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Socioeconomic status, obesity, individual behaviors, diabetes, and risk for frozen shoulder

A Mendelian randomization study

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Abstract

There are few studies on risk factors for frozen shoulder, and even fewer Mendelian randomization (MR) studies on frozen shoulder. Therefore, we conducted a two-sample MR study to explore whether socioeconomic status (years of schooling, average total household income before tax), obesity (body mass index and waist circumference), individual behaviors (smoking initiation, alcohol intake frequency, coffee intake, nonoily fish intake, tea intake, beef intake, bread intake, cheese intake, oily fish intake, and fresh fruit intake), and diabetes (type 1 and type 2 diabetes) are associated with frozen shoulder. The exposure datasets and the outcome dataset were extracted from the MRC Integrative Epidemiology Unit at the University of Bristol Open genome-wide association studies project (https://gwas.mrcieu.ac.uk/). We conducted MR analyses using the inverse variance weighted (primary method), MR-Egger, and weighted median methods and conducted heterogeneity and pleiotropy analyses. Type 1 diabetes (OR: 1.103; 95% CI: 1.053–1.156; $P = .0000410$) was associated with an increased risk of frozen shoulder. Cheese intake (OR: 0.490; 95% CI: 0.267–0.899; $P = .0213$), non-oily fish intake (OR: 0.0993; 95% CI: 0.0220–0.448; $P = .00267$), years of schooling (OR: 0.453; 95% CI: 0.349–0.588; $P = .00000000277$), and average total household income before tax (OR: 0.434; 95% CI: 0.253–0.743; $P = .00236$) were discovered as protective factors. No horizontal pleiotropy was found in all analyzes we performed ($P > .05$). Our study indicated that type 1 diabetes was a risk factor for frozen shoulder while cheese intake, non-oily fish intake, years of schooling, and average total household income before tax were considered as protective factors for frozen shoulder.

Abbreviations: GWAS = genome-wide association studies, IEU = the MRC Integrative Epidemiology Unit at the University of Bristol, IVs = instrumental variables, IVW = inverse variance weighted, MR = Mendelian randomization, SNPs = single nucleotide polymorphisms.

Keywords: diabetes, frozen shoulder, individual behaviors, Mendelian randomization, obesity, socioeconomic status

1. Introduction

Adhesive capsulitis of the shoulder, also known as frozen shoulder, is a self-limiting disease that usually resolves spontaneously after 2 to 4 years.[1] Frozen shoulder often presents with stiffness, inability to stretch, and pain. The term frozen shoulder was first used in 1934 to describe pain on the affected side, inability to sleep, limited activity, and normal imaging studies.[2] In 1945, Neviaser redefined it as "Adhesive capsulitis of the shoulder".[3] The incidence of frozen shoulder is about 3%, and the incidence in childhood is very low.[4] It is more common in women between the ages of 40 and 70.[5,6] Previous study has identified thyroid and adrenal function, and diabetes as systemic risk factors for frozen shoulder.[7] And a possible genetic predisposition for frozen shoulder was found in a meta-analysis.[8] A study has found a link between frozen shoulder and Dupuytren disease.[9] Those researches on the risk factors of frozen shoulder has been quite limited, so it is still of great significance to explore the risk and protective factors of the frozen shoulder by using the Mendelian randomization (MR) method. MR is designed to study the causal effect between exposure and outcome.[10] The statistical nature of MR is to utilize genetic variation (usually single nucleotide polymorphisms, SNPs) irrelative to individual behaviors and environment as

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instrumental variables to identify causal relationships between exposures and outcomes.[10,11] Although there are many MR studies, few of them involve frozen shoulder, which is the main purpose of our study.

2. Methods

2.1. Study design

MR is based on the following basic assumptions. First, the association assumption: the instrumental variables (IVs) must be strongly correlated with the exposure factor. Second, the exclusivity assumption: IVs cannot be directly related to the outcome. Third, the independence assumption: IVs cannot be related to any possible confounding factors. This study used the genome-wide association studies (GWAS) summary data released by the MRC Integrative Epidemiology Unit at the University of Bristol (IEU) open GWAS project, which are derived from published articles, UK Biobank and FinnGen biobank. All datasets included in this study were anonymized, de-identified, and publicly available, and therefore did not require the Ethical Review Authority approval.

