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Evidence of a Causal Relationship Between Body Mass Index and Immune-Mediated and Inflammatory Skin Diseases and Biomarkers: A Mendelian Randomization Study

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Aim: Increasing observational studies are revealing a positive correlation between body mass index (BMI) and the risk of Immune-mediated and Inflammatory Skin Diseases (IMID), however the causal relationship is not yet definite.

Objective: The aim of the study was to conduct a two-sample Mendelian randomization (TSMR) to explore the potential causality between BMI, and IMID and biomarkers.

Methods: The summary statistics for BMI (n = 322,154), at genome-wide significant level, were derived from the Genetic Investigation of Anthropometric Traits consortium (GIANT). The outcome data for IMID (Psoriasis, vitiligo, Atopic dermatitis (AD), acne, Bullous diseases, Dermatitis herpetiformis, Systemic lupus erythematosus (SLE), Alopecia Areata (AA), Hidradenitis suppurativa (HS) and Systemic sclerosis), and biomarkers were obtained from genome-wide association studies (GWAS). The TSMR analyses were performed in four methods, including inverse variance weighted (IVW) method, MR-Egger regression, the weighted median estimator (WME) and simple mode.

Results: The IVW analysis showed that the per standard deviation (SD) increase in BMI increased a 57% risk of psoriasis. We also observed the suggestive evidence of a causal relationship between BMI and AD and HS. This analysis did not support causality of Vitiligo, Acne, Bullous pemphigoid, Dermatitis herpetiformis, SLE, AA and Systemic sclerosis. The higher risk of BMI may be explained by higher levels of Triglycerides, C-reactive protein (CRP), Interleukin 6, Erythrocyte sedimentation rate (ESR) and Neutrophil count. The high-density lipoprotein (HDL) has an inverse relationship with BMI. No influences were defined for Total cholesterol, low-density lipoprotein (LDL), Rheumatoid factor (RF), Basophil count and Eosinophil count.

Conclusion: Our two-sample MR analysis proved the causal evidence for the associations between BMI and IMID, including psoriasis, AD and HS, which might be related to the elevated expression of biomarkers, including Triglycerides, CRP, Interleukin 6, ESR and neutrophil count.

Keywords: Mendelian randomization, BMI, immune-mediated and inflammatory skin diseases, biomarkers, causal association

Introduction

In the last 10 years, basic research has increasingly revealed the immunological mechanisms of immune-mediated and inflammatory skin diseases (IMID), including Psoriasis, vitiligo, Atopic dermatitis, acne, Bullous diseases, Dermatitis herpetiformis, Systemic lupus erythematosus, Alopecia Areata, Hidradenitis suppurativa and Systemic sclerosis, which share a chronic inflammatory background of the skin. The therapeutic management of IMID involves extraordinary long-term disease control, accompanied by the emergence of problems.[1]

Obesity has become one of the leading health issues of the 21st century, with over one-quarter of the United Kingdom population now obese and similarly high obesity levels in many other parts of the world.[2] The body mass index (BMI) is

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an objective way to define obesity, which is calculated by dividing a person's weight in kilograms by the square of height in meters.

Researchers have found that obesity causes alterations in skin physiology that predisposes obese individuals to the development of various skin manifestations and diseases, such as many inflammatory skin diseases.[3] The possible mechanisms of this predisposition are the association of obesity with a proinflammatory state, decreased cell-mediated immune responses.[4] Obesity also affects skin barrier integrity and increases the sebum and sweat production.[5–7] A clearer understanding of the cutaneous and systemic metabolic effects associated with obesity and IMID is important to enact treatment and prevention strategies for these patients.

As we all know, many biomarkers, especially inflammatory markers, were proved to be related to IMID and obesity. Researchers found that obesity was associated with higher levels of CRP, and bariatric surgery could reduce CRP levels.[8] In addition, a study[9] showed that CRP was valuable to identify the severity and activity of Hidradenitis suppurativa patients. It was proved that adipose tissue could produce proinflammatory cytokines, Interleukin 6, which might exacerbate psoriasis.[10] It was analyzed that Cutibacterium acnes could cause a large raising in primary lipids, including triglycerides.[11] Obesity was inferred to be associated with reduced bacterial diversity, leading to skin colonization with lipophilic bacteria and intestinal colonization with pro-inflammatory species, which induced the severity of Atopic dermatitis symptoms.[12] A statistical significant relationship[13] was explored between psoriasis severity and inflammation biomarkers including CRP and ESR.

