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Association Between Atopic Dermatitis and Major Cardiovascular Outcomes: a Two-Sample Mendelian Randomization Study

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ABSTRACT

Introduction: Atopic dermatitis (AD) has been linked to cardiovascular disease (CVD) in population-based studies, however, their causal relationship is still unclear.

Objectives: To evaluate the causal association of AD with risk of cardiovascular outcomes using a Mendelian randomization (MR) approach.

Methods: We extracted summary-level data for AD, stroke, heart failure, coronary artery disease (CAD), myocardial infarction, angina pectoris from published, nonoverlapping genome-wide association studies (GWAS). Inverse variance weighted (IVW) method was used as the primary analysis. Alternative methods, including weighted median, MR Egger, MR-Pleiotropy Residual Sum and Outlier, weighted mode, and leave-out analysis, were performed to examine potential pleiotropy.

Results: Thirteen SNPs (13,287 cases and 41,345 controls) were selected as instrumental variables (IVs). No associations of AD with risks of stroke (odds ratio [OR] = 1.03, 95% confidence interval [CI]: 0.97-1.09, P = 0.3630), heart failure (OR = 1.04, 95%CI: 0.99-1.09, P= 0.119), coronary artery disease (OR = 1.00, 95%CI: 0.96-1.05, P = 0.988), myocardial infarction (OR = 1.00, 95%CI: 1.00-1.00, P = 0.322), and angina pectoris (OR = 1.00, 95%CI: 1.00-1.00, P = 0.369) was found. No significant effect of pleiotropy was detected.

Conclusions: This MR study does not support a causal effect of AD on stroke, heart failure, CAD, myocardial infarction, angina pectoris.

Introduction

Atopic dermatitis (AD, atopic eczema, eczema) is a common chronic, inflammatory, relapsing, skin diseases [1]. The prevalence of AD is 15 to 20% among children

And 7% to 14% among adults [2,3]. It is characterized by eczematous lesions, varying degrees of pruritus, and a chronic or relapsing disease course [4]. AD broadly decreases health-related quality of life [5].

Recently, there has been a growing interest in the putative cardiovascular comorbidities of AD in population-based observational studies [6-11]. However, owning to the nature of being susceptible to potential confounders and reverse causation in observational study design [12], it remains unclear whether the elevated risk of CVD in patients with AD is caused by AD or introduced by confounding factors of AD and CVD. Understanding the causal relationship between AD and CVD could have implications for appropriate identification, clinical surveillance, and management of high-risk population. Mendelian randomization (MR) analysis is a novel epidemiological approach to assess the causal relationship between an exposure and an outcome [12], with less susceptibility to unmeasured confounders and reverse causation by using genetic variants (i.e., single nucleotide polymorphisms, SNPs) as instrumental variables (IVs) [13,14].

Objectives

In this study, we explored the causal associations between AD and CVD events using the MR method.

Methods

We carried out a two-sample MR analysis based on summary statistics to investigate the causal relationship between AD and CVD events including stroke, heart failure, CAD, myocardial infarction, and angina pectoris. Single nucleotide polymorphisms (SNPs) were selected as instruments variables because they are randomly allocated and less probable to be affected by confounding or reverse causation[15]. We used publicly available data, informed patients consents and ethical approvals were available in original genome-wide association studies (GWAS) studies.

Data Sources and Selection of SNPs

Summary-level data for AD were extracted from the EArly Genetics and Lifecourse Epidemiology (EAGLE) eczema consortium, including 13,287 cases and 41,345 controls of mostly European ancestry [16]. Summary-level data stroke were extracted from the MEGASTROKE Consortium, a meta-analysis of 29 GWAS including a total of 40,585 cases and 406,111 non-cases of European ancestry [17]. Summary-level data for heart failure were extracted from the Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) Consortium [18], comprising 47,309 cases and 930,014 non-cases of European ancestry across 26 studies. Summary-level data for CAD from UKBiobank-CardioMetabolic-Consortium CHD working group included 10801 cases and 137914 non-cases of European ancestry [19]. Summary-level data for myocardial infarction from UKBiobank included 4837 cases and 332,362 non-cases of European ancestry. Summary-level data for angina pectoris from UKBiobank included 4,837 cases and 332,362 non-cases of European ancestry.