2.2. Instrument variables selection

SNPs related to socioeconomic status (years of schooling, average total household income before tax), obesity (body mass index and waist circumference), individual behaviors (smoking initiation, alcohol intake frequency, coffee intake, non-oily fish intake, tea intake, beef intake, bread intake, cheese intake, oily fish intake, and fresh fruit intake), and diabetes (type 1 diabetes and type 2 diabetes) were extracted from the IEU GWAS database project (https://gwas.mrcieu.ac.uk/), which was developed by the IEU at the University of Bristol. we screened the SNPs were strongly associated with exposures at the genome-wide significance level ($P < 5 \times 10^{-8}$), the linkage disequilibrium level ($r^2 < 0.001$), and clumping window > 10,000 kb. We used the F statistic to ensure a strong correlation between IVs and exposure, and it is generally believed that the F statistic >10 is considered to meet the strong correlation requirement.[12] More information about the exposure datasets is shown in Table 1.

2.3. GWAS data for frozen shoulder

The summary statistics for frozen shoulder used in this study, including 2942 case data and 167,641 control data, were extracted from the FinnGen biobank by the IEU GWAS database project. FinnGen study launched in Finland in 2017 is a study that combines genome information with digital health care data.

2.4. Statistical analysis

The inverse variance weighted (IVW) method was used as the main MR analysis method (the Wald ratio method was used if only one SNP is eligible and the random-effects IVW method was used as the major analytical method). As the method with the strongest ability to detect causality in two-sample MR analysis,[13] the IVW method is widely used. We then compared the consequences of the IVW method with other methods, including the weighted median and MR-Egger methods, except for the exposure "Oily fish intake" because only one SNP was eligible. More information is in Table 1. We assessed the heterogeneity of the IVW model using Cochran Q test. Potential heterogeneity was indicated when Cochrane Q test $P < .05$. However, Cochran Q-test $P < .05$ does not necessarily mean that the random effect IVW model is invalid. MR-Egger regression was used to detect directional pleiotropy because it allows a nonzero intercept.[14] Leave-one-out analyses were conducted to evaluate whether there were single SNPs that strongly affected the causal relationship between exposures and outcome. The MR-PRESSO method was then used to check and remove outliers. All analyzes were performed using the TwoSampleMR packages[15] in the R software (version 4.2.0).

3. Results

This study analyzed the causal relationship between Socioeconomic status, obesity, individual behaviors, diabetes, and frozen shoulder using 16 different exposure factors. More information on exposures and outcome can be obtained from Table 1. After the SNP filtering operation, the final number of SNPs used for each phenotype ranged from 1 to 475. The F statistic ranges from 12.00 to 22655.09, indicating that the instrumental variables we use meet the requirements of strong correlation with the exposures. In the analysis using the

Table 1

Information of the exposure and outcome datasets.

