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ORIGINAL RESEARCH

The Effect of Epigenetic Age Acceleration on Atopic Dermatitis: A Mendelian Randomization Study

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Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin disorder with a complex etiology involving genetic and immune factors. Emerging evidence suggests that epigenetic age acceleration, measured by DNA methylation clocks, may contribute to immune dysregulation and aging-related processes. However, the causal link between epigenetic age acceleration and AD remains unclear.

Methods: We conducted a two-sample Mendelian randomization (MR) analysis to evaluate the causal association between epigenetic age acceleration and AD. Summary statistics were obtained from the FinnGen consortium (394,476 AD cases and 421,381 controls) and a large genome-wide association study meta-analysis of epigenetic age acceleration in 34,710 European participants. Genetic instruments were constructed for four widely used epigenetic clocks: HannumAge, HorvathAge, PhenoAge, and GrimAge. Causal estimates were primarily derived from inverse variance weighted analysis, complemented by MR-Egger regression, weighted median, and weighted mode approaches. Sensitivity analyses included Cochran's Q test, MR-Egger intercept, MR-PRESSO, and leave-one-out tests.

Results: Genetically predicted AD was positively associated with HannumAge acceleration (IVW, p = 0.046, 95% CI: 0.003–0.276), with no evidence of heterogeneity or pleiotropy. No significant associations were observed between AD and HorvathAge, PhenoAge, or GrimAge. Reverse MR analysis did not reveal a causal effect of epigenetic age acceleration on AD. Sensitivity analyses confirmed the robustness of the findings.

Conclusion: This study provides genetic evidence that AD is causally related to acceleration of HannumAge, suggesting a potential role of immune system aging in AD pathogenesis. These findings highlight epigenetic aging as a novel perspective in dermatology and support further research into the mechanisms linking AD, inflammaging, and biological aging. Future studies in diverse populations and mechanistic experiments are warranted to validate and expand upon these results.

Keywords: atopic dermatitis, epigenetic age acceleration, DNA methylation clocks, Hannum age, Mendelian randomization

Introduction

Atopic dermatitis (AD), commonly referred to as atopic eczema, is a chronic inflammatory condition distinguished by the occurrence of recurrent eczematous skin lesions accompanied by severe itching. This persistent pruritus is a hallmark symptom, significantly contributing to the disease burden and impacting the quality of life of affected individuals.[1] Recent epidemiological studies conducted in Europe and the United States report that AD affects nearly 20% of children. In adults, the prevalence exhibits some variation, ranging between 7% and 14%, underscoring the significant public health impact of AD across different age groups.[2] The development of AD is a multifaceted process influenced by various interconnected factors, including genetic predisposition, compromised epidermal barrier function, alterations in the skin microbiome, immune system imbalances, and neuroimmune interactions. These mechanisms collectively drive disease progression.[3–7] Beyond its clinical manifestations, AD represents a significant non-fatal dermatological condition, exerting profound psychological and social impacts on both patients and their families.[8]

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Aging is characterized by a series of progressive biological alterations that accumulate over time, contributing to the onset of diseases and ultimately culminating in mortality. This intricate phenomenon underscores the interplay between genetic, environmental, and molecular factors in determining health outcomes over a lifetime.[9] A panel of common biomarkers has been employed to predict biological age, encompassing epigenetic clocks, telomere length, transcriptomic profiles, proteomic signatures, metabolomic datasets, and composite biomarker-based predictors.[10]

