

products,⁶ but asthma-related risk associated with use of these products is poorly understood.

Few studies examined stress as a potential mechanism underlying sexual orientation–related differences. Although limited findings suggest that adverse childhood experiences and general stress may increase asthma risk among SM adults, no studies examined the role of minority stressors (eg, discrimination, stigma) or victimization, despite the known effects of minority stress on health. Minority stress may affect physical health via its effects on immune dysregulation, hypothalamic pituitary adrenal function, and autonomic nervous system reactivity.⁷ These processes set the stage for health disparities by worsening symptom severity and increasing risk of acute and chronic health conditions.⁷ High levels of minority stress and negative affect are associated with negative health behaviors, such as unhealthy eating, drinking, and smoking. Indeed, studies have found that SM adults have multiple risk factors, such as high BMI (particularly lesbian women)⁸ and higher rates of unhealthy behaviors, such as smoking,⁹ that increase overall health risks, including asthma risk. Complicating this higher-risk profile is lower access to health care and use of preventive care among SM adults.¹⁰

Knowledge about risk factors for asthma among SM adults is currently limited. However, given findings that indicate sexual identity–related disparities, researchers should assess sexual identity and include measures that go beyond the presence or absence of lifetime asthma to improve understanding of asthma risk, severity, and control and the temporality of asthma and risk factors. Given the sparse literature and inconclusive findings among the studies in our review, more research is needed on the associations between smoking and asthma among SM adults, including prospective work on mechanisms that drive these associations. Greater understanding of asthma risk among SM adults is critically important if practitioners are to reduce asthma-related health disparities among their SM patients.

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Cockroach, dust mite, and shrimp sensitization correlations in the National Health and Nutrition Examination Survey

Shellfish allergy is a common condition, affecting 1% to 2% of the U.S. population.¹ Tropomyosin, the primary allergen in shrimp, is a muscle protein found in other arthropods, including cockroaches and dust mites (DMs), and cross-sensitization to these allergens has been hypothesized to drive shrimp sensitization.^{2,3} In the National Health and Nutrition Examination Survey (NHANES), it was recently demonstrated that there was a marked decrease in the

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References

1. Murphy KR, Meltzer EO, Blaiss MS, Nathan RA, Stoloff SW, Doherty DE. Asthma management and control in the United States: results of the 2009 Asthma Insight and Management survey. *Allergy Asthma Proc*. 2012;33(1):54–64.
2. Centers for Disease Control and Prevention. Trends in asthma prevalence, health care use, and mortality in the United States, 2001–2010. *NCHS Data Brief*. 2012;(94):1–8.
3. Gao J, Mansh M. Sexual orientation disparities in the prevalence of asthma and allergic rhinitis among US adults. *Ann Allergy Asthma Immunol*. 2016;117(4):435–437.
4. Gonzales G, Przedworski J, Henning-Smith C. Comparison of health and health risk factors between lesbian, gay, and bisexual adults and heterosexual adults in the United States. *JAMA Intern Med*. 2016;176(9):1344–1348.
5. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol*. 2014;67(12):1291–1294.
6. Nayak P, Salazar LF, Kota KK, Pechacek TF. Prevalence of use and perceptions of risk of novel and other alternative tobacco products among sexual minority adults: results from an online national survey, 2014–2015. *Prev Med*. 2017;104:71–78.
7. Lick DJ, Durso LE, Johnson KL. Minority stress and physical health among sexual minorities. *Perspect Psychol Sci*. 2013;8(5):521–548.
8. VanKim NA, Austin SB, Jun H-J, Hu FB, Corliss HL. Dietary patterns during adulthood among lesbian, bisexual, and heterosexual women in the Nurses' Health Study II. *J Acad Nutr Diet*. 2017;117(3):386–395.
9. Dorn-Medeiros CM, Dykeman C, Bergquist T. Alcohol and tobacco use among women who have sex with women. *Vistas Online*. 2016;(87):1–14.
10. Heck JE, Sell RL, Gorin SS. Health care access among individuals involved in same-sex relationships. *Am J Public Health*. 2006;96(6):1111–1118.

prevalence of shrimp sensitization between NHANES III (1988–1994) and NHANES 2005–2006.⁴ The objective of this study was to test the hypothesis that this decrease in shrimp sensitization was associated with concomitant changes in cockroach and DM sensitization.

