to aeroallergens is a common phenomenon and a crucial step in the development of allergic diseases. Nonetheless, the influence of tobacco smoke exposure on the development of allergic sensitization in adults is quite complex and not totally understood.

Therefore, our objective was to systematically review the existing evidence regarding this topic and to perform a meta-analysis of the data collected from the included studies.

The search for studies that potentially matched the inclusion criteria (for inclusion and exclusion criteria, see this article's Online Repository at www.jacionline.org) was performed independently by 2 authors, in several databases (Fig 1). Discrepancies were resolved through discussion with the involvement of a third author when necessary. All data were independently extracted by 2 review authors, who also independently assessed the risk of bias in the included studies considering the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement for observational studies. For description of statistical methods, see this article's Online Repository at www.jacionline.org.

Fig 1 represents the flowchart of the inclusion and exclusion criteria used in the selection process. Of the 1387 retrieved studies, 16 were included in the meta-analysis.

Regarding the random-effects' meta-analysis for specific IgE, 6 studies with a total of 25,218 participants were included. The random-effects estimate showed that tobacco smoke exerted a statistically significant protective effect in the development of allergic sensitization among smokers, when compared with never smokers (odds ratio [OR], 0.692; 95% CI, 0.596-0.804; $P < .001$) (Fig 2, *A*). For summary of the meta-analysis, sensitivity analysis, and evaluation of publication bias, see this article's Online Repository at www.jacionline.org.

Concerning the fixed-effect meta-analysis for house dust mite (HDM)-specific IgE, 5 studies with a total of 31,782 participants were included. The fixed-effect estimate revealed that tobacco smoke exposure increases significantly the risk of allergic sensitization to HDM in smokers, when compared with never smokers (OR, 1.184; 95% CI, 1.113-1.259; $P < .001$) (Fig 2, *B*). For summary of the meta-analysis, sensitivity analysis, and evaluation of publication bias, see this article's Online Repository.

Relatively to the random-effects' meta-analysis for skin prick tests, 7 studies with a total of 11,041 participants were included. The random-effects estimate revealed that tobacco smoke exposure exerted a significant protective effect in the development of allergic sensitization among smokers when compared with never smokers (OR, 0.714; 95% CI, 0.596-0.856; $P < .001$) (Fig 2, *C*). For summary of the meta-analysis, sensitivity analysis,

