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Dietary factors and the risk of atopic dermatitis: a Mendelian randomisation study

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Abstract

Previous studies have revealed an association between dietary factors and atopic dermatitis (AD). To explore whether there was a causal relationship between diet and AD, we performed Mendelian randomisation (MR) analysis. The dataset of twenty-one dietary factors was obtained from UK Biobank. The dataset for AD was obtained from the publicly available FinnGen consortium. The main research method was the inverse-variance weighting method, which was supplemented by MR–Egger, weighted median and weighted mode. In addition, sensitivity analysis was performed to ensure the accuracy of the results. The study revealed that beef intake (OR = 0·351; 95 % CI 0·145, 0·847; $P = 0·020$) and white bread intake (OR = 0·141; 95 % CI 0·030, 0·656; $P = 0·012$) may be protective factors against AD. There were no causal relationships between AD and any other dietary intake factors. Sensitivity analysis showed that our results were reliable, and no heterogeneity or pleiotropy was found. Therefore, we believe that beef intake may be associated with a reduced risk of AD. Although white bread was significant in the IVW analysis, there was large uncertainty in the results given the wide 95 % CI. Other factors were not associated with AD in this study.

Keywords: **Mendelian randomisation: Atopic dermatitis: Dietary habits: GWAS**

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterised by recurrent eczematous lesions. These lesions are ill-defined and are often accompanied by erythema, early exudation, blistering and crusting; later, they may present with scaling, dehiscence and lichenisation. AD patients are also prone to allergic rhinitis, asthma, intense itching and discomfort[1,2]. The prevalence of AD is estimated to be 15–20 % in children and 1–3 % in adults, with the incidence of AD increasing 2–3-fold in industrialised countries over the past decades[3,4]. It is the leading non-fatal health burden attributable to skin diseases and inflicts a substantial psychosocial burden on patients[5–9]. A strong link between AD and food allergies has been established in childhood. Food allergies are also present in up to 37 % of infants with AD, whereas they are present in approximately 10 % of adults with AD[10]. There is some debate about the role of food allergies in AD[11–13]. In assessing allergen triggers in AD patients, doctors typically perform a range of tests, including tests for food allergens. These tests may ask patients to avoid certain foods to determine whether they improve symptom control for AD[14]. However, this 'elimination diet' approach does not fully determine the role of food allergies in the development of AD because there are many other factors that may affect the control of the disease, such as genetics, the environment and the microbiome.

Mendelian randomisation (MR) studies are defined as any study that uses genetic variation as a robust proxy for modifiable environmental exposures to make causal inferences about the outcomes of modifiable exposures[15]. MR have been likened to 'natural' randomised controlled trials. MR exploits the fixity of genes and Mendel's first and second laws of inheritance; namely, at meiotic gamete formation, alleles from parents are randomly assigned to offspring. MR uses genetic variants associated with risk factors of interest to explore their association with disease outcome[16–18]. The process is similar to that of a traditional randomised controlled trials; in that, patients are randomised into treatment and control groups. However, MR studies use random allocation of genetic variation to avoid the interference of reverse causality and potential confounding factors encountered in traditional randomised controlled trials[19,20].

Abbreviations: AD, atopic dermatitis; IV, instrumental variable; IVW, inverse-variance weighting; MR, Mendelian randomisation.

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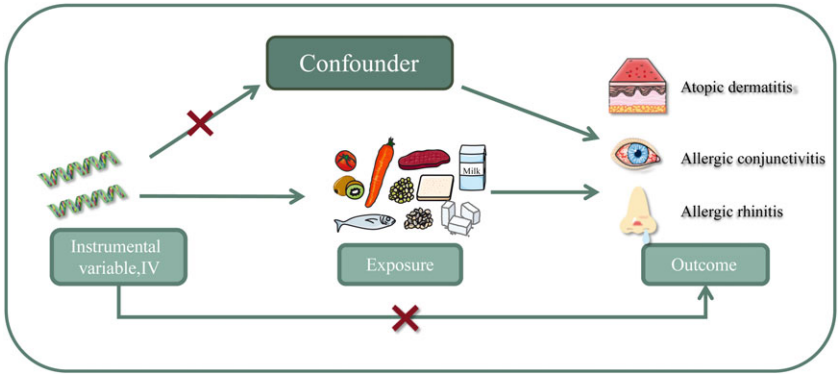

Fig. 1. The relationship between exposure factors (dietary habits), instrumental variables (IV) and outcomes (AD).

Table 1. Baseline characteristics of atopic dermatitis patients in FinnGen consortium

	All	Female	Male
Number of individuals	32 457	23 022	9435
Unadjusted period prevalence (%)	6·78	7·85	4·16
Median age at first event (years)	34·24	33·47	36·11

Previous studies have shown that different dietary patterns have varying degrees of impact on the risk of AD. However, the causal relationship between AD and dietary patterns has not been assessed systematically. Excessive restriction of dietary intake may lead to nutritional deficiencies. Our study is the first to explore the association between dietary factors and AD risk using MR. The primary objective of our research was to substantiate the existence of a causal relationship between diet and AD at the genetic level. By establishing this connection, our study aimed to provide valuable insights that can guide the development of tailored dietary recommendations for individuals with AD.

Methods

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology–Mendelian randomisation reporting guidelines (online Supplementary Table S1)[21]. This study used only publicly available summary data, which were approved for human experimentation by an ethical standards committee. Therefore, additional ethical approval was not required for the current study. MR uses genetic variants to assess causal relationships using observational data[22,23]. The principle of MR is based on Mendelian laws of inheritance and instrumental variable (IV) estimation methods, which enable the inference of causal effects in the presence of unobserved confounding factors[18]. The relationships among exposure factors (dietary habits), IV and the outcome (AD) are detailed in Fig. 1. MR analysis must satisfy the following three model assumptions[24]: (1) IV are strongly correlated with intermediate phenotypes or exposure factors; (2) IV are not correlated with confounding factors; and (3) conditional independence between IV and disease outcome, that is, IV affect outcome only through exposure

