OPEN ACCESS

Increased advanced glycation end product and meat consumption is associated with childhood wheeze: analysis of the National Health and Nutrition Examination Survey

Jing Gennie Wang ,[1,2] Bian Liu,[3] Francesca Kroll,[4] Corrine Hanson,[5] Alfin Vicencio,[6] Steven Coca,[7] Jaime Uribarri,[7] Sonali Bose [1]

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2020-216109).

For numbered affiliations see end of article.

Correspondence to
Dr Sonali Bose, Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York City, New York, USA; sonali.bose@mssm.edu

Received 28 August 2020
Accepted 1 October 2020
Published Online First 21 December 2020

Listen to Podcast
thorax.bmj.com

Linked

► http://dx.doi.org/10.1136/thoraxjnl-2020-216369

Check for updates

To cite: Wang JG, Liu B, Kroll F, *et al*. *Thorax* 2021;**76**:292–294.

ABSTRACT

We examined 4388 children from the 2003 to 2006 National Health and Nutrition Examination Survey and used survey-design-adjusted multivariable logistic regression to evaluate associations between dietary advanced glycation end product (AGE) and meat consumption frequencies and respiratory symptoms. Higher AGE intake was significantly associated with increased odds of wheezing (adjusted OR 1.18; 95% CI 1.02 to 1.36), wheeze-disrupted sleep (1.26; 95% CI 1.05 to 1.51) and exercise (1.34; 95% CI 1.08 to 1.67) and wheezing requiring prescription medication (1.35; 95% CI 1.13 to 1.63). Higher intake of non-seafood meats was associated with wheeze-disrupted sleep (2.32; 95% CI 1.11 to 4.82) and wheezing requiring prescription medication (2.23; 95% CI 1.10 to 4.54).

INTRODUCTION

Dietary advanced glycation end products (AGEs) are highly oxidant, proinflammatory compounds, with highest levels present in cooked meats.[1] AGEs are ligands for the AGE receptor (RAGE), a pattern recognition and danger signal receptor, with highest expression in the lungs, and an important driving force behind downstream Th-2 inflammation.[2] The relationship between AGEs and inflammatory airways disease is unclear.[1] We investigated the effects of dietary AGE intake and meat consumption on respiratory symptoms within a paediatric cohort from the National Health and Nutrition Examination Survey (NHANES), a cross-sectional survey assessing the health and nutritional status of the US population.[3]

METHODS

We included 4388 children aged 2–17 years from NHANES 2003–2006 (online supplemental figure S1), for whom data on dietary patterns (assessed by the 139-item Food Frequency Questionnaire (FFQ)), and respiratory symptoms were available. Only participants from NHANES 2003–2006 were included, as FFQ data were unavailable in other years. We calculated unitless meat consumption frequency scores using the FFQ, and AGE scores in keeping with prior published methodology (online supplemental appendix 1, online supplemental figure S2).[4] The primary outcome was presence of wheezing over the past year; secondary outcomes included the presence of more specific wheezing symptoms (online supplemental table S1).

The covariates age, sex, race/ethnicity, poverty to income ratio, body mass index (BMI) percentile, asthma status, total Healthy Eating Index (HEI) score and total caloric intake were collected from questionnaires. Survey logistic regression models were used to investigate associations between AGE and meat consumption scores, and dichotomised respiratory outcomes, adjusting for covariates. Interaction effects by age, sex, BMI percentile, asthma status and race/ethnicity were assessed, and total HEI score was removed from the multivariable model as a sensitivity analysis. Further analytical details are described in online supplemental appendix 1.

RESULTS

Survey-weighted demographics of the 4388 paediatric participants are summarised in table 1, with 537 (13%) reporting wheezing in the past year (online supplemental table S2). In the adjusted models, higher AGE scores were significantly associated with increased odds of wheezing (OR 1.18; 95% CI 1.02 to 1.36), at least one sleep disturbance due to wheezing (OR 1.26; 95% CI 1.05 to 1.51), wheezing during exercise (OR 1.34; 95% CI 1.08 to 1.67) and wheezing requiring prescription medication (OR 1.35; 95% CI 1.13 to 1.63) in the past year (table 2).