The epigenetic clock has emerged as one of the most promising biomarkers in the field of aging research.[11] This tool enables the evaluation of biological age at the molecular level, with DNA methylation (DNAm) age serving as a key metric. By analyzing specific methylation patterns, researchers can gain insights into the biological processes underlying aging and assess individual age-related changes with high precision.[12] DNA methylation, characterized by the addition of a methyl group to the 5-carbon position of cytosine within CpG dinucleotides, represents a stable yet reversible form of epigenetic modification. Building on the dynamic nature of these epigenetic changes throughout the human lifespan, researchers have developed various epigenetic clocks. These tools enable remarkably precise estimations of biological age, reflecting the complex interplay between genetic and environmental factors over time.[13] The first generation of epigenetic clocks, such as HannumAge and HorvathAge, relies predominantly on CpG sites from blood or tissue samples, together with select biological covariates. In prior studies, HannumAge was classified as "extrinsic" epigenetic age acceleration (EEAA); it now serves as a robust biomarker for immune system aging. Importantly, this biomarker explicitly captures hallmarks of immune senescence—including age-dependent changes in blood cell counts—and correlates with lifestyle factors and health-relevant phenotypes.[14] By contrast, HorvathAge, previously termed "intrinsic" epigenetic age acceleration (IEAA) in the literature, is a valid marker of cell-intrinsic aging—a property that remains consistent across multiple tissue types, likely due to the conserved epigenetic regulatory pathways underlying intrinsic aging.[15] These clocks excel in accurately predicting chronological age. In comparison, second-generation epigenetic clocks—exemplified by PhenoAge and GrimAge—build on this foundation by incorporating a larger repertoire of CpG sites, along with clinical biomarkers that directly associate with disease and mortality. To develop the PhenoAge metric, researchers integrated data from mortality-associated CpGs and a panel of clinically relevant biomarkers. In parallel, Horvath et al initially defined GrimAge using two key sets of molecules: CpGs robustly linked to smoking exposure, and disease-relevant proteins that serve as proxies for health status.[16,17] This evolution enhances their capability to provide more refined assessments of an individual's susceptibility to age-related health conditions and mortality risk.[18]

Previous research has suggested a potential link between epigenetic age and the development of AD.[19,20] However, it is crucial to recognize that much of this evidence derives from case reports or experimental studies, both of which are susceptible to confounding variables and the influence of reverse causation bias. These methodological challenges may contribute to the observed inconsistencies across study findings, underscoring the need for more robust and comprehensive investigations.

Mendelian randomization (MR) represents a powerful genetic epidemiological method that leverages genetic variations, such as single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to explore potential causal relationships between exposures and outcomes.[21] By relying on the random inheritance of alleles from parents to offspring, this method ensures that fertilization and the establishment of genotypes occur independently of disease status. Consequently, MR is particularly effective in addressing challenges related to confounding bias and reverse causation.

In the present study, we employed MR analysis at the genetic level to examine the causal relationship between epigenetic age and the risk of developing AD. This approach provides valuable insights into the genetic underpinnings of immune-mediated skin conditions.

Materials and Methods

Study Design

To accurately infer the potential causal relationship between AD and epigenetic age through MR analysis, three criteria must be met: (1) genetic variants must be significantly associated with the exposure; (2) when extracted as instrumental variables for the exposure, genetic variants must be independent of other confounding factors; and (3) genetic variants should influence disease outcomes solely through their effect on exposure.[22,23] Figure 1 illustrates the workflow of the MR study. As all data were sourced from publicly accessible open databases, ethical review was not required.

