reduce IL-33 bioavailability, providing a second mechanism to reduce IL-33 function *in vivo*. These results are in accord with the odds ratio, indicating the variants in *IL1RL1* confer protection against asthma susceptibility and further corroborate other genetic and functional studies implicating a role for the IL-33/ST2 pathway in asthma pathogenesis.

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Disclosure of potential conflict of interest: The authors declare that they are employees of Genentech, hold stock and/or options in the Roche group, and are named inventors on patents pending related to asthma diagnosis and treatment.

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Maternal selenium status in pregnancy, offspring glutathione peroxidase 4 genotype, and childhood asthma

To the Editor:

Two prospective birth cohort studies have suggested that prenatal selenium status may play a role in the inception of childhood asthma. In the Avon Longitudinal Study of Parents and Children (ALSPAC), umbilical cord tissue concentration of selenium was negatively associated with risk of wheezing in early childhood[1]; in another United Kingdom cohort, maternal and cord plasma selenium concentrations were negatively associated with wheezing in the second year of life, but not at 5 years.[2] Associations between biomarkers of prenatal selenium exposure and asthma and wheezing later in childhood have not been reported.

Glutathione peroxidase (GPX) 4 is a unique membrane-associated selenium-dependent antioxidant enzyme that can directly reduce phospholipid hydroperoxides and protect against oxidative stress in mammalian cells.[3] Aside from its antioxidant role, *GPX4* has been implicated in lipoxygenase metabolism,[4] which has major relevance to leukotriene synthesis and inflammatory signaling in asthma. Thus, demonstration of an interaction between selenium status and *GPX4* genotype on asthma risk could strengthen the evidence for a causal role of selenium.

In the ALSPAC birth cohort, we investigated whether higher maternal blood concentration of selenium in pregnancy is associated with a lower risk of asthma and wheezing at age 7 years and whether associations are modified by the *GPX4* genotype (rs713041). Details of the ALSPAC protocol can be found at http://www.alspac.bris.ac.uk. Methods for maternal selenium analysis have been described in detail previously[5]; whole blood samples were obtained from 4484 women as early as possible in pregnancy, and selenium analysis was performed by the Centers for Disease Control and Prevention, Atlanta, Georgia, in 2009-2010. After excluding assay failures, selenium measurements were complete for 4287 women. The mean (interquartile range) of the gestational timing of blood samples was 11.7 (9-13) weeks (median, 11 weeks; range, 2-42 weeks). Maternal blood selenium concentrations were log transformed for analysis. Children were defined as having current doctor-diagnosed asthma at 7.5 years if mothers responded positively to the question "Has a doctor *ever* actually *said* that your study child has asthma?" *and* positively to questions about wheezing and/or asthma in the past 12 months at 7.5 years. A single nucleotide polymorphism (SNP) in *GPX4* (rs713041, at position 718) was typed by LGC Genomics Ltd (Hoddesdon, Herts, United Kingdom; www.lgcgenomics.com) in mothers and children using a competitive allele-specific PCR system (KASPar). Maternal and child *GPX4* genotype frequencies did not deviate from Hardy-Weinberg equilibrium. All analyses were restricted to white mothers and their offspring. The median blood selenium concentration was 110.37 μg/L (range, 27.4-324.07 μg/L); the arithmetic mean was 113.82 ± 24.53 μg/L. The 20% centile concentration was 96 μg/L, which approximates to the whole blood concentration of 100 μg/L needed to saturate glutathione peroxidase activity in adults *in vivo*.[6] After controlling for confounders, including gestational timing of maternal blood samples (see this article's Online Repository at www.jacionline.org for the full list), it was found that maternal blood selenium concentration was not associated with childhood asthma (N = 2298) or wheezing (N = 2326) overall (see Table E1 in this article's Online Repository at www.jacionline.org), nor was maternal or child *GPX4* genotype associated with these outcomes (see Table E2 in this article's Online Repository at www.jacionline.org). Table I presents the adjusted associations between maternal blood selenium concentrations and asthma and wheezing, stratified by maternal and child *GPX4* genotypes. Maternal genotype did not modify the associations.

