A Transethnic Mendelian Randomization Study Identifies Causality of Obesity on Risk of Psoriasis

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TO THE EDITOR

Psoriasis is a chronic disorder characterized by cutaneous and systemic manifestations. Epidemiological studies have reported increased comorbidity of psoriasis with numerous complex diseases such as metabolic clinical measurements (Greb et al., 2016; Naito and Imafuku, 2016). However, interpretation of the comorbidity remains controversial to date, because causal inference between correlated phenotypes is difficult when depending solely on epidemiological studies. Identification of causal inference between correlated phenotypes has significant clinical impacts, because modification of the causal phenotypes could benefit treatment of the outcome phenotypes. Drugs indicated by the causal phenotypes could also be promising targets of drug repositioning for the outcome phenotypes (Holmes et al., 2017). Therefore, alternative approaches to strengthen causal inference on psoriasis are warranted.

An approach becoming popular for this purpose is use of genetic data (Pingault et al., 2018). Genetically determined phenotype profiles are robust to confounding factors acquired during a lifetime, which could be interpreted as ideal randomization of subjects. Mendelian randomization (MR) is an approach to infer causal inference between phenotypes using the genome-wide association study (GWAS) results (Holmes et al., 2017; Hemani et al., 2018). Because of (i) achievement of large-scale GWASs of a variety of human phenotypes with public data deposit and (ii) development of MR analytical methods that robustly infer causality, such as MR-Egger (Burgess and Thompson, 2017), MR is now one of the best approaches to infer causality. Generally, the largest available GWAS result within a single ancestry is used for an MR analysis to afford robust conclusions. Thus, confirmation of the MR analysis results requires additional validation using GWAS with independent ancestry.

Here, we conducted a transethnic MR analysis to estimate causal inference on psoriasis. We obtained the genome-wide summary statistics of the previously reported psoriasis GWAS of European populations (13,229 case and 21,543 control individuals) (Tsoi et al., 2017) and Japanese population (282 case and 426 control individuals) (Hirata et al., 2018) (see Supplementary Table S1 online). Both of the psoriasis GWASs were conducted by applying whole-genome sequencing–based genotype imputation, which yielded high coverage of the genome-wide variants suitable for the MR analysis (>6,000,000 variants). As for the European GWAS, the participants in the cohort collected by 23andMe (Mountain View, CA) were excluded because of their policies on summary data sharing. We thus reconducted the GWAS meta-analysis after sample exclusion for our MR analyses. We admit that the sample size of the Japanese GWAS was relatively smaller, which warrants further accumulation of participants.

We focused on metabolic clinical measurements as exposure phenotypes, for which the large-scale GWAS results have been released in both populations. We selected nine measurements: obesity (body mass index [BMI]); levels of triglycerides, total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, blood sugar, and hemoglobin A1c; and systolic and diastolic blood pressure (on average 149,958 subjects per trait) (see Supplementary Table S2 online) (Akiyama et al., 2017; Ehret et al., 2011; Kanai et al., 2018; Locke et al., 2015; Scott et al., 2012; Wheeler et al., 2017; Willer et al., 2013). After selection of the lead variants (or the proxy single nucleotide polymorphisms [SNPs] in linkage disequilibrium of $r^2 \geq 0.5$ in the corresponding 1000 Genomes Project phase1v3 populations) at the loci with genome-wide significance threshold ($P < 5.0 \times 10^{-8}$) and exclusion of the highly pleiotropic locus of the major histocompatibility complex region, on average 41.3 loci per trait were obtained.

We adopted two-sample MR, one of the MR analysis approaches that handles summary statistics obtained from separate studies. In addition to the typical method of inverse variance weighted (IVW), we adopted MR analysis based on Egger regression (i.e., MR-Egger), which is statistically less powerful but more robust to bias caused by directional pleiotropy (Burgess and Thompson, 2017). We used the MR-Base platform implemented as a package of R statistical software (R Core Development Team, Vienna, Austria) (Hemani et al., 2018).

For Europeans, significant causality of genetically increased BMI on risk of psoriasis was estimated ($\beta = 0.464$ and $P = 3.1 \times 10^{-5}$ in IVW, and $\beta = 0.697$ and $P = 0.0093$ in MR-Egger) (Table 1 and Figure 1). For Japanese, significant causality of BMI on psoriasis risk was also observed in the IVW analysis with a concordant directional effect ($\beta = 1.275$ and $P = 0.0069$). Although the MR-Egger result was not significant ($\beta = 1.499$ and $P = 0.27$), the effect size estimate was larger than that of

Abbreviations: BMI, body mass index; GWAS, genome-wide association study; IVW, inverse variance-weighted; MR, Mendelian randomization; SNP, single nucleotide polymorphism

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Table 1. Results of the transethnic MR analyses inferring causality of the clinical metabolic measurements on psoriasis

