Assessment of a causal relationship between body mass index and atopic dermatitis

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Assessment of a causal relationship between body mass index and atopic dermatitis

To the Editor:

Atopic dermatitis (AD) is an itchy, inflammatory skin condition associated with multiple comorbidities. Observational epidemiology suggests an increased prevalence of obesity in patients with AD, but (1) whether there is a causal effect and (2) whether obesity leads to AD or *vice versa* remain unclear. Genetic predisposition to obesity has been shown to promote psoriasis,[1] but dermatologic disorders can also lead to reduced participation in physical activity, resulting in weight gain. We aimed to investigate evidence of causality in the association of AD with elevated body mass index (BMI).

We meta-analyzed 33 published studies examining the association between obesity or elevated BMI and AD to summarize available observational data (see Fig E1 in this article's Online Repository at www.jacionline.org). The odds ratio (OR) for AD in overweight individuals was 1.05 (95% CI = 0.94-1.19) in adults (n = 51,008) and 1.08 (95% CI = 1.00-1.16) in children (n = 506,202) (see Fig E2 in this article's Online Repository at www.jacionline.org). For obese individuals, the OR for having AD was 1.19 (95% CI = 0.95-1.49) in adults (n = 1,400,679) and 1.20 (95% = CI 1.11-1.30) in children (n = 796,514) (see Fig E3 in this article's Online Repository at www.jacionline.org); the methods and results are detailed in the Methods and Results sections of the Online Repository (at www.jacionline.org). We extended the observational analysis by using 2 large population-based studies from the United Kingdom and Norway[2,3] (for details, see the Online Repository and Tables E1-E4). Among overweight individuals (BMI of 25-30 kg/m^2), the OR of AD was 1.02 per each 1-kg/m^2 increase in BMI (95% CI = 1.00-1.04; $P = .07$; 4,820 cases and 130,776 controls); a similar estimate was found among obese individuals (BMI >30 kg/m^2) (ie, OR =1.02 [95% CI = 1.01-1.03; $P = 3.3 \times 10^{-4}$] in a sample of 2,741 cases and 73,907 controls) (see Fig E4 in this article's Online Repository at www.jacionline.org).

Observational epidemiology has several limitations, including bias from confounding and reverse causation; this restricts its utility for causal inference. However, causality and the direction of effect can be investigated by mendelian randomization (MR). MR uses genetic variants as a proxy for the exposure (eg, BMI) to estimate the effect on an outcome (eg, AD). Genetic variants are randomly allocated at fertilization, therefore avoiding confounding; they are not affected by outcomes later in life, thus avoiding reverse causation. Genome-wide association studies (GWASs) have identified single-nucleotide polymorphisms (SNPs) associated with BMI (≤941 loci[4,5]) and AD (24 loci in European populations[6]). These SNPs can be combined into a genetic risk score (GRS) or "genetic instrument" that acts as a proxy for the specified trait during MR.

We conducted MR analysis by using data from the largest population-based studies in the United Kingdom (UK Biobank[2]) and Norway (Nord-Trøndelag Health Study, Norway[3] [HUNT, 2006-08]) along with the largest published GWASs for BMI[4,5] and AD[6] to date, representing a total of 742,611 individuals (see Table E5 in this article's Online Repository at www.jacionline.org). One-sample MR was performed in the UK Biobank and HUNT data sets with the individuals' BMI SNPs, measured BMI, and AD status. Two-sample MR using published GWAS data[4-6] was performed and meta-analyzed with the 1-sample estimate to obtain an overall causal estimate. Similarly, reverse MR was conducted to investigate the effect of AD genetic risk on BMI. Methodologic details and sensitivity analysis are described in the Online Repository, including Fig E5.

