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Causal Relationship Between Dietary Factor, Chronic Disease and Idiopathic Inflammatory Myopathies: A Two-Sample Mendelian Randomization Study

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Abstract. Idiopathic inflammatory myopathies are rare autoimmune diseases marked by chronic skeletal muscle inflammation and systemic manifestations. Observational links between diet, metabolic traits, and IIM risk may reflect confounding or reverse causation. A two-sample Mendelian randomization study employed germline variants as instruments for 28 dietary exposures (e.g., coffee, red meat, alcohol) from the UK Biobank and the NHGRI-EBI GWAS Catalog, and for obesity, type 1 diabetes, and depression from FinnGen. IIM outcomes comprised two FinnGen dermatomyositis GWASs and two European meta-analyses of myositis and idiopathic pulmonary fibrosis. SNPs reaching $P < 5\times10^{-8}$ were clumped at $r^2 < 0.01$, and outliers were removed via MR-PRESSO. Inverse-variance weighted MR provided primary causal estimates, with MR-Egger, weighted median, and mode-based methods for sensitivity. Heterogeneity and pleiotropy were evaluated by Cochran's Q and the MR-Egger intercept. Genetically predicted coffee consumption was inversely associated with dermatomyositis risk. In contrast, red meat and white wine intake showed positive causal Relationship with IPF. Genetic liability to obesity (OR = 1.25; $P = 1\times10^{-4}$) and type 1 diabetes (OR = 1.18; $P = 3\times10^{-4}$) increased overall IIM susceptibility. No evidence of significant heterogeneity or pleiotropy was observed. These findings support a protective causal role for coffee and harmful effects of high red meat, alcohol consumption, obesity, and type 1 diabetes on IIM risk, highlighting targets for dietary and metabolic interventions.

Keywords: idiopathic inflammatory myopathies, Mendelian randomization, dietary exposures, chronic diseases, coffee consumption

1. Introduction

Chronic low-grade systemic inflammation underlies both the initiation and progression of idiopathic inflammatory myopathies (IIM), a group of rare autoimmune disorders primarily targeting skeletal muscle [1]. Muscle pathology is often accompanied by extramuscular involvement—interstitial lung disease and characteristic cutaneous lesions being the most frequent manifestations [1]. The IIM spectrum encompasses four principal subtypes—dermatomyositis, polymyositis, inclusion-body myositis, and immune-mediated necrotizing myopathy—each defined by distinct clinical and

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histopathological criteria [2]. Although precise etiological triggers remain to be fully defined, current evidence implicates an interplay of genetic susceptibility, aberrant immune responses, and environmental exposures.

Type 2 diabetes, cardiovascular disease, and obesity all exhibit strong associations with chronic, low-grade inflammation and disrupted immune–metabolic homeostasis [3]. In this context, dietary factors have emerged as key, modifiable determinants of these conditions by modulating inflammatory signaling, gut microbiota composition, and metabolic function [4,5]. For example, increased consumption of dietary fiber reinforces intestinal barrier integrity and attenuates systemic inflammation via short-chain fatty acid production [4]. Similarly, supplementation with omega-3 fatty acids has been linked to reductions in circulating inflammatory markers such as C-reactive protein and interleukin-6 [5]. Moreover, both observational investigations and Mendelian randomization analyses targeting gut microbial dynamics suggest that nutritional exposures may alter IIM susceptibility by shaping host immune responses and microbial metabolite profiles [6].

Genetic variants that influence modifiable exposures can serve as unconfounded instruments in causal inference. In Mendelian randomization (MR), alleles associated with an exposure—such as a dietary nutrient—are used as proxies to test for direct effects on disease outcomes. Because these variants are assigned at gamete formation and remain fixed thereafter, MR reduces bias from confounding variables and eliminates reverse-causal interpretations [7]. The two-sample MR approach further leverages GWAS summary data from distinct, large-scale cohorts, thereby increasing statistical precision and enabling independent validation of results [8]. In this study, a two-sample MR framework was applied to quantify the causal influence of selected nutritional exposures and their related chronic-disease traits on IIM susceptibility, with the goal of identifying targets for precision prevention.