TABLE I. Associations between maternal blood selenium concentrations during pregnancy and childhood asthma and wheezing, stratified by maternal and child *GPX4* rs713041 genotype

GPX4 rs713041 genotype	N	Adjusted OR (95% CI) per doubling selenium concentration	*P* value	N	Adjusted OR (95% CI) per doubling selenium concentration	*P* value
Asthma		Stratified by maternal genotype			Stratified by child genotype	
C:C	560	0.51 (0.17-1.54)	.23	573	0.92 (0.31-2.74)	.88
T:C	852	0.95 (0.41-2.22)	.91	877	1.18 (0.50-2.78)	.70
T:T	326	0.92 (0.29-2.92)	.88	298	0.17 (0.04-0.72)	.02
P for interaction*		.64			.068	
Wheezing		Stratified by maternal genotype			Stratified by child genotype	
C:C	567	0.74 (0.24-2.27)	.60	577	0.69 (0.26-1.86)	.46
T:C	865	1.41 (0.57-3.45)	.46	893	1.99 (0.81-4.93)	.13
T:T	329	1.14 (0.35-3.66)	.83	302	0.16 (0.04-0.66)	.01
P for interaction*		.68			.011	

OR, Odds ratio.
*Testing difference in selenium associations according to genotype.

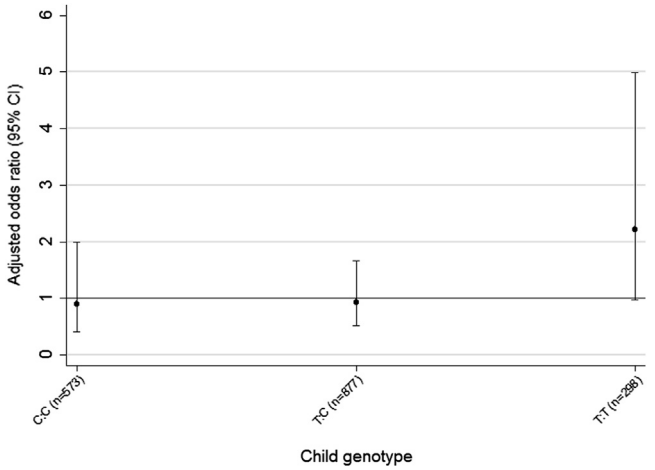

FIG 1. Odds ratio for asthma, comparing children of mothers in the bottom quintile for blood selenium concentration with children of mothers in the top 4 quintiles, and stratifying by child *GPX4* rs713041 genotype.

However, there was evidence of interaction between maternal selenium status and child *GPX4* genotype on asthma (*P* interaction .068) and wheezing (*P* interaction .011), with an odds reduction of 83% to 84% per doubling increase in blood selenium concentration in children who were homozygous for the minor T allele of rs713041; maternal blood selenium concentration was not associated with these outcomes in children carrying the C allele. Similarly, children of mothers below the 20th centile for blood selenium concentration were more likely to have asthma than were children of mothers with higher blood selenium concentration if they were homozygous for the T allele of rs713041 (odds ratio, 2.21; 95% CI, 0.98-4.99; $P = .057$), but not if they were carrying the C allele (*P* interaction .18) (Fig 1). The main findings were unchanged when we carried out 2 sensitivity analyses: first, excluding 3 mother-child pairs with outlying maternal blood selenium values (>300 μg/L); second, after controlling for 10 variables derived by principal-components analysis from the ALSPAC genomewide association study data to address possible residual confounding by population substructure.

In this population-based birth cohort study, we have found a novel, and plausible, interaction between maternal blood selenium concentration in pregnancy and child *GPX4* genotype (rs713041) on the risk of asthma and wheezing at age 7 years. Our data indicate that low maternal blood selenium concentration increases the risk and higher blood selenium concentration reduces the risk but only in genetically susceptible children, namely, those who are homozygous for the minor T allele of *GPX4*. Villette et al[4] proposed that the rs713041 SNP in the 3′ untranslated region of *GPX4* may influence how efficiently selenocysteine is incorporated into *GPX4*, leading to altered *GPX4* synthesis in response to variations in selenium supply.[4] There is other evidence confirming that T/C variation (rs713041) has functional consequences,[7] including a study showing that in individuals with the *GPX4* (rs713041) TT genotype, oxidative stress decreased as *in vivo* selenium concentrations Furthermore, *in vitro*, selenium is necessary for the maximum expression of *GPX4* in human lung epithelial cells.[9] We therefore propose that low maternal blood selenium concentration leads to suboptimal *GPX4* activity and impaired antioxidant defenses against oxidative stress in fetal airway epithelium, leading to epithelial damage, which, in turn, contributes to the pathogenesis of asthma. Alternatively, prenatal selenium status might influence the development of asthma through the involvement of *GPX4* in lipoxygenase metabolism.[4] However, because we cannot exclude the possibility that the main findings have arisen through type 1 error, replication of the interaction we observed is needed in another birth cohort of sufficient size.