The BMI GRS was strongly associated with BMI in both the UK Biobank and HUNT data sets (see Figs E6 and E7 in this article's Online Repository at www.jacionline.org), supporting its use as a genetic instrument. Potential confounders of the GRS-BMI association were detected (see Figs E6-E9), but the magnitudes were minimal in comparison with the strength of association with BMI. Similarly, the AD GRS was a good predictor of AD in both the UK Biobank (OR = 1.26 [95% CI = 1.23-1.28]; F-statistic = 2036; R^2 = 0.7%) and HUNT (OR = 1.15 [95% CI = 1.11-1.21]; F-statistic = 97;

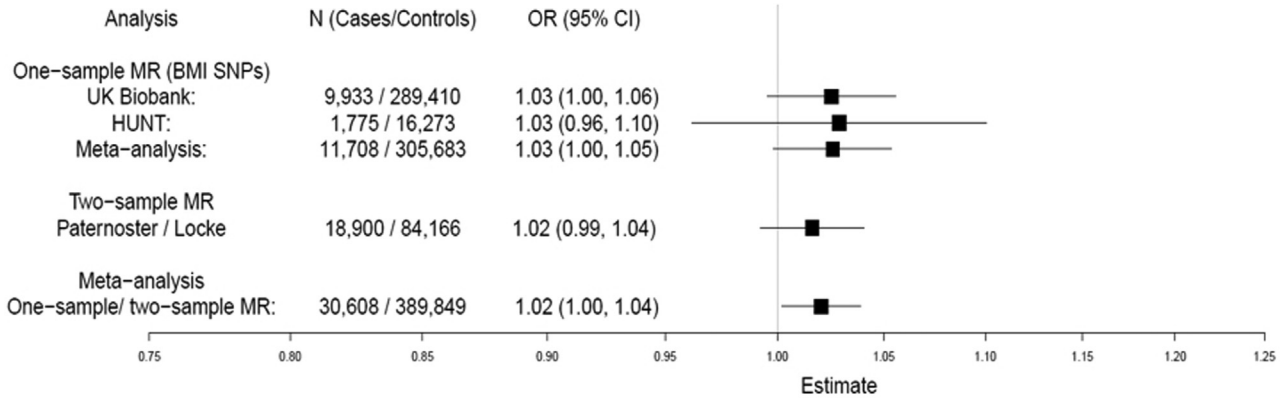

FIG 1. MR analysis of the causal effect of BMI on AD. Meta-analysis of 1-sample and 2-sample MR estimates using individual BMI SNPs as instruments. Estimates are given per 1-kg/m^2 increase in BMI.

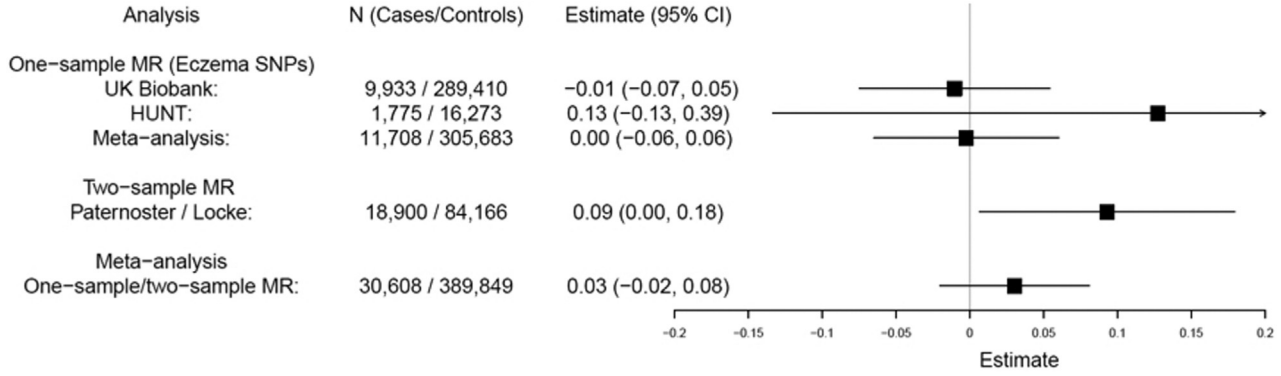

FIG 2. Reverse direction MR analysis: effect of AD genetic risk on BMI. Meta-analysis of 1-sample and 2-sample MR estimates using individual AD SNPs as instrumental variables. Estimates represent change in BMI (kg/m^2) per doubling odds of AD.

