

**Epidemiology Publish Ahead of Print**

**DOI: 10.1097/EDE.0000000000000640**

**The Unintended Consequences of a Gluten-Free Diet**

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**Conflict of Interest Disclosures:** No disclosures to report.

**Funding/Support:** This work was supported by the National Institutes of Health grant numbers R01 ES024423, R21 ES024834, R01 CA107431, P42 ES010349, and T32 HL125294.

**Keywords:** gluten-free diet; arsenic; cross-sectional study

**To the Editor:**

Gluten-free diets have become immensely popular in the United States. Despite <1% of Americans having diagnosed celiac disease, an estimated 25% of American consumers reported consuming gluten-free food in 2015, a 67% increase from 2013.<sup>1,2</sup> Gluten is a protein found in a variety of grains including wheat, rye, and barley and their flours. Commercial gluten-free products primarily contain rice flour as a substitute.<sup>3</sup> Emerging evidence suggests rice-based products can contain high levels of toxic metals; rice is a recognized source of arsenic and methylmercury exposure.<sup>4,5</sup> Despite such a dramatic shift in the diet of many Americans, little is known about how gluten-free diets might affect exposure to toxic metals found in certain foods.

**Methods:**

We used 2009-2014 nationally representative data from the National Health and Nutrition Examination Survey (NHANES) to analyze cross-sectional associations between self-reported gluten-free diet status and urinary and blood biomarkers of exposure to toxic metals.<sup>6</sup> Trained staff conducted in-person interviews with all participants 12 years and older; for younger children, a parent or caretaker was interviewed. A gluten-free diet was defined as an affirmative response to “Are you on a gluten-free diet?” during the medical questionnaire or “Gluten-free/Celiac diet” response to “What kind of diet are you on?” during the dietary interview. We calculated two estimates of total arsenic exposure in addition to the measured urinary total arsenic: estimated total arsenic 1 was defined as urinary total arsenic minus arsenobetaine and arsenocholine, and estimated total arsenic 2 was defined as the sum of arsenite, arsenate, monomethylarsonic acid, and dimethylarsinic acid.<sup>4,7</sup> Arsenobetaine and arsenocholine were subtracted or excluded since they are considered nontoxic forms of organic arsenic.<sup>4</sup> Any resulting negative values for estimated total arsenic 1 were set to 0.01 µg/L. Biomarker

concentrations below the detection limit were substituted with the limit divided by the square root of 2. If the limit of detection changed between survey cycles, the highest limit was used for this substitution. Since the distributions of the biomarkers were skewed, geometric means were calculated. We adjusted for age, sex, race/ethnicity, and survey cycle, and used urinary creatinine to adjust for dilution of urinary biomarkers. We accounted for the complex sampling design of NHANES (multistage sampling design involving stratification, clustering, and oversampling of certain subgroups) by using Taylor series linearization and sampling weights, per the NHANES analytic guidelines, to ensure unbiased and nationally representative estimates.<sup>6</sup> This study met the criteria of “non-human subjects” research since the investigators accessed de-identified information.

### **Results:**

Among the 7,471 NHANES participants in our analysis, 73 (weighted prevalence: 1.2%) self-reported being on a gluten-free diet. In adjusted analyses, we found higher concentrations of urinary total arsenic, estimated total arsenic 1, estimated total arsenic 2, dimethylarsonic acid, urinary cadmium, and blood total mercury among those on a gluten-free diet (Table). For example, the weighted geometric mean concentration of estimated urinary total arsenic 1 was nearly double among those on a gluten-free diet versus not on a gluten-free diet (geometric mean ratio=1.9, 95% CI: 1.3-2.6), adjusted for sociodemographic characteristics and urinary creatinine. Associations with gluten-free diet for urinary and blood lead, blood cadmium, and blood inorganic mercury were near null (Table). Results from sensitivity analyses restricting the sample to adults (aged >20 years) with additional adjustment for income and educational attainment were not appreciably different (data not shown).

**Discussion:**

To our knowledge, this is the first analysis to suggest that Americans on gluten-free diets may be exposed to higher levels of arsenic and mercury. With the increasing popularity of gluten-free diets, these findings may have important health implications since the health effects of low-level arsenic and mercury exposure from food sources are uncertain but may increase the risk for cancer and other chronic diseases.<sup>4,8</sup> Although we can only speculate, rice may be contributing to the observed higher concentrations of metal biomarkers among those on a gluten-free diet as the primary substitute grain in gluten-free products.<sup>3</sup> While our study is cross-sectional and relies on self-reported data regarding gluten-free diets, it does suggest that future studies are needed to more fully examine exposure to toxic metals from consuming gluten-free foods.