2. Methods

2.1. Study design

A two-sample Mendelian randomization (MR) framework was employed to evaluate causal relationships between genetically instrumented dietary exposures, chronic-disease traits, and IIM risk. Three core assumptions underpin this analysis: (1) selected single-nucleotide polymorphisms (SNPs) must exhibit genome-wide significant associations with each exposure ($P < 5 \times 10^{-8}$); (2) genetic instruments must be independent of potential confounders; and (3) any effect on IIM risk should operate exclusively via the specified exposure pathways. Reporting followed the STROBE-MR guidelines for Mendelian randomization studies [7].

2.2. Data sources

Exposure GWAS summary statistics for dietary factors and chronic diseases were obtained from the NHGRI-EBI GWAS Catalog [9] and the FinnGen consortium (accessed on June 12, 2025) in individuals of European ancestry [10]. Dietary exposures included genetically proxied indicators of food and beverage intake from the UK Biobank cohort [11]. Outcome data for IIM comprised two GWAS datasets from FinnGen and two European GWAS meta-analyses: one for myositis susceptibility and one for idiopathic pulmonary fibrosis (IPF), a common dermatomyositis complication, used for external validation (Table 1) [12].

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2.3. Instrumental variable selection

Single-nucleotide polymorphisms (SNPs) associated with each exposure at genome-wide significance ($P<5\times10^{-8}$, $r^2 = 0.01$, kb=10000) were identified via the TwoSampleMR R package . To ensure independence, SNPs were clumped using an r^2 threshold of 0.01 within a 10000 kb window [10]. Instrument strength was evaluated by calculating F-statistics for each variant. After harmonizing effect alleles between exposure and outcome datasets, any SNP demonstrating a genome-wide association with the outcome ($P < 0.05$) was excluded to minimise the risk of reverse causation. Horizontal pleiotropy was further addressed by detecting and removing outlier instruments through the MR-PRESSO global test [13].

Table 1. Summary table of GWAS data sources

Exposure/Outcome	trait	Case	Sample size	First author
	Chronic Diseases			
KRA_PSY_ANXIETY_EXMORE	Anxiety disorders	50486	330460	Kurki, M.I. et.al
F5_BIPO	Bipolar affective disorders	8209	394756	Kurki, M.I. et.al
F5_ALZHDEMENT	Dementia in Alzheimer disease	6741	428053	Kurki, M.I. et.al
F5_DEPRESSION_DYSTHYMIA	Depression or dysthymia	63608	236510	Kurki, M.I. et.al
I9_HYPTENS	Hypertension	137312	316345	Kurki, M.I. et.al
E4_OBESITY	Obesity	27711	425881	Kurki, M.I. et.al
SLEEP	Sleep disorders	57251	391891	Kurki, M.I. et.al
T2D	Type 2 diabetes	71728	369007	Kurki, M.I. et.al
T1D	Type1 diabetes	4526	369007	Kurki, M.I. et.al
	Dietary Factors			
GCST90096893	Overall healthy diet	/	258758	Pirastu N. et.al
GCST90096901	Beef consumption	/	241092	Pirastu N. et.al
GCST90096902	Beer or cider consumption	/	168237	Pirastu N. et.al
GCST90096903	Spread on bread consumption	/	445506	Pirastu N. et.al
GCST90096904	Bread consumption	/	438853	Pirastu N. et.al
GCST90096905	Champagne or white wine consumption	/	175549	Pirastu N. et.al
GCST90096906	Cheese consumption	/	365842	Pirastu N. et.al
GCST90096907	Cooked vegetables consumption	/	435417	Pirastu N. et.al
GCST90096908	Decaffeinated coffee consumption	/	62072	Pirastu N. et.al
GCST90096909	Dried fruit consumption	/	409125	Pirastu N. et.al
GCST90096910	Drink temperature	/	444097	Pirastu N. et.al
GCST90096912	Fresh fruit consumption	/	433186	Pirastu N. et.al
GCST90096913	Ground coffee consumption	/	72276	Pirastu N. et.al
GCST90096914	Instant coffee consumption	/	180764	Pirastu N. et.al
GCST90096915	Lamb consumption	/	189984	Pirastu N. et.al
GCST90096916	Percentage fat in milk consumption	/	411503	Pirastu N. et.al