R^2 = 0.4%) data sets, despite lacking an *FLG* null genotype (R501X/rs61816761), which is known to show strong association with AD.

Meta-analyzed 1- and 2-sample MRs show evidence of a small causal effect of higher BMI increasing the risk of AD (OR = 1.02 [95% CI = 1.00-1.04]; P = .03) (Fig 1). This represents an increase in AD risk by approximately 2% for each 1-kg/m^2 increase in BMI, which is remarkably similar to the observational estimate (see Figs E2 and E3 in the Online Repository). Importantly, sensitivity analyses showed little evidence of pleiotropy (for details, see the Sensitivity Analysis section, Table E6, Fig E10, and Fig E11 in this article's Online Repository at www.jacionline.org) or heterogeneity among the individual SNP effect estimates (UK Biobank Q = 101.07 [P = .32]; HUNT Q = 100.04 [P = .37]). Two-sample MR using the larger number of recently published BMI SNP estimates (941 SNPs)[4] gave similar evidence of a causal effect on AD risk (OR = 1.08 [95% CI = 1.01-1.16]; P =.02).

In the reverse direction, meta-analysis gave weak evidence of a very small causal effect (Fig 2): a 0.03-kg/m^2 change in BMI per doubling odds of AD (95% CI = –0.02 to 0.08; P = .24). There was little evidence of pleiotropy but modest heterogeneity among the individual SNP effects (see Fig E12 and Table E7 in in this article's Online Repository at www.jacionline.org). The difference in BMI between patients with AD and controls estimated in 1-sample MR (0.15 kg/m2, 95% CI -1.97 to 2.27) was small compared with observational estimates (see Tables E1 and E2), indicating that the association is mainly explained by the causal effect of BMI on AD.

The association of obesity with cardiometabolic disease and systemic inflammation is now well recognized, and clinical guidelines recommend screening patients with psoriasis for obesity. The presence of a *causal* effect and the *direction* of effect are both clinically relevant, to define a primary target (ie, obesity) for intervention. Our MR analysis shows evidence that higher BMI increases the risk of AD (ie, a 2% increase in disease risk for each 1-kg/m^2 increase in BMI). Conversely, there was no strong evidence of a causal effect of AD genetic risk on BMI; the estimate of 0.03 kg/m^2 suggests that genetic risk for AD has little meaningful influence on an individual's BMI. These findings may be compared with the causal effect of BMI on psoriasis and lack of effect of psoriasis genetic risk on BMI.[1] The effect of BMI on AD is more modest than the effect size observed in psoriasis, but the high prevalence of obesity (in more than one-third of US adults) and AD (in ≤10% of adults) demonstrate the potential importance of this causal effect on a population scale.

The molecular mechanisms by which obesity contributes to skin inflammation remain unclear. Excess adipose tissue secretes proinflammatory cytokines and hormones,[7] and atopic

inflammation may be promoted by disruption of the epidermal barrier in obese individuals.[8] Changes in the adipocytes and lymphatic vessels may also contribute to obesity-related skin inflammation.[8] Research to define mechanisms underlying the causal relationship demonstrated by MR may identify novel therapeutic targets.

