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Causal effects of diabetes and alcohol intake on Dupuytren's disease: a two-sample Mendelian randomization study in UK Biobank and FinnGen

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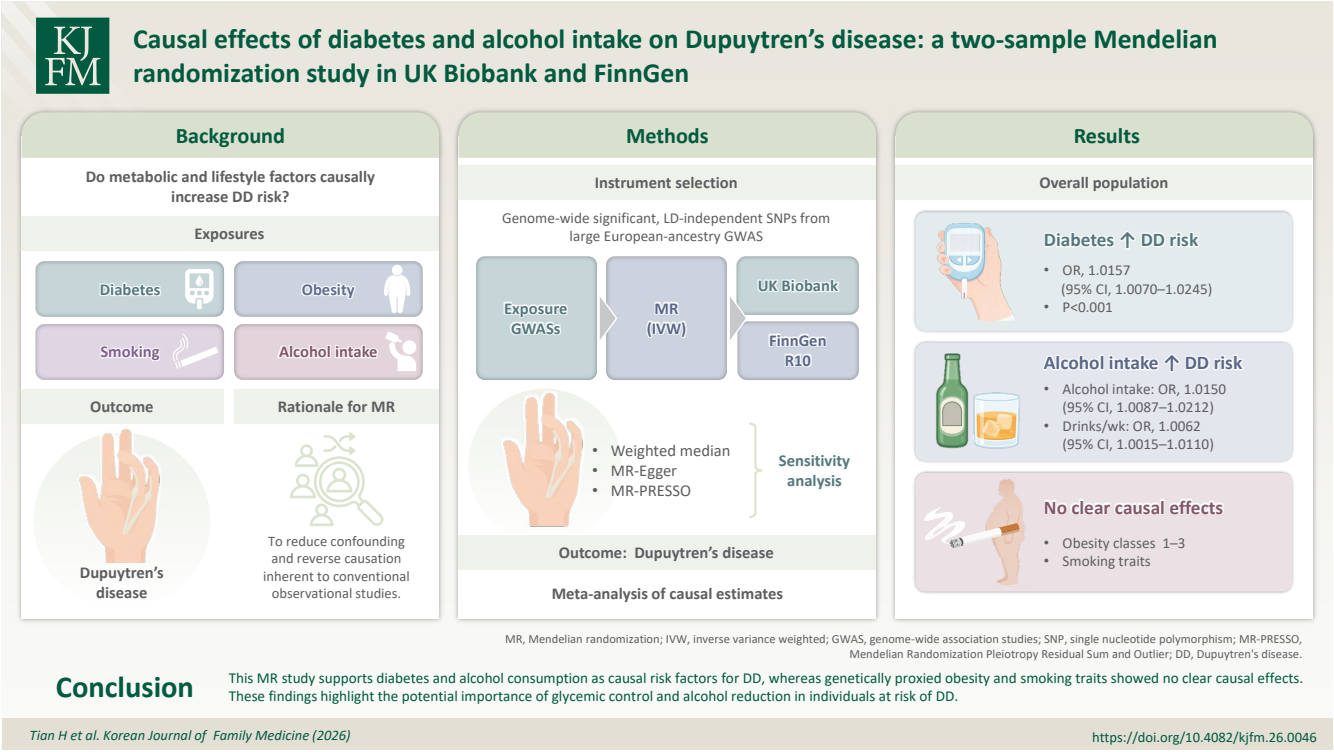

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ABSTRACT

Background: Dupuytren's disease (DD) is associated with metabolic and lifestyle traits. However, these associations remain uncertain because exposures frequently cluster, and conventional studies are vulnerable to residual confounding and reverse causation.

Methods: A two-sample Mendelian randomization (MR) analysis using genetic instruments for diabetes, obesity-related, smoking, and alcohol-related traits from genome-wide association studies of large European ancestry was conducted. Summary statistics of DD were obtained from UK Biobank and FinnGen and combined using meta-analysis. Multiplicative random-effects inverse variance weighted MR was used as the primary method, with complementary sensitivity analyses to test robustness.