There were no significant interactions by age (p_{int}=0.46), sex (p_{int}=0.31), BMI percentile (p_{int}=0.73) or asthma status (p_{int}=0.26), but a significant interaction effect for race (p_{int}=0.04) (online supplemental appendix 2). Removing the total HEI score covariate from the main model did not significantly alter the associations between AGE intake and respiratory symptoms (data not shown).

We found a moderate but statistically significant positive correlation between AGE score and any non-seafood meat consumption (Pearson's correlation coefficient of r=0.69, p<0.0001) (online supplemental figure S3), consistent with meats containing high amounts of AGEs.[1] Higher consumption of non-seafood meat was associated with increased odds of wheezing requiring prescription medication (OR 2.23; 95% CI 1.10 to 4.54), and wheezing disrupting sleep (OR 2.32; 95% CI 1.11 to 4.82) (figure 1, online supplemental table S3).

DISCUSSION

To our knowledge, this is the first study in a national paediatric population demonstrating an association between dietary AGE intake and wheezing symptoms,

Table 1 Analytical population characteristics in relation to AGE intake

Participant characteristics (categorical variables)	Weighted % (crude frequency)*	Weighted AGE score median (25–75th percentiles)**
Sex		
Male	51.29 (2148)	5.32 (3.19–8.73)
Female	48.71 (2240)	5.99 (3.67–9.09)
Race/ethnicity		
Non-Hispanic whites	63.28 (1320)	5.43 (3.42–8.45)
Non-Hispanic blacks	14.74 (1404)	7.71 (4.52–12.8)
Hispanics	15.85 (1425)	5.43 (2.9–8.57)
Others	6.14 (239)	5.31 (3.5–8.73)
Current asthma		
No	89.02 (3907)	5.74 (3.48–9)
Yes	10.98 (481)	5.05 (2.94–8.32)
Participant characteristics (continuous variables)	**Weighted median (25–75th percentiles)***	
Age (years)	9.3 (5.3–13.2)	
Poverty to income ratio	2.3 (1.1–4.0)	
Body mass index percentile	68.7 (39.1–89.7)	
Total Healthy Eating Index (HEI) score†	46.1 (37.8–54.8)	
AGE score‡	5.70 (3.4–9.0)	
Red meat consumption score§	18.6 (15.8–21.5)	
Poultry consumption score§	8.6 (6.9–10.2)	
Processed meat consumption score§	16.1 (13.5–19.5)	
Non-seafood meat consumption score§	44.4 (38.7–50.5)	
Seafood consumption score§	8.5 (7.0–10.6)	
All meat consumption score§	53.6 (46.9–60.3)	

*Survey procedures were used to account for the NHANES survey design and to obtain population weighted estimates for proportions, medians, and 25–75th percentiles. All continuous variables were non-normally distributed. AGE and meat consumption scores were natural log transformed.
†Total HEI scores range from 0 to 100, with higher scores representing better compliance with the 2010 Dietary Guidelines for Americans.
‡The AGE score represents the daily average AGE intake, standardised for total caloric intake per participant. The score was calculated based on the FFQ and prior published food AGE content data.
§Meat consumption scores were derived using the FFQ in a similar fashion to the AGE score.
AGE, advanced glycation end-product; FFQ, Food Frequency Questionnaire.

including wheezing disruptive enough to interfere with exercise and sleep, and require prescription medication. Similarly, higher non-seafood meat consumption was associated with wheezing interfering with sleep and requiring prescription medication. Importantly, as non-seafood meats are a major dietary source of AGEs,[1] our results suggest that a AGE-rich diet is adversely associated with childhood wheeze independent of overall diet quality.

Our results expand on current literature supporting a link between a proinflammatory dietary pattern and wheezing.[4 5] The Western dietary pattern, characterised by increased consumption of AGE-rich foods, namely meats and saturated fats, may promote activation of the toll-like receptor 4 pathway and NF-κB inflammatory cascade, thereby contributing to airway inflammation and asthma pathogenesis.[6] Additionally, a recent cohort study demonstrated that a pro-inflammatory diet measured by the Dietary Inflammatory Index, was associated with increased wheezing in atopic children.[5] Conversely, the Mediterranean dietary pattern, characterised by lower consumption of saturated fatty acids and red meats, may have important anti-inflammatory effects, with one systematic review and meta-analysis demonstrating that adoption of a Mediterranean diet in children was associated with lower risk of wheezing symptoms and having ever had asthma.[7] Finally, as several cohort studies have suggested an adverse effect of meat consumption on paediatric airways health,[8 9] confirmation of a positive correlation between AGE intake and non-seafood meat consumption in our cohort strengthens our a priori hypothesis that dietary AGEs may have an important role in airway inflammation in children.