Our MR analyses have various strengths as well as weaknesses. The large sample size is powerful, and the genetic instruments are strong. The 2-sample analysis included an overlap of data sources (from the HUNT study), which has the potential to bias the causal estimate, but this bias would be in the direction of the null. There is the possibility of misclassification of AD, and because AD often shows remission in childhood, this phenotype may be particularly susceptible to recall bias in adult studies; however, this would likely drive any estimate toward the null. It is also important to note that the MR methodology applied here does not define temporal relationship. Genetic risk has a lifetime effect and therefore predates disease onset, but a causal effect determined by MR does not rely on obesity occurring before the onset of AD. However, when we attempted to mitigate this issue by repeating the MR analyses using SNPs that are strongly associated with childhood BMI,[9] a causal estimate with the same direction of effect was obtained (OR = 1.04; 95% CI = 1.01-1.07; P = .01). Nevertheless, replication of these analyses within pediatric cohorts with large sample sizes would be valuable future work.

In conclusion, we have found evidence of a small but potentially important causal effect of BMI on AD. Clinical trials have shown that interventions to promote weight loss can lead to improvement in psoriasis, but this approach has not been tested in AD. The results of our study provide support for the investigation of obesity management strategies and/or targeting of the adipocyte-keratinocyte cross-talk as therapeutic opportunities for AD. This may contribute to the prevention of AD, as well as to a reduction in the population prevalence of this chronic disease.

This research was conducted by using data from the UK Biobank Resource (application number 10074) and the Nord-Trøndelag Health Study (the HUNT Study). Details of patient and public involvement in the UK Biobank are available online (http://www.ukbiobank.ac.uk/about-biobank-uk/ and https://www.ukbiobank.ac.uk/wp-content/uploads/2011/07/Summary-EGF-consultation.pdf?phpMyAdmin=trmKQlYdjjnQIgJ%2CfAzikMhEnx6). The UK Biobank data set used to conduct the research in this article is available via application directly to the UK Biobank. Applications are assessed for meeting the required criteria for access, including legal and ethics standards. More information regarding data access can be found at the following website: http://www.ukbiobank.ac.uk/scientists-3/. Data from the HUNT Study used in research projects will, when reasonably requested by others, be made available on request to the HUNT Data Access Committee (hunt@medisin.ntnu.no). The HUNT data access information (available at: http://www.ntnu.edu/hunt/data) describes in detail the policy regarding data availability. No patients were specifically involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of this study. No patients were asked to advise on interpretation or writing up of results. There are no specific plans to disseminate the results of the research to study participants, but the UK Biobank and the HUNT Study disseminate key findings from projects on their websites. The HUNT Study is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. We acknowledge the permission of the EAGLE consortium (including 23andMe) to use results from their previous GWAS of AD (Paternoster et al[6]).

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Cross-reactivity between vancomycin, teicoplanin, and telavancin in patients with *HLA-A*32:01*–positive vancomycin-induced DRESS sharing an HLA class II haplotype

To the Editor:

Vancomycin is a glycopeptide antibiotic used to treat resistant gram-positive infections. It is associated with a life-threatening, delayed T-cell–mediated reaction, drug reaction with eosinophilia and systemic symptoms (DRESS) presenting with fever, rash, hematologic abnormalities, lymphadenopathy, and organ involvement that occurs 2 to 6 weeks after initiation of vancomycin treatment.[1] We demonstrated that *HLA-A*32:01* is strongly associated with vancomycin-induced DRESS in European populations.[2] All glycopeptide antibiotics contain a heptapeptide core structure, and cross-reactivity should be considered when treating patients who have had a previous hypersensitivity reaction to vancomycin (see Fig E1 in this article's Online Repository at www.jacionline.org).[3] Cross-reactivity remains controversial, as some patients presenting with teicoplanin-induced DRESS showed subsequent tolerability to vancomycin[4-7] and patients with teicoplanin-induced DRESS confirmed by a positive intradermal skin test result had a negative result of a skin test to vancomycin.[8]

To examine the immunologic cross-reactivity among 4 glycopeptide antibiotics (ie, vancomycin, teicoplanin, dalbavancin, and telavancin), adults who were at least 18 years old with a probable diagnosis of vancomycin-induced DRESS defined as having a corresponding Naranjo adverse drug reaction score of 5 or higher (probable adverse drug reaction), having a Registry of Severe Cutaneous Adverse Reactions score of 4 or higher (probable DRESS), and carrying *HLA-A*32:01* (the recently described risk allele for vancomycin-induced DRESS) were recruited between January 2010 and September 2019 through drug allergy clinics and inpatient facilities at participating institutions (Vanderbilt University Medical Center in Nashville, Tennessee, and Austin Health, Peter MacCallum Cancer Centre, Fiona Stanley Hospital and Royal Perth Hospital in Perth, Western Australia, Australia). All patients provided informed consent for collection of saliva and blood to be stored as DNA and PBMCs.