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Table 1. (continued)

GCST90096917	Non-oily fish consumption	/	318136	Pirastu N. et.al
GCST90096918	Oily fish consumption	/	297881	Pirastu N. et.al
GCST90096919	Pork consumption	/	187202	Pirastu N. et.al
GCST90096920	Poultry consumption	/	399716	Pirastu N. et.al
GCST90096921	Processed meat consumption	/	312220	Pirastu N. et.al
GCST90096922	Red wine consumption	/	211628	Pirastu N. et.al
GCST90096923	Salad consumption	/	422542	Pirastu N. et.al
GCST90096924	Added salt consumption	/	323995	Pirastu N. et.al
GCST90096926	Tea consumption	/	434171	Pirastu N. et.al
GCST90096928	Water consumption corrected for coffee	/	400642	Pirastu N. et.al
GCST90096929	Water consumption	/	445799	Pirastu N. et.al
	IIM Outcomes			
GCST90399720	IPF	6257	947616	Zhou W. et.al
DERMATOPOLY_FG	Dermatopolymyositis	459	341375	Kurki, M.I. et.al
M13_POLYMYO	Polymyositis	261	439424	Kurki, M.I. et.al
GCST90044617	Myositis	437	455911	Jiang L. et.al

2.4. MR analysis

Causal estimates were derived using five complementary methods: inverse-variance weighted (IVW), MR-Egger regression, weighted median, simple mode, and weighted mode approaches. Statistical significance was defined by an IVW P-value < 0.05, provided that the direction of effect was consistent across all sensitivity estimators. The IVW method aggregates SNP-specific ratio estimates by weighting each estimate inversely by its variance, producing unbiased results when all instruments are valid. All analyses—including calculation of odds ratios (ORs) with 95% confidence intervals (CIs)—were performed using the TwoSampleMR R package.

2.5. Sensitivity analyses

Sensitivity analyses assessed heterogeneity, horizontal pleiotropy and SNP-level influence. Cochran's Q-test within the MR-Egger framework quantified heterogeneity; where Q indicated significance, causal estimates were re-computed using a random-effects IVW model. Scatter and funnel plots provided visual inspection of heterogeneity. Horizontal pleiotropy was evaluated via the MR-Egger intercept test.

2.6. Validation MR analysis

Complementary validation analyses were performed using two independent datasets for IIM. In these analyses, outcome data were substituted with large-scale GWAS summary statistics from European cohorts, representing myositis and idiopathic pulmonary fibrosis (IPF) phenotypes. IPF—a common manifestation of autoimmune disease and frequent complication of dermatomyositis—served as an IIM-associated syndrome phenotype. After excluding potential confounders, the corresponding two-sample Mendelian randomization analyses were undertaken. Additional sensitivity analyses were conducted to assess the stability of the causal estimates. These procedures

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enhance external validity and minimize biases arising from sample heterogeneity or population-specific effects.

3. Results

3.1. The causal effects of dietary factor on IIM

To explore the potential causal effect of diet on IIM, the author conducted two-sample Mendelian randomization (MR) analyses using 28 common dietary exposures across four independent GWAS datasets. Soluble coffee consumption showed a consistent and statistically significant protective association across two datasets. In the dermatomyositis dataset, the IVW estimate corresponded to an odds ratio (OR) of 0.0096 (P = 0.0288). Similarly, the polymyositis cohort yielded an OR of 0.0018 (P = 0.0248). Myositis (OR = 0.66; P > 0.05) and IPF (OR = 0.61; P > 0.05) datasets exhibited analogous inverse trends that did not reach significance. Ground coffee intake was also inversely associated with dermatomyositis risk (OR = 0.0051; P = 0.0311), suggesting that habitual coffee consumption may causally reduce IIM susceptibility.

Conversely, beef consumption significantly increased the risk of IIM in the IPF dataset (OR = 770.6, P = 0.0104), although positive associations were observed in the other three cohorts without reaching statistical significance. Similarly, champagne or white wine intake was associated with markedly increased risk only in the IPF dataset (OR = 945.0; 95% CI: 17.5–50940; P = 7.6×10^{-4}), with non-significant trends observed in other cohorts (P > 0.05). In the dermatopolymyositis dataset, red wine, cheese, and dried fruit each showed significant protective associations (ORs = 3.4×10^{-5}, 6.0×10^{-6}, and 0.0340, respectively; all P < 0.05). Although similar protective trends were observed across the other three datasets, none reached statistical significance (P > 0.05). Detailed results are summarized in Table 2 and depicted graphically in Figure 1.