NHANES consists of a series of cross-sectional studies conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. Food specific IgE (sIgE) to shrimp was measured using ImmunoCAP (Phadia) in participants aged 6 to 19 years in NHANES III and NHANES 2005–2006, as previously described.^{4,5} Two children included in the previous analyses of food sensitization were not included in this study because they did not have shrimp sIgE measured due to sample availability. Shrimp sIgE levels were used to define 3 a priori overlapping categories: overall (sIgE ≥ 0.35 kU/L), moderate (sIgE ≥ 2 kU/L), and high (sIgE ≥ 5 kU/L) level sensitization. Aeroallergen sensitization was defined by skin prick testing (SPT) in NHANES III and by sIgE measurements in NHANES 2005–2006. Further details about these methods can be found in the eAppendix.



Table 1Adjustment for Cockroach and Dust Mite Sensitization in Shrimp Sensitization Models Among Children Aged 6 to 19 Years in NHANES^a

Sensitization	Crude model (n = 7797)		Dust mite adjustment (n = 7435)		Cockroach adjustment (n = 7433)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Overall shrimp sensitization						
NHANES 2005–2006 vs III	0.52 (0.40–0.66)	<.001	0.60 (0.46–0.79)	<.001	0.94 (0.69–1.3)	.70
Dust mite sensitization	NA		12.7 (9.5–17.0)	<.001	NA	
Cockroach sensitization	NA		NA		24.6 (17.8–33.8)	<.001
Moderate shrimp sensitization						
NHANES 2005–2006 vs III	0.39 (0.27–0.58)	<.001	0.45 (0.29–0.69)	<.001	0.72 (0.47–1.12)	.14
Dust mite sensitization	NA		19.0 (11.8–30.6)	<.001	NA	
Cockroach sensitization	NA		NA		38.4 (19.3–76.4)	<.001
High shrimp sensitization						
NHANES 2005–2006 vs III	0.26 (0.17–0.39)	<.001	0.28 (0.18–0.43)	<.001	0.44 (0.27–0.70)	.001
Dust mite sensitization	NA		27.9 (14.9–52.2)	<.001	NA	
Cockroach sensitization	NA		NA		36.4 (13.7–96.3)	<.001

Abbreviations: NA, not applicable; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

^aAll models adjusted for age, sex, race/ethnicity, income, asthma, and allergic rhinitis.

To assess whether cockroach and DM sensitization explained the differences seen in shrimp sensitization between these surveys, multiple logistic regression models with and without cockroach and DM sensitization were assessed. These models were adjusted for age, sex, race/ethnicity, income, asthma, and allergic rhinitis. Only survey weights were used for these models because the NHANES sampling units and pseudo-strata could not be combined between these 2 surveys. Correlation coefficients for shrimp, cockroach, and DM were calculated for each survey independently because of the differences in aeroallergen sensitization measurements. Finally, lowess (locally weighted scatterplot smoothing) curves were generated to visually depict the association among cockroach, DM, and oak (as a representative allergen not thought to be related to shrimp) sIgEs in NHANES 2005–2006.

Overall, 7894 children were included in these analyses (NHANES III, n = 4994; NHANES 2005–2006, n = 2900). The prevalence of shrimp sensitization significantly decreased from 11.2% (95% CI, 10.0%–12.5%) in NHANES III to 6.1% (95% CI, 4.5%–7.7%, $P < .001$) in NHANES 2005–2006, as previously reported.⁴ Similarly, there was a significant decrease in the prevalence of sensitization to cockroach (23% [95% CI, 21%–24%] vs 10% [95% CI, 9%–2%]; $P < .001$) and DM (28% [95% CI, 26%–31%] vs 22% [95% CI, 19%–24%]; $P < .001$) over this time. Cockroach and DM sensitization both had moderate positive correlations with shrimp sensitization (NHANES III: cockroach, 0.48; DM, 0.37; NHANES 2005–2006: cockroach, 0.53; DM, 0.45).