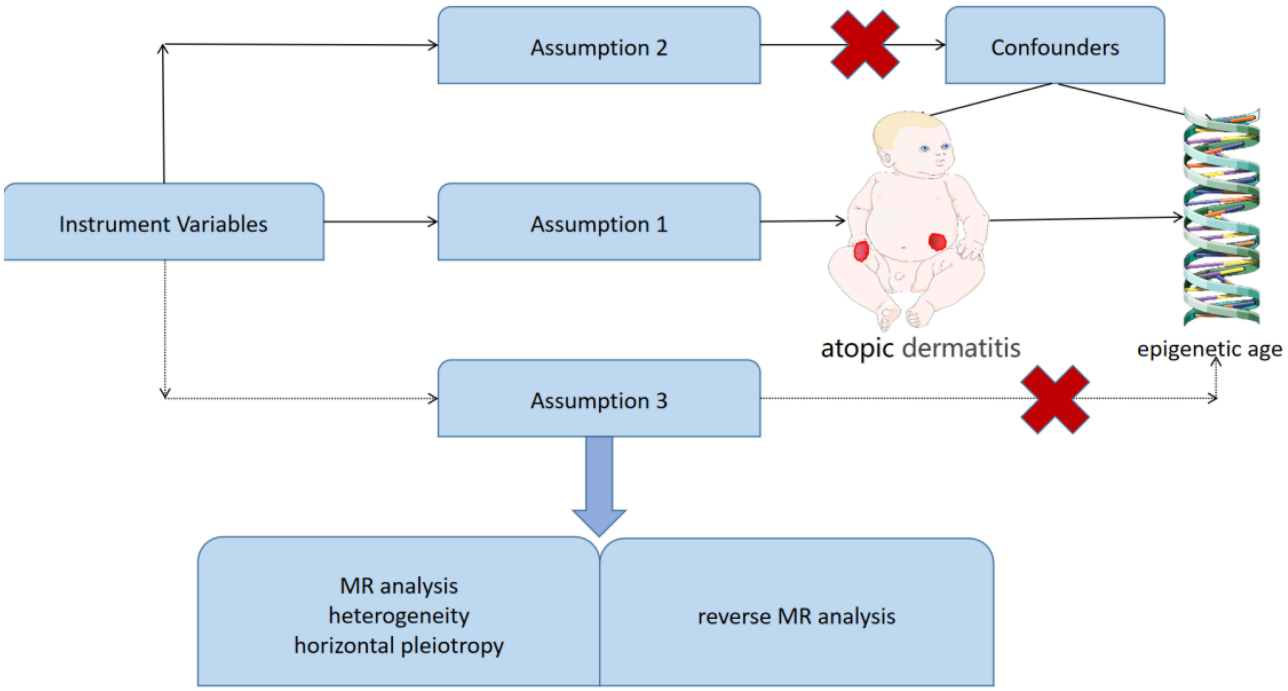

Figure 1 Flowchart of the MR study between AD and epigenetic age acceleration.

Data Sources

Public summary statistics from GWAS were obtained to conduct our MR analysis. Summary statistics for atopic dermatitis (AD) were obtained from the FinnGen release R11, including 394,476 AD cases and 421,381 controls. AD diagnosis in FinnGen is defined using national health registries based on ICD-10 codes and corresponding ICD-9 codes, supplemented by hospital discharge and prescription records.[24] The Finnish GWAS database is a dedicated bioinformatics platform designed to aggregate and integrate genome-wide association study data specific to the Finnish population. This resource leverages the unique genetic profile of the Finnish demographic, characterized by high homogeneity and distinct regional genetic bottlenecks, making it an ideal cohort for investigating genetic disorders and traits. Epigenetic age data were sourced from the GWAS meta-analysis conducted by McCartney et al.[25] This analysis was based on 28 cohorts comprising 34,710 participants of European ancestry, with ages ranging from 27.2 to 79.1 years (mean age 54.8 years), of whom 57.3% were female. Epigenetic age was calculated using the Horvath epigenetic age calculator software. The study identified 137 DNA biomarker loci associated with aging.

IV Selection

To strengthen the robustness of the MR analyses, genetic IVs for exposures were meticulously selected, adhering to the genome-wide significance threshold of $p < 5 \times 10^{-8}$. Given the potential for linkage disequilibrium (LD) to introduce bias, LD adjustments were applied to ensure the independence of selected SNPs, with parameters set at $r^2 = 0.001$ and a 10,000 kb window. This approach emphasizes the critical importance of rigorous selection criteria and LD adjustment in the construction of genetic instruments, aiming to minimize bias and facilitate accurate causal inferences in genetic epidemiology.[26] Additionally, to improve data quality, palindromic sequences were excluded from the analysis to maintain higher data integrity. To assess potential biases from weak instrumental variables, the proportion of variance explained (R^2) was evaluated, and the F-statistic for each SNP was calculated. Only instrumental variables with an

average F-statistic greater than 10 were retained, establishing a threshold to ensure that the selected instruments were sufficiently robust for reliable causal inference.[27]

Statistical Analysis

To evaluate the causal relationship between AD and epigenetic age acceleration, we employed a MR approach using four distinct methods: Inverse Variance Weighted (IVW) analysis, MR Egger regression, weighted median, and weighted mode.[28–30] The IVW method, utilizing a fixed-effect meta-analysis model to combine causal estimates from individual SNPs, is widely recognized for its reliability and was therefore selected as our primary analytical technique. This comprehensive methodology facilitates a robust assessment of genetic instrumental variables, providing a rigorous causal inference regarding the association between AD and epigenetic age acceleration.[31] The results from the IVW analysis were regarded as the primary outcome, with the other three methods serving as supplementary analyses. A *p*-value of less than 0.05 was considered indicative of a statistically significant association between the exposure and the outcome. The list of SNPs included in the analysis is provided in Supplementary Material 1.