Table 2. Significant causal effect estimates of dietary exposures on IIM derived from Mendelian randomization analyses (nsnp, number of single nucleotide polymorphisms)

Outcome	Exposure	Nsnp	Beta	Standard error	P value
Dermatopolymyositis	Ground coffee consumption	4	-5.282	2.450	0.031
Dermatopolymyositis	Instant coffee consumption	12	-4.647	2.125	0.029
Dermatopolymyositis	Red wine consumption	7	-10.288	4.528	0.023
IPF	Beef consumption	4	6.647	2.595	0.010
IPF	Champagne or white wine consumption	6	6.851	2.034	0.001
IPF	Cheese consumption	11	-6.102	1.933	0.002
IPF	Lamb consumption	15	5.294	2.142	0.013
IPF	Pork consumption	4	6.705	2.652	0.011
Myositis	Cheese consumption	18	-12.004	5.529	0.030
Myositis	Dried fruit consumption	42	-3.382	1.340	0.012
Polymyositis	Instant coffee consumption	12	-6.338	2.824	0.025
Polymyositis	Water consumption corrected for coffee	44	-0.739	0.504	0.142
Polymyositis	Water consumption	57	0.297	0.453	0.512

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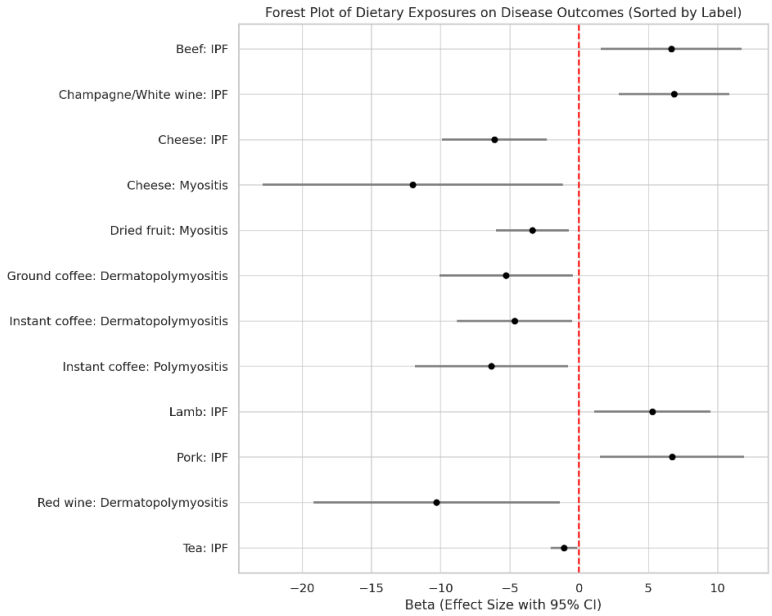


Figure 1. Forest plot illustrates the significant causal effect from Mendelian randomization analyses of dietary exposures on IIM risk

(Picture credit: Original)

3.2. Sensitivity analyses of dietary factor in IIM

Across all four IIM outcome datasets and 28 dietary exposures, MR-Egger intercept tests yielded $P > 0.05$, indicating absence of directional pleiotropy. Likewise, Cochran's Q statistics were non-significant ($P > 0.05$), consistent with homogeneity of instrument–outcome associations. Scatter plots indicated linear SNP–exposure versus SNP–outcome associations, while funnel plots were symmetrical and free of apparent outliers. Leave-one-out analyses confirmed that the exclusion of any single SNP had minimal effect on IVW estimates, reinforcing the robustness of protective associations for coffee and risk-enhancing effects of meat and alcohol intake (Table 3-4).