Our findings suggest that in a susceptible subgroup of mother-child pairs in the population, namely, pregnant women with suboptimal selenium status and offspring with the homozygous minor variant of *GPX4* rs71304, there may be potential to reduce the incidence of childhood asthma through selenium supplementation in pregnancy. Whether primary prevention of asthma can be achieved in this way can be determined only through a clinical trial; the efficacy of such a trial is likely to be maximized by adopting a stratified approach.

We are extremely grateful to all the families who took part in this study, to the midwives for their help in recruiting them, and to the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

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Eczema is associated with osteoporosis and fractures in adults: A US population-based study

To the Editor:

Patients with eczema have multiple potential risk factors for decreased bone mineral density (BMD), including using large quantities of topical corticosteroids, systemic corticosteroids, and chronic inflammation. Furthermore, eczema is associated with distraction from itch, mental health comorbidities, and sleep disturbance,[1] all of which predispose to fractures and other injuries.[2,3] However, previous studies examining BMD in adults with eczema found conflicting results[4-6] and their risk of fractures has not been fully explored. In the present study, we analyzed data from a large-scale US-population–based study to assess the burden of fractures in adult eczema.

We used the 2005-2006 National Health and Nutrition Examination Survey. Household surveys were performed in-person in English and Spanish, as well as health examinations, blood collection, and dual-energy x-ray absorptiometry (DEXA) in mobile examination centers. Survey results were weighted to represent the population of US adults using data from the US Census Bureau. Approval by the Northwestern University institutional review board was waived.

Sociodemographic characteristics included age, sex, race, education level, and household income. Lifetime history of doctor-diagnosed osteoporosis and prednisone/cortisone use daily for at least 30 days were assessed. Daily tobacco and alcohol consumption habits were assessed. History of eczema was assessed by a positive response to the question, "Has a doctor or other health professional ever told (you/sample person) that (you have/sample person has) eczema?" To improve the specificity of self-reported eczema, subjects who reported a health care provider diagnosis of psoriasis were excluded from analyses. History of fractures was determined by asking "Has a doctor ever told (you/sample person) that (you/s/he) had broken or fractured … (your/his/her) hip?", "… (your/his/her) spine?", "… (your/his/her) wrist?", "… any other bone after (you were/s/he was) 20 years of age?" A composite binary variable was created on the basis of the above responses.

The BMD (g/cm^2) of the hip and spine was measured by using DEXA on all eligible participants. Total femur, femoral neck, trochanter, and spine scans were performed with a Hologic QDR-4500A fan-beam densitometer (Hologic, Inc, Bedford, Mass) as previously described.[7] BMD-for-age, sex, and race/ethnicity *t* scores were also determined on the basis of National Health and Nutrition Examination Survey reference standards.[8] Physical examination was performed,[9] body mass index was calculated, and blood samples were collected.

Bivariate and multivariate analyses were performed with SURVEY procedures in SAS (version 9.4; SAS Institute, Cary, NC). Bivariate associations between eczema, fracture, metabolic factors, and sociodemographic variables were tested via logistic regression models. Bivariate associations between eczema and BMD were tested via linear regression models. Complete data analysis was performed. Two-way interaction terms between eczema and age, sex, race, and household income were tested. Interactions were included in final models if P was less than .01 and modification of estimates was more than 20%. A 2-sided P value of less than .05 was taken to indicate statistical significance.