Results: Genetic liability for diabetes was associated with a higher risk of DD (meta-analyzed odds ratio [OR], 1.0157; 95% confidence interval [CI], 1.0070–1.0245; P<0.001). Genetically predicted alcohol intake was also positively associated with DD (alcohol intake OR, 1.0150; 95% CI, 1.0087–1.0212; P<0.001; drinks per week OR, 1.0062; 95% CI, 1.0015–1.0110; P=0.0103). However, we found no convincing evidence that obesity traits or smoking intensity had causal effects on DD. Sensitivity analyses were directionally consistent, the instruments were adequately strong, and there was no substantial evidence of horizontal pleiotropy for the main associations. Although the observed effect sizes were modest, consistent with the multifactorial nature of DD, supporting directional risk associations rather than large individual-level effects.

Conclusion: This MR study supported diabetes liability and higher alcohol intake as causal risk factors for DD, whereas genetically proxied obesity and smoking traits showed no clear causal effects. These findings suggest that better glycemic management and lower alcohol exposure may help reduce the risk of DD.

Keywords: Dupuytren Contracture; Diabetes; Obesity; Lifestyle; Mendelian Randomization Analysis

Introduction

Dupuytren's disease (DD), a prevalent benign fibroproliferative condition, is characterized by aberrant collagen proliferation in the palms and fingers, resulting in progressive finger contractures that impair hand functionality and diminish the overall quality of life. According to a meta-analysis report [1], its global prevalence is 8.2%, with different prevalence rates in different continents (15.3%, Asia; 10.3%, Europe; 17.2%, Africa; and 2.3%, the Americas).

Many observational studies have reported an association between DD and metabolic or lifestyle factors including diabetes, obesity, smoking, and alcohol use [2-4]. However, these associations are difficult to interpret causally. Diabetes and obesity coexist commonly, and smoking and alcohol consumption are often correlated with each other. Patients with chronic metabolic diseases may also differ from unaffected individuals in several socioeconomic and clinical factors. Therefore, conventional epidemiological studies are vulnerable to residual confounding factors and reverse causation. Consequently, it remains uncertain whether these factors are the true causal drivers of DD or markers of broader risk profiles.

Several biological mechanisms may explain these associations. In diabetes, chronic hyperglycemia may promote advanced glycation end-product accumulation, abnormal collagen cross-linking, microvascular dysfunction, and fibroproliferative remodeling of the palmar fascia. Alcohol exposure has also been linked to oxidative stress, altered cytokine signaling, and dysregulated extracellular matrix turnover, which may contribute to fibrotic changes. In contrast, the mechanisms linking obesity and smoking to DD are less consistent and previous studies have reported conflicting findings. Distinguishing the epidemiological associations from biological plausibility further supports the need for causal inferences.

Although several observational studies and a limited number of Mendelian randomization (MR) reports have examined individual DD risk factors, important gaps remain. Previous studies have often evaluated single exposures in isolation, relied on one outcome dataset, or were unable to disentangle the correlated metabolic and behavioral traits. Consequently, the putative risk factors with the strongest causal relevance in DD remain unclear. In this study, we used a two-sample MR framework with replication across the UK Biobank and FinnGen databases to systematically evaluate diabetes, obesity, smoking, and alcohol-related traits in relation to DD. We hypothesized that genetic liability to diabetes and higher alcohol intake would increase the risk of DD, whereas the causal roles of obesity and smoking would be weaker or uncertain because prior evidence has been inconsistent.

Methods

Ethics statement

This study used publicly available, deidentified genome-wide association studies (GWAS) summary statistics; therefore, additional institutional review board approval and informed consent were not required. Ethical approval and informed consent were obtained in the original studies.

Study design and data sources

Figure 1 summarizes the study workflow and the core MR assumptions. We conducted a two-sample MR study using publicly available GWAS summary statistics [5]. Genetic instruments were selected for diabetes- and obesity-related traits and lifestyle factors. Summary statistics for DD were obtained from two independent European ancestry resources (UK Biobank and FinnGen). As this study used aggregated summary-level data from prior GWAS, no additional ethical approval was required. We report this study in line with STROBE-MR (strengthening the reporting of observational studies in epidemiology using Mendelian randomization) and current MR guidance [6]. The details of the data sources used are listed in Table 1.