Table 3. Cochran's Q-test outcomes for assessing heterogeneity of dietary exposures on IIM risk

Outcome	Exposure	method	Q	Q pvalue
IPF	Beef consumption	MR Egger	0.475	0.789
IPF	Beef consumption	Inverse variance weighted	1.111	0.774
IPF	Champagne or white wine consumption	MR Egger	8.573	0.073
IPF	Champagne or white wine consumption	Inverse variance weighted	14.060	0.015
IPF	Cheese consumption	MR Egger	3.378	0.947
IPF	Cheese consumption	Inverse variance weighted	5.773	0.834
IPF	Lamb consumption	MR Egger	29.856	0.005
IPF	Lamb consumption	Inverse variance weighted	33.695	0.002
IPF	Pork consumption	MR Egger	2.212	0.331
IPF	Pork consumption	Inverse variance weighted	2.924	0.403
IPF	Tea consumption	MR Egger	14.186	0.821

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Table 3. (continued)

IPF	Tea consumption	Inverse variance weighted	14.191	0.861
Myositis	Cheese consumption	MR Egger	9.436	0.894
Myositis	Cheese consumption	Inverse variance weighted	10.838	0.865
Myositis	Dried fruit consumption	MR Egger	41.639	0.399
Myositis	Dried fruit consumption	Inverse variance weighted	42.070	0.424
Dermatopolymyositis	Ground coffee consumption	MR Egger	0.536	0.765
Dermatopolymyositis	Ground coffee consumption	Inverse variance weighted	0.926	0.819
Dermatopolymyositis	Instant coffee consumption	MR Egger	7.102	0.716
Dermatopolymyositis	Instant coffee consumption	Inverse variance weighted	7.560	0.752
Dermatopolymyositis	Red wine consumption	MR Egger	4.460	0.485
Dermatopolymyositis	Red wine consumption	Inverse variance weighted	5.068	0.535
Polymyositis	Instant coffee consumption	MR Egger	10.745	0.378
Polymyositis	Instant coffee consumption	Inverse variance weighted	11.180	0.428

Table 4. MR-Egger Intercept test results for evaluating horizontal pleiotropy in dietary exposure–IIM analyses

Outcome	Exposure	Egger intercept	P value
IPF	Beef consumption	-0.087	0.509
IPF	Champagne or white wine consumption	-0.116	0.185
IPF	Cheese consumption	-0.047	0.156
IPF	Lamb consumption	-0.051	0.219
IPF	Pork consumption	-0.077	0.506
IPF	Tea consumption	0.001	0.941
Myositis	Cheese consumption	0.108	0.254
Myositis	Dried fruit consumption	0.034	0.524
Dermatopolymyositis	Ground coffee consumption	0.071	0.596
Dermatopolymyositis	Instant coffee consumption	0.033	0.514
Dermatopolymyositis	Red wine consumption	0.134	0.471
Polymyositis	Instant coffee consumption	-0.042	0.539

3.3. Causal effects of chronic disease on IIM

To further investigate comorbidities, the author performed forward two-sample MR analyses on ten common disease traits. Obesity showed consistent and significant risk-increasing effects in two datasets: IPF (OR = 1.18; P = 4.86×10^{-4}) and Dermatopolymyositis (OR = 1.39; P = 0.034). Although positive trends were observed in the Polymyositis and MYOSITIS datasets, they did not achieve statistical significance (P > 0.05), suggesting that obesity may contribute to disease progression.

Genetic predisposition to depression or dysthymia was associated with increased IIM susceptibility in the IPF dataset (OR = 1.35; P = 6.49×10^{-3}). Combined definitions of type 1 diabetes showed significant positive associations in the dermatomyositis cohort (OR = 1.16; P =

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3.93×10^{-7}) and the polymyositis cohort (OR = 1.19; P = 4.47×10^{-4}). Liability to sleep disorders conferred a significant risk elevation only in the polymyositis dataset (OR = 2.96; P = 0.0264). No other comorbid traits reached statistical significance in any cohort (P > 0.05). Complete estimates are presented in Table 5 and visualized in Figure 2.