Exposure or outcome	Participants included in analysis	Identified SNPs	F-statistic	IEU GWAS id
Body mass index	681,275 European-descent individuals	475	77.41865778	ieu-b-40
Waist circumference	462,166 European-descent individuals	342	43.19888508	ukb-b-9405
Smoking initiation	632,802 European-descent individuals	83	171.3922051	ieu-b-4877
Alcohol intake frequency	462,346 European-descent individuals	92	115.1974417	ukb-b-5779
Coffee intake	428,860 European-descent individuals	38	41.75147731	ukb-b-5237
Type 2 diabetes	298,957 European-descent individuals	67	503.2514538	ebi-a-GCST007515
Type 1 diabetes	189,113 European-descent individuals	16	22655.08934	finn-b-E4_DM1
Tea intake	447,485 European-descent individuals	39	62.78192661	ukb-b-6066
Beef intake	461,053 European-descent individuals	14	27.84088854	ukb-b-2862
Bread intake	452,236 European-descent individuals	25	38.33874056	ukb-b-11348
Cheese intake	451,486 European-descent individuals	60	44.88006354	ukb-b-1489
Non-oily fish intake	460,880 European-descent individuals	11	27.54398116	ukb-b-17627
Oily fish intake	64,949 European-descent individuals	1	11.99728714	ukb-b-10546
Fresh fruit intake	446,462 European-descent individuals	52	15.50163436	ukb-b-3881
Years of schooling	766,345 European-descent individuals	295	54.7197388	ieu-a-1239
Average total household income before tax	397,751 European-descent individuals	43	57.85854034	ukb-b-7408
Adhesive capsulitis of shoulder	2942 adhesive capsulitis of shoulder cases and 167,641 controls of European descent	NA	NA	finn-b-M13_ADHCAPSULITIS

The information of the exposure and outcome datasets.

GWAS = genome-wide association studies; IEU = integrative epidemiology unit; SNPs = single-nucleotide polymorphism.

Table 2

The results of Mendelian randomization analyses.

Exposure	Used SNPs	Inverse variance weighted method (Wald ratio)		Weighted median method		MR-Egger method		Cochrane Q test		Pleiotropy			MR-PRESSO*					
													Raw			Outlier-corrected		
		OR(95% CI)	*P*-value	OR(95% CI)	*P*-value	OR(95% CI)	*P*-value	Q	*P*-value	MR-Egger intercept	se	*P*-value	casual estimate	sd	*P*-value	casual estimate	sd	*P*-value
Body mass index	475	1.045 (0.867–1.260)	0.641	0.861 (0.629–1.180)	0.353	0.781 (0.478–1.278)	0.326	579.76	0.000620	0.00511	0.00408	0.211	0.0444	0.0953	0.641	NA	NA	NA
Waist circumference	342	1.055 (0.830–1.340)	0.662	0.957 (0.670–1.367)	0.808	0.770 (0.391–1.518)	0.451	444.04	0.000141	0.00520	0.00536	0.332	0.0533	0.122	0.663	NA	NA	NA
Smoking initiation	83	1.005 (0.782–1.291)	0.968	1.175 (0.809–1.705)	0.397	0.976 (0.278–3.425)	0.970	80.43	0.528	0.000777	0.0166	0.963	0.00510	0.127	0.968	NA	NA	NA
Alcohol intake frequency	92	1.068 (0.785–1.453)	0.157	1.103 (0.697–1.745)	0.234	2.221 (0.866–5.695)	0.480	118.78	0.027	-0.0184	0.0114	0.110	0.0659	0.157	0.675	NA	NA	NA
Coffee intake	38	0.846 (0.426–1.678)	0.632	1.637 (0.631–4.250)	0.311	1.723 (0.437–6.794)	0.442	44.62	0.182	-0.0134	0.0115	0.249	-0.167	0.350	0.635	NA	NA	NA
Type 2 diabetes	67	1.018 (0.896–1.157)	0.780	1.041 (0.861–1.258)	0.680	1.011 (0.740–1.380)	0.947	85.10	0.057	0.000558	0.0104	0.958	0.0183	0.0653	0.781	NA	NA	NA
Type 1 diabetes	16	1.103 (1.053–1.156)	0.0000410	1.109 (1.055–1.167)	0.0000551	1.113 (1.029–1.203)	0.0178	26.22	0.0357	-0.00541	0.0196	0.786	0.0982	0.0239	0.000943	NA	NA	NA
Tea intake	39	1.019 (0.545–1.905)	0.953	1.444 (0.643–3.246)	0.374	2.258 (0.581–8.775)	0.247	56.26	0.0285	-0.0171	0.0132	0.205	0.0189	0.319	0.953	NA	NA	NA
Beef intake	14	1.584 (0.391–6.426)	0.520	1.533 (0.248–9.472)	0.646	629.160 (0.198–2000256.000)	0.143	14.84	0.317	-0.0760	0.0515	0.166	0.460	0.714	0.531	NA	NA	NA
Bread intake	25	0.762 (0.310–1.876)	0.554	0.608 (0.170–2.173)	0.443	0.0620 (0.000989–3.886)	0.201	28.50	0.239	0.0364	0.0299	0.236	-0.272	0.460	0.560	NA	NA	NA
Cheese intake	60	0.490 (0.267–0.899)	0.0213	0.475 (0.219–1.033)	0.0603	2.756 (0.213–35.738)	0.441	90.35	0.00538	-0.0298	0.0220	0.179	-0.713	0.309	0.0248	NA	NA	NA
Non-oily fish intake	11	0.0993 (0.0220–0.448)	0.00267	0.0821 (0.00102–0.663)	0.0190	0.0000977 (0.0000000745–0.128)	0.0327	8.89	0.542	0.0860	0.0445	0.0851	-2.308	0.725	0.00974	NA	NA	NA
Oily fish intake	1	0.0711 (0.00000125–4053.899)	0.636	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Fresh fruit intake	52	1.095 (0.448–2.679)	0.842	1.183 (0.310–4.508)	0.806	4.130 (0.197–86.612)	0.365	48.397	0.578	-0.0128	0.0143	0.375	0.0910	0.445	0.839	NA	NA	NA
Years of schooling	295	0.453 (0.349–0.588)	2.77E-09	0.424 (0.285–0.630)	0.0000217	0.477 (0.174–1.312)	0.153	274.34	0.789	-0.000738	0.00702	0.916	-0.792	0.129	2.47E-09	NA	NA	NA
Average total household income before tax	43	0.434 (0.253–0.743)	0.00236	0.406 (0.197–0.836)	0.0144	1.069 (0.0673–16.990)	0.962	50.69	0.168	-0.0176	0.270	0.518	-0.835	0.275	0.00406	NA	NA	NA