IFN-γ release in response to overnight incubation with implicated drugs was performed by ELISpot assay (3420-2H; Mabtech, Stockholm, Sweden) in triplicate from thawed PBMCs (rested overnight) and included negative (unstimulated) and positive (anti-CD3 Mabtech antibody, staphylococcal enterotoxin B, and/or cytomegalovirus pp65) controls. Control PBMCs from glycopeptide unexposed *HLA-A*32:01*–positive and *HLA-A*32:01*–negative individuals were also used. PBMCs plated at 200,000 cells per well were incubated with vancomycin, teicoplanin, dalbavancin, telavancin, and other implicated drugs at concentrations representative of maximum serum concentrations, as well as those 10-fold higher and 10-fold lower (Fig 1). A positive response was defined as more than 50 spot-forming units per million cells after background removal as per previous the definitions.[9] High-resolution 4-digit HLA-A, HLA-B, HLA-C, HLA-DP, HLA-DR, and HLA-DQ typing was performed by using sequence-based typing with previously published protocols.[2]

A total of 15 patients who met the clinical inclusion criteria for vancomycin-induced DRESS syndrome were enrolled into this study. Their demographics, clinical characteristics, and DRESS history are described in Table E1 (in this article's Online Repository at www.jacionline.org), and full HLA typing of all patients is described in Table E2 (in this article's Online Repository at www.jacionline.org).

All patients with vancomycin-induced DRESS exhibited a dose-dependent positive IFN-γ ELISpot response to vancomycin (Fig 1 and see Table E3 in this article's Online Repository at www.jacionline.org); all had a clear negative response to both concentrations of dalbavancin (Fig 1). Three patients overall showed cross-reactivity, with all 3 showing a positive response to telavancin and 2 of them also demonstrating a positive IFN-γ ELISpot response to teicoplanin. One of the 2 patients who had positive IFN-γ ELISpot responses to vancomycin, teicoplanin, and telavancin (patient 15 and see Table E3) was intradermally skin-tested to both vancomycin and teicoplanin and showed positive responses to both (see Fig E2 in this article's Online Repository at www.jacionline.org), which was not seen in glycopeptide-unexposed controls (n = 5) and 3 patients (patients 9, 10, and 11) with *HLA-A*32:01*–positive vancomycin-induced DRESS who showed positive delayed intradermal testing and IFN-γ ELISpot results to vancomycin but negative IFN-γ ELISpot and intradermal testing results to teicoplanin. Patients 1, 3, and 5 also tolerated ingestion challenges with medications concurrently administered at the time of vancomycin-induced DRESS.

In samples with sufficient cell numbers, PBMCs were tested against other concurrently administered medications potentially implicated in DRESS development (see Fig E3 in this article's Online Repository at www.jacionline.org). IFN-γ ELISpot was also performed on PBMCs from non–HLA-matched healthy donors (n = 5) and a *HLA-A*32:01*–positive vancomycin naive control (n = 1), with all exhibiting a negative response to all 4 drugs (data not shown).

Vancomycin is implicated in up to 40% of patients with antibiotic-related DRESS.[1] The prevalence of vancomycin-induced DRESS appears to be increasing, and it is the second most common cause of DRESS overall reported to the US Food and Drug Administgration Adverse Event Reporting System between 1999 and 2019 (https://open.fda.gov/data/faers/ [accessed March 2, 2020]). *HLA-A*32:01* has recently been reported as a