A total of 4972 people aged 20 to 85 years were included in this analysis. The prevalence (95% CI) of eczema was 7.4% (6.5% to 8.3%), of which 24.7% (18.8% to 30.5%) also had a lifetime history of asthma. The prevalence of any fracture was 32.3% (30.7% to 33.9%). Hip or spine fractures were described in 3.9% (3.3% to 4.6%), whereas 30.6% (29.0% to 32.2%) reported having "other" fractures. Associations with the prevalence of eczema and fractures are presented in Table E1 in this article's Online Repository at www.jacionline.org. Adult eczema was not associated with 25-OH vitamin D, calcium, parathyroid hormone, alkaline phosphatase, albumin, lactate dehydrogenase, C-reactive protein, or peripheral white blood cell counts compared with those without AD (see Table E2 in this article's Online Repository at www.jacionline.org).

CONFOUNDERS

In multivariate analyses, we controlled for the following potential confounders: maternal factors during pregnancy (smoking, infections, anxiety score, and use of antibiotics, alcohol, and paracetamol); other maternal factors (educational level, housing tenure, financial difficulties, body mass index, age, parity, and history of asthma, eczema, rhinoconjunctivitis, and migraine); sex of child, season of birth, multiple pregnancy, gestational age, birth weight, head circumference, and birth length; and postnatal factors (breast-feeding, day care, pets, damp/mold, environmental tobacco smoke exposure, antibiotic and paracetamol use in infancy, number of younger siblings, and body mass index at age 7 years). We also controlled for the gestational timing of maternal blood samples because whole blood selenium concentrations are known to decline as pregnancy progresses.[E1]

STATISTICAL ANALYSIS

To test for interaction, we included the genotype and selenium variables, as well as a Genotype $\times$ Selenium interaction term, in the regression models.

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E1. Butler JA, Whanger PD, Tripp MJ. Blood selenium and glutathione peroxidase activity in pregnant women: comparative assays in primates and other animals. Am J Clin Nutr 1982;36:15-23.

TABLE E1. Associations between maternal blood selenium concentrations during pregnancy and childhood asthma and wheezing

Disease	Selenium concentration (μg/L)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Asthma (N = 2298)	Q1 (≤96)	1.0	1.0
	Q2 (96-105.74)	0.77 (0.52-1.14)	0.82 (0.54-1.26)
	Q3 (105.8-115.47)	0.61 (0.40-0.92)	0.76 (0.49-1.18)
	Q4 (115.5-128.7)	0.73 (0.49-1.08)	0.85 (0.55-1.31)
	Q5 (128.8-324.07)	0.72 (0.48-1.07)	0.83 (0.53-1.30)
	Per doubling	0.66 (0.42-1.04)	0.74 (0.45-1.21)
		P value for trend = .07	*P* value for trend = .24
Wheezing (N = 2326)	Q1 (≤96)	1.0	1.0
	Q2 (96-105.74)	0.92 (0.60-1.40)	0.97 (0.61-1.54)
	Q3 (105.8-115.47)	0.77 (0.50-1.20)	0.96 (0.59-1.54)
	Q4 (115.5-128.7)	1.05 (0.70-1.59)	1.16 (0.73-1.84)
	Q5 (128.8-324.07)	0.95 (0.62-1.45)	1.07 (0.66-1.72)
	Per doubling	0.84 (0.52-1.33)	0.87 (0.52-1.45)
		P value for trend = .45	*P* value for trend = .59

OR, Odds ratio.

TABLE E2. Association between maternal and child *GPX4* rs713041 genotype and childhood asthma and wheezing

Disease	Maternal *GPX4* rs713041 genotype		OR (95% CI)
Asthma (N = 1738)	N		
	560	C:C	1.0
	852	T:C	0.90 (0.64-1.25)
	326	T:T	1.29 (0.87-1.93)
		Per allele	1.11 (0.91-1.37)
Wheezing (N = 1761)	N		
	567	C:C	1.0
	865	T:C	0.83 (0.59-1.19)
	329	T:T	1.28 (0.85-1.94)
		Per allele	1.10 (0.89-1.37)

Disease	Child *GPX4* rs713041 genotype		OR (95% CI)
Asthma (N = 1748)	N		
	573	C:C	1.0
	877	T:C	1.23 (0.88-1.73)
	298	T:T	1.24 (0.80-1.94)
		Per allele	1.13 (0.91-1.40)
Wheezing (N = 1772)	N		
	577	C:C	1.0
	893	T:C	0.88 (0.63-1.24)
	302	T:T	1.10 (0.71-1.71)
		Per allele	1.02 (0.82-1.28)

OR, Odds ratio.