Sensitivity analyses could not be performed for oily fish intake due to few SNPs (only 1 SNP).

CI = confidence interval; NA = not available; OR = odds ratio; SNPs = single-nucleotide polymorphisms.

* The results of MR-PRESSO are presented in the form of beta values, and there is a conversion relationship between beta values and OR, specifically beta = log(OR).

IVW method, a total of 5 causal relationships were identified ($P < .05$). And this study also showed the results of the weighted median and MR-Egger methods.

We found that type 1 diabetes (OR: 1.103; 95% CI: 1.053–1.156; $P = .0000410$) was associated with an increased risk of frozen shoulder. This finding was further confirmed by the results of the weighted median (OR: 1.109; 95% CI: 1.055–1.167; $P = .0000551$) and MR-Egger (OR:1.113; 95% CI: 1.029–1.203; $P = .0178$) model. Cheese intake (OR: 0.490; 95% CI: 0.267–0.899; $P = .0213$), non-oily fish intake (OR: 0.0993; 95% CI: 0.0220–0.448; $P = .00267$), years of schooling (OR: 0.453; 95% CI: 0.349–0.588; $P = .00000000277$), and average total household income before tax (OR: 0.434; 95% CI: 0.253–0.743; $P = .00236$) were discovered as protective factors. Only non-oily fish intake showed positive conclusions in the 3 models, years of schooling and average total household income before tax only showed positive conclusions in the IVW and weighted median models, and cheese intake only found positive results in the IVW model. More results from these analyses are given in Table 2. Leave-one-out analyses (Fig. 1) showed that these causal relationships were very robust. Although heterogeneity was detected in some exposures, the consequences of the MR-Egger intercept indicated that no directional pleiotropy was detected (Table 2). As shown in Table 2, the MR-PRESSO analysis consequences are highly consistent with the IVW model, and an outlier was detected in Tea intake, and no positive results were observed after removing the outlier.