Statistical Analysis

For each CVD outcome, we carried out two-sample MR analysis to estimate the causal effect of AD, using the "TwoSampleMR" package of R. The inverse-variance weighted (IVW) linear regression was conducted as the primary analysis. IVW is an efficient analysis method which assumes that all genetic variants are valid IVs, and that there is no horizontal pleiotropy [20]. We calculated the odds ratio (OR) with 95% confidence interval (CI) and created the SNP effect scatter plot.

Besides, we assessed the potential violations of the assumptions of MR analysis by performing a number of complementary sensitivity analysis: weighted median approach for examining result robustness when some instruments may be potentially invalid [20], MR-Egger regression for evaluating the directional pleiotropy of instruments [21,22], weighted mode, which generally has low bias and low Type 1 error rate inflation [23], MR Pleiotropy RESidual Sum and Outlier (MR PRESSO) for outlier instrument detection [24], and leave-one-out analysis to evaluate whether the MR estimate was influenced by single proxy SNP. We also calculated the Cochran Q test from the IVW analysis to examine potential horizontal pleiotropy.

All statistical analyses were performed using R software 4.0.3 (R Foundation for Statistical Computing). All statistical tests were two-sided with $\alpha=0.05$.

Results

Genetic Instruments

Thirteen SNPs were identified as associated with AD ($P<5\times10^{-8}$), with independent inheritance ($r^2<0.01$), and without linkage disequilibrium (LD) in summary statistics. All of these 13 SNPs were available in GWAS for stroke, heart failure, CAD, myocardial infarction, angina pectoris. Details of the included SNPs are shown in Tables S1, Tables S2, S3, S4, and S5 respectively.

Two-sample MR of AD and CVD

No significant evidence was found for a causal effect of AD on stroke, heart failure, CAD, myocardial infarction, angina pectoris using the IVW analysis (stroke: OR = 1.03, 95%CI: 0.97-1.09, P = 0.363; heart failure: OR = 1.04, 95%CI: 0.99-1.09, P = 0.119; CAD: OR = 1.00, 95%CI: 0.94-1.06, P = 0.961; myocardial infarction: OR = 1.00, 95%CI: 1.00-1.00, P = 0.322; angina pectoris: OR = 1.00, 95%CI: 1.00-1.00, P = 0.369). The results neither weighted median, MR Egger, weighted mode nor MR PRESSO analyses were significant for all of the diseases above (Table 1 and Figures S1, S2, S3, S4, S5).

Leave-one-out analysis indicated no influence of single SNP on the risk estimates of AD on stroke, heart failure, CAD, myocardial infarction, angina pectoris. P values of Cochrane Q test and MR Egger intercept for AD on stroke were 0.481 and 0.695, respectively; for AD on heart failure were 0.150 and 0.224, respectively; for AD on CAD were 0.146 and 0.583, respectively; for AD on myocardial infarction were 0.417 and 0.993, respectively; for AD on angina pectoris were 0.080 and 0.752, respectively, suggesting no evidence of potential horizontal pleiotropy and heterogeneity.

Conclusions

To the best of our knowledge, this is the first study to explore the causal relationship between AD and CVD based on an MR approach. Our results did not support a causal effect of AD on CVD.

Previous studies on the link between AD and stroke are controversial. In a Danish matched cohort study, patients with severe AD had an increased risk of ischemic stroke, but after adjustment for socioeconomic status, smoking, comorbidities, and medication use, the risk was similar with controls [6]. In a cohort from the Nurses' Health Study 2, the risk of stroke was significantly increased in female nurses with AD in the age and models adjusted for demographic, lifestyle risk factors, family history of MI, and