Data sources

The diet-related exposure factors used in this study included meat intake (processed meat, poultry, beef, non-oily fish, oily fish, pork and lamb/mutton intake), staple food intake (white bread and cereal intake), vegetable intake (salad/raw vegetable intake and cooked vegetable intake), beverage intake (weekly number of alcoholic beverages consumed and frequency of alcohol consumption, tea intake, milk intake and coffee intake), fruit intake (dried fruit intake and fresh fruit intake) and intake of other foods (cheese intake, whole egg intake and unsalted peanut intake). Genome-wide association study (GWAS) summary-level data were extracted directly or indirectly from UK Biobank using the IEU Open GWAS project, and details of the design, such as quality control procedures and statistical analyses, are available on the website (http://www.nealelab.is/UK-biobank/c). Dietary intake was measured by questionnaires as the average intake over the past year. GWAS summary-level data for AD were extracted from the FinnGen consortium (https://r5.finngen.fi)[25]. The R5 release data of the FinnGen consortium include 7024 AD patients and 198 740 control participants. Cases were ascertained by hospital discharge and cause of death (code L20 of the ICD-10), 6918 (with the exclusion of 6918X) of the ICD-9, and 691 of the ICD-8. FinnGen consortium researchers define AD as 'A chronic inflammatory genetically determined disease of the skin marked by increased ability to form reagin (Ig E), with increased susceptibility to allergic rhinitis and asthma, and hereditary disposition to a lowered threshold for pruritus. It is manifested by lichenification, excoriation, and crusting, mainly on the flexural surfaces of the elbow and knee'. Table 1 shows the baseline characteristics of AD patients in the FinnGen consortium.

Selection of instrumental variables

All the statistical analyses were performed using the 'MendelianRandomization' and 'TwoSampleMR' packages in R (3.6.1). We performed analyses using a two-sample MR model with dietary factors as the exposure variables and AD as the outcome variable. In MR analysis, IV are utilised as mediators between exposure factors and outcomes to explore the causal relationship between exposure and outcomes and are generally genetic variations, among which SNP are the most commonly

used[26]. In this study, SNP sites associated with significant dietary factors were selected in advance based on the criterion (P1 = 5e-8); dietary factors with no significant sites were extracted, and the criterion was adjusted to 5e-6. In the first step, we used standard parameters (aggregation window of 10 000 kb and an r^2 cut-off of 0·001) to eliminate the interference of linkage disequilibrium[27]. In the second step, SNP with genome-wide significance ($P < 5 \times 10 - 5$) for AD risk were excluded. Then, SNP with the same alleles in the dietary factor data and AD data were collated to harmonise the effect sizes of exposure and outcome[28]. To avoid potential weak instrumental bias, the F statistic ($F = beta^2/se^2$) was used to assess the strength of the IV; if F > 10, the correlation between IV and exposure was considered strong enough that the results of the MR analysis could be protected from weak instrumental bias[29].

Mendelian randomisation analysis

We performed a two-sample MR analysis to assess the causal relationship between exposure (dietary factors) and outcome (AD). We utilised the inverse-variance weighting (IVW), weighted median, weighted mode and MR–Egger methods for the main MR analysis[30–32]. First, associations were made for each SNP, and the IVW method was used to combine Wald ratios to assess associations between dietary factors and AD. The IVW method adopted in this study mainly uses the inverse of variance of each IV as a weight for weighting calculation. The results of the random-effects IVW method were regarded as the predominant analysis[33]. This process is carried out under the premise of ensuring that all IVs are valid to evaluate horizontal pleiotropy[34]. MR–Egger regression uses the inverse of the variance of the outcome as a weight for fitting, which adds an intercept term to the regression[35]. The weighted median method[31] involves the median of a weighted empirical density function defined as a ratio estimate that still provides consistent effect estimates when the proportion of invalid IV is as high as 50 % and the accuracy of the estimates varies widely among IV.

Sensitivity analysis

To ensure the reliability of our conclusions, six sensitivity analyses were used to verify whether heterogeneity and pleiotropy in genetic variables biased the MR results. First, MR–Egger regression was applied to detect and adjust for the effect of potential horizontal pleiotropy among the selected IV by assessing the intercept[36,37]. Second, MR pleiotropy residual and outlier (MR-PRESSO) tests were used to detect potential horizontal pleiotropy, and MR-PRESSO global heterogeneity tests were performed to identify potential horizontal pleiotropy, which were immediately removed once outliers were found. Third, the asymmetry of the funnel plot was used as an indicator of horizontal pleiotropy. Fourth, the Cochran Q test was used to quantify the heterogeneity of the selected genetic instruments[36,37]. Fifth, leave-one-out sensitivity analysis was implemented by deleting each SNP, which ensured that the MR estimates were not driven by certain strong SNP. Finally, after removing outliers, the MR analysis was performed again.

Results

The flow chart of the study design, data collection, data processing and analysis, and exclusion of SNP numbers is shown in Fig. 2

Selection of instrumental variables

The causal relationships between dietary factors and AD were analysed using twenty-one different exposure factors. The number of European-descent individuals included in the study ranged from 335 394 to 462 346. The outcomes included 7024 European-descent AD patients and 198 740 European-descent control participants from the FinnGen consortium, and there was little overlap between the populations involved in the exposures and outcomes. The number of SNP used for different exposures in this study ranged from 7 to 90. The F statistic for all SNP was greater than 10, which indicates that the IV used in our study satisfied the requirements of strong associations with the exposures. Table 2 provides detailed information on the twenty-one exposure factors.

Causal effect in the main analysis and sensitivity analyses

In this study, we found that beef intake (OR = 0·351; 95 % CI 0·145, 0·847; $P = 0·020$) was associated with a decreased risk of AD, which was further verified by the results of the MR–Egger model (OR = 0·002; 95 % CI 0·000, 0·341; $P = 0·036$) despite the negative results of the weighted median and weighted mode models. The IVW results for white bread suggested that white bread might be a protective factor against AD (OR = 0·141; 95 % CI 0·030, 0·656; $P = 0·012$). However, the wide CI indicates uncertainty about the protective effect of white bread on AD. Therefore, we cannot verify the protective effect of white bread on AD.