4. Discussion

This MR analysis found that type 1 diabetes, non-oily fish intake, years of schooling, and average total household income before tax were associated with frozen shoulder risk and there may be a causal relationship between cheese intake and frozen shoulder. This study also indicated that body mass index, waist circumference, smoking initiation, alcohol intake frequency, oily fish intake, coffee intake, type 2 diabetes, tea intake, beef intake, bread intake, and fresh fruit intake were not associated with frozen shoulder. To our knowledge, there are few MR studies for frozen shoulder. Therefore, our study is of great value in understanding the risk factors and protective factors of frozen shoulder.

Although previous research has suggested a link between frozen shoulder and diabetes, few studies have examined their relationship. A population-based follow-up study showed that the risk of developing frozen shoulder was significantly increased after developing diabetes (hazard ratio 1.33).[16] In addition, Lo SF et al found that diabetes is an independent risk factor for frozen shoulder.[17] However, their study did not differentiate between type 1 and type 2 diabetes. A study found that frozen shoulder is more common in people with type 1 and type 2 diabetes, and people with type 2 diabetes have a higher risk of developing frozen shoulder than people with type 1 diabetes (22.4% vs 10.3%).[18] However, they included fewer people with diabetes (291 with type 1 diabetes and 134 with type 2 diabetes), so their conclusions were not convincing. Therefore, we included type 1 diabetes (including 5928 cases and 183,185 controls) and type 2 diabetes (48,286 cases and 250,671 controls) in this study for analysis, and found a causal relationship between type 1 diabetes and frozen shoulder. Although a causal relationship between type 1 diabetes and frozen shoulder was shown in the IVW, weighted median, and MR-Egger model, MR is not a substitute for randomized controlled trials, but can only be used as a supplement to randomized controlled trials.[19]

To our knowledge, this study is the first to examine the relationship between socioeconomic status and frozen shoulder. Several previous MR studies have involved socioeconomic factors. MR studies found that socioeconomic status (Educational Attainment) was associated with COVID-19 severity,[20] ischemic stroke,[21] mental disorders,[22] and lung cancer.[23] This research indicated that there is a causal relationship between socioeconomic status and frozen shoulder. However, there may be an extremely complicated mechanism between socioeconomic status and frozen shoulder. We cannot simply say that years of schooling and average total household income before tax directly reduce the risk of frozen shoulder. risk, it is worth noting. In a study from China, body mass index was found to be related to the occurrence of frozen shoulder.[24] This study found that body mass index and waist circumference were not associated with frozen shoulder. In addition, in this study, it was found that most factors in individual behaviors (smoking initiation, alcohol intake frequency, coffee intake, tea intake, beef intake, bread intake, oily fish intake, and fresh fruit intake) were not