The probability of shrimp sensitization increased with higher levels of cockroach sIgE, and a weaker association was seen between shrimp and DM and oak (eFig 1). In multiple logistic regression models, the odds for overall, moderate-, and high-level shrimp sensitization were significantly lower in NHANES 2005–2006 vs NHANES III. When adjusting for cockroach, the decreased odds of overall and moderate-level, but not high-level, shrimp sensitization between years were no longer significant (Table 1), suggesting that changes in shrimp sensitization are not independent of changes in cockroach sensitization. In contrast, adjusting for DM sensitization did not account for the decrease observed in shrimp sensitization between the surveys.

In this study, we found that shrimp sensitization correlated with cockroach and, to a lesser extent, DM sensitization. We further demonstrated that the decrease in overall and moderate-level shrimp sensitization seen over time was attenuated when adjusting for cockroach sensitization. Although cross-reactivity among cockroach, DM, and shrimp has been hypothesized to drive shrimp sensitization, to our knowledge, this is the first report of longitudinal trends in sensitization to these allergens in the United States.

Previous studies have suggested that sensitization to environmental allergens, such as DM and cockroach, may drive shrimp sensitization because individuals who have never ingested shellfish

have detectable sIgE levels to shrimp.³ In this study, we found that although the decrease in shrimp sensitization was attenuated by adjusting for cockroach sensitization, no such decrease was seen when adjusting for DM. This finding extends a previous observation by Wang et al² in which exposure to cockroach allergen, but not DM, in the homes of inner-city US children was associated with higher shrimp and cockroach sIgE levels. Furthermore, in rural China, sensitization to shrimp was recently reported to be driven by cockroach but not DM sensitization, and tropomyosin was not the dominant cross-reactive allergen.⁶ Other proteins that cross-react with DM and cockroach include arginine kinase and hemocyanin, whereas myosin light chain and troponin C uniquely cross-react with cockroach.⁷ It is possible that cross-sensitization to these other allergens may drive shrimp sensitization, but the extent to which this occurs remains unclear.

In this study, we additionally found that although the decrease in overall and moderate-level shrimp sensitization was attenuated when adjusting for cockroach, there was no change in the association with high-level shrimp sensitization. One possible explanation for this finding is the fact that we were unable to adjust for the magnitude of cockroach sensitization in our model, which may have further attenuated the association with high-level shrimp sensitization. Alternatively, it is well known that not all individuals with shrimp sensitization are clinically allergic, and those who are clinically allergic have higher sIgE levels to shrimp extract than those who are asymptotically sensitized.⁸ It is thus possible that individuals with lower sIgE levels to shrimp may represent those who are asymptotically sensitized, likely from cross-reactive allergens, and further studies evaluating the predictive value of SPT size and sIgE levels for diagnosing clinical allergy vs asymptomatic shrimp sensitization are needed. While the factors that may promote or protect against the development of clinical food allergy among those who are sensitized are unknown, one could hypothesize that geographic variation of exposure to allergens, infectious exposures, and consumption of shrimp could also play important roles in this association.

This study is limited by the different methods used to measure aeroallergen sensitization in NHANES III (SPT) and NHANES 2005–2006 (sIgE). SPT is a more sensitive test than sIgE,⁹ so this difference may explain the decrease seen in DM and cockroach sensitization between the 2 surveys. However, because both allergens were assessed in the same manner, it is unlikely that this explains the differential correlation seen with shrimp sensitization. Our study is further limited by the lack of clinical data regarding shrimp allergy or allergic rhinitis in these surveys, as well as the lack of sIgE to specific components of shrimp, DM, and cockroach. In addition, without other data, we cannot exclude the possibility that changes in sensitization between these surveys are due to sampling differences

between the surveys rather than time. However, these weaknesses are balanced by the fact that NHANES are large cross-sectional surveys designed to be nationally representative, and our results are thus generalizable to the US population. Furthermore, this is the only study to date, to our knowledge, examining the association among DM, cockroach, and shrimp sensitization over time.