Genetic instrument selection

For each exposure, single nucleotide polymorphisms (SNPs) were selected at genome-wide significance ($P<5\times10^{-8}$). To ensure independence, linkage disequilibrium clumping was performed using a European reference panel ($r^2<0.01$) with a 10,000 kb window, retaining the variant with the smallest P-value. Palindromic variants with ambiguous strand alignment were excluded, and proxy SNPs ($r^2\geq0.8$) were sought when an index SNP was unavailable in an outcome dataset. Instrument strength was evaluated using the F statistic ($F=\beta^2/SE^2$), with F<10 indicating potential weak instruments. Additionally, the exposure and outcome alleles were harmonized to ensure a consistent direction of the effect. When applicable, variants that were considered potentially weak were removed from the sensitivity checks. For each exposure, the instrument strength was summarized by reporting the mean F-statistics of the retained SNPs, all of which exceeded the conventional weak-instrument threshold of F>10.

Dupuytren's disease data sources

Outcome summary statistics for DD were obtained from the UK Biobank and FinnGen to enable independent replications. The UK Biobank DD phenotype was defined using the International Classification of Diseases, 10th Revision (ICD-10), code M72.0 and included 1,537 patients and 461,473 controls [7]. For FinnGen R10, the DD endpoint included 5,542 cases and 299,606 controls [8]. All participants in the exposure and outcome GWAS datasets were of European ancestry. Therefore, we restricted the primary analysis to European ancestry populations to minimize bias from population stratification, ancestry-specific linkage disequilibrium structures, and allele-frequency differences between the exposure and outcome datasets. Accordingly, the present findings should be interpreted as directly applicable to populations of European descent.

Statistical analysis

Causal estimates were derived using multiplicative random-effects inverse variance weighted (IVW) MR. We selected IVW as the primary estimator because it provides an efficient pooled estimate when the instruments are overall valid or when horizontal pleiotropy is balanced. It also allows for heterogeneity across SNP-specific estimates. Weighted median [9], MR-Egger [10], MR-PRESSO [11], Cochran's Q, and leave-one-out analyses

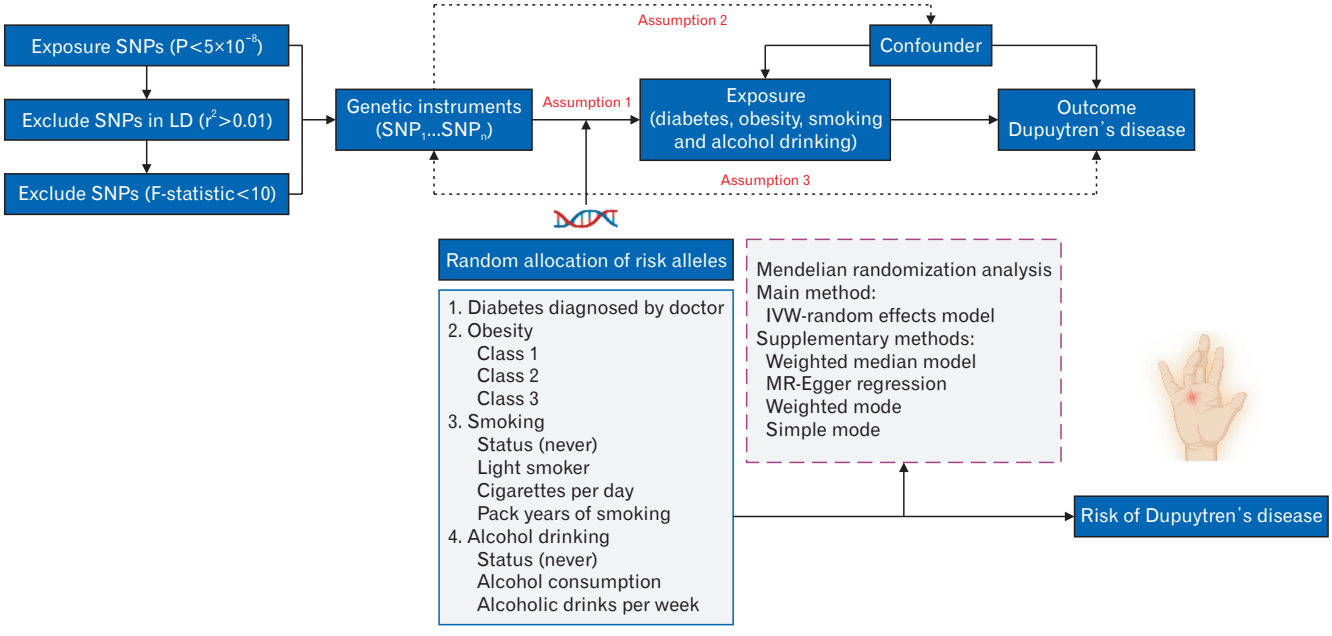

Figure 1. The study design flow chart and assumptions of Mendelian randomization (MR) studies. SNP, single nucleotide polymorphism; LD, linkage disequilibrium; IVW, inverse variance weighted.