However, it should be noted that the observed associations could not be well determined due to the limitations of conventional statistical methods, namely potential confounders either or both reverse causalities.

Recently, mendelian randomization (MR) has been widely used to resolve these limitations, assessing the potential causal relationships between various exposures and clinical outcomes.[14] MR could avoid systematic biases by selecting genetic variants associated with exposure as instrumental variables (IVs), analogous to randomized controlled trials (RCT), and alleles are assigned randomly at conception according to Mendel's second law.[15]

Based on the increasing genome-wide association studies (GWASs) in the past decade, other studies already used MR to explore the causal relationships between BMI and IMID, such as psoriasis[16] and atopic dermatitis.[17] Nevertheless, the evidence for the effects of BMI on IMID and biomarkers is still limited and unclear, which requires the further exploration of causality.

In this case, we conducted the two-sample MR analysis to answer the two key questions: (1) what is the causal association of BMI and immune-mediated and inflammatory skin diseases: negatively, neutrally, or positively? (2) what is the influence of BMI on biomarkers?

Materials and Methods

Workflow Design

The flow chart of the research design, and the three key assumptions of MR are shown in Figure 1 as followings: (A) single nucleotide polymorphisms (SNPs) are strongly related to body mass index; (B) SNPs are isolated from known confounders; (C) SNPs only influence IMID and biomarkers via BMI (Figure 1).

Data Sources

In this article, ethics approval was not required for the current analysis because all included genome-wide association studies (GWAS) data are publicly available and had been approved by the corresponding ethical review boards. Based on this fact, Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University had agreed with exemption from examination application. We searched the published summary-level data from GWAS (https://gwas.mrcieu.ac.uk/) with the primary population of European individuals and included both males and females. GWAS summary statistics for BMI (n = 322,154) were derived from the Genetic Investigation of Anthropometric Traits consortium (GIANT) (https://portals.broadinstitute.org/collaboration/giant/index.php/

GIANT_consortium_data_files., accessed on 28 April 2021) reported by Locke AE et al.[18] The outcome data for Psoriasis (n = 216,752), vitiligo (n = 337,159), Atopic dermatitis (n = 205,764), acne (n = 212,438), Bullous pemphigoid

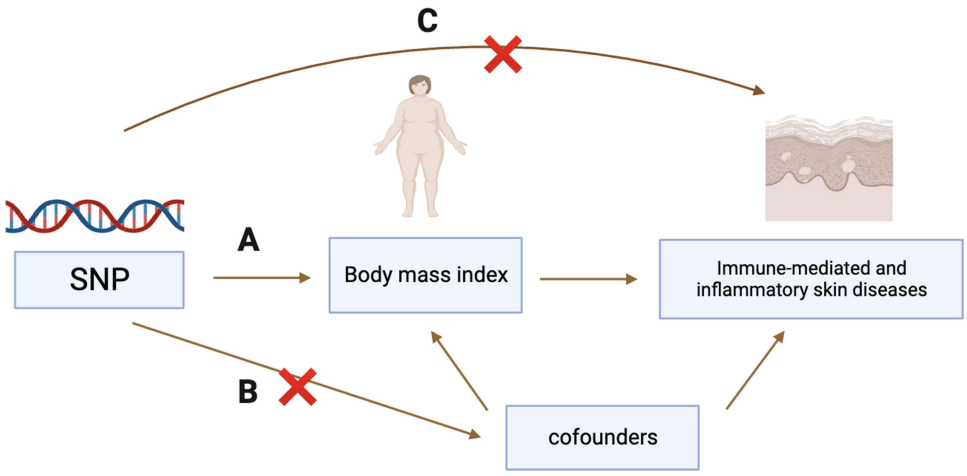

Figure 1 Workflow design overview and assumptions of the Mendelian randomization (MR) design. (**A**) single nucleotide polymorphisms (SNPs) are strongly related to body mass index; (**B**) SNPs are isolated from known confounders; (**C**)SNPs only influence IMID and biomarkers via BMI. SNP: single-nucleotide polymorphism.