This study also found that the number of alcoholic drinks per week (OR: 0·721; 95 % CI 0·441, 1·179; $P = 0·192$), alcohol consumption frequency (OR: 1·027; 95 % CI 0·856, 1·233; $P = 0·771$), processed meat intake (OR: 0·638; 95 % CI 0·300, 1·353; $P = 0·241$), poultry intake (OR: 2·565; 95 % CI 0·668, 9·847; $P = 0·170$), non-oily fish intake (OR: 1·125; 95 % CI 0·299, 4·241; $P = 0·862$), oily fish intake (OR: 0·980; 95 % CI 0·647, 1·485; $P = 0·923$), pork intake (OR: 0·920; 95 % CI 0·313, 2·710; $P = 0·880$), lamb/mutton intake (OR: 0·828; 95 % CI 0·403, 1·702; $P = 0·607$), cheese intake (OR: 0·856; 95 % CI 0·598, 1·224; $P = 0·393$), cooked vegetable intake (OR: 1·586; 95 % CI 0·636, 3·952; $P = 0·322$), tea intake (OR: 0·714; 95 % CI 0·495, 1·030; $P = 0·071$), fresh fruit intake (OR: 0·618; 95 % CI 0·338, 1·129; $P = 0·118$), cereal intake (OR: 1·283; 95 % CI 0·720, 2·286; $P = 0·399$), salad/raw vegetable intake (OR: 1·732; 95 % CI 0·606, 4·952; $P = 0·306$), coffee intake (OR: 0·902; 95 % CI 0·593, 1·373; $P = 0·631$), milk intake (OR: 0·994; 95 % CI 0·493, 2·001; $P = 0·986$), whole egg intake (OR: 1·238; 95 % CI 0·631, 2·426; $P = 0·535$), unsalted peanuts intake (OR: 1·404; 95 % CI 0·555, 2·426; $P = 3·553$) and dried fruit intake (OR: 0·864; 95 % CI 0·448, 1·666; $P = 0·662$) were not associated with AD. Additional MR analysis results are shown in Table 3.

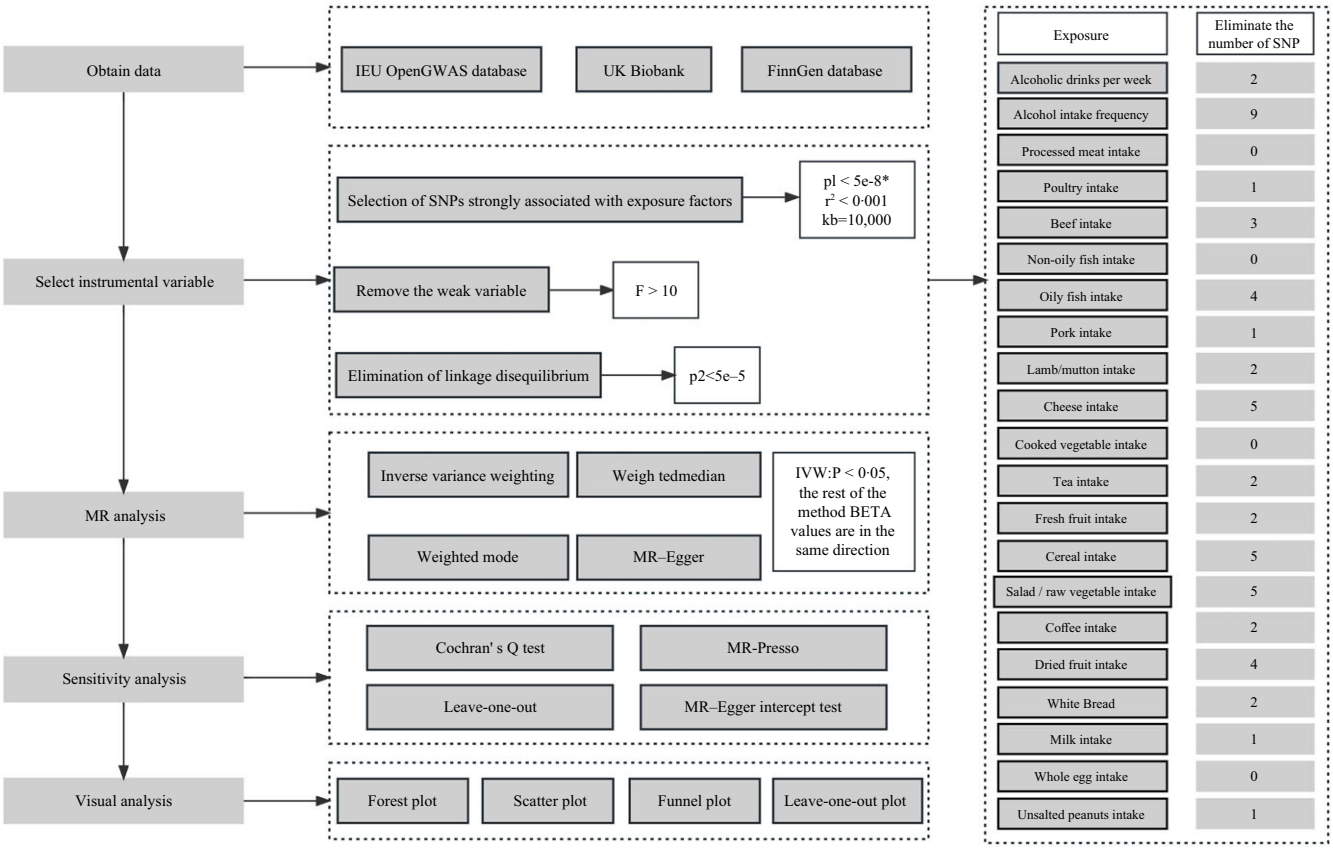

Fig. 2. Study flow diagram. *p1 = 5e-8, p1 changed to 5e-6 if tool variables are insufficient.

The analysis of beef intake showed that the *P* value of the IVW method was less than 0·05, and the direction of the β-coefficient was consistent for the remaining methods. Therefore, we concluded that beef intake was a protective factor against AD. To ensure the robustness of the positive results, we performed a sensitivity analysis. Heterogeneity was not detected in the exposures (Cochran's Q test $P > 0·05$), and the results of the MR–Egger intercept suggested that no directional pleiotropy was present (Table 4). A scatter plot of the individual causal effect estimates is shown in Fig. 3. The diagnostic funnel plot showed visually apparent symmetry, which excluded the possible influence of directional pleiotropy on our estimates (Fig. 3). A forest plot is shown in Fig. 3. Leave-one-out analysis indicated that the causality of the associations was robust (Fig. 3). As shown in Table 3, the results of the MR-PRESSO analysis were consistent with those of the IVW model.

