

Peer Review File

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Reviewer A

Air pollution in women is a significant exposure for developing asthma at all stages of life. Exposure to woodstoves and gas stoves is a major trigger in childhood and adulthood for asthma especially in women. More mention of these exposures in the article would be helpful.

Reply: Thank you very much for pointing out this very important issue.

Indoor and outdoor pollutions affect respiratory health, increasing the prevalence of asthma and triggering the symptoms of asthma, and this effect is more pronounced in all age groups in women. Among children with allergic predisposition, positive associations between air pollutants and respiratory symptoms and diseases have been detected in females¹. Among girls, but not boys, lifetime exposures to black carbon (a constituent of traffic-related particulate matter 2.5 [PM_{2.5}]) and PM_{2.5} are associated with greater odds of early and mid-childhood asthma². Adult women living in households that use biomass and solid fuels have a significantly higher risk of asthma than those living in households that use cleaner fuels, even after controlling for a number of potentially confounding factors, but this effect has not been found among men³. PM_{2.5} exposure increases the risk of developing asthma, and PM_{2.5} and nitrogen dioxide (NO₂) increase the risk of developing wheezing, the cardinal symptom of asthma, in adult women⁴. Vinod Mishra⁵ examined the effect of cooking smoke on the reported prevalence of asthma among elderly men and women, and found that adjusted effect of cooking smoke on asthma was greater among women than among men.

We added the above discussion in the context (**Line 70, Page 4**).

References

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Dietary intake also has an effect on inducing Th2 inflammation and is an important contributor to obesity and asthma. Central adiposity in women is associated with asthma and type II inflammation. This is not seen in adolescent clinically obese girls. Distribution of adiposity is an important comment to make when discussing obesity in women.

Reply: We completely agree with your comments.

Dietary intake plays an important role in obesity and asthma. Carla E found that better diet quality was associated with lower odds of asthma¹. According to Eun-kyung Kim, higher consumption of fish and seaweed and a high ratio of n-3 to n-6 polyunsaturated fatty acids (PUFA) may be associated with a lower prevalence of asthma in adult women². A cross-sectional study has suggested that dietary arachidonic acid is a promoter of allergic disease in women³. In elderly women, a healthy diet is associated with fewer asthma symptoms, and, among women with asthma, a healthy diet is linked to reduced uncontrolled asthma and metabolic-related multimorbidity⁴. There is a complex association between asthma and obesity, especially in females. Victoria J Vieira investigated the prevalence of atopy among healthy obese and nonobese women and found that the frequency of specific IgE in the obese group was almost three times higher

than that in the nonobese group, confirming a direct relation between obesity and a T helper 2 cell immune response in women⁵. Body fat distribution affects the obesity–asthma relationship, and when stratifying by sex, the association between trunk-predominant adiposity (higher trunk/total fat and trunk/legs fat, or lower legs/total fat) and asthma has only been found in adult women⁶.

We have added the above discussion to the manuscript, please refer to **Line 885, Page 45**.

References

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The gut microbiome from infancy through adulthood has been shown to be very interrelated with prevention of asthma and atopic disease in children and also interacts in respiratory health in adults (both men and women) and down regulation of type 2 inflammation. More reference to the benefit of a healthy microbiota and its effect on type II inflammation asthma should be included.

Reply: We sincerely thank the reviewer for reminding us to address this important issue.

Race, mode of delivery, breastfeeding, and cord blood vitamin D levels are associated

with infant gut microbiome composition, with potential long-term implications for immune system modulation and asthma/allergic disease incidence¹. A Western lifestyle, which overly hygienically limits the general microbial exposure, alters the infant gut microbiome, subsequently disrupting the development of the immune system and ultimately leading to allergic disease². A study performed in Southern China also showed that rural children from an agricultural background exhibited a reduced risk of asthma owing to rural environmental exposure modulating the gut microbiota, which was essential in reducing allergy in children³⁻⁴.

We have included the above discussion in the revised manuscript, please refer to Line 371, Page 19.

References

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Reviewer B

Interesting review on the pathophysiology and management of asthma at different periods of life. Good bibliographical references.

Reply: Thank you very much. We appreciate your kind, positive comment.