(n = 218,285), Dermatitis herpetiformis (n = 218,344), Systemic lupus erythematosus (n = 213,683), Alopecia Areata (n = 211,428), Hidradenitis suppurativa (n = 211,548) and Systemic sclerosis (n = 213,447) were obtained from the Genome Reference Consortium (GRC).

For biomarkers, total cholesterol (n = 187,365), triglycerides (n = 177,861), high-density lipoprotein (HDL, n = 187,167), and low-density lipoprotein (LDL, n = 173,082) were derived from the Global Lipids Genetics Consortium (GLGC) analyzed by Willer CJ et al.[19] C-reactive protein (CRP, n = 61,308) was obtained from the Within family GWAS consortium. Interleukin 6 (n = 3,394) was analyzed by Folkersen et al.[20] Rheumatoid factor (nSNPs = 13,538,539) and Erythrocyte sedimentation rate (n = 213,097), Eosinophil count (n = 6,262) were obtained from the Genome Reference Consortium (GRC). Basophil count (n = 171,846) was reported by Astle WJ et al.[21] Neutrophil count (n = 7,542) was analyzed by Chen MH et al.[22]

Instrumental Variable Selection and Validation of SNPs

The extracted genetic variants were selected as suitable instrumental variables (IVs) to evaluate causal effects of BMI on the risk of IMID according to three criteria: (1) being predictive of BMI, (2) being independent of confounders, and (3) no alteration of the outcome via an independent pathway other than BMI.[23] Then, the independence among the selected SNPs was assessed according to the pairwise-linkage disequilibrium.[24] When r^2 >0.001 (clumping window of 10,000 kb), the SNP correlated with more SNPs or with a higher *p*-value was deleted. When the F-statistic being greater than ten, SNPs were regarded to be powerful enough to alleviate the effects of potential bias.[25] Then, we also conducted data-harmonization analysis before the MR analysis, as the effects of an SNP on the exposure and the outcome had to correspond to the identical allele.

Mendelian Randomization Analyses

A random-effects inverse-variance weighted (IVW) meta-analysis was regarded as the primary method to accurately evaluate the correlated influence of the exposure's impact on outcomes when every inherited mutation meets the IV assumptions. IVW uses the Wald Ratio method and conducts a weighted linear regression with a forced intercept of zero.[26]

In addition, for the sensitivity analyses, we conducted the weighted median,[27] MR-Egger,[28] weighted mode and simple mode[29] to assess the strength of the primary IVW estimates to horizontal pleiotropy. We also applied the MR pleiotropy residual sum and outlier (MR-PRESSO)[30] to evaluate potential IV violations. Additionally, a leave-one-out sensitivity analysis for horizontal pleiotropy was conducted to assess the robustness of significant results. If the combined effect is consistent with the major effect analysis result, no single SNP has an excessive influence on the MR analysis. Besides, Cochrane's Q-value was used to suggest heterogeneities among selected IVs.

Bonferroni-corrected thresholds of $p < 0.005$ (α = 0.05/10 outcomes) and $p < 0.0045$ (α = 0.05/11 biomarkers) were employed for IMID outcomes and biomarkers to account for multiple comparisons in univariate MR. Results between the Bonferroni threshold and 0.05 were regarded as suggestive evidence of a potential causal relationship, requiring further validation.

All the MR analysis was performed with R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) using the "Two Sample MR", "MVMR", and "MRPRESSO" packages.

Results

SNP Selection and Validation

In general, we included studies, which were published between 2013 and 2021 with the main population of European and American (Supplementary Table S1). Sixty-nine SNPs of the BMI variation as IVs were extracted for causal estimations, and all F-statistics were greater than ten (Supplementary Table S2). After detecting outliers identified by MR-PRESSO and removing disambiguation and palindromic SNP by harmonizing processes, no single SNP has been picked out, and all of the SNPs were then selected as instrumental variables.