Discussion

An increase in the incidence of AD is associated with an increase in food allergies, but the relationship is complex. Opinion is divided on the use of dietary elimination as an effective treatment option for AD because of growing evidence that other factors are driving the development of AD, independent of food consumption[38]. Furthermore, excessive dietary restriction may cause nutritional deficiencies. To our knowledge, the present study is the first to verify the causal relationship between diet and AD at the genetic level. The most important finding of this MR analysis was that beef intake was associated with a reduced risk of AD. Therefore, when beef allergies are excluded, AD patients can eat some beef appropriately, which may help to improve their skin condition. Due to the wide 95 % CI (0·030–0·656), we could not determine the exact protective effect of white bread against AD. The width of the CI was influenced by the sample size, the variability of the data or the statistical methods used. Therefore, further studies are needed to verify this conclusion. In addition, this study revealed that the number of alcoholic drinks per week, alcohol consumption frequency, processed meat intake, poultry intake, non-oily fish intake, oily fish intake, pork intake, lamb/mutton intake, cheese intake, cooked vegetable intake, dried fruit intake, fresh fruit intake, tea intake, cereal intake, salad/raw vegetable intake, whole egg intake, unsalted peanuts intake, milk intake and coffee intake were not associated with AD. Therefore, after the exclusion of foods that trigger an allergic response, rational food intake should be used to avoid excessive use of dietary avoidance to treat AD. Excessive avoidance of certain foods may lead to nutritional deficiency, which is detrimental to the health of patients. For patients with food allergies, we recommend regular food allergy monitoring combined with one-on-one consultation from a dietician on food intake for better management and

Table 2. Information of the exposures and outcome datasets

IEU GWAS ID	Year	Trait	SNP	Consortium	Sample size
ieu-b-73	2019	Alcoholic drinks per week	33	GWAS and Sequencing Consortium of Alcohol and Nicotine use	335 394
ukb-b-5779	2018	Alcohol intake frequency	90	MRC-IEU	462 346
ukb-b-6324	2018	Processed meat intake	23	MRC-IEU	461 981
ukb-b-8006	2018	Poultry intake	7	MRC-IEU	461 900
ukb-b-2862	2018	Beef intake	14	MRC-IEU	461 053
ukb-b-17627	2018	Non-oily fish intake	11	MRC-IEU	460 880
ukb-b-2209	2018	Oily fish intake	59	MRC-IEU	460 443
ukb-b-5640	2018	Pork intake	13	MRC-IEU	460 162
ukb-b-14179	2018	Lamb/mutton intake	30	MRC-IEU	460 006
ukb-b-1489	2018	Cheese intake	60	MRC-IEU	451 486
ukb-b-8089	2018	Cooked vegetable intake	17	MRC-IEU	448 651
ukb-b-6066	2018	Tea intake	39	MRC-IEU	447 485
ukb-b-3881	2018	Fresh fruit intake	52	MRC-IEU	446 462
ukb-b-15926	2018	Cereal intake	38	MRC-IEU	441 640
ukb-b-1996	2018	Salad/raw vegetable intake	17	MRC-IEU	435 435
ukb-b-5237	2018	Coffee intake	38	MRC-IEU	428 860
ukb-b-16576	2018	Dried fruit intake	39	MRC-IEU	421 764
ukb-d-1448_1	2018	White bread	20	NA	348 424
ukb-b-2966	2018	Milk intake*	20	MRC-IEU	64 943
ukb-b-4075	2018	Whole egg intake*	6	MRC-IEU	64 949
ukb-b-15555	2018	Unsalted peanuts intake*	47	MRC-IEU	64 949

IEU, Integrated Epidemiology Unit; GWAS, genome-wide association study;
* P1 = 5e-6. In addition to the marked exposure, the remaining *P*-values are 5e-8.

Table 3. The results of Mendelian randomisation analyses

Exposure	Method	BETA	SE	*P*	OR	95 % lower	95 % upper
Alcoholic drinks per week	Inverse-variance weighted	33	−0·327	0·251	0·192	0·721	0·441
	MR–Egger		0·107	0·572	0·853	1·112	0·363
	Weighted median		−0·325	0·346	0·347	0·722	0·366
	Weighted mode		0·059	0·491	0·906	1·060	0·405
Alcohol intake frequency	Inverse-variance weighted	90	0·027	0·093	0·771	1·027	0·856
	MR–Egger		0·231	0·285	0·419	1·260	0·721
	Weighted median		0·027	0·133	0·841	1·027	0·792
	Weighted mode		0·053	0·260	0·839	1·054	0·633
Processed meat intake	Inverse-variance weighted	23	−0·450	0·384	0·241	0·638	0·300
	MR–Egger		−0·038	1·971	0·985	0·963	0·020
	Weighted median		−0·494	0·416	0·235	0·610	0·270
	Weighted mode		−0·737	0·694	0·299	0·479	0·123
Poultry intake	Inverse-variance weighted	7	0·942	0·686	0·170	2·565	0·668
	MR–Egger		−19·401	20·626	0·390	0·000	0·000
	Weighted median		0·646	0·917	0·481	1·907	0·316
	Weighted mode		1·016	1·242	0·445	2·763	0·242
Beef intake	Inverse-variance weighted	14	−1·047	0·450	0·020	0·351	0·145
	MR–Egger		−6·393	2·713	0·036	0·002	0·000
	Weighted median		−1·036	0·629	0·099	0·355	0·103
	Weighted mode		−0·667	1·353	0·630	0·513	0·036
Non-oily fish intake	Inverse-variance weighted	11	0·118	0·677	0·862	1·125	0·299
	MR–Egger		−1·622	3·349	0·640	0·197	0·000
	Weighted median		0·102	0·740	0·891	1·107	0·260
	Weighted mode		0·351	1·055	0·746	1·421	0·180
Oily fish intake	Inverse-variance weighted	59	−0·020	0·212	0·923	0·980	0·647
	MR–Egger		0·097	0·909	0·915	1·102	0·186
	Weighted median		−0·004	0·283	0·988	0·996	0·571
	Weighted mode		−0·079	0·686	0·909	0·924	0·241
Pork intake	Inverse-variance weighted	13	−0·083	0·551	0·880	0·920	0·313
	MR–Egger		3·881	3·437	0·283	48·481	0·058
	Weighted median		−0·204	0·719	0·776	0·815	0·199
	Weighted mode		−0·776	1·115	0·500	0·460	0·052
Lamb/mutton intake	Inverse-variance weighted	30	−0·189	0·368	0·607	0·828	0·403
	MR–Egger		1·440	1·545	0·359	4·221	0·204
	Weighted median		0·027	0·520	0·959	1·027	0·371
	Weighted mode		−0·252	0·822	0·761	0·777	0·155
Cheese intake	Inverse-variance weighted	60	−0·156	0·183	0·393	0·856	0·598
	MR–Egger		0·449	0·777	0·565	1·567	0·342
	Weighted median		−0·431	0·264	0·102	0·650	0·387
	Weighted mode		−1·099	0·720	0·132	0·333	0·081

Table 3. (*Continued*)