To mitigate potential biases arising from heterogeneity and pleiotropy, sensitivity analyses were performed. Cochran's Q test was utilized to assess heterogeneity in the causal estimates between exposure and outcome, with a p-value less than 0.05 indicating significant heterogeneity. Horizontal pleiotropy was evaluated using the MR-Egger regression intercept, with statistical significance defined at $p < 0.05$. Furthermore, MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) analysis was employed to identify and correct for outliers, thereby providing a critical evaluation of genetic variants that may affect the outcome through pathways other than the primary exposure. This comprehensive approach ensures the robustness and validity of the MR analysis.[32]

Finally, A leave-one-out analysis was additionally performed to assess whether the causal association was driven by any single SNP.

All statistical analyses in this study were conducted using R software (version 4.3.2), with the MR analysis carried out using the TwoSampleMR package (version 0.6.7).

Results

In the MR analysis, we observed a causal relationship between genetically predicted AD and Hannum age ($p = 0.046$, 95% CI 0.003–0.276). Subsequent sensitivity analyses revealed no evidence of heterogeneity or horizontal pleiotropy (Table 1). However, we did not find a significant causal relationship between AD and other epigenetic clocks, as illustrated in Figure 2. The results of the scatter plots are presented in the Supplementary Material 2. The Supplementary Material 3 encompass a leave-one-out sensitivity analysis.

In the reverse MR analysis, the parameters are the same as those shown above, where epigenetic age acceleration was treated as the exposure and AD as the outcome, we did not identify any significant causal associations across the four epigenetic clocks. Sensitivity analyses were consistent with these findings, suggesting no evidence of reverse causality. The results of the reverse analysis are detailed in the Supplementary Materials 4–6.

Table 1 Heterogeneity and Horizontal Pleiotropy Analysis

Outcome	Q	Q_pval	MR-PRESSO Global Test	MR-Egger Intercept	pval	Filtered SNP(s)
HannumAge	61.616	0.126	0.129	−0.011	0.531	NA
GrimAge	71.124	0.026	0.024	−0.006	0.758	NA
PhenoAge	72.118	0.0220	0.025	0.0153	0.537	NA
HorvathAge	79.768	0.005	0.007	0.006	0.783	"rs10774624"

Outcome	No.of SNP	Method	BETA(95% CI)	P
HannumAge	51	IVW	0.139 (0.003 to 0.276)	0.046
		MR Egger	0.258 (−0.136 to 0.652)	0.205
		Weighted median	0.093 (−0.101 to 0.286)	0.348
		Weighted mode	0.042 (−0.274 to 0.357)	0.797
GrimAge	51	IVW	0.134 (−0.015 to 0.283)	0.079
		MR Egger	0.199 (−0.238 to 0.635)	0.377
		Weighted median	0.110 (−0.095 to 0.316)	0.292
		Weighted mode	0.100 (−0.251 to 0.450)	0.579
PhenoAge	51	IVW	0.082 (−0.109 to 0.273)	0.399
		MR Egger	−0.085 (−0.645 to 0.475)	0.767
		Weighted median	0.182 (−0.060 to 0.424)	0.141
		Weighted mode	0.321 (−0.108 to 0.749)	0.148
HorvathAge	51	IVW	0.097 (−0.063 to 0.257)	0.236
		MR Egger	0.035 (−0.430 to 0.500)	0.883
		Weighted median	0.144 (−0.055 to 0.343)	0.156
		Weighted mode	0.256 (−0.135 to 0.648)	0.205

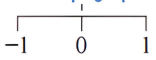

Figure 2 Forest plot of MR analysis (95% CI, 95% confidence interval; $P < 0.05$ was considered statistically significant).

Discussion

In this study, we explored the relationship between AD and epigenetic age acceleration from a Mendelian randomization perspective and identified a positive correlation between AD and Hannum Age. Conversely, the reverse MR analysis did not reveal any significant associations, providing a novel perspective on the relationship between AD and epigenetic age acceleration.

AD is typically characterized by inflammatory dermatitis and involves a complex pathophysiological process, including epidermal barrier dysfunction, alterations in the skin microbiome, and immune dysregulation.[33]

One of the primary functions of Hannum Age is its ability to mirror the natural, age - associated alterations in blood cell composition, which are hallmarks of immune system deterioration. As individuals age, the immune system undergoes a series of well - characterized changes, including shifts in the relative proportions of different blood cell types. For instance, there is a decrease in the number of naive T cells and an increase in memory T cells, along with alterations in the function and number of B cells, monocytes, and neutrophils. Hannum Age captures these changes, providing a comprehensive reflection of the immune system's aging process.[14]

A variety of biological mechanisms have been implicated in the process of aging driven by AD. Among these, the contribution of epigenetic modifications has gained significant attention, as they are increasingly acknowledged as a fundamental basis for the development and persistence of inflammation.[19] Numerous prior investigations have identified a significant link between DNA methylation patterns and the pathogenesis of AD.