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Table 1. Detailed information on used studies and consortia

No.	Trait	GWAS ID	Consortium	Unit	Participants included in analysis	SNPs	PMID or URL
Exposure							
1	Diabetes diagnosed by doctor	ukb-b-10753	MRC-IEU	SD	European (22,340 cases and 439,238 controls)	9,851,867	GWAS
2	Obesity class 1	ieu-a-90	GIANT	Log odds	European (32,858 cases and 65,839 controls)	2,380,428	23563607
3	Obesity class 2	ieu-a-91	GIANT	Log odds	European (9,889 cases and 62,657 controls)	2,331,456	23563607
4	Obesity class 3	ieu-a-92	GIANT	Log odds	European (2,896 cases and 50,364 controls)	2,250,779	23563607
5	Smoking status (never)	GCST90042704	-	-	European ancestry (245,064 cases and 209,365 controls)	11,842,647	34737426
6	Light smokers	GCST90043646	-	-	European ancestry (56,073 cases and 65,972 controls)	11,842,647	34737426
7	Cigarettes per day	ieu-b-25	GSCAN	SD	337,334	11,913,712	30643251
8	Pack years of smoking	ukb-b-10831	MRC-IEU	SD	142,387	9,851,867	GWAS
9	Alcohol drinker status (never)	GCST90042707	-	-	European ancestry (14,532 cases and 441,123 controls)	11,842,647	34737426
10	Alcohol consumption	ieu-a-1283	UK Biobank	NA	112,117	12,935,395	28937693
11	Alcoholic drinks per week	ieu-b-73	GSCAN	NA	335,394	11,887,865	30643251
Outcome							
1	Palmar fascial fibromatosis (Dupuytren's disease)	finngen_R10_M13_DUPUTRYEN	-	-	European (5,542 cases and 299,606 controls)	-	FinnGen consortium
2	Palmar fascial fibromatosis (Dupuytren's disease)	ukb-b-4772	-	-	European (1,537 cases and 461,473 controls)	9,851,867	UK Biobank

GWAS, genome-wide association studies; SNP, single nucleotide polymorphism; MRC-IEU, Medical Research Council Integrative Epidemiology Unit; SD, standard deviation; GIANT, Genetic Investigation of Anthropometric Traits; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use; NA, not available.

were used as complementary sensitivity analyses to assess the robustness of the findings to invalid instruments, heterogeneity, and horizontal pleiotropy. For analyses across multiple exposure traits, Bonferroni correction was applied to control for multiple testing. Results from the UK Biobank and FinnGen were meta-analyzed using fixed-effect models. Random-effects models were explored in sensitivity analyses when heterogeneity was present. All analyses were performed in R ver. 4.3.2 (The R Foundation for Statistical Computing) using the TwoSampleMR [12], MR-PRESSO, and MendelianRandomization packages [13].

Results

Metabolic traits (diabetes and obesity)

Diabetes and Dupuytren's disease

Higher genetically predicted diabetes was associated with an elevated risk of DD in UK Biobank data, FinnGen Consortium data, and the meta-analysis (P<0.001). Genetic predisposition to diabetes was positively associated with DD in both the FinnGen and UK Biobank, and these associations remained directionally consistent in both. The combined odds ratio (OR) was 1.0157 (95% confidence interval [CI], 1.0070–1.0245) for diabetes diagnosed by a physician on the log-odds liability scale (Figure 2). Although the magnitude of the effect was modest, this estimate reflected the expected change in DD risk per unit increase in genetically