Exposure	Method	BETA	SE	*P*	OR	95 % lower	95 % upper
Cooked vegetable intake	Inverse-variance weighted	17	0·461	0·466	0·322	1·586	0·636
	MR–Egger		−2·013	5·114	0·699	0·134	0·000
	Weighted median		0·065	0·622	0·917	1·067	0·316
	Weighted mode		−0·224	1·042	0·833	0·800	0·104
Tea intake	Inverse-variance weighted	39	−0·337	0·187	0·071	0·714	0·495
	MR–Egger		−0·283	0·414	0·498	0·753	0·335
	Weighted median		−0·323	0·264	0·222	0·724	0·432
	Weighted mode		−0·385	0·294	0·199	0·680	0·382
Fresh fruit intake	Inverse-variance weighted	52	−0·481	0·307	0·118	0·618	0·338
	MR–Egger		−0·972	1·045	0·357	0·378	0·049
	Weighted median		−0·253	0·476	0·595	0·776	0·305
	Weighted mode		−0·093	0·802	0·909	0·912	0·189
Cereal intake	Inverse-variance weighted	38	0·249	0·295	0·399	1·283	0·720
	MR–Egger		−1·766	1·230	0·160	0·171	0·015
	Weighted median		0·341	0·345	0·323	1·407	0·715
	Weighted mode		0·427	0·594	0·477	1·533	0·479
Salad/raw vegetable intake	Inverse-variance weighted	17	0·549	0·536	0·306	1·732	0·606
	MR–Egger		0·455	2·480	0·857	1·576	0·012
	Weighted median		0·296	0·732	0·686	1·345	0·320
	Weighted mode		−0·875	1·172	0·466	0·417	0·042
Coffee intake	Inverse-variance weighted	38	−0·103	0·214	0·631	0·902	0·593
	MR–Egger		−0·767	0·431	0·083	0·464	0·200
	Weighted median		−0·288	0·327	0·378	0·750	0·395
	Weighted mode		−0·464	0·331	0·170	0·629	0·329
Dried fruit intake	Inverse-variance weighted	39	−0·146	0·335	0·662	0·864	0·448
	MR–Egger		−0·736	1·499	0·626	0·479	0·025
	Weighted median		−0·083	0·410	0·841	0·921	0·412
	Weighted mode		−0·226	0·902	0·803	0·797	0·136
Bread type: white	Inverse-variance weighted	20	−1·957	0·783	0·012	0·141	0·030
	MR–Egger		−4·209	5·523	0·456	0·015	0·000
	Weighted median		−2·224	0·965	0·021	0·108	0·016
	Weighted mode		−3·768	2·007	0·076	0·023	0·000
Milk intake*	Inverse-variance weighted	20	−0·006	0·357	0·986	0·994	0·493
	MR–Egger		−1·062	0·744	0·170	0·346	0·080
	Weighted median		0·220	0·465	0·637	1·246	0·500
	Weighted mode		−0·029	0·791	0·971	0·972	0·206
Whole egg intake*	Inverse-variance weighted	6	0·213	0·343	0·535	1·238	0·631
	MR–Egger		−0·740	0·830	0·423	0·477	0·094
	Weighted median		0·568	0·457	0·215	1·764	0·720
	Weighted mode		0·738	0·711	0·347	2·091	0·519
Unsalted peanuts intake*	Inverse-variance weighted	46	0·340	0·474	0·474	1·404	0·555
	MR–Egger		0·198	0·958	0·837	1·219	0·186
	Weighted median		0·650	0·734	0·376	1·916	0·455
	Weighted mode		0·541	1·017	0·598	1·718	0·23

*P1 = 5e-6. In addition to the marked exposure, the remaining *P*-values are 5e-8.

Table 4. The results of sensitivity analyses

Method			Beef intake
Cochrane's Q test		Q	12·979
		P-value	0·449
Pleiotropy		MR-Egger intercept	0·068
		SE	0·034
		P-value	0·069
MR-PRESSO	Raw	casual estimate	−1·047
		SD	0·449
		P-value	0·037
	outlier-corrected	casual estimate	NA
		SD	NA
		P-value	NA
	Global Test *P* value		0·427

treatment of AD. In conclusion, this study provides comprehensive dietary guidance for AD patients and helps them improve their skin condition while maintaining balanced nutrition. Moreover, this study provides more specific suggestions and treatment options for patients with food allergies.

However, studies on beef allergies are rare. In a study by Ogle *et al.*, beef was considered hypoallergenic. In contrast, Chandra *et al.* considered beef to be a strong allergen[39]. Our study suggested that beef may be a protective factor against AD. Unlike observational studies, MR studies using genetic variants (mainly SNP) as IV are not affected by confounding factors or reverse causality. We hypothesised that beef type, ethnicity and age would have some effect on the results.

There is currently some controversy about the relationship between alcohol use and AD. A study of dietary habits in Japanese adult patients with AD revealed a negative association between alcohol consumption and the development of AD[40]. However, several epidemiological studies suggest that increased alcohol consumption is also associated with increased risk of developing AD[41,42]. Nonetheless, we did not find a clear causal