Immune-Mediated and Inflammatory Skin Diseases

The IVW analysis displayed that the BMI per standard deviation (SD) increase was directly significantly associated with a higher risk of psoriasis (odds ratio (OR) = 1.57; 95% confidence interval (CI), 1.21–2.02; $p < 0.001$) (Figure 2). Suggestive evidence of causal relationship between BMI and two of the ten IMID, including Atopic dermatitis (odds ratio (OR) = 1.27; 95% confidence interval (CI), 1.035–1.55; $p = 0.022$) and Hidradenitis suppurativa (odds ratio (OR) = 2.74; 95% confidence interval (CI), 1.32–5.71; p = 0.007), was also observed (Figure 2). Conversely, the MR estimates for BMI did not support causal relationship with Vitiligo, Acne, Bullous pemphigoid, Dermatitis herpetiformis, Systemic lupus erythematosus, Alopecia Areata and Systemic sclerosis (Figure 2).

For most IMID, the weighted-median and MR-Egger analyses suggested consistent estimates but of low precision (Table 1). Additionally, no evidence of directional pleiotropy was identified. Therefore, an IVW meta-analysis under a random-effects model was applied to mitigate the influence of heterogeneity.

Consistent results can be observed in the scatter plot and forest plot of the causal association between BMI and IMID, which were displayed in Supplementary Figure S1 and Supplementary Figure S2, separately. The leave-one-out sensitivity analysis (Supplementary Figure S3) proved that any individual SNP could not disproportionately affect the overall estimates. In addition, no evidence of horizontal pleiotropy was observed in the funnel plot (Supplementary Figure S4).

Biomarkers

The IVW analysis showed that the BMI per standard deviation (SD) increase was directly significantly associated with a higher risk of triglycerides (effect estimate = 0.2; 95% CI, from 0.15 to 0.26; $p < 0.001$), CRP (effect estimate = 0.21; 95%

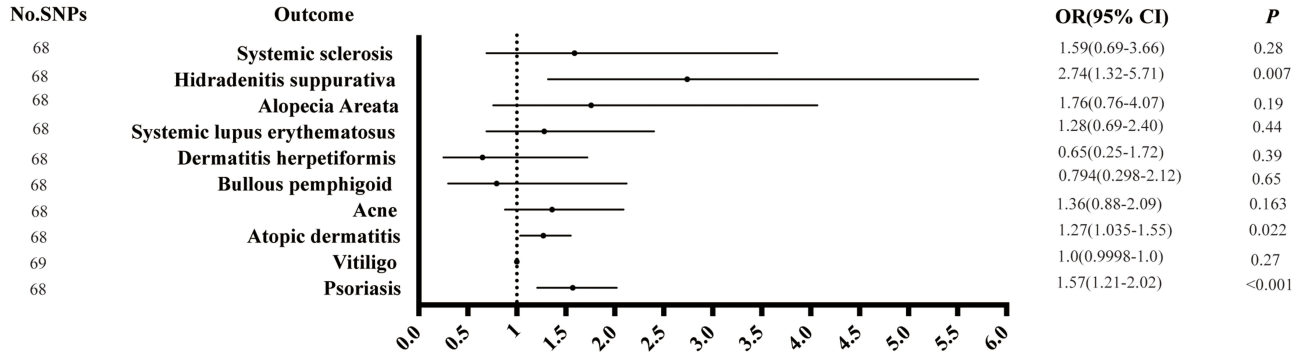

Figure 2 Associations of BMI with IMID. The outcome of IVW meta-analysis was used to accurately evaluate the correlated influence of the BMI on IMID.
Abbreviations: IVW, inverse-variance weighted; IMID, Immune-mediated and inflammatory skin diseases; CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.