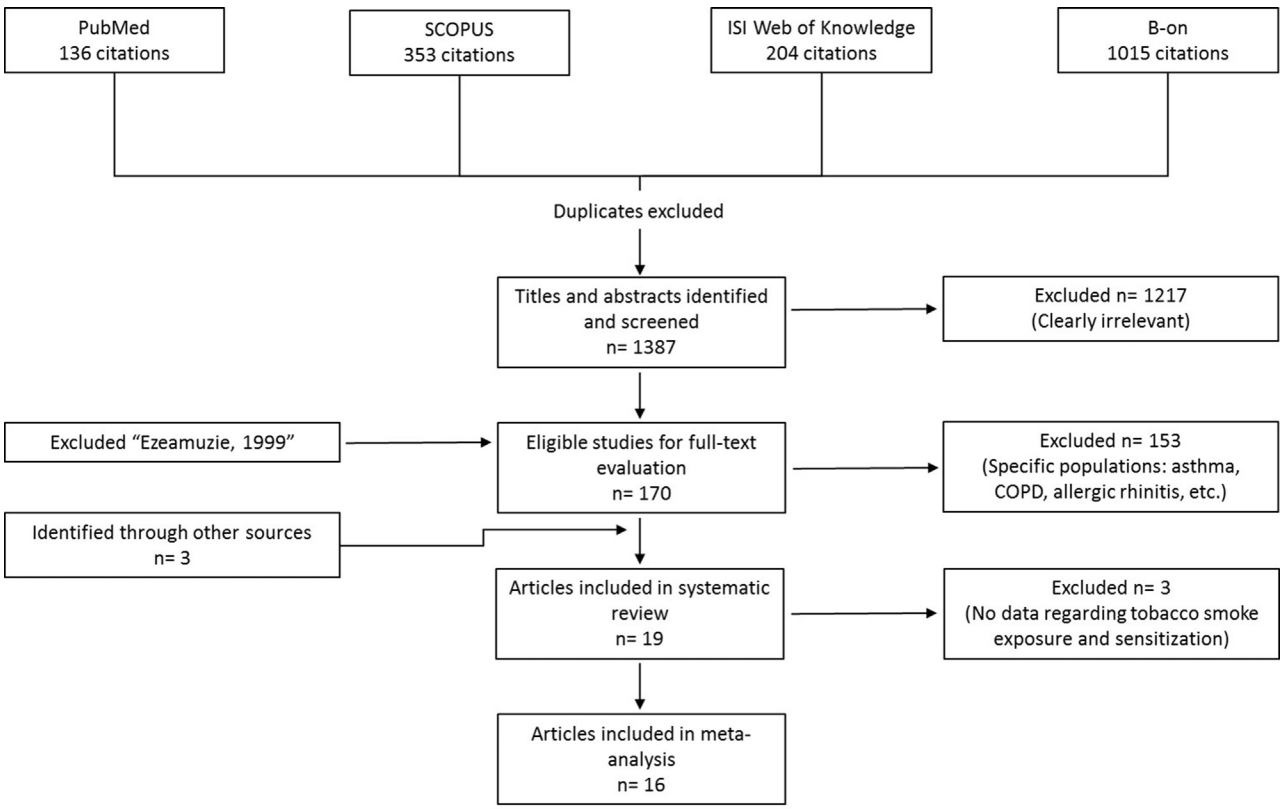

FIG 1. Flowchart of the inclusion and exclusion criteria used in this systematic review and meta-analysis. *COPD*, Chronic obstructive pulmonary disease.

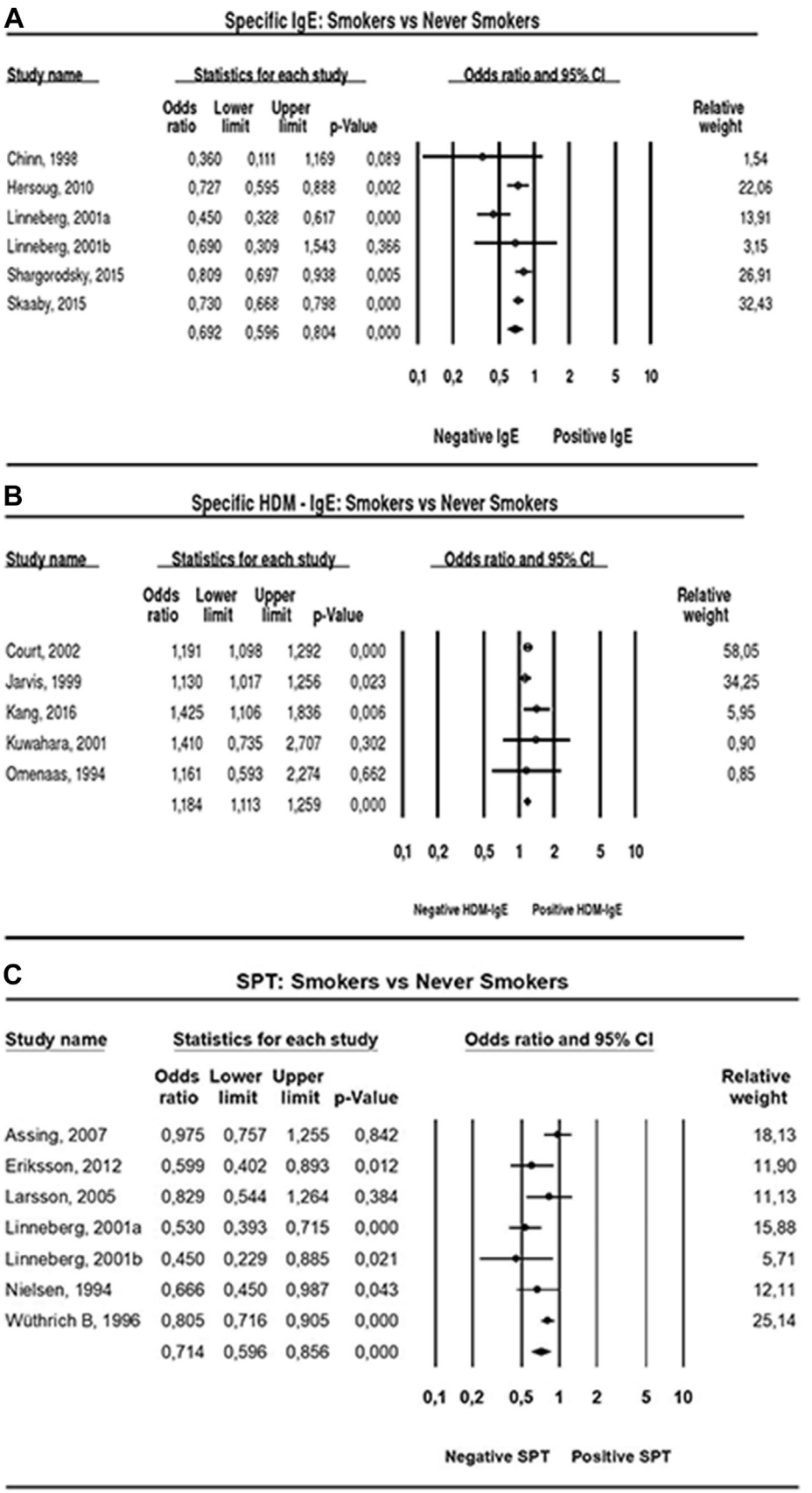

FIG 2. **A,** Forest plot representing the comparison of tobacco smoke exposure on specific IgE in smokers vs never smokers. **B,** Forest plot representing the comparison of tobacco smoke exposure on HDM-specific IgE in smokers vs never smokers. **C,** Forest plot representing the comparison of tobacco smoke exposure on SPTs in smokers vs never smokers. *SPT*, Skin prick test.

and evaluation of publication bias, see this article's Online Repository.