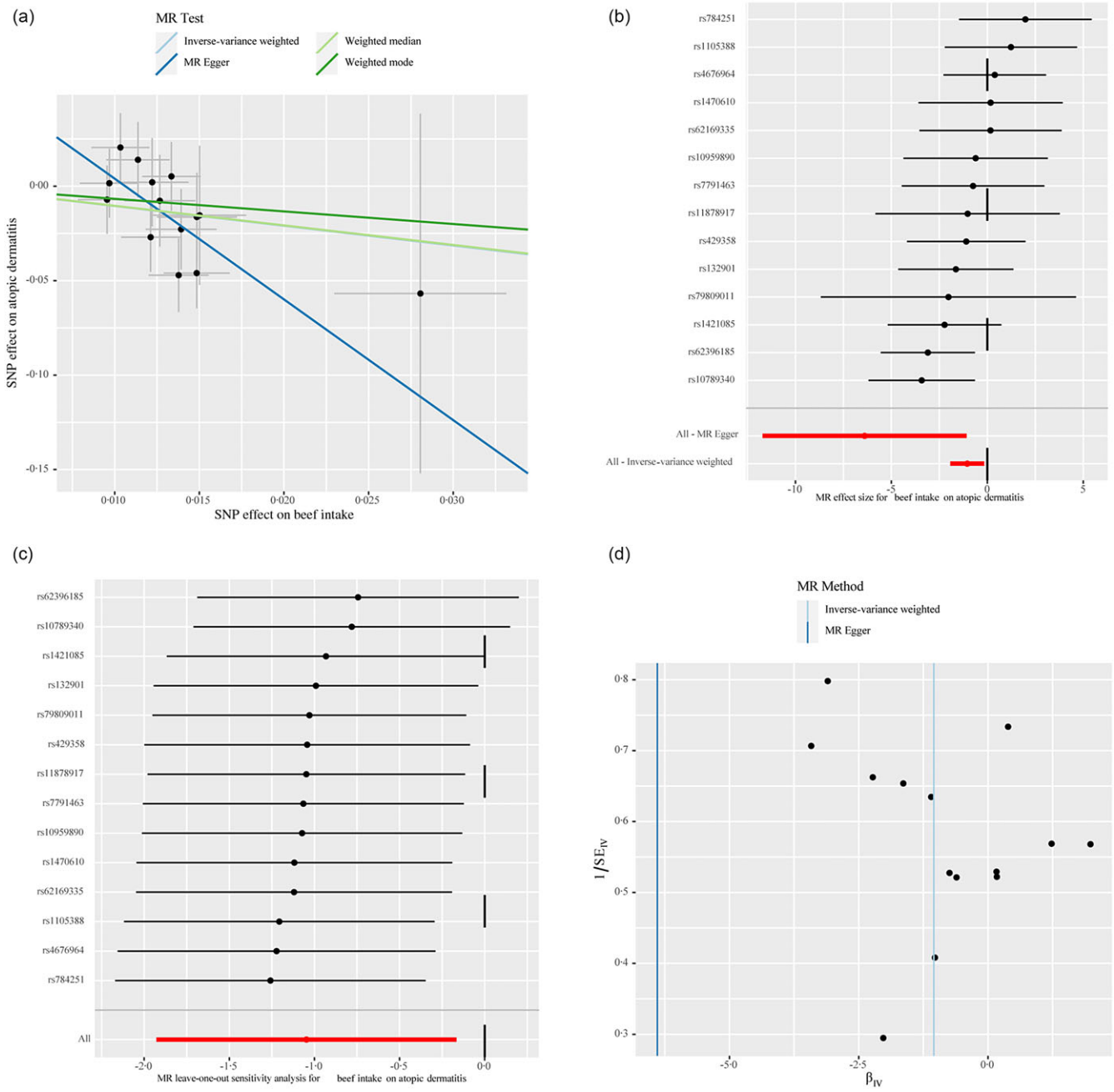

Fig. 3. MR results of beef intake and atopic dermatitis (AD): (a) scatter plot of genetic correlations of beef intake and AD using different MR methods. The slopes of line represent the causal effect of each method, respectively; (b) forest plot of the causal effects of beef intake associated SNP on AD. The red and black dot/bar indicate the causal estimate of beef intake on risk of patients with AD;(c) MR results of leave-one-out sensitivity analysis for beef intake and AD; (d) funnel plot the causal effects of beef intake associated SNP on AD.

relationship between alcohol consumption and AD according to the MR analysis. Therefore, further research and discussion of the relationship between alcohol consumption and AD are still needed. Alcohol consumption and AD appear to be associated to some extent, but the specific mechanism of this association is not clear. Several studies have shown that high alcohol consumption is associated with elevated IgE levels but does not necessarily indicate an increased risk of allergic disease[43]. Another study revealed a sex difference between alcohol consumption and IgE sensitisation. However, the specific effects of alcohol on allergic diseases may vary by individual and alcohol type[44]. Observational studies are susceptible to confounding factors, such as alcohol consumption, which may be accompanied by other confounding factors such as smoking and excessive energy intake. These confounding factors may influence the accuracy of the results. In contrast, MR analysis is able to remove these confounders and more accurately reflect the relationship between the variables. However, due to sample

size limitations in the database, our study only verified the association between alcohol consumption and AD in the European population. Therefore, our results only apply to European populations and cannot be generalised to other populations. In addition, the relationship between alcohol consumption and AD still needs further investigation. Future research should focus on the specific effects of alcohol consumption on allergic diseases and how that relationship is impacted by sex and quantity and type of alcohol consumed to attain a more accurate assessment of that relationship.

A study from the Swedish Prospective Birth Cohort showed that fish consumption during infancy was associated with the development of allergic disease by the age of 12 years and that regular fish consumption during infancy reduced the risk of allergic disease up to the age of 12 years[45]. Another study of a primary population of patients over 14 years of age with AD showed that allergy to fish in AD patients was associated with persistent eczematous skin lesions[46]. However, our study showed no causal relationship between fish intake (neither oily nor non-oily) and AD. A cross-sectional study of dietary modifications in patients with AD showed that the consumption of vegetables and fruits improved the skin condition of patients[47]. This study used MR analysis methods and did not find a causal relationship between vegetable intake or fruit intake and AD. Notably, previous studies have shown that the consumption of meat[48], wheat[48], processed foods[49,50] and coffee is associated with the onset of AD[51]. In contrast, our study did not find a causal relationship between the above factors. Cows' milk, eggs, peanuts, wheat, soya, nuts and fish are responsible for > 90 % of food allergies in children with AD[52]. Previous studies support the association between milk, egg, and nut intake (e.g. peanuts) and an elevated risk of AD[48,53–57]. Using a significance threshold of P1 = 5e-8, we were unable to perform effective studies on milk, egg or peanut intake due to the lack of sufficient IV for MR analysis. To address this problem, we relaxed the significance threshold to P2 = 5e-6. After using this relaxed threshold, our IVW results showed no significant associations between milk, eggs, or peanuts and the risk of AD. However, future studies with larger sample sizes are needed to verify the accuracy of our conclusions.

Although some studies have shown that food allergies may play a role in the development of AD in some patients, not all AD patients exhibit food allergy reactions. Furthermore, even if a person is allergic to a certain food, this does not mean that the food is the cause of AD[38]. We speculate that there is most likely a common pathogenesis between food allergy and AD. This study provides strong new evidence for the relationship between dietary factors and AD. A possible pathway for dietary factors to affect AD is through the gut microbiome, as the intake of different foods can affect the composition of bacteria in the gut, thereby affecting nutrient metabolism[58,59]. There is growing evidence that the establishment of the gut microbiome early in life influences the development of AD[60]. A two-sample MR study demonstrated bidirectional causality between the gut flora and AD[61]. Therefore, these studies revealed a role for the gut flora in the pathogenesis of AD.