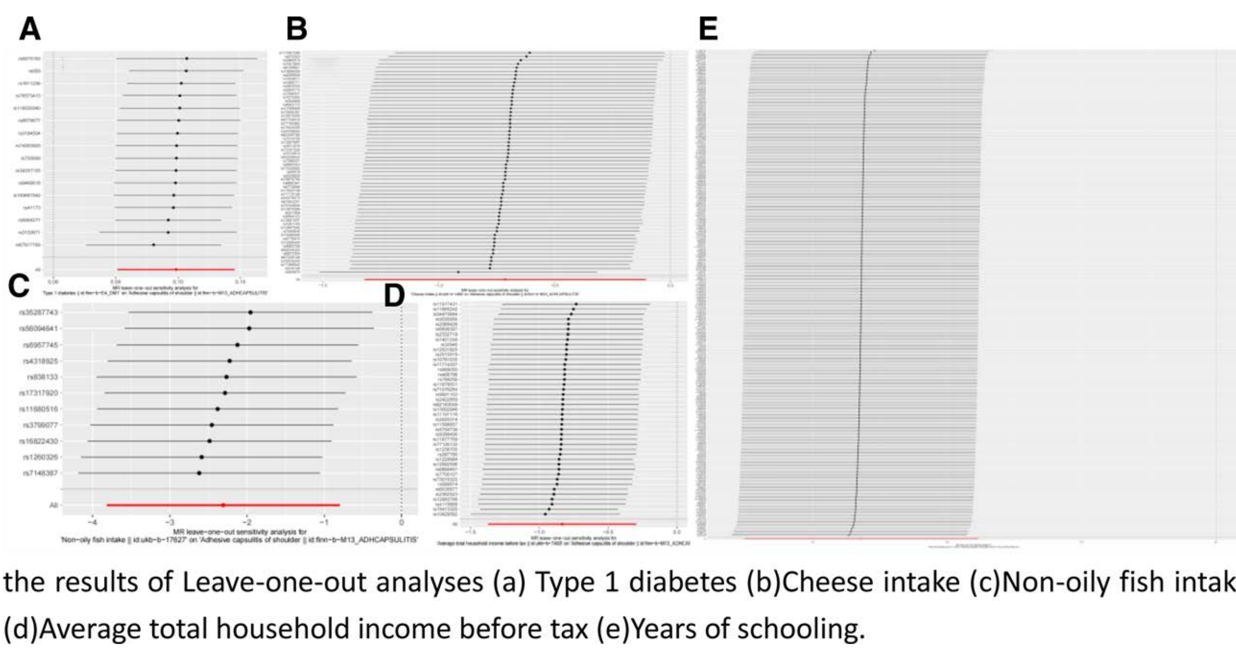

Figure 1. The results of Leave-one-out analyses. the results of leave-one-out analyses: (A) type 1 diabetes, (B) cheese intake, (C) non-oily fish intake, (D) average total household income before tax, (E) years of schooling.

related to frozen shoulder, only non-oily fish intake and cheese intake were related to frozen shoulder.

Although our work demonstrated some causal relationship between socioeconomic status, obesity, individual behaviors, and diabetes in frozen shoulder, the interpretation of MR studies should be more prudent. The causality demonstrated by MR reflects the effects of long-term or even lifetime exposure to risk factors. Therefore there may be no clinical significance in short-term exposure to risk factors.[25] In addition, there is another problem worth noting that MR cannot distinguish causality between different periods. For example, a MR study found a causal relationship between vitamin D and the risk of multiple sclerosis. For example, a MR study found a causal relationship between vitamin D and reduced risk of multiple sclerosis.[26] However, previous research has shown that this effect only exists in childhood or earlier.[27] Therefore, we must be cautious about the results of MR. First, univariate MR analysis does not directly reveal the direct effect of exposures on outcomes, but only the overall effect between them. There may be extremely complex mechanisms between exposure and outcome. Secondly, the conclusions of MR studies help to screen specific populations susceptible to diseases, but there may be greater limitations in guiding clinical intervention. Finally, the results of MR studies cannot replace randomized controlled trials. As a supplement to randomized controlled trials, they can verify past randomized controlled trials and explore directions for future trials. MR uses genetic variants as instrumental variables to infer the causal relationship between exposure and outcome, which can effectively overcome the bias caused by confounding and reverse causality.[28] We performed pleiotropic and sensitivity analysis to ensure the accuracy of the conclusions of MR analysis. And we used populations from Europe in both exposures and outcome to avoid unnecessary bias.

Several limitations in this study are also worth noting. First, F-statistics show that the instrumental variables we selected meet the requirement of strong correlation with exposure (F-statistics > 10), however, a considerable part of F-statistics is lower than 100, so this may affect the accuracy of the results. And more GWAS data can help avoid this problem. Second, this study used summary-level GWAS data, so we were unable to perform gender-stratified analysis. Third, for Cheese intake and Non-oily fish intake, it is impossible to distinguish the impact of different types of cheese and non-oily fish. Fourth, because of the lack of complete GWAS data for some exposures, we did not perform reverse MR analysis. Therefore, it is necessary to complete the two-way MR analysis when the data requirements are met in the future.

5. Conclusion

Our research found that type 1 diabetes, cheese intake, non-oily fish intake, years of schooling, and average total household income before tax were associated with the occurrence of frozen shoulder.

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