Trait	MR Method	MR Result in Europeans		MR Result in Japanese		Meta-Analysis
		Beta (SE)	*P*	Beta (SE)	*P*	*P*
Body mass index	Inverse variance weighted	0.464 (0.112)	3.1×10^{-5}	1.275 (0.472)	0.0069	1.2×10^{-6}
	MR-Egger	0.697 (0.262)	0.0093	1.499 (1.342)	0.27	0.0088
Triglyceride	Inverse variance weighted	0.085 (0.088)	0.33	0.139 (0.369)	0.71	0.34
	MR-Egger	−0.064 (0.129)	0.62	0.748 (0.561)	0.19	0.56
Total cholesterol	Inverse variance weighted	0.054 (0.063)	0.39	−0.595 (0.476)	0.21	0.78
	MR-Egger	0.126 (0.115)	0.28	−0.663 (0.900)	0.47	0.80
HDL cholesterol	Inverse variance weighted	−0.026 (0.072)	0.72	0.190 (0.318)	0.55	0.87
	MR-Egger	0.024 (0.109)	0.82	−0.048 (0.509)	0.93	0.92
LDL cholesterol	Inverse variance weighted	0.051 (0.054)	0.35	−0.300 (0.385)	0.44	0.91
	MR-Egger	0.180 (0.088)	0.046	−0.134 (0.535)	0.80	0.22
Blood sugar	Inverse variance weighted	−0.537 (0.269)	0.046	0.235 (0.671)	0.73	0.24
	MR-Egger	−0.685 (0.943)	0.47	1.940 (2.550)	0.46	0.99
HbA1c	Inverse variance weighted	−0.143 (0.273)	0.60	−0.289 (0.417)	0.49	0.39
	MR-Egger	0.064 (0.552)	0.91	1.811 (1.661)	0.29	0.41
Systolic blood pressure	Inverse variance weighted	0.006 (0.010)	0.54	1.080 (0.781)	0.17	0.16
	MR-Egger	0.048 (0.033)	0.16	3.818 (2.823)	0.19	0.055
Diastolic blood pressure	Inverse variance weighted	0.017 (0.017)	0.31	1.010 (0.963)	0.29	0.14
	MR-Egger	0.099 (0.058)	0.10	1.560 (3.043)	0.62	0.13

Abbreviations: HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MR, Mendelian randomization; SE, standard error.

IVW. Because phenotype normalization methods were different among the original GWAS, direct comparison of the estimated causal effect sizes of the BMI-associated SNPs on psoriasis between the studies was difficult. We assessed potential bias in the results of MR analyses, mostly caused by SNP pleiotropy, by applying a set of sensitivity analyses including heterogeneity test, leave-one-out analysis, and funnel plots implemented in the MR-Base platform, but we did not find existence of apparent bias (see Supplementary Figure S1 online). We applied the reverse MR analysis inferring causality of psoriasis on BMI, but we did not observe significant causality ($P > 0.75$) (see Supplementary Figure S2 online).

We then conducted a transethnic meta-analysis of the MR results, using weighted summation of *z*-scores considering directional concordance of the causal effect estimates. As expected, significant causality of BMI on risk of psoriasis was observed ($P = 1.2\times10^{-6}$ in IVW, and $P = 0.0088$ in MR-Egger). Although suggestive relationships of LDL cholesterol and blood sugar were observed in Europeans ($P < 0.05$ in IVW or MR-Egger), these associations were not replicated in Japanese, and transethnic MR analyses did not indicate significant causality of these traits ($P > 0.22$).

By using large-scale GWAS results of psoriasis in European and Japanese populations, our transethnic MR

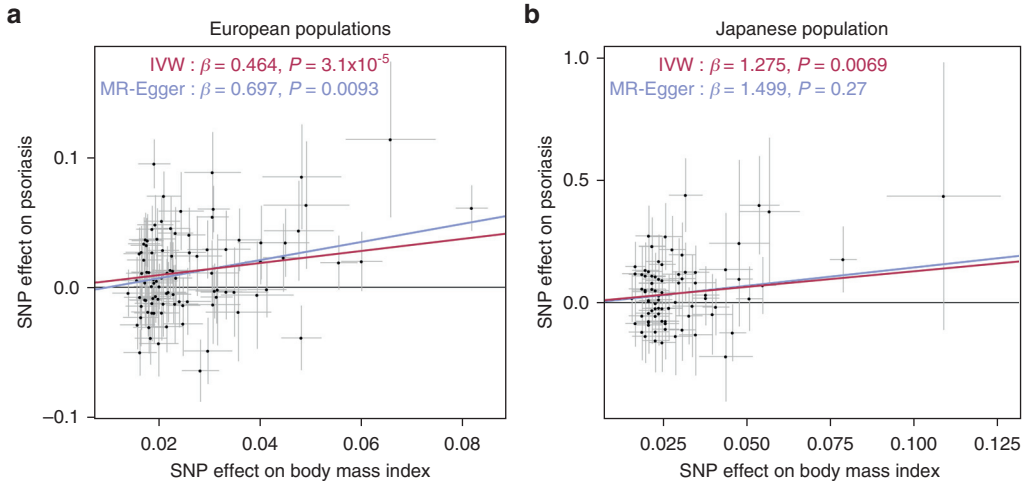

Figure 1. Regression plots of the BMI-associated variants on psoriasis risk. Dots represent the BMI-associated SNPs plotted along with effect size estimates on BMI (x-axis) and psoriasis risk (y-axis) with 95% confidence intervals in (**a**) the European populations and (**b**) the Japanese population. Regression lines obtained from the MR analyses are plotted in red (by IVW) and blue (by MR-Egger). BMI, body mass index; IVW, inverse variance weighted; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

analyses identified a causal link for obesity on risk of psoriasis. This study has value as one of the initial successful examples of transethnic MR analysis. Epidemiological studies have pointed to a link between higher BMI and increased incidence or severity of psoriasis (Greb et al., 2016; Naito and Imafuku, 2016), with which our MR analysis results were concordant. Moreover, because our study validated causality (i.e., directional link) of obesity on psoriasis, interventional improvement of obesity itself could be a promising treatment strategy toward better management of psoriasis. Further application of the MR analysis of psoriasis to a wider range of phenotypes, as well as validations in additional ethnicities, is warranted.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2018.11.023.

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