Biologic plausibility for our findings draws from emerging literature demonstrating that AGEs interact with RAGE, a critical modulator of type 2 cytokine signal transduction with a prominent role in allergic asthma pathogenesis.[2 10] However, whether increased dietary AGE intake leads to overactivation and upregulation of RAGE-mediated airways inflammation remains unclear and warrants further exploration.

There are several limitations. First, causality cannot be implied due to the cross-sectional design, although these novel, hypothesis-generating findings provide a foundation for subsequent longitudinal studies to assess AGE intake as a modifiable dietary risk factor in the development of airways disease. Second, while there is no validated method of quantifying AGE consumption, AGE scores presented reasonably represent relative intake within our cohort, and associations between meat intake and wheezing were

Table 2 Associations between age scores and respiratory symptoms

Outcomes	Weighted % (crude frequency: 'yes'/total)*	OR	95% CI	P value
Primary outcome				
Wheezing in chest	13.04 (537/4388)	1.18	1.02 to 1.36	0.03
Secondary outcomes				
At least one sleep disturbance due to wheezing	7.04 (304/4388)	1.26	1.05 to 1.51	0.01
Wheezing during exercise	6.91 (292/4385)	1.34	1.08 to 1.67	0.007
At least one doctor, hospital or emergency room visit for wheezing	8.17 (325/4388)	1.05	0.87 to 1.27	0.64
Wheezing requiring prescription medication use	9.45 (399/4388)	1.35	1.13 to 1.63	0.001
Limitation of usual activities due to wheezing	5.39 (229/4388)	1.20	0.98 to 1.47	0.08
At least 1 day of school or work missed due to wheezing	4.31 (169/4245)	1.12	0.90 to 1.40	0.34
Dry nocturnal cough	2.63 (124/4386)	1.15	0.83 to 1.61	0.41

*Survey procedures were used to account for the NHANES survey design and to obtain population weighted estimates for prevalence and OR estimates. OR estimates were based on logistic models adjusted for age, sex, race/ethnicity, poverty to family income ratio, body mass index percentile, current asthma and total Healthy Eating Index score.
AGE, advanced glycation end product; NHANES, National Health and Nutrition Examination Survey.

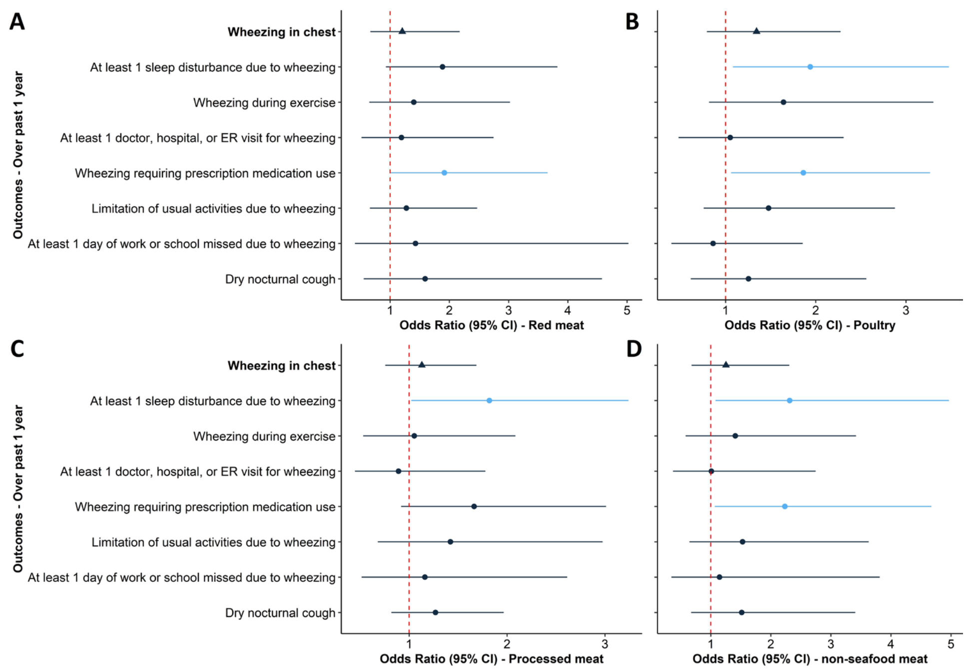

Figure 1 Associations between consumption scores for (A) red meat, (B) poultry, (C) processed meat and (D) any non-seafood meat (combination intake frequencies of red meat, poultry and processed meat) and respiratory symptoms, adjusted for age, sex, race/ethnicity, poverty to family income ratio, body mass index percentile, current asthma, total health eating index score and total caloric intake. ER, emergency room.