In conclusion, we found that the decrease seen in overall and moderate-level shrimp sensitization between 1988–1994 and 2005–2006 was attenuated when adjusting for cockroach sensitization. These findings provide further support of the hypothesis that sensitization to shrimp is largely driven by sensitization to other arthropods, and it provides further evidence of changing patterns of sensitization over time in the United States.

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References

- McGowan EC, Keet CA. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007–2010. *J Allergy Clin Immunol*. 2013;132(5):1216–1219.e5.
- Wang J, Calatroni A, Visness CM, Sampson HA. Correlation of specific IgE to shrimp with cockroach and dust mite exposure and sensitization in an inner-city population. *J Allergy Clin Immunol*. 2011;128(4):834–837.
- Fernandes J, Reshef A, Patton L, Ayuso R, Reese G, Lehrer SB. Immunoglobulin E antibody reactivity to the major shrimp allergen, tropomyosin, in unexposed Orthodox Jews. *Clin Exp Allergy*. 2003;33(7):956–961.
- McGowan EC, Peng RD, Salo PM, Zeldin DC, Keet CA. Changes in food-specific IgE over time in the National Health and Nutrition Examination Survey (NHANES). *J Allergy Clin Immunol Pract*. 2016;4(4):713–720.
- Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol*. 2010;126(4):798–806.e13.
- Yang Z, Zhao J, Wei N, et al. Cockroach is a major cross-reactive allergen source in shrimp-sensitized rural children in southern China. *Allergy*. 2018;73(3):585–592.
- Faber MA, Pascal M, El Kharbouchi O, et al. Shellfish allergens: tropomyosin and beyond. *Allergy*. 2017;72(6):842–848.
- Gamez C, Sanchez-Garcia S, Ibanez MD, et al. Tropomyosin IgE-positive results are a good predictor of shrimp allergy. *Allergy*. 2011;66(10):1375–1383.
- Calabria CW, Dietrich J, Hagan L. Comparison of serum-specific IgE (ImmunoCAP) and skin-prick test results for 53 inhalant allergens in patients with chronic rhinitis. *Allergy Asthma Proc*. 2009;30(4):386–396.

Drug-induced enterocolitis syndrome (DIES)

A clinical entity that deserves more awareness



Drug-induced enterocolitis syndrome (DIES) is a rare, non-IgE-mediated hypersensitivity reaction provoked by drugs that can be severe and lead to shock. Despite the potential severity of the reactions, awareness of DIES is low. In contrast, enterocolitis syndrome induced by food proteins (FPIES) has been better documented. Previous studies have reported the occurrence of hypovolemic shock in approximately 15% of reactions, which indicates that FPIES is a potentially life-threatening disease.¹ To increase clinical awareness of DIES, we report a case of a child who was referred to our pediatric allergy clinic and was diagnosed with DIES by amoxicillin. In addition, we propose diagnostic criteria for DIES to improve both clinical and scientific knowledge.

A 4-year-old boy was referred to the pediatric allergy unit of the Erasmus University Medical Center (Rotterdam, The Netherlands) for a suspected drug hypersensitivity. At the age of 2 years, he developed an erythematous skin reaction and a short period of drowsiness after the administration of amoxicillin. The symptoms spontaneously disappeared within 24 hours. At the age of 4 years, he developed an acute episode of repetitive vomiting and lethargy 1.5 hours after ingestion of a first dose of amoxicillin for treatment of a dental infection. His parents called an ambulance, and he was treated with intramuscular adrenaline and intravenous injection of clemastine and dexamethasone. He was admitted to the emergency department, and physical examination showed a blood pressure of 100/80 mm/Hg, a heart rate of 125 beats/minute, and a normal

respiratory rate and oxygen saturation. Further physical examination showed no classic immunoglobulin E (IgE)-mediated skin or respiratory symptoms. The vomiting and lethargy persisted for approximately 2 hours and was followed by complete clinical recovery. He was referred to our allergy unit for further analysis of the hypersensitivity reactions to amoxicillin.

