that the choice is more complex and still others avoid using relative measures because of this dilemma, as described by Kjellsson et al.[1,4] Some authors have discussed the implications of relative inequality in adverse outcomes and relative inequality in favorable outcomes between two population groups moving in opposite direction.[5] One way to avoid this situation when monitoring changes in disparities over time is to measure relative disparities of health only in terms of adverse events.[6] Even though one could select a relative measure for trend analysis based on a value judgment, it is also informative to know under what conditions these situations could arise. Knowing the patterns of change under which these paradoxical results could occur may assist researchers to make implicit value judgments explicit.

Ramal Moonesinghe
Ana Penman-Aguilar
Office of Minority Health and Health Equity
Centers for Disease Control and Prevention
Atlanta, GA
rmoonesinghe@cdc.gov

Gloria L. A. Beckles
National Center for Chronic Disease
Prevention and Health Promotion
Centers for Disease Control and Prevention
Atlanta, GA

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The Unintended Consequences of a Gluten-free Diet

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.[1,2] 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.[3] Emerging evidence suggests rice-based products can contain high levels of toxic metals; rice is a recognized source of arsenic and methylmercury exposure.[4,5] 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.[6] 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.[4,7] Arsenobetaine and arsenocholine were subtracted or excluded because they are considered nontoxic forms of organic arsenic.[4] 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. As 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.[6] This study met the criteria of "nonhuman subjects" research because the investigators accessed deidentified 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

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The data are publicly available through the National Health and Nutrition Examination Survey, Centers for Disease Control and Prevention, National Center for Health Statistics. Statistical code is available from the authors upon request for replication.

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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 (ages >20 years) with additional adjustment for income and educational attainment were not appreciably different (data not shown).

TABLE. Urinary and Blood Metal Concentrations by Gluten-free Diet Status

	Gluten-free Diet[a] N = 73	Non-gluten-free Diet N = 7,398	
Metal	Geometric Mean (SE)[b]	Geometric Mean (SE)[b]	Geometric Mean Ratio (95% CI)[b]
Urinary concentrations			
Total arsenic (μg/L)	12.1 (1.5)	7.8 (0.23)	1.5 (1.2, 2.0)
Estimated total arsenic 1 (μg/L)[c]	6.1 (1.0)	3.2 (0.14)	1.9 (1.3, 2.6)
Estimated total arsenic 2 (μg/L)[d]	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)
Blood concentrations			
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)

[a]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.

[b]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.

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

[d]Estimated as [arsenite in μg/L + arsenate in μg/L + monomethylacrsonic acid in μg/L + dimethylarsonic acid in μg/L].

CI indicates confidence interval, SE standard error.

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 because 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.[4,8] 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.[3] 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.

Catherine M. Bulka
Division of Epidemiology and Biostatistics
School of Public Health
University of Illinois at Chicago
Chicago, IL

Matthew A. Davis
School of Nursing
University of Michigan
Ann Arbor, MI

Margaret R. Karagas
Department of Epidemiology
Geisel School of Medicine at Dartmouth
Hanover, NH

Habibul Ahsan
Department of Public Health Sciences
The University of Chicago
Chicago, IL

Maria Argos
Division of Epidemiology and Biostatistics
School of Public Health
University of Illinois at Chicago
Chicago, IL
argos@uic.edu

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