The strengths of this study are that it is the first large-scale MR analysis to explore the causal relationship between twenty-one dietary factors and AD. Our findings provide stronger evidence than traditional observational studies. This study has several limitations, and the results of MR need to be interpreted with caution. First, the causal relationship found in the MR analysis reflects the effects of long-term exposure; thus, short-term exposure may not be clinically meaningful. Second, we were unable to distinguish between causal relationships at different time points; for example, allergies in AD patients usually occur in childhood, and patients gradually tolerate sensitisation with age. Therefore, our findings may not be meaningful for infants. Furthermore, the univariable MR analysis showed only an overall effect between exposure and outcome and not a direct effect between them. Extremely complex mechanisms may exist between exposure and outcome. The most important point is that due to the database sample size and sample type, we were unable to study the AD population by age and disease severity. In future studies with suitable samples, more detailed analysis should be performed. Finally, this study mainly included data from individuals of European ancestry, preventing us from extrapolating these findings to other ethnic groups. We were unable to further subdivide the different types of dietary intake or distinguish the effects of different dietary combinations. Therefore, further studies with larger sample sizes are needed to validate our findings.

Conclusions

The study showed that beef intake may be associated with a reduced risk of AD. Due to the wide 95 % CI((0·030–0·656), we could not determine the exact protective effect of white bread against AD. In addition, the number of alcoholic drinks per week, alcohol consumption frequency, processed meat intake, poultry intake, non-oily fish intake, oily fish intake, pork intake, lamb/mutton intake, cheese intake, cooked vegetable intake, dried fruit intake, fresh fruit intake, cereal intake, salad/raw vegetable intake, whole egg intake, unsalted peanut intake, milk intake and coffee intake were not associated with AD. Our study revealed a causal relationship between diet and AD at the genetic level, with beneficial implications for AD patients. Through personalised dietary advice, they can better cope with and manage diseases.

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Y. C., J. Y. and Q. W. designed the study, drafted the manuscript and verified the data; Y. C., M. L., D. T. and M. C. conducted the statistical analyses; J. Z. and J. G. drafted the manuscript and revised it critically for important intellectual content; X. X., Y. P. and S. C. substantially contributed to the interpretation of data; and W. H. and Z. X. were accountable for all aspects of the work. All authors critically reviewed and approved the final manuscript.

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as potential.

This study used only publicly available summary data, which were approved for human experimentation by an ethical standards committee. Therefore, additional ethical approval was not required for the current study.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114524000436

References

1. Weidinger S, Beck LA, Bieber T, *et al.* (2018) Atopic dermatitis. *Nat Rev Dis Primers* **4**, 1.
2. Weidinger S & Novak N (2016) Atopic dermatitis. *Lancet (London, England)* **387**, 1109–1122.
3. Nutten S (2015) Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab* **66**, 8–16.
4. Avena-Woods C (2017) Overview of atopic dermatitis. *Am J Managed Care* **23**, S115–S123.
5. Ständer S (2021) Atopic dermatitis. *N Engl J Med* **384**, 1136–1143.
6. Gochnauer H, Valdes-Rodriguez R, Cardwell L, *et al.* (2017) The psychosocial impact of atopic dermatitis. *Adv Exp Med Biol* **1027**, 57–69.
7. Filanovsky MG, Pootongkam S, Tamburro JE, *et al.* (2016) The Financial and Emotional Impact of Atopic Dermatitis on Children and Their Families. *J Pediatr* **169**, 284–290.e285.
8. Chang YS & Chiang BL (2018) Sleep disorders and atopic dermatitis: a 2-way street? *J Allergy Clin Immunol* **142**, 1033–1040.
9. Boguniewicz M, Fonacier L, Guttman-Yassky E, *et al.* (2018) Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. *Ann Allergy Asthma & Immunol: Offic Publ Am Coll Allergy, Asthma, Immunol* **120**, 10–22.e12.
10. Manam S, Tsakok T, Till S, *et al.* (2014) The association between atopic dermatitis and food allergy in adults. *Curr Opin Allergy Clin Immunol* **14**, 423–429.
11. Roerdink EM, Flokstra-de Blok BM, Blok JL, *et al.* (2016) Association of food allergy and atopic dermatitis exacerbations. *Ann Allergy, Asthma Immunol: Offic Publ Am Coll Allergy Asthma Immunol* **116**, 334–338.
12. Breuer K, Heratizadeh A, Wulf A, *et al.* (2004) Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy: J Br Soc Allergy Clin Immunol* **34**, 817–824.
13. Niggemann B, Sielaff B, Beyer K, *et al.* (1999) Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy: J Br Soc Allergy Clin Immunol* **29**, 91–96.
14. Singh AM, Anvari S, Hauk P, *et al.* (2022) Atopic dermatitis and food allergy: best practices and knowledge gaps-a work group report from the AAAAI allergic skin diseases committee and leadership institute project. *J Allergy Clin Immunol Pract* **10**, 697–706.
15. Lawlor DA, Harbord RM, Sterne JA, *et al.* (2008) Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med* **27**, 1133–1163.
16. Burgess S, Davey Smith G, Davies NM, *et al.* (2019) Guidelines for performing Mendelian randomization investigations. *Wellcome Open Res* **4**, 186.
17. Davies NM, Holmes MV & Davey Smith G (2018) Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ (Clin Res ed)* **362**, k601.
18. Sanderson E, Glymour MM, Holmes MV, *et al.* (2022) Mendelian randomization. *Nat Rev Meth Primers* **2**, 6.
19. Hingorani A & Humphries S (2005) Nature's randomised trials. *Lancet (London, England)* **366**, 1906–1908.
20. Davey Smith G & Ebrahim S (2005) What can mendelian randomisation tell us about modifiable behavioural and environmental exposures? *BMJ (Clin Res Ed)* **330**, 1076–1079.
21. Skrivankova VW, Richmond RC, Woolf BAR, *et al.* (2021) Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: the STROBE-MR statement. *JAMA* **326**, 1614–1621.
22. Burgess S, Scott RA, Timpson NJ, *et al.* (2015) Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. *Eur J Epidemiol* **30**, 543–552.
23. Davey Smith G & Hemani G (2014) Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet* **23**, R89–98.
24. Didelez V & Sheehan N (2007) Mendelian randomization as an instrumental variable approach to causal inference. *Stat Meth Med Res* **16**, 309–330.
25. Kurki MI, Karjalainen J, Palta P, *et al.* (2022) FinnGen: unique genetic insights from combining isolated population and national health register data. MedRxiv https://doi.org/10.1101/2022.03.03.22271360
26. Smith GD & Ebrahim S (2003) 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* **32**, 1–22.
27. Slatkin M (2008) Linkage disequilibrium–understanding the evolutionary past and mapping the medical future. *Nat Rev Genet* **9**, 477–485.
28. Hartwig FP, Davies NM, Hemani G, *et al.* (2016) Two-sample Mendelian randomization: avoiding the downsides of a powerful, widely applicable but potentially fallible technique. *Int J Epidemiol* **45**, 1717–1726.
29. Burgess S & Thompson SG (2011) Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol* **40**, 755–764.
30. Nikolakopoulou A, Mavridis D & Salanti G (2014) How to interpret meta-analysis models: fixed effect and random effects meta-analyses. *Evidence-Based Mental Health* **17**, 64.