Table 1. The Causal Effect of Atopic Dermatitis on Stroke

Type of CVD	Method	OR (95% CI)	P Value	No. of SNPs
Stroke	IVW	1.03 (0.97-1.09)	0.363	13
	Weighted median	0.99 (0.92-1.05)	0.681	13
	MR Egger	0.96 (0.79-1.17)	0.694	13
	Weighted mode	0.97 (0.88-1.07)	0.529	13
	MR PRESSO	1.01 (0.96-1.06)	0.659	13
Heart failure	IVW	1.04 (0.99-1.09)	0.119	13
	Weighted median	1.05 (1.00-1.11)	0.069	13
	MR Egger	1.13 (0.98-1.30)	0.110	13
	Weighted mode	1.06 (0.98-1.14)	0.176	13
	MR PRESSO	1.04 (0.99-1.09)	0.145	13
Coronary artery disease	IVW	1.00 (0.96-1.05)	0.988	13
	Weighted median	0.99 (0.94-1.05)	0.760	13
	MR Egger	0.96 (0.84-1.10)	0.608	13
	Weighted mode	0.98 (0.90-1.07)	0.654	13
	MR PRESSO	1.00 (0.96-1.05)	0.988	13
Myocardial infarction	IVW	1.00 (1.00-1.00)	0.322	13
	Weighted median	1.01 (1.00-1.00)	0.789	13
	MR Egger	1.00 (1.00-1.00	0.724	13
	Weighted mode	1.00 (1.00-1.00)	0.574	13
	MR PRESSO	1.00 (1.00-1.00)	0.328	13
Angina pectoris	IVW	1.00 (1.00-1.00)	0.369	13
	Weighted median	1.01 (1.00-1.00)	0.416	13
	MR Egger	1.00 (1.00-1.00)	0.992	13
	Weighted mode	1.00 (1.00-1.00)	0.627	13
	MR PRESSO	1.00 (1.00-1.00)	0.386	13

CI = Confidence interval; CVD = cardiovascular disease; IVW = inverse variance–weighted; MR = mendelian randomization; OR = odds ratio; SNP = single-nucleotide polymorphism.

postmenopausal hormone replacement use. However, after further controlling for hypertension, hypercholesterolemia, and diabetes, the association between AD and stroke was no longer significant [7]. In a Swedish nationwide case-control study, only severe AD was associated with ischemic stroke [8]. A cross-sectional study conducted among primary care and community settings patients found only adult patients with moderate to severe AD was significantly associated with higher prevalence rates of prior stroke compared to the control: 4.4% versus 2.4% [25]. In a large population-based study including three surveys in US, AD was not associated with stroke in NHANES 2005-2006, but was significantly associated with higher odds of stroke in NHIS 2010 and 2012 in crude models and multivariate models adjusted for demographic, lifestyle factors, hay fever and asthma [9]. A population-based cohort study with data from the UK Clinical Practice Research Datalink reported very modest association between AD and stroke in adjusted models, and the associations were considerably stronger in patients with severe or active AD [10]. Two recent large German studies also found no association between AD and stroke [26,27]. Moreover, a large Canadian cohort even found AD was associated with lower risk of stroke in adjusted model [28].

Though there are only few studies on the link between AD and heart failure, the results are still inconsistent. An US cross-sectional inpatient study reported a significant relationship between AD and heart failure [29]. A cohort study also found positive association between AD and heart failure [10].

CAD is a cause of major morbidity and mortality worldwide. It includes stable ischemic heart disease, MI and unstable angina [30]. Several studies provided estimates for the association of AD with the risk of CAD. The abovementioned study conducted by Silverberg et al. showed AD was associated with significantly higher odds of CAD, the associations attenuated but remained significant in the three adjusted models [9]. But Kwa et al. study reported AD was not significantly associated with CAD [29]. Findings about associations between AD and angina were also mixing. Standl et al. and Silverwood et al. reported a significantly positive association between AD and angina [10,26]. However, AD was not found to be significantly associated with angina in NHANES [9]. The situation is similar to MI. There is a significant association between AD and MI in NHANES, but after controlling risk factor of CVD, the association did not remain significant [9]. Studies of Drucker et al. and Standl et al. also suggested no evidence of the association between AD and MI [7,26,28]. However, Silverwood et al., the NHIS 2010, and a recent cross-sectional study suggested AD was associated with an increased risk of MI, even adjusted for potential confounding factors [9,10,31]. AD and CVD related studies are shown in Table S6.

There are some limitations to the present study. First, the summary-level GWAS data we used were based mainly on people of European ancestry. Therefore, results in this study may not be applicable to other populations. Second, onset age and disease severity of AD might influence the association between AD and comorbidities, but because the limitation of data, we were not able to perform subgroup analyses by age and severity of AD. Third, an important limitation for MR study is potential pleiotropy. In this study, we applied various MR approaches to test for potential pleiotropy, and no evidence of pleiotropy for all the analyses was observed. Moreover, the definitions of AD and comorbidities used in the data is a mixture of self-reported diagnosis together with doctor diagnosed cases, which may cause bias to our findings.

Conclusion

In conclusion, MR study does not support a causal effect of AD on stroke, heart failure, CAD, myocardial infarction, angina pectoris.

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