

Table 1

Characterization of Penicillin Allergy Obtained via Patient Interview Compared With EMR Documentation

Characterization	No. of patients (N = 100)
Patient did not report a penicillin allergy but was documented to have a penicillin allergy in the EMR	0
Patient reported a penicillin allergy reaction that was consistent with EMR documentation	32
Patient described a penicillin allergy reaction that was different from EMR documentation	19
Patient described a penicillin allergy reaction but the EMR reaction field was empty	13
Patient described a penicillin allergy reaction but the EMR reaction field was incomplete	32
Patient described a history of a penicillin allergy but had subsequently tolerated penicillin-like antibiotics	1
The penicillin allergy reaction was a nonimmunologically mediated intolerance incorrectly classified as an allergy	1
The penicillin allergy reaction was documented as family history without a patient history of an allergic reaction	2

Abbreviation: EMR, electronic medical record.

IgE-mediated penicillin allergy lose their sensitivity within 10 years.² The time elapsed since a possible penicillin reaction is a critical factor that is often disregarded and remains undocumented in most patients.

Accurate documentation of a penicillin allergy history occurred in less than 50% of patients across all professions. Accurate entries for advanced practice professionals (eg, physician assistants and nurse practitioners) occurred in 18 (43%) of 42 entries, followed by nurses (18 [32%] of 57), physicians (8 [28%] of 29), and pharmacists (3 [23%] of 13). Although our findings are provocative, they offer little explanation as to why discrepancies in allergy documentation occur. Given poor documentation across all professions, we hypothesize that there is a general lack of knowledge regarding the importance of qualifying medication allergies and relevant details surrounding the sentinel reaction. This is particularly important with penicillin allergy given the robust literature surrounding the deleterious effects of this label. There were at least 7 professions that modified or updated our study participants' allergy fields, ranging from a respiratory therapist to an attending physician, each with widely varying degrees of knowledge and experience pertaining to allergy and immunology.

It is possible that health care professionals are more thoroughly assessing penicillin allergies but are not documenting information into the EMR. There are various reasons why this may be occurring, including significant time constraints and/or cumbersome EMR allergy documentation requirements. All these potentially contributing factors emphasize the need for a standardized electronic approach that prompts the health care professional to ask strategic and analytical questions when modifying or adding a penicillin allergy to the allergy field. Our logic may not be applicable to all medication allergies but should certainly be considered for penicillin antibiotics because penicillin remains the most commonly reported drug allergy and the label carries significant implications for health care costs and antimicrobial resistance.³

There are several limitations to our study. First, we describe disparities in penicillin allergy EMR documentation in adult inpatients only. It is possible that our findings may not translate to the ambulatory, pediatric, and/or paper record settings. Of note, prior studies in these environments have reported similar results.^{5–7} In addition, our survey was susceptible to recall bias or inaccurate patient recollection; however, because most medication allergy reactions occur outside medical facilities or in the absence of a medical professional, patient history is often the only obtainable information.⁸

In patients with a penicillin allergy, antimicrobial stewardship begins with a thorough allergy history and verification of the allergy label. Our findings reveal that most EMR penicillin allergy histories documented at our institution are inconsistent with the histories described by patients. Although our institution is in the minority of health care systems that provide allergy and immunology services, most medication allergy assessments are conducted by non-allergy-trained health care professionals. Implementation of a standardized approach to thoroughly, accurately, and consistently obtain a penicillin allergy history could serve to improve EMR allergy documentation across all professions and may lead to reduction in the use of second-line, high-risk antibiotic exposure.