Table 1 Associations Between Genetically Predicted Body Mass Index and Immune-Mediated and Inflammatory Skin Diseases (IMID) in Sensitivity Analyses Using the Inverse Variance Weighted, Weighted-Median and MR-Egger Methods

Outcome	Weighted median		MR Egger		Heterogeneity		Pleiotropy	
	OR (95% CI)	*p*	OR (95% CI)	*p*	Q	*p*	Intercept	*p*
Psoriasis	1.83(1.29–2.61)	<0.001	1.97(0.92–4.23)	0.087	84	0.071	−0.0065	0.535
Vitiligo	1.0(0.9995–1.0)	0.67	1.0(0.999–1.0)	0.55	67	0.976	−4.06E-6	0.809
Atopic dermatitis	1.08(0.81–1.44)	0.6	1.13(0.62–2.05)	0.71	66	0.141	0.003	0.681
Acne	1.07(0.56–2.02)	0.84	0.49(0.14–1.73)	0.27	66	0.278	0.029	0.098
Bullous pemphigoid	0.57(0.13–2.47)	0.45	0.85(0.05–15.71)	0.92	66	0.868	−0.002	0.96
Dermatitis herpetiformis	0.69(0.19–2.57)	0.58	0.56(0.03–10.21)	0.699	66	0.071	0.004	0.917
Systemic lupus erythematosus	1.17(0.46–2.97)	0.73	0.84(0.13–5.43)	0.86	66	0.46	0.012	0.641
Alopecia Areata	1.89(0.55–6.48)	0.31	0.38(0.03–4.57)	0.45	66	0.63	0.044	0.204
Hidradenitis suppurativa	2.42(0.78–7.52)	0.13	1.38(0.16–12.24)	0.77	66	0.339	0.0196	0.514
Systemic sclerosis	2.21(0.62–7.81)	0.22	1.55(0.13–18.9)	0.73	66	0.48	0.0006	0.987

Abbreviations: CI, confidence interval; MR, Mendelian randomization; OR, odds ratio.

CI, from 0.15 to 0.27; $p < 0.001$), Interleukin 6 (effect estimate = 0.44; 95% CI, from 0.17 to 0.7; p=0.001), ESR (effect estimate = 0.72; 95% CI, from 0.26 to 1.17; p=0.002) and Neutrophil count (effect estimate = 0.24; 95% CI, from 0.08 to 0.41; $p = 0.004$) (Figure 3). Table 2 revealed the inverse relationship between BMI and HDL (effect estimate = −0.27; 95% CI, from −0.36 to −0.18; $p < 0.001$). However, no causal associations were observed for Total cholesterol, LDL, RF, Basophil count and Eosinophil count (Figure 3). The weighted-median and MR-Egger analyses revealed similar estimates but of low precision. Meanwhile, no evidence of directional pleiotropy was observed in the majority of biomarkers except for RF (Table 2).

Scatter plot, forest plot, the results of the leave-one-out sensitivity analysis, and the funnel plot of the association between BMI and biomarkers are illustrated in Supplementary Figure S5–Supplementary Figure S7, and Supplementary Figure S8, respectively, where similar results can be detected.

Discussion

In summary, our two-sample MR analysis results revealed that BMI was directly associated with the risk of psoriasis and 1 kg/m increase in BMI is associated with 57% higher odds of PSO. It also unveiled the suggestive evidence of causal relationships between BMI and Atopic dermatitis as well as Hidradenitis suppurativa. These results might be explained by increased Triglycerides, CRP, Interleukin 6, ESR and neutrophil count. Our findings are in accordance with previous