## References

1. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. *Am J Gastroenterol*. 2012; 107(10):1538-1544.
2. Mintel Group, Ltd. “Half of Americans Think Gluten-Free Diets are a Fad While 25% Eat Gluten-Free Foods.” <http://www.mintel.com/press-centre/food-and-drink/half-of-americans-think-gluten-free-diets-are-a-fad-while-25-eat-gluten-free-foods/>. Accessed August 1, 2016.
3. Bascuñán KA, Vespa MC, Araya M. Celiac disease: understanding the gluten-free diet. *Eur J Nutr*. 2016; Epub ahead of print.
4. Davis MA, Mackenzie TA, Cottingham KL, Gilbert-Diamond D, Punshon T, Karagas MR. Rice consumption and urinary arsenic concentrations in U.S. children. *Environ Health Perspect*. 2012; 120(10):1418-1424.
5. Zhang H, Feng X, Larssen T, Qiu G, Vogt RD. In Inland China, Rice, Rather than Fish, Is the Major Pathway for Methylmercury Exposure. *Environ Health Perspect*. 2010; 118(9): 1183–1188.
6. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. <http://www.cdc.gov/nchs/nhanes>
7. Cardenas A, Smit E, Houseman EA, Kerkvliet NI, Bethel JW, Kile ML. Arsenic exposure and prevalence of the varicella zoster virus in the United States: NHANES (2003-2004 and 2009-2010). *Environ Health Perspect*. 2015; 123(6):590-596.

8. Karagas MR, Choi AL, Oken E, Horvat M, Schoeny R, Kamai E, Cowell W, Grandjean P, Korrick S. Evidence on the human health effects of low-level methylmercury exposure. *Environ Health Perspect.* 2012;120(6):799-806.

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**Table. Urinary and Blood Metal Concentrations by Gluten-Free Diet Status**

Metal	Gluten-Free Diet <sup>a</sup> N=73	Non-Gluten-Free Diet N=7,398	Geometric Mean Ratio (95% CI) <sup>b</sup>
	Geometric Mean (SE) <sup>b</sup>	Geometric Mean (SE) <sup>b</sup>	
<b>Urinary Concentrations</b>			
Total arsenic (µg/L)	12.1 (1.5)	7.8 (0.23)	1.5 (1.2-2.0)
Estimated total arsenic 1 (µg/L) <sup>c</sup>	6.1 (1.0)	3.2 (0.14)	1.9 (1.3-2.6)
Estimated total arsenic 2 (µg/L) <sup>d</sup>	8.2 (0.5)	6.4 (0.07)	1.3 (1.1-1.4)
Dimethylarsonic acid (µg/L)	5.3 (0.5)	3.7 (0.06)	1.4 (1.2-1.7)
Cadmium (µg/L)	0.18 (0.01)	0.16 (0.00)	1.1 (1.0-1.3)
Lead (µg/L)	0.40 (0.04)	0.37 (0.01)	1.1 (0.9-1.3)
<b>Blood Concentrations</b>			
Cadmium (µg/L)	0.29 (0.03)	0.29 (0.00)	1.0 (0.8-1.2)
Lead (µg/dL)	1.1 (0.10)	0.96 (0.01)	1.1 (0.9-1.3)
Inorganic mercury (µg/L)	0.30 (0.02)	0.28 (0.00)	1.1 (1.0-1.2)
Total mercury (µg/L)	1.3 (0.25)	0.80 (0.02)	1.7 (1.1-2.4)

<sup>a</sup> For NHANES 2009-2010 and 2011-2012, a gluten free diet was defined as a “yes” response to “Are you on a gluten-free diet?” (MCQ086) in the medical questionnaire or “Gluten-free/Celiac diet” (DRQSDT11) to “What kind of diet are you on?” in the dietary interview day 1; for NHANES 2013-2014, a gluten free diet was defined as a “yes” response to “Are you on a gluten-free diet?” (MCQ086) in the medical questionnaire.

<sup>b</sup> Calculated using survey-weighted linear regression, adjusting for age (continuous), sex (male/female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican, Hispanic, or other), and survey cycle (2009-2010, 2011-2012, or 2013-2014) with additional adjustment for urinary creatinine (continuous) in urinary concentration models.

<sup>c</sup> Estimated as [total arsenic in µg/L – (arsenocholine in µg/L + arsenobetaine in µg/L)] with negative values set to 0.01 µg/L.

<sup>d</sup> Estimated as [arsenite in µg/L + arsenate in µg/L + monomethylarsonic acid in µg/L + dimethylarsonic acid in µg/L].

CI indicates confidence interval, SE standard error.