Trait	Source	OR (95% CI)	P-value
Diabetes diagnosed by doctor	FinnGen	6.1782 (1.6192–23.5739)	0.0077
	UK Biobank	1.0156 (1.0069–1.0244)	<0.001
	Meta-analysis	1.0157 (1.0070–1.0245)	<0.001
Obesity class 1	FinnGen	0.9288 (0.8367–1.0310)	0.1656
	UK Biobank	0.9995 (0.9988–1.0002)	0.1576
	Meta-analysis	0.9995 (0.9988–1.0002)	0.1550
Obesity class 2	FinnGen	0.9676 (0.8750–1.0700)	0.5216
	UK Biobank	0.9997 (0.9991–1.0003)	0.2564
	Meta-analysis	0.9997 (0.9991–1.0002)	0.2548
Obesity class 3	FinnGen	0.9940 (0.7845–1.2595)	0.9604
	UK Biobank	0.9995 (0.9989–1.0000)	0.0643
	Meta-analysis	0.9995 (0.9989–1.0000)	0.0642
Smoking status (never)	FinnGen	0.8798 (0.7564–1.0233)	0.0967
	UK Biobank	1.0003 (0.9991–1.0014)	0.6643
	Meta-analysis	1.0003 (0.9991–1.0014)	0.6737
Light smokers	FinnGen	1.0479 (0.7066–1.5541)	0.8160
	UK Biobank	1.0016 (0.9982–1.0051)	0.3573
	Meta-analysis	1.0016 (0.9982–1.0051)	0.3562
Cigarettes per day	FinnGen	0.9453 (0.8262–1.0815)	0.4125
	UK Biobank	1.0008 (0.9997–1.0019)	0.1481
	Meta-analysis	1.0008 (0.9997–1.0019)	0.1500
Pack years of smoking	FinnGen	0.9298 (0.6269–1.3791)	0.7174
	UK Biobank	1.0007 (0.9979–1.0036)	0.6149
	Meta-analysis	1.0007 (0.9979–1.0036)	0.6168
Alcohol drinker status (never)	FinnGen	0.9567 (0.8671–1.0556)	0.3781
	UK Biobank	0.9996 (0.9985–1.0007)	0.4796
	Meta-analysis	0.9996 (0.9985–1.0007)	0.4734
Alcohol consumption	FinnGen	3.0001 (0.8135–11.0634)	0.0989
	UK Biobank	1.0149 (1.0087–1.0212)	<0.001
	Meta-analysis	1.0150 (1.0087–1.0212)	<0.001
Alcoholic drinks per week	FinnGen	3.0219 (1.8659–4.8941)	<0.001
	UK Biobank	1.0061 (1.0014–1.0109)	0.0117
	Meta-analysis	1.0062 (1.0015–1.0110)	0.0103

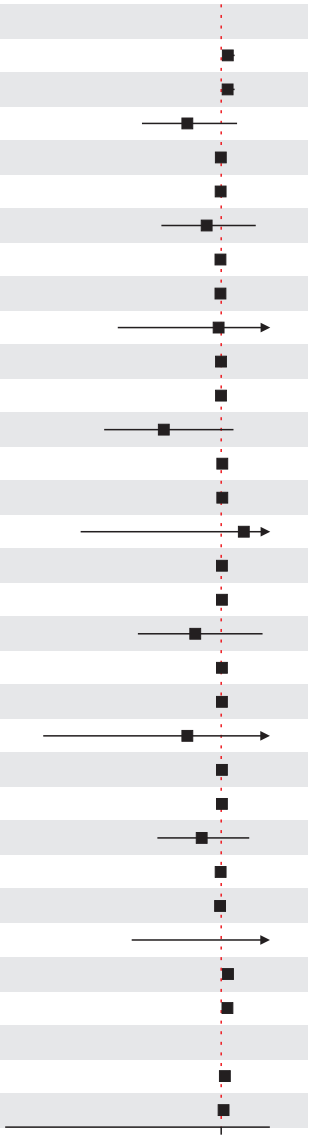

Figure 2. Univariable associations between metabolic and lifestyle factors and Dupuytren's disease were examined in the FinnGen and UK Biobank datasets. OR, odds ratio; CI, confidence interval.

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predicted diabetes liability and was consistent with a small but directionally robust contribution to a multifactorial disease.

Obesity and Dupuytren's disease

Genetically predicted obesity showed no association with an increased risk of DD, and the obesity associations remained directionally consistent for both data sources. The combined ORs were 0.9995 (95% CI, 0.9988–1.0002; P=0.1550) for obesity class 1, 0.9997 (95% CI, 0.9991–1.0002; P=0.2548) for obesity class 2, and 0.9995 (95% CI, 0.9989–1.0000; P=0.0642) for obesity class 3, respectively (Figure 2).