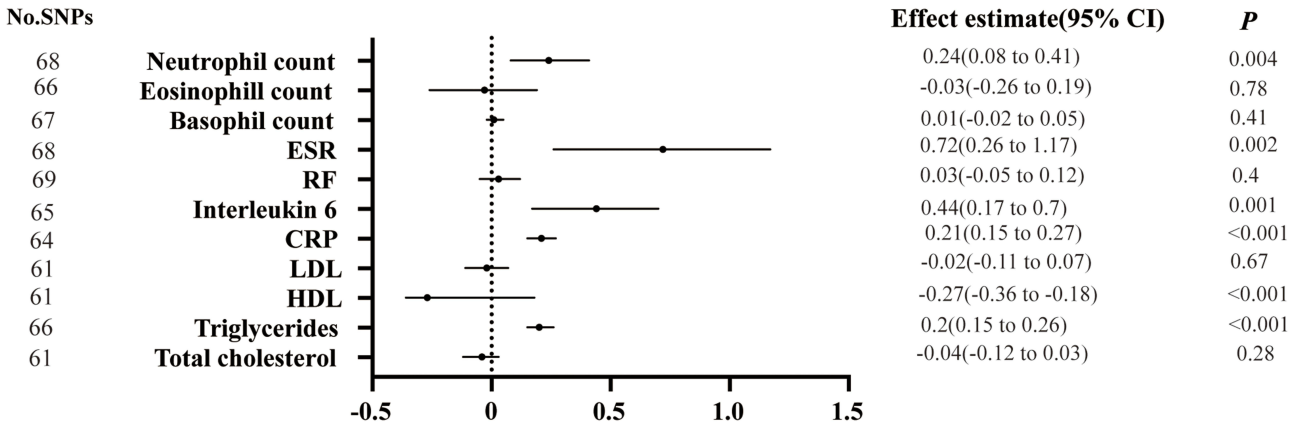

Figure 3 Associations of BMI with IMID immune-makers. The outcome of IVW meta-analysis was used to accurately evaluate the correlated influence of the BMI on IMID immune-makers.

Abbreviations: IVW, inverse-variance weighted; IMID, Immune-mediated and inflammatory skin diseases; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ESR: Erythrocyte sedimentation rate; RF: Rheumatoid factor; CRP: C-Reactive protein; CI, confidence interval; SNP, single-nucleotide polymorphism.

Table 2 Associations Between Genetically Predicted Body Mass Index and Immune-Mediated and Inflammatory Skin Diseases (IMID) Biomarkers in Sensitivity Analyses Using the Inverse Variance Weighted, Weighted-Median and MR-Egger Methods

Outcome	Weighted median		MR Egger		Heterogeneity		Pleiotropy	
	Effect Estimate (95% CI)	*p*	Effect Estimate (95% CI)	*p*	Q	*p*	Intercept	*p*
Total cholesterol	−0.08(−0.15 to −0.01)	0.02	−0.19(−0.41 to 0.03)	0.09	57	<0.001	0.004	0.16
Triglycerides	0.2(0.14 to 0.26)	<0.001	0.13(−0.03 to 0.28)	0.12	62	<0.001	0.002	0.303
HDL	−0.21(−0.28 to −0.14)	<0.001	−0.22(−0.47 to 0.04)	0.097	58	<0.001	−0.002	0.67
LDL	0.008(−0.06 to 0.08)	0.83	−0.14(−0.39 to 0.11)	0.28	58	<0.001	0.003	0.31
CRP	0.17(0.09 to 0.26)	0.0001	0.25(0.07 to 0.42)	0.007	59	1.48	−0.001	0.67
Interleukin 6	0.29(−0.1 to 0.67)	0.15	−0.12(−0.9 to 0.66)	0.76	63	0.38	0.016	0.14
RF	−0.04(−0.16 to 0.09)	0.55	−0.22(−0.46 to 0.02)	0.07	67	0.55	0.007	0.03
ESR	0.53(−0.12 to 1.17)	0.11	0.33(−1.03 to 1.69)	0.64	66	0.31	0.011	0.56
Basophil count	0.02(−0.03 to 0.07)	0.45	0.03(−0.07 to 0.14)	0.52	65	0.49	−0.0006	0.7
Eosinophil count	−0.25(−0.59 to 0.09)	0.15	−0.45(−1.07 to 0.18)	0.17	63	0.84	0.012	0.17
Neutrophil count	0.27(0.04 to 0.5)	0.02	−0.01(−0.51 to 0.49)	0.96	65	0.98	0.007	0.29

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ESR: Erythrocyte sedimentation rate; RF: Rheumatoid factor; CRP: C-Reactive protein; MR, Mendelian randomization; OR, odds ratio.

observational studies of obesity deteriorating psoriasis,[31] Atopic dermatitis,[32] Hidradenitis suppurativa,[33] alopecia,[34] and so on.

However, MR analysis could provide a more reliable conclusion than observational studies, avoiding the influence of confounders or reverse causalities, based on the random distribution of genotypes in the general population.