This study revealed that, in general, smokers have a lower risk of developing allergic sensitization to common aeroallergens, when compared with never smokers (for IgE: OR, 0.692; 95% CI, 0.596-0.804; $P < .001$; for skin prick tests: OR, 0.714; 95% CI, 0.596-0.856; $P < .001$). These results support the hypothesis that tobacco smoke exerts a protective effect in the development of allergic sensitization to some aeroallergens, most likely through its immunosuppressant effects. Chronic exposure to tobacco smoke affects both innate and adaptive immune responses.[1] Various components of tobacco smoke were found to induce an increase in suppressor T cells, a decrease in T_H cells,[2] a significant reduction in natural killer cells, and a decrease in serum levels of immunoglobulins.[1] Furthermore, high-dose cigarette smoke has also been shown to directly suppress T-cell function, including T_H2-cell response, which plays an important role in IgE production and in the development of immediate hypersensitivity.[2] This suppression in T_H2-cell function might result in a lower risk of developing allergic sensitization to certain aeroallergens. Nevertheless, the higher risk for HDM sensitization that was observed among smokers still remains to be explained.

Regarding HDM sensitization, the observed results show that smokers have a higher risk of developing allergic sensitization to HDM allergens, when compared with never smokers (OR, 1.184; 95% CI, 1.113-1.259; $P < .001$). The differences observed may be due to a difference in biochemical function. Almost all inhalant allergens are proteases.[3] HDM proteases other than the group 1 allergens, to which belongs the major HDM allergen *Dermatophagoides pteronyssinus* 1 (a cysteine protease), induce only low levels of sensitization, and very few allergens from other sources are cysteine proteases.[3,4] This may be a possible explanation to why tobacco smoke exposure is able to exert a protective effect on most aeroallergens, but not on *Der p* 1.

Der p 1 can act as an adjuvant in the sensitization process and elicit allergic responses both to itself and to other allergens. The 4 main mechanisms by which *Der p* 1 induces allergic sensitization are through (1) cleavage of CD23[5] (a low-affinity IgE Fc receptor), which leads to IgE-mediated immune responses[4]; (2) degradation and inactivation of lung surfactant proteins A and D,[6] which inhibit the binding of inhalant allergens to cell-sequestered IgE; (3) cleavage of α1-antitrypsin,[7] a pulmonary antiprotease, whose activity in smokers is already significantly reduced; and (4) disruption of the epithelial barrier function, which increases permeability to other allergens, facilitating their access to dendritic cells[4] and promoting the development of allergic sensitization.

The mechanism by which tobacco smoke exerts a protective effect on allergic sensitization to some aeroallergens, but not others, has not yet been clarified. A study performed by Lanckacker et al[8] showed that cigarette smoke short exposure was sufficient to promote dendritic cell–mediated transport of HDM allergens to lymph nodes and elicit a T_H2 immune response, thus facilitating the process of allergic sensitization to HDM allergens. Moreover, some components of tobacco smoke may be able to alter allergenic properties of some proteins, potentiating or abating their allergenic potential.[9]

These hypotheses may explain, at least partially, the differences observed between sensitization to HDM allergens and sensitization to other aeroallergens. Regardless, tobacco smoke has deeply detrimental effects in human health, and these results suggest that a protective effect in the development of allergic sensitization should not be considered an argument in favor to initiate or perpetuate this harmful habit. In the future, more studies that illustrate the mechanism by which tobacco smokes induces allergic sensitization to HDM and prevents sensitization to other aeroallergens are needed, as well as enlightenment on other factors involved in the process.

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Lower perinatal exposure to Proteobacteria is an independent predictor of early childhood wheezing

To the Editor:

We postulated that perinatal risk factors for asthma would be associated with early exposure to bacteria or bacterial products. To evaluate this hypothesis, we assessed circulating-free bacterial DNA (cfbDNA) in umbilical cord blood from mother-child pairs (see Table E1 in this article's Online Repository at www.jacionline.org) from Project Viva, a longitudinal study from birth through childhood.[1] To assess cfbDNA, we used 16s rRNA sequencing of the V1-3 region from circulating DNA