Table 5. Mendelian randomization estimates of the causal effects of chronic diseases on IIM (nsnp, number of single nucleotide polymorphisms)

Outcome	Exposure	Nsnp	Beta	Standard error	P value
Dermatopolymyositis	Anxiety disorders	13	-0.505	0.474	0.287
Dermatopolymyositis	Dementia in Alzheimer disease	28	0.037	0.066	0.575
Dermatopolymyositis	Depression or dysthymia	31	-0.238	0.311	0.445
Dermatopolymyositis	Hypertension	303	0.184	0.099	0.062
Dermatopolymyositis	Obesity	47	0.333	0.157	0.034
Dermatopolymyositis	Sleep disorders	16	0.474	0.371	0.201
Dermatopolymyositis	Type 2 diabetes	257	-0.010	0.083	0.902
Dermatopolymyositis	Type1 diabetes	70	0.149	0.029	3.93E-07
Myalgia and myositis	Anxiety disorders	13	0.419	0.479	0.382
Myalgia and myositis	Dementia in Alzheimer disease	26	0.063	0.073	0.387
Myalgia and myositis	Depression or dysthymia	31	0.235	0.307	0.443
Myalgia and myositis	Hypertension	293	-0.092	0.108	0.394
Myalgia and myositis	Obesity	42	-0.278	0.162	0.087
Myalgia and myositis	Sleep disorders	14	0.020	0.509	0.969
Myalgia and myositis	Type 2 diabetes	243	-0.033	0.090	0.718
Myalgia and myositis	Type1 diabetes	65	0.058	0.034	0.090
IPF	Anxiety disorders	12	0.020	0.134	0.882
IPF	Dementia in Alzheimer disease	24	-0.018	0.024	0.465
IPF	Depression or dysthymia	24	0.302	0.111	0.006
IPF	Hypertension	237	-0.057	0.037	0.126
IPF	Obesity	38	0.163	0.047	4.86E-04
IPF	Sleep disorders	10	0.192	0.150	0.200
IPF	Type 2 diabetes	201	-0.006	0.028	0.820
IPF	Type1 diabetes	57	-0.008	0.012	0.520
Polymyositis	Anxiety disorders	13	-0.110	0.526	0.834
Polymyositis	Dementia in Alzheimer disease	28	0.026	0.082	0.753
Polymyositis	Depression or dysthymia	31	-0.010	0.366	0.977
Polymyositis	Hypertension	304	0.118	0.133	0.374
Polymyositis	Obesity	47	0.270	0.211	0.201
Polymyositis	Sleep disorders	16	1.085	0.489	0.026
Polymyositis	Type 2 diabetes	256	0.077	0.112	0.493
Polymyositis	Type1 diabetes	72	0.173	0.049	4.47E-04

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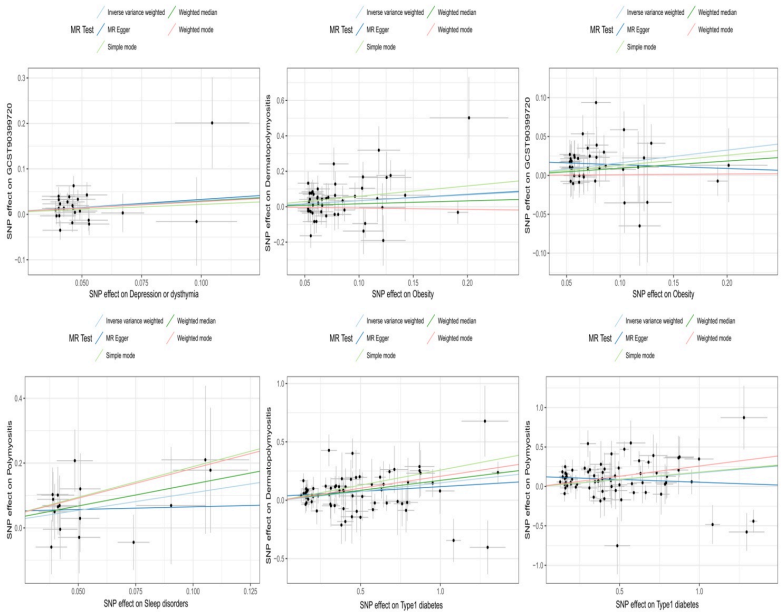


Figure 2. Scatter plot presents significant Mendelian randomization results for the causal effect of dietary factors on IIM

(Picture credit: Original)

3.4. Sensitivity analyses of chronic disease traits

For the four comorbid traits showing significant associations in at least one dataset, MR-Egger intercept and Cochran's Q-tests found no evidence of pleiotropy or heterogeneity across all relevant datasets ($P > 0.05$). Scatter and funnel plots revealed symmetrical and linear distributions, and leave-one-out analyses indicated minimal variation in causal effect. These results provide consistent and robust evidence supporting links between IIM and obesity, depression, type 1 diabetes, and sleep disorders across multiple independent cohorts (Table 6-7).