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Vitamin D and asthma A Mendelian randomization study

Several studies have associated low levels of 25-hydroxyvitamin D (25[OH]D) with higher risk of asthma.^{1,2} However, these studies

could have residual confounding or reverse causation, making it difficult to draw conclusions on whether 25(OH)D is causally associated with asthma. Instrumental variable analysis was developed for assessing causality using genetic variants in epidemiologic

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research known as Mendelian randomization (MR). The rationale of MR is to find genetic variants associated with the exposure (eg, 25 [OH]D) but not with other risk factors (eg, obesity) that affect the outcome (eg, asthma). This means any observed associations of genetic variants with the outcome must be through the exposure, which affects the outcome, thus implying a causal effect of exposure on outcome. A recent MR study evaluating 25(OH)D on asthma risk found low levels of 25(OH)D were unlikely causative for asthma risk.³ However, this study included 1,203 cases and 3,877 controls and might have a low statistical power for MR analysis to detect a small effect size. In the present study, we investigated the causal effect of 25(OH)D on asthma by applying the MR method to publicly available summary statistics from the GABRIEL Consortium, a large-scale genomewide association study (GWAS) of asthma (eTable 1).⁴

Four single-nucleotide polymorphisms (SNPs) have been identified as associated with variation in circulating 25(OH)D levels in previous GWAS publications.⁵ These variants (rs2282679, rs7944926, rs2060793, and rs17217119) are at loci (GC, *DHCR7*, *CYP2R1*, and *CYP24A1*) with plausible links to 25(OH)D metabolism and synthesis and have been used as instrumental variables in several MR studies.⁶ The effects of the 4 SNPs on concentrations of 25(OH)D were 5.48 nmol/L for rs2282679 (per T allele), 2.40 nmol/L for *DHCR7* rs7944926 (per G allele), 3.22 nmol/L for rs2060793 (per T allele), and 2.62 nmol/L for rs17217119 (per T allele).⁶ The 4 SNPs together accounted for 3.6% of the variation.⁶ We also extracted the final estimates of these SNPs on asthma from the GABRIEL Consortium.⁴ This study involved multiple cohorts composed of 10,365 asthma cases and 16,110 controls. The participants in the GABRIEL study included individuals recruited from across Europe and cases and controls of European descent from Canada, Australia, and the United States. The outcome examined was physician-diagnosed asthma.⁴ To estimate the causal effect of 25(OH)D on asthma using a genetic risk score as the instrumental variable, we applied the MR methods developed specifically for summary statistics. We carried out 4 different estimating methods (inverse variance weighting method,⁷ weighted median method,⁸ and MR-Egger regression and robust MR-Egger regression methods⁹) for the MR analyses (eSupplement). These methods yielded similar results to those obtained from the genetic risk score approach using individual-level data. Statistical analyses were performed in R 3.3 (R Project for Statistical Computing).

The methods were carried out in accordance with approved guidelines. People of predominantly European descent were included in the study. Each study was specifically approved by the ethical committees of the original studies and all participants provided a written informed consent. This analysis of publicly available summary data does not require ethical approval.

Figure 1 shows the effects of 25(OH)D-increasing alleles on asthma risk. None of these SNPs were nominally significantly associated with asthma. None of the estimates using the different methods supported a protective causal role of 25(OH)D in decreasing asthma risk (odds ratio [OR] 1.00, 95% confidence interval [CI] 0.99–1.01, $P = .45$ for inverse variance weighting method; OR 1.00, 95% CI 0.99–1.01, $P = .65$ for weighted median method; OR 1.00, 95% CI 0.93–1.08, $P = .98$ for MR-Egger regression method; OR 1.00, 95% CI 0.94–1.06, $P = .99$ for robust MR-Egger regression method).

In this study, we performed an MR analysis of the largest asthma GWAS, the GABRIEL study,⁴ to examine the causal effects of 25(OH)D on asthma risk and found that the MR evidence did not support a causal protective role against asthma risk. This suggests that previous results from observational epidemiologic studies could be due to unmeasured confounders or reverse causation. Although the effects of 25(OH)D on intermediate biomarkers (eg, cytokines) or asthma-related complications (eg, osteoporosis and cataracts) are