As a long-standing inflammatory condition, AD is marked by continuous stimulation of the innate immune response. This dysregulation results in an increased production of pro-inflammatory cytokines in the circulatory system, notably TNF-α, IL-1β, and IL-6, which play critical roles in sustaining the inflammatory state characteristic of the disease.[34]

The impact of genetic variations in human leukocyte antigens (HLA) on the development of allergic diseases is a critical area of investigation. These variations are widely recognized for their significant role in influencing susceptibility to a range of allergic conditions, highlighting their importance in understanding the underlying genetic mechanisms of such disorders.[35] Interestingly, genetic variations in HLA-DQB1 have been associated with the regulation of lipid metabolism. This connection suggests a potential pathway through which these genetic differences might contribute to variations in lifespan, emphasizing the broader implications of HLA-DQB1 in metabolic and longevity-related processes.[36]

A genome-wide methylation analysis, comparing 12 AD patients to 6 healthy individuals, identified substantial disparities in methylation profiles between the two groups.[20] This finding aligns with further research by Rodríguez et al, which highlights pronounced differences in methylation and epigenetic modifications in AD. Notably, their study demonstrated that the methylation patterns at numerous CpG sites within the lesional epidermis of AD patients were markedly distinct from those observed in healthy counterparts.[37] Furthermore, localized to chromosome 1q2, the filaggrin (FLG) gene undertakes the role of encoding FLG (filaggrin protein)—a primary structural protein residing within the stratum corneum (SC).[38] A well-validated finding across dermatological and genetic studies is that FLG null mutations impair skin barrier integrity and increase the predisposition to AD.[39] Findings from research indicate that DNA methylation of the FLG gene plays a role in augmenting the susceptibility to eczema associated with loss of function variants,[40] this phenomenon may be attributed to the combined effects of genetic variants within the FLG genomic region and adjacent differential DNA methylation.[41]

While our findings reveal the association between AD and epigenetic age acceleration in a large population, several limitations should be acknowledged. First, our cohort study and MR analysis were conducted solely in European populations, so caution is warranted when generalizing these findings to other ethnic groups. Second, the lack of detailed clinical information—such as sex, age, and disease severity—limited our ability to perform subgroup analyses. Third, although we identified a statistically significant causal effect of AD on HannumAge acceleration ($p = 0.046$), this association is borderline. Importantly, our heterogeneity and sensitivity analyses, including MR-Egger intercept and MR-PRESSO, did not reveal evidence of pleiotropy or instability, lending support to the robustness of the result. Nevertheless, as multiple epigenetic clocks were tested, the possibility of type I error after correction for multiple comparisons cannot be excluded. Thus, replication in independent cohorts and further mechanistic studies are warranted to validate this observation. Finally, while we established an association between AD and epigenetic age acceleration, the precise mechanisms underlying this relationship remain to be further explored.

Conclusion

In conclusion, our Mendelian randomization analysis suggests a possible causal relationship between atopic dermatitis and acceleration of HannumAge, an epigenetic marker reflecting immune system aging. However, this association was borderline significant ($p=0.046$) and may be influenced by multiple testing considerations. No robust evidence was found for other epigenetic clocks, and reverse MR analyses did not support a causal effect of epigenetic age acceleration on AD. These findings should therefore be interpreted with caution. While the results provide preliminary genetic evidence linking AD with accelerated immune-related aging, further replication in independent cohorts, validation in diverse populations, and mechanistic studies are needed to clarify the biological relevance of this relationship and its potential implications for AD pathogenesis and management.

Ethics Statement

According to Article 32 of the Ethical Review Measures for Life Science and Medical Research Involving Human Beings of the People's Republic of China, the data used in this study will not cause any form of harm to human beings, nor will it involve sensitive personal privacy or trade secrets; therefore, ethical review can be exempted. Furthermore, the databases applied in this study are publicly and legally available. No original data were collected, and no direct involvement with study participants occurred. All data is publicly available in public databases.

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Disclosure

All authors declare no conflicts of interest in this work.

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