Table 6. Heterogeneity test results for the causal effect of chronic disease on IIM

Outcome	Exposure	method	Q	Q_df	Q pvalue
Dermatopolymyositis	Type1 diabetes	MR Egger	83.703	68	0.095
Dermatopolymyositis	Type1 diabetes	Inverse variance weighted	87.013	69	0.070
Dermatopolymyositis	Obesity	MR Egger	57.593	45	0.099
Dermatopolymyositis	Obesity	Inverse variance weighted	57.599	46	0.117
IPF	Obesity	MR Egger	30.045	36	0.747
IPF	Obesity	Inverse variance weighted	33.716	37	0.624
IPF	Depression or dysthymia	MR Egger	27.873	22	0.180
IPF	Depression or dysthymia	Inverse variance weighted	27.877	23	0.220
Polymyositis	Sleep disorders	MR Egger	8.848	14	0.841
Polymyositis	Sleep disorders	Inverse variance weighted	9.200	15	0.867
Polymyositis	Type1 diabetes	MR Egger	122.560	70	0.105
Polymyositis	Type1 diabetes	Inverse variance weighted	145.242	71	0.050

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Table 7. MR-Egger intercept test results evaluating horizontal pleiotropy in chronic disease–IIM analyses

Outcome	Exposure	Egger intercept	P value
Dermatopolymyositis	Type1 diabetes	0.035	0.106
Dermatopolymyositis	Obesity	-0.002	0.948
IPF	Obesity	0.018	0.063
IPF	Depression or dysthymia	-0.002	0.956
Polymyositis	Sleep disorders	0.048	0.563
Polymyositis	Sleep disorders	0.048	0.563

4. Discussion

Genetic evidence implicates specific dietary behaviors and metabolic comorbidities in IIM pathogenesis, with coffee intake—both instant and ground—demonstrating a marked protective effect against dermatomyositis. This inverse association parallels findings from a recent two-sample MR study in which higher genetically instrumented caffeine concentrations were linked to lower odds of obesity and osteoarthritis (OR = 0.97 per SD increase in caffeine) [14]. Bioactive compounds in coffee (e.g., caffeine, chlorogenic acids) possess anti-inflammatory and immunomodulatory properties, enhancing natural killer cell activity and suppressing excessive T-cell responses, thereby offering protection against autoimmune diseases [15]. Thus, the causal link between genetically predicted coffee intake and reduced IIM risk is biologically plausible. Crucially, the use of genetic instruments mitigates confounding, strengthening the evidence for coffee's potential protective role against IIMs.

Conversely, high red meat consumption and intake of certain alcoholic beverages (e.g., champagne/white wine) showed positive genetic correlations with increased IIM risk. These findings are biologically supported: diets rich in saturated fats (red meat) and excessive ethanol intake are known to induce systemic inflammation and oxidative stress [16]. In support of these pathways, a bidirectional MR analysis shows that increased circulating saturated fatty acid levels causally elevate rheumatoid arthritis risk [16]. Chronic alcohol use promotes inflammation through multiple routes: it alters the gut microbiome, increases intestinal permeability—allowing endotoxins to enter the circulation—and directly engages innate immune receptors such as Toll-like receptors and the NLRP3 inflammasome, resulting in elevated pro-inflammatory cytokines and reactive oxygen species [17]. Inflammatory and oxidative-stress pathways implicated in rheumatoid arthritis and immune-mediated hepatic disorders also underlie the positive associations observed for high red meat and alcohol intake in IIM. Chronic exposure to saturated fats and ethanol thus appears to create a pro-inflammatory milieu that may promote IIM onset.