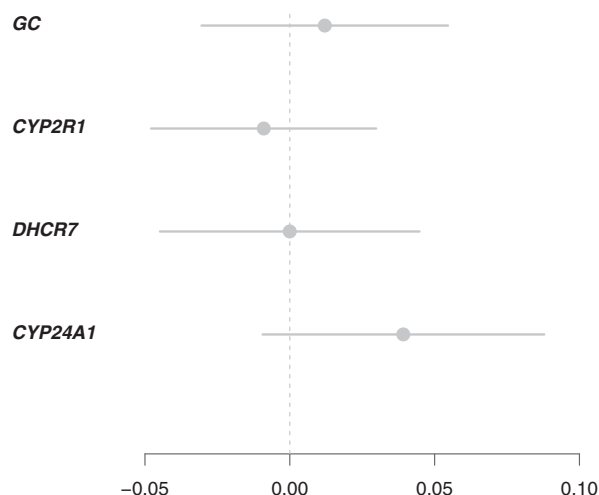


Figure 1. Effects of vitamin D-increasing single-nucleotide polymorphisms on asthma, log(odds ratio) with 95% confidence interval.

of interest, the present study could not examine these hypotheses using the MR design because the summary GWAS statistics for these traits are not available. In summary, our results suggest that increasing 25(OH)D might not translate to decreased risk for asthma. However, our analysis included a relatively small number of SNPs that explained less than 5% of the variability in 25(OH)D levels and might have had limited power to detect an association.¹⁰ Moreover, it was based on participants of European ancestry. Studies including more variants that explain a larger proportion of 25(OH)D variability and focus on other populations will be needed to confirm our findings.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2017.05.018>.

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Supplementary Data

eSupplement

A special MR approach has been developed to draw causal inference using summary GWAS statistics (not individual-level data), in which the associations of SNPs with outcome were published and made publically available. Here, we briefly describe the estimation methods when using summary GWAS statistics for an MR study.

The causal estimate from the inverse variance weighted (IVW) method (β_{IVW}) is calculated by the following equation:

$$\beta_{IVW} = \frac{\sum_{i=1}^N \beta_{exp,i} \beta_{out,i} \sigma_{out,i}^{-2}}{\sum_{i=1}^N \beta_{exp,i} \sigma_{out,i}^{-2}}$$

The SE is estimated by:

$$se(\beta_{IVW}) = \frac{1}{\sum_{i=1}^N \beta_{exp,i} \sigma_{out,i}^{-2}}$$

where N is total number of genetic variants, $\beta_{exp,i}$ is the effect of the i-th genetic variant on the exposure, $\beta_{out,i}$ is the i-th genetic variant on the outcome, and $\sigma_{out,i}$ is the SE of $\beta_{out,i}$.

The weighted median method provides a valid estimate of the causal effect of exposure on disease if at least half the genetic variants are valid instruments. The MR-Egger method performs a weighted linear regression of the SNP disease coefficients on the

SNP exposure coefficients. Tutorial and corresponding codes for these methods can be found in the supplementary file for the article cited in the main text.

eTable 1
Study Participants in GABRIEL Consortium

Study	Country	Cases, n	Controls, n
ALSPAC	United Kingdom	607	609
B58C	United Kingdom	445	420
BAMSE	Sweden	239	246
BUSSELTON	Australia	398	809
CAPPS and SAGE	Canada	267	554
ECRHS	multiple countries	664	1,546
EGEA	France	676	1,252
GABRIEL Advanced Surveys	Germany	841	851
GAIN	multiple countries	1,475	1,668
Karelia Allergy Study	Finland	73	75
KSMU	Russia	291	277
MAGICS	Germany	630	572
MAS	Germany	171	
MRCA-UKC	United Kingdom	177	399
PIAMA	Holland	172	157
SAPALDIA	Switzerland	608	913
SLSJ Familial Collection	Canada	586	613
TOMSK	Russia	259	422
UFA	Russia	330	348
Occupational asthma	multiple countries	529	698
AUGOSA	United Kingdom	637	2,677
SEVERE	United Kingdom	290	974