More and more children and adolescents are being identified with obesity-associated metabolic problems, which would cause inflammation-related diseases, previously described only in adults.[35] It was revealed that inflammation-related proteins, such as CRP, IL-6, or TNFα, had higher expression level.[36]

It has been proved that obesity could induce psoriasis severity.[37] Immoderation skin adipose tissue leads to hormone secretion and pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNFα) and interleukin 6 (IL-6), which are directly implicated in the pathology of psoriasis.[38] Researchers found that psoriasis shared pro-inflammatory mechanisms with obesity, such as the cytotoxic T-lymphocyte antigen 4 and toll-like receptor 3.[39] Leptin, a hormone largely secreted by adipocytes that inhibits hunger, can increase keratinocyte proliferation and pro-inflammatory protein secretion,[40,41] and adipokines accelerate the metabolism of the stratum corneum and promote keratinocyte activation,[42] which are characteristics of psoriasis.

The severity of atopic dermatitis (AD) is reported to be correlated well with BMI.[43] The sub-clinical systemic inflammation with obesity as well as the immune modulating characteristics of adipokines, such as leptin, resistin, and ghrelin explain plausibly for the increased incidence of AD in patients with obesity.[44,45] As we all known, damage of barrier integrity, such as xerosis and altered transepidermal water loss (TEWL), have been linked to obesity.[6] It is acknowledged that a defective epidermal barrier allows entry of allergen and pathogen, stimulating a Th2 immune response, which initiates the acute AD cutaneous pathology.[46]

Because of larger skin folds and thicker layers of subcutaneous fat, obese patients have more sweat and humid environment could exacerbate local inflammation inducing HS.[47] The pathomechanism might be intrafollicular keratin hydration from skin occlusion, leading to the higher levels of proinflammatory cytokines.[48]

It was hypothesized[49] that adipose tissue-resident macrophages had two different phenotypes, including pro-inflammatory M1 ("classically activated") and anti-inflammatory M2 ("alternatively activated"). Obesity induced a switch from the M2 to the M1 phenotype. Researches revealed that adipose tissue secreted a kind of adipokines named leptin, which could stimulate monocyte proliferation and differentiation in macrophages and modulate the activation of natural killer lymphocytes to disrupt the immune system.[50]

This study has some limitations for that it only reports the lifetime impact of higher BMI on IMID and biomarkers, rather than the specific action of a short-term prevention aiming to reduce BMI in clinical practice. Secondly, the stratified analysis upon gender and age is not performed because of the lack of sufficient information. What is more, the individuals of European and American populations inhibited the popularization to other ancestries. Our MR analysis revealed that the prevention and treatment of IMID might focus on losing weight to influence the biomarkers and pathways in skin. Finally, a two-step MR approach for investigating the potential causal relationships among BMI, biomarkers such as triglycerides, and psoriasis, is necessary. Further future research will focus on how BMI affects biomarkers and, in turn, how these biomarkers mediate the effect of BMI on the risk of psoriasis, which could provide a clearer understanding of the underlying mechanisms.

Conclusion

In summary, our analysis indicated the positive associations between BMI and psoriasis, which might be affected by higher levels of biomarkers, such as Triglycerides, CRP, Interleukin 6, ESR and Neutrophil count. The suggestive relationships between BMI, and Atopic dermatitis as well as Hidradenitis suppurativa, were observed. Thus, our results can provide a guideline for dermatologists to manage obesity in patients with IMID, especially psoriasis, Atopic dermatitis and Hidradenitis to achieve a better prognosis in addition to the traditional pharmacologic or biological treatments.

Abbreviation

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; GWAS, genome-wide association study; IV, instrumental variable; IVW, inverse-variance weighted; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MR, Mendelian randomization; OR, odds ratio; RR, relative ratio; SNP, single-nucleotide polymorphism; ESR, Erythrocyte sedimentation rate; RF, Rheumatoid factor; MID, Immune-mediated and Inflammatory Skin Diseases; SD, standard deviation.

Disclosure

The authors report no conflicts of interest in this work.

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