Lifestyle factors (smoking and alcohol drinking)

Smoking and Dupuytren's disease

Genetic predisposition to smoking was not associated with the development of DD. MR analysis showed no causal effect of genetic liability on cigarettes per day (OR, 1.0008; 95% CI, 0.9997–1.0019; P=0.1481) or pack years of smoking (OR, 1.0007; 95% CI, 0.9979–1.0036; P=0.6168) on DD risk (Figure 2). These findings suggest that smoking intensity is not causally associated with DD development.

Alcohol drinking and Dupuytren's disease

Higher genetic predisposition to alcohol consumption was associated with an increased risk of DD in the UK Biobank and in the meta-analysis (OR, 1.0150; 95% CI, 1.0087–1.0212; P<0.001) (Figure 2). Similarly, genetic liability to higher alcoholic drinks per week was associated with an increased risk of DD (OR, 1.0062; 95% CI, 1.0015–1.0110; P=0.0103). These results indicated that a genetic predisposition to greater alcohol intake is causally associated with a higher risk of developing DD.

Sensitivity test

The results of the associations of genetically predicted risk factors with DD in the MR sensitivity analyses are presented in Table 2, based on the weighted median, weighted mode, and MR-Egger results. The MR-Egger regression for most exposure factors revealed no significant pleiotropy, with intercepts close to zero. The results of the weighted-median and weighted-mode methods were broadly consistent, indicating that the effect estimates were robust. Exceptions included factors such as obesity class 3 in both data sources and alcohol consumption in the UK Biobank owing to an insufficient number of SNPs. Additionally, UK Biobank smoking status (never), alcoholic drinks per week, and FinnGen obesity class 2 showed significant pleiotropic effects (P<0.05).

Discussion

Using two-sample MR across the UK Biobank and FinnGen, we found genetic support for diabetes liability and higher alcohol intake as probable causal contributors to DD. In contrast, obesity traits and smoking intensity did not show any convincing causal effects. These findings refine the current understanding of the risk of DD by suggesting that some commonly reported observational associations may reflect confounding factors, comorbidity clustering, or correlated behaviors rather than direct biological effects. Although the effect sizes were modest, this pattern is consistent with the multifactorial nature of DD and helps prioritize exposures that may be more relevant to disease susceptibility.

Comparison with Prior Genetic Evidence: Previous MR analyses typically evaluated individual exposures (e.g., body mass index or lifestyle factors) in isolation and often relied on a single DD outcome source [14,15]. In contrast, we examined a broader panel of clinically relevant and potentially modifiable metabolic and lifestyle traits in a unified MR framework, incorporated obesity severity strata, and replicated the results across UK Biobank and FinnGen using meta-analytic synthesis. This triangulated approach improved the robustness and provided clinically actionable targets supported by genetic triangulation.

Diabetes, a metabolic disorder, is widely recognized as a significant risk factor for various diseases, including DD [16]. There is an increase in the likelihood of developing palmar aponeurosis contracture among individuals with diabetes, with the presence of poor glycemic control in such patients showing a positive correlation with the incidence of DD [17,18]. There are numerous complications associated with diabetes stemming from nonenzymatic glycation of proteins, contributing to fibrotic diseases related to diabetes [19]. A hyperglycemic milieu results in increased collagen cross-linking in the connective tissue and the development of glycation end products, fostering the proliferation and contraction of fibrous tissue [20,21]. Diabetes-related microvascular diseases may also impair blood flow to the hands. This may promote local hypoxia and aggravate connective tissue remodeling. The systematic review and meta-analysis conducted by further substantiated the robust correlation between DD and diabetes [22]. Our findings are consistent with those of the broader literature and support diabetes-related biology as a plausible contributor to the pathogenesis of DD. In particular, the MR design strengthens the interpretation that the association cannot be solely explained by confounding factors or reverse causation.