consistent with these findings. Finally, we recognise that the aetiology of wheezing may be highly variable in the wide age range of our cohort; however, we demonstrated no significant interaction effects by age.

In conclusion, higher dietary intake of AGEs, in part from non-seafood meat consumption, was associated with increased risk of clinically impactful wheezing in children. Further longitudinal studies examining the impact of dietary AGEs on airways disease in children are warranted.

Author affiliations
[1]Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York City, New York, USA
[2]Division of Pulmonary, Critical Care Medicine and Sleep Medicine, Department of Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA
[3]Department of Population Health Science and Policy, Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York City, New York, USA
[4]Krieger School of Arts and Science, Johns Hopkins University, Baltimore, Maryland, USA
[5]Division of Medical Nutrition Education, College of Allied Health Professions, University of Nebraska Medical Center, Omaha, Nebraska, USA
[6]Division of Pediatric Pulmonology, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York City, New York, USA
[7]Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York City, New York, USA

Twitter Jing Gennie Wang @jing_gennieWang

Contributors JGW and SB took responsibility for the integrity of the data and accuracy of the analyses. SB, JGW and BL contributed to the conception of the study. BL, JGW and JU contributed to the data collection. BL, JGW, SC, FK, CH, AV and SB contributed to data analysis and interpretation. JGW and SB drafted the manuscript. All authors revised the manuscript for intellectual content and approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests SC reports personal fees, equity and stock options from REnalytixAI, personal fees and stock options from pulseData and personal fees from CHF Solutions, Quark, Takeda, Janssen, Goldfinch, Relypsa and Bayer.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Jing Gennie Wang http://orcid.org/0000-0001-5705-9917
Sonali Bose http://orcid.org/0000-0002-8639-4789

REFERENCES

1 Uribarri J, Woodruff S, Goodman S, *et al*. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc* 2010;110:911–6.
2 Oczypok EA, Perkins TN, Oury TD. All the "RAGE" in lung disease: The receptor for advanced glycation endproducts (RAGE) is a major mediator of pulmonary inflammatory responses. *Paediatr Respir Rev* 2017;23:40–9.
3 Zipf G, Chiappa M, Porter KS, *et al*. National health and nutrition examination survey: plan and operations, 1999-2010. *Vital Health Stat 1* 2013;1:1–37.
4 Guilleminault L, Williams EJ, Scott HA, *et al*. Diet and asthma: is it time to adapt our message? *Nutrients* 2017;9. doi:10.3390/nu9111227. [Epub ahead of print: 08 Nov 2017].
5 Han Y-Y, Forno E, Shivappa N, *et al*. The dietary inflammatory index and current wheeze among children and adults in the United States. *J Allergy Clin Immunol Pract* 2018;6:834–41.
6 Wood LG, Gibson PG. Dietary factors lead to innate immune activation in asthma. *Pharmacol Ther* 2009;123:37–53.
7 Garcia-Marcos L, Castro-Rodriguez JA, Weinmayr G, *et al*. Influence of Mediterranean diet on asthma in children: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2013;24:330–8.
8 Nagel G, Weinmayr G, Kleiner A, *et al*. Effect of diet on asthma and allergic sensitisation in the International study on allergies and asthma in childhood (Isaac) phase two. *Thorax* 2010;65:516–22.
9 Hallit S, Raherison C, Abou Abdallah R, *et al*. Correlation of types of food and asthma diagnosis in childhood: a case-control study. *J Asthma* 2018;55:966–74.
10 Oczypok EA, Milutinovic PS, Alcorn JF, *et al*. Pulmonary receptor for advanced glycation end-products promotes asthma pathogenesis through IL-33 and accumulation of group 2 innate lymphoid cells. *J Allergy Clin Immunol* 2015;136:747–56.