Genetic analyses further identified causal associations between IIM susceptibility and metabolic or psychological comorbidities, notably obesity, type 1 diabetes and depression. Elevated body mass index (BMI) promotes a state of low-grade chronic inflammation; a recent two-sample MR analysis across 15 autoimmune diseases showed that genetically elevated BMI significantly increases the risk of multiple autoimmune conditions (e.g., OR~1.22 for RA, OR~1.55 for T1D per 1-SD BMI increase; [18]), supporting its pathogenic role. Similarly, genetically predicted T1D susceptibility was associated with IIM risk, consistent with reported shared genetic mechanisms between T1D and other autoimmune diseases—MR evidence indicates T1D genetic risk elevates the risk of systemic

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lupus erythematosus, RA, and multiple sclerosis [19]. Notably, depressive symptoms also showed a potential causal effect on IIM risk. Chronic psychological stress and depression are closely linked to systemic inflammation: depressed patients exhibit elevated pro-inflammatory cytokines, and persistent activation of inflammatory pathways is considered a contributor to comorbid autoimmune diseases [20]. Controlling chronic inflammation in treatment-resistant depression may reduce future autoimmune disease risk [20]. Collectively, metabolic dysregulation (obesity, diabetes) and psychological stress may promote IIM onset via immune dysregulation and increased inflammatory mediators. The causal inferences in this study are highly robust.

From public health and clinical prevention perspectives, the author's findings highlight important implications. They support anti-inflammatory dietary strategies as feasible measures to reduce IIM risk. Specifically, promoting diets rich in antioxidants and unsaturated fats, moderate coffee and fiber intake, and reducing red meat and alcohol consumption may help mitigate systemic inflammatory burden and lower IIM incidence. This aligns with recent nutritional research: the Mediterranean dietary pattern—characterized by abundant omega-3 polyunsaturated fatty acids, vitamin D and various polyphenolic compounds—has been linked to reduced inflammatory activity in rheumatic conditions [21]. Mechanistic investigations suggest that this diet modulates key immunometabolic pathways and attenuates sustained muscle inflammation [21]. Rheumatoid arthritis management guidelines already advocate this dietary pattern while advising limits on saturated fats and alcohol consumption [16]. For individuals with IIM or at elevated risk, strategies that support metabolic balance—such as maintaining a healthy body weight and preventing obesity—as well as measures to preserve mental health, including stress management and depression prevention, may offer additional protection given the emerging links between systemic metabolic homeostasis, neuroimmune regulation, and autoimmunity.

However, several limitations must be considered when interpreting these findings. First, while the use of genetic instruments strengthens causal inferences, the potential for weak instrument bias remains a concern. Although the author applied sensitivity analyses to mitigate pleiotropy, undetected pleiotropic effects could still influence the author's results. Second, this study relies on summary-level data predominantly from populations of European descent, which may limit the generalizability of the author's findings to other ethnic groups. Further research incorporating diverse cohorts is necessary to confirm these results across different populations. Third, while the author assumed a linear relationship between dietary exposures and IIM risk, future studies should explore non-linear effects and potential time-dependent relationships. Finally, the measurement of dietary exposures through self-reported data may introduce some degree of bias, and further validation of these exposures in prospective cohort studies is warranted.

Future studies should investigate the precise immunometabolic mechanisms through which these dietary and comorbid factors influence IIM pathogenesis and progression. For instance, mitochondrial dysfunction and aberrant energy metabolism in IIM patients suggest immunometabolic reprogramming may drive inflammatory damage [22]. Elucidating such mechanisms could identify novel therapeutic targets and inform primary prevention strategies. Validation of dietary interventions and comorbidity-management strategies in prospective cohort studies and randomized controlled trials is essential to establish their efficacy in reducing IIM incidence and improving clinical outcomes, thereby translating genetic insights into evidence-based prevention and treatment guidelines [22].

Overall, these findings deliver novel causal evidence for IIM pathogenesis and underscore the value of integrating genetic and lifestyle data to inform personalized prevention and management strategies.

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5. Conclusion

This two-sample MR study provides evidence that habitual coffee intake may exert a protective effect against IIM, whereas frequent consumption of red meat and alcohol may elevate disease risk. Obesity, type 1 diabetes, and depressive disorders were found to exert causal effects on IIM risk, emphasizing the pivotal role of adjustable metabolic and lifestyle factors in determining autoimmune susceptibility.

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