A skin prick test with amoxicillin was performed, and blood levels of specific IgE to amoxicillin were measured; both test results were negative. An intradermal skin test was not performed because of the relative young age of the patient. Consecutively, an open 3-step graded oral challenge with amoxicillin was performed according to the European Network for Drug Allergy (ENDA) guidelines.² One and one-half hours after the last dose intake, he developed severe abdominal pain, started to vomit, and became pale and lethargic. Because of persistent vomiting, he was given intramuscular adrenaline and an oral antihistaminic approximately 15 minutes after onset of symptoms. Despite administration of intramuscular adrenaline, the vomiting persisted, and approximately 25 minutes after onset of the reaction, an intravenous catheter was inserted. Ondansetron and hydrocortisone were given intravenously, after which the abdominal pain and vomiting diminished. Approximately 90 minutes after onset of the reaction, he again started to complain of abdominal pain and vomited again. Intramuscular adrenaline was given a second time, after which he showed progressive improvement to a complete recovery 2.5 hours after onset of symptoms. During the reaction, he had no skin or respiratory symptoms, and he remained hemodynamically stable. A blood test (which was performed 2 hours after the last dose of

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The National Health and Nutrition Examination Survey (NHANES) III was conducted from 1988 to 1994, and since 1999, NHANES has been conducted continuously in 2-year blocks. Sampling is designed to be representative of the overall noninstitutionalized US population, with oversampling of certain groups to ensure power for subgroup analyses. Interviews are initially conducted in participants' homes, followed by physical examinations in mobile centers. Response rate for the examination portion of the survey was 78% for NHANES III and 77% for NHANES 2005-2006. The surveys and use of stored serum samples from NHANES III were approved by the institutional review board of the National Center for Health Statistics, and all participants provided informed consent.

In NHANES III, skin prick testing, using the prick-puncture technique, was assessed to rye grass, Bermuda grass, white oak,

Russian thistle, short ragweed, *Alternaria alternata*, German cockroach, *Dermatophagoides farinae* (dust mite), and cat, as well as histamine and glycerinated diluent for the positive and negative controls, respectively. A positive test result was defined as a difference of 3 mm or more between the wheal length of the allergen and that of the negative control. In NHANES 2005-2006, allergen specific IgE was measured to the same allergens, with the addition of dog, birch tree, mouse, rat, *Aspergillus fumigatus*, and *Dermatophagoides pteronyssinus*. A positive test result was defined as 0.35 kU/L or greater for the measured allergen. Aeroallergen sensitization in both years was defined as a positive response to at least 1 of the inhaled aeroallergens, and only the aeroallergens measured in both surveys were included. Asthma and allergic rhinitis were defined as positive responses to questions regarding physician diagnosis of these conditions.

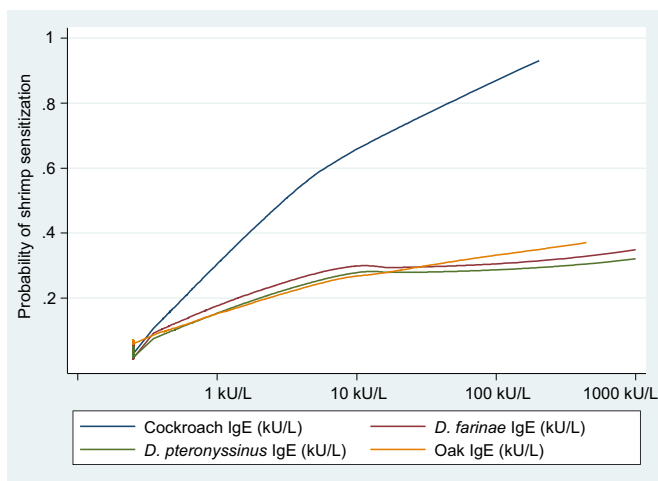


Figure 1. Lowess (locally weighted scatterplot smoothing) curve of the association among level of cockroach, dust mite, and oak IgE and probability of shrimp sensitization. Cockroach, oak, and dust mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) IgE were measured and log transformed. Shrimp sensitization was defined as shrimp specific IgE levels of 0.35 kU/L or greater. Bandwidth was 0.6.