31. Bowden J, Davey Smith G, Haycock PC, *et al.* (2016) Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol* **40**, 304–314.
32. Bowden J, Del Greco MF, Minelli C, *et al.* (2017) A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med* **36**, 1783–1802.
33. Zuber V, Colijn JM, Klaver C, *et al.* (2020) Selecting likely causal risk factors from high-throughput experiments using multivariable Mendelian randomization. *Nat Commun* **11**, 29.
34. Burgess S, Bowden J, Fall T, *et al.* (2017) Sensitivity analyses for robust causal inference from mendelian randomization analyses with multiple genetic variants. *Epidemiol (Cambridge, Mass)* **28**, 30–42.
35. Slob EAW, Groenen PJF, Thurik AR, *et al.* (2017) A note on the use of Egger regression in Mendelian randomization studies. *Int J Epidemiol* **46**, 2094–2097.
36. Burgess S & Thompson SG (2017) Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol* **32**, 377–389.
37. Verbanck M, Chen CY, Neale B, *et al.* (2018) Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet* **50**, 693–698.
38. Oykhman P, Dookie J, Al-Rammahy H, *et al.* (2022) Dietary elimination for the treatment of atopic dermatitis: a systematic review and meta-analysis. *J Allergy Clin Immunol Pract* **10**, 2657–2666.e2658.
39. Chandra RK, Puri S, Suraiya C, *et al.* (1986) Influence of maternal food antigen avoidance during pregnancy and lactation on incidence of atopic eczema in infants. *Clin Allergy* **16**, 563–569.
40. Ito M, Morita T, Okazaki S, *et al.* (2019) Dietary habits in adult Japanese patients with atopic dermatitis. *J Dermatol* **46**, 515–521.
41. Sawada Y, Saito-Sasaki N, Mashima E, *et al.* (2021) Daily lifestyle and inflammatory skin diseases. *Int J Mol Sci* **22**, 5204.
42. Lim JJ, Lim YYE, Ng J, *et al.* (2022) An update on the prevalence, chronicity, and severity of atopic dermatitis and the associated epidemiological risk factors in the Singapore/Malaysia Chinese young adult population: a detailed description of the Singapore/Malaysia Cross-Sectional Genetics Epidemiology Study (SMCGES) cohort. *World Allergy Organ J* **15**, 100722.
43. Lomholt FK, Nielsen SF & Nordestgaard BG (2016) High alcohol consumption causes high IgE levels but not high risk of allergic disease. *J Allergy Clin Immunol* **138**, 1404–1413.e1413.
44. Roh D, Lee DH, Lee SK, *et al.* (2019) Sex difference in IgE sensitization associated with alcohol consumption in the general population. *Sci Rep* **9**, 12131.
45. Magnusson J, Kull I, Rosenlund H, *et al.* (2013) Fish consumption in infancy and development of allergic disease up to age 12 years. *Am J Clin Nutr* **97**, 1324–1330.
46. Čelakovská J, Josef B, Vaneckova J, *et al.* (2020) Food hypersensitivity reactions to seafish in atopic dermatitis patients older than 14 year of age - the evaluation of association with other allergic diseases and parameters. *Indian J Dermatol* **65**, 97–104.
47. Nosrati A, Afifi L, Danesh MJ, *et al.* (2017) Dietary modifications in atopic dermatitis: patient-reported outcomes. *J Dermatol Treatment* **28**, 523–538.
48. Yang YS, Byun YS, Kim JH, *et al.* (2015) Food hypersensitivity in adult patients with atopic dermatitis in Korea. *Clin Exp Dermatol* **40**, 6–10.
49. Park S, Choi HS & Bae JH (2016) Instant noodles, processed food intake, and dietary pattern are associated with atopic dermatitis in an adult population (KNHANES 2009–2011). *Asia Pac J Clin Nutr* **25**, 602–613.
50. Li Y, Su J, Luo D, *et al.* (2021) Processed food and atopic dermatitis: a pooled analysis of three cross-sectional studies in Chinese adults. *Front Nutr* **8**, 754663.
51. Uenishi T, Sugiura H & Uehara M (2003) Role of foods in irregular aggravation of atopic dermatitis. *J Dermatol* **30**, 91–97.
52. Sicherer SH & Sampson HA (1999) Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. *J Allergy Clin Immunol* **104**, S114–122.
53. Estrada-Reyes E, García-Hernández G, Martínez-Gimeno A, *et al.* (2006) Effect of extensively hydrolyzed milk formula on growth and resistance to bronchitis and atopic dermatitis in infants and toddlers. *J Investig Allergol Clin Immunol* **16**, 183–187.
54. Monti G, Muratore MC, Peltran A, *et al.* (2002) High incidence of adverse reactions to egg challenge on first known exposure in young atopic dermatitis children: predictive value of skin prick test and radioallergosorbent test to egg proteins. *Clin Exp Allergy: J Br Soc Allergy Clin Immunol* **32**, 1515–1519.
55. Huffaker MF, Kanchan K, Bahnson HT, *et al.* (2023) Epidermal differentiation complex genetic variation in atopic dermatitis and peanut allergy. *J Allergy Clin Immunol* **151**, 1137–1142.e1134.
56. Du Toit G, Katz Y, Sasieni P, *et al.* (2008) Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* **122**, 984–991.
57. Du Toit G, Roberts G, Sayre PH, *et al.* (2015) Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* **372**, 803–813.
58. Kau AL, Ahern PP, Griffin NW, *et al.* (2011) Human nutrition, the gut microbiome and the immune system. *Nature* **474**, 327–336.
59. Muegge BD, Kuczynski J, Knights D, *et al.* (2011) Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. *Science (New York, NY)* **332**, 970–974.
60. Chu Y, Meng Q, Yu J, *et al.* (2023) Strain-level dynamics reveal regulatory roles in atopic eczema by gut bacterial phages. *Microbiol Spectr* **11**, e0455122.
61. Jin Q, Ren F, Dai D, *et al.* (2023) The causality between intestinal flora and allergic diseases: insights from a bi-directional two-sample Mendelian randomization analysis. *Front Immunol* **14**, 1121273.

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