We did not find convincing evidence that obesity traits causally increased the risk of DD. This finding differs from those of observational reports [23,24]. First, the observational associations between obesity and DD may reflect residual confounding due to diabetes, occupational exposure, metabolic comorbidities, or healthcare contact. Second, body mass index- or obesity-based genetic instruments capture the lifelong liability to adiposity, which may not correspond to the specific metabolic or hormonal pathways most relevant to palmar fibrosis. Third, the true association could be nonlinear or modified by sex, diabetes status, or body composition patterns that are not fully captured by standard summary-level MR. Taken together, our findings suggest that

Table 2. Associations of genetically predicted risk factors with Dupuytren's disease in MR sensitivity analyses

Exposure	SNP	P-value[a]	MR-Egger			Weighted median		Weighted mode	
			OR (95% CI)	P-value	P-value[b]	OR (95% CI)	P-value	OR (95% CI)	P-value
UK Biobank									
Diabetes	49	0.452	1.0226 (1.0026–1.0430)	0.0312	0.3086	1.0177 (1.0036–1.0319)	0.0133	1.0192 (1.0049–1.0338)	0.011
Obesity class 1	12	0.9983	0.9995 (0.9977–1.0013)	0.5986	0.6229	0.9992 (0.9983–1.0000)	0.0659	0.9992 (0.9981–1.0003)	0.1824
Obesity class 2	6	0.4944	0.9991 (0.9976–1.0006)	0.3207	0.8175	0.9995 (0.9988–1.0002)	0.1731	0.9994 (0.9986–1.0002)	0.1773
Obesity class 3	2	-	-	-	-	-	-	-	-
Smoking status (never)	81	0.0428	0.9938 (0.9875–1.0000)	0.0555	0.0056	0.9997 (0.9982–1.0000)	0.6783	0.9985 (0.9955–1.0014)	0.3054
Light smokers	3	0.5083	0.9974 (0.9884–1.0066)	0.6786	0.0697	1.0008 (0.9987–1.0028)	0.4705	1.0006 (0.9984–1.0028)	0.6429
Cigarettes per day	17	0.3388	1 (0.9982–1.0019)	0.9469	0.1771	1.0001 (0.9988–1.0015)	0.8185	0.9999 (0.9986–1.0013)	0.9855
Pack years of smoking	7	0.3544	0.9979 (0.9918–1.0041)	0.5351	0.3673	0.9993 (0.9960–1.0026)	0.671	0.9995 (0.996–1.003)	0.8149
Alcohol drinker status (never)	18	0.8918	1.0007 (0.9855–1.016)	0.9325	0.0717	0.9998 (0.9984–1.0011)	0.736	1.0002 (0.9977–1.0027)	0.8874
Alcohol consumption	2	-	-	-	-	-	-	-	-
Alcoholic drinks per week	26	0.042	1.0231 (1.0069–1.0394)	0.0096	0.0162	1.0091 (1.0038–1.0144)	0.0007	1.0127 (1.0055–1.0199)	0.0019
FinnGen									
Diabetes	78	0.5346	2.4181 (0.0948–61.698)	0.5947	0.0648	7.1221 (0.8889–57.063)	0.0644	13.463 (1.2162–149.04)	0.0373
Obesity class 1	18	0.1466	0.7583 (0.5736–1.0026)	0.07	0.2938	0.9013 (0.7843–1.0358)	0.1433	0.8993 (0.7726–1.0469)	0.189
Obesity class 2	11	0.0299	0.7176 (0.5637–0.9135)	0.0246	0.3695	0.929 (0.8368–1.0313)	0.1672	0.9195 (0.8232–1.0271)	0.1681
Obesity class 3	2	-	-	-	-	-	-	-	-
Smoking status (never)	125	0.5586	1.0592 (0.5595–2.005)	0.8602	0.0004	0.9474 (0.7789–1.1525)	0.589	1.295 (0.6779–2.4759)	0.4347
Light smokers	5	0.9042	1.1344 (0.3179–4.0477)	0.8583	0.0408	1.0243 (0.7304–1.4364)	0.8895	1.0536 (0.7258–1.5295)	0.7971
Cigarettes per day	29	0.5638	0.8916 (0.703–1.1309)	0.3527	0.7555	0.9306 (0.7658–1.1308)	0.4695	0.9298 (0.7772–1.1125)	0.4333
Pack years of smoking	11	0.5816	0.7299 (0.2913–1.8294)	0.5188	0.7528	0.8619 (0.5187–1.4324)	0.5664	0.8121 (0.4718–1.3976)	0.4697
Alcohol drinker status (never)	30	0.7864	0.976 (0.8199–1.1617)	0.7862	0.3716	1.0312 (0.8837–1.2033)	0.6965	1.0319 (0.8945–1.1904)	0.6692
Alcohol consumption	5	0.2746	463.7871 (0.2553–842,613.1921)	0.2072	0.1903	2.7949 (0.8461–9.2331)	0.0918	2.672 (0.9296–7.6798)	0.1421
Alcoholic drinks per week	38	0.4376	1.9847 (0.6245–6.307)	0.2529	0.273	4.0166 (2.0202–7.9857)	0.0001	5.625 (1.8473–17.128)	0.0043

Sensitivity analyses for obesity class 3 and alcohol consumption were not feasible due to the limited number of SNPs available for analysis.
MR, Mendelian randomization; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.
[a]The significance of pleiotropy was assessed through the P-values obtained from the MR-Egger intercept test, with a threshold of P<0.05 indicating statistical significance of the pleiotropic effect. [b]P-value associated with the heterogeneity Q statistic.

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obesity may be more of a correlated clinical characteristic than a direct causal determinant of DD.

Similarly, we found no convincing causal effect of smoking on DD. However, this null result does not necessarily invalidate prior observational associations. Smoking behavior is difficult to accurately measure, and the dose, duration, cessation, and cumulative exposure may not be fully represented by available genetic proxies. In addition, smoking may indirectly influence DD through vascular, inflammatory, or occupational pathways, which are only partially captured by MR instruments [25-27]. Therefore, the discrepancy between MR and observational studies may reflect differences between lifelong genetic liability and measured behavioral exposure as well as residual confounding in conventional epidemiology.

Alcoholism is a lifestyle factor that affects health, with epidemiological studies and clinical observations suggesting a correlation between alcohol consumption and palmar aponeurosis contracture. However, the precise mechanism remains unclear. Alcohol consumption is significantly associated with a higher prevalence of DD in men, as evidenced by a large cohort study conducted in France [27]. One perspective posits that alcohol consumption stimulates the generation of reactive oxygen species within the body, resulting in oxidative stress and subsequent damage to cells and tissues [15,26]. On the contrary, an alternative perspective posits that the consumption of alcohol could potentially augment the synthesis of growth factors, including transforming growth factor-beta, that play a role in the formation of fibrous tissue [28]. Alcohol disrupts collagen metabolism by inhibiting fibroblast activity and increasing the levels of collagen-degrading enzymes. This may reduce tissue resilience and increase susceptibility to DD [29,30]. Taken together, these observations suggest that alcohol contributes to DD through oxidative stress, profibrotic signaling, and disturbed extracellular matrix remodeling. Our MR findings extend the observational literature by supporting alcohol exposure as a likely causal risk domain, rather than a simple behavioral correlate.

A key strength of this study was the use of an MR design with replication across two independent outcome datasets. This approach reduced vulnerability to residual confounding and reverse causation, and strengthened causal inference for the main associations.

Limitations

This study had several limitations. First, although we applied multiple pleiotropy-robust methods, horizontal pleiotropy could not be completely excluded, and some exposure-outcome pairs showed heterogeneity in single datasets. Second, all analyses were restricted to populations of European ancestry to improve ancestry matching and instrument validity. Therefore, generalizability to other populations remains uncertain. Third, MR estimates were reported on a genetic liability or genetically predicted exposure scale and should not be interpreted as the direct effect size of short-term clinical interventions. Fourth, because some exposure GWAS datasets included UK Biobank participants, a partial sample overlap with the UK Biobank DD outcome dataset is possible and may have biased estimates toward observational associations, although replication in FinnGen reduces this concern. Fifth, some secondary traits had relatively few instruments, limiting the statistical power and precision of the sensitivity analyses.

Conclusion

Using a two-sample MR study, we found that genetic liability for diabetes and higher alcohol consumption were associated with an increased risk of DD, whereas obesity and smoking traits showed no convincing causal effects. These findings strengthen the evidence that diabetes-related biology and alcohol exposure are associated with susceptibility to DD. However, the estimated effects were small, and the results should be interpreted primarily as evidence of a risk association on a genetic liability scale. From a clinical perspective, these findings support further investigation of glycemic control and alcohol exposure as potentially modifiable domains of DD risk, although direct preventive implications remain to be established.

Article Information

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

All data used in this study are openly accessible without any limitations and can be obtained upon request.

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