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Risk Factors for Carpal Tunnel Syndrome: Mendelian Randomization Study

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Abstract

Background: This study aimed to investigate potential risk factors for carpal tunnel syndrome (CTS). We used a Mendelian randomization (MR) approach to identify causal associations. It is contributing to the understanding of CTS development.

Methods: We employed MR analysis to investigate the potential links between 88 different risk factors and CTS. The analysis was conducted using data from a genome-wide association study (GWAS) that involved a large cohort of individuals with European ancestry, including 48,843 cases of CTS and 1,190,837 controls.

Results: Among the 88 potential risk factors, 19 traits, including Type 2 diabetes, obesity-related factors, psychiatric factors, hormone-related factors, lifestyle factors, and socioeconomic status, were significantly associated with CTS risk. Additionally, suggestive associations were observed with 17 other factors, including fasting glucose, depression, sleep duration, alcohol intake, and vitamin levels. However, no causal evidence was found for associations between autoimmune diseases, inflammatory biomarkers, acromegaly, and wrist fractures with the risk of CTS.

Conclusion: This Mendelian randomization study identifies several potential risk factors for CTS, shedding light on its multifactorial nature. These findings underscore the importance of metabolic, hormonal, lifestyle, and socioeconomic factors in CTS development, providing valuable implications for preventive measures and interventions.

Keywords

Carpal Tunnel Syndrome, Mendelian Randomization, Risk Factors

Introduction

As the most common peripheral nerve entrapment syndrome worldwide, carpal tunnel syndrome (CTS) is a condition where the median nerve in the carpal tunnel of the wrist becomes compressed, leading to nerve entrapment. CTS is a common cause of work disability, affecting approximately 1–5% of the general population, and it imposes significant healthcare costs on society [1,2].

Several observational studies have identified several factors associated with CTS, including gender, age, race, obesity, alcohol consumption, drug toxicity and exposure to toxins, endocrine diseases, and specific occupations [1,3–9]. Nearly all research findings indicate that CTS is more prevalent in females, particularly during pregnancy and breastfeeding, with incidence rates up to three times higher than in males [7,10]. This gender difference can be partially attributed to hormonal factors. Postmenopausal women who take oral contraceptives or hormone replacement therapy in the first year after menopause, as well as those who undergo oophorectomy, seem to have a lower incidence of CTS [6,11,12]. The likelihood of developing CTS is 2.5 times higher in individuals who are obese compared to those who are not obese. Research suggests that trauma, such as wrist fractures, and inflammatory conditions like rheumatoid arthritis, may increase the capacity of the carpal tunnel, leading to CTS [13]. Some cases of CTS are associated with endocrine disorders, such as hypothyroidism, acromegaly, and diabetes.

Additionally, carpal tunnel narrowing due to trauma or inflammation caused by conditions such as inflammatory rheumatic diseases also pose risk factors. Extensive research has shown a positive correlation between CTS and occupations involving highly repetitive wrist motion, the use of vibratory tools, increased hand force, and prolonged or repetitive flexion/extension of the wrist [14,15]. In 2008, Thomsen et al. [16] and in 2014, Mediouni et al. [17] further investigated this association between computer work and CTS. Despite the fact that carpal tunnel pressure increases during computer keyboarding and mouse use, it remains below levels that are considered harmful. However, associations from observational studies can be potentially biased by confounding and reverse causality.

One way to address this issue is through MR analysis, which can help overcome the limitations of observational studies related to confounding factors and reverse causality [18,19]. The estimated familial occurrence of CTS is 17–39% [20,21] and the heritability of CTS has been estimated to be 0.46 in women [22]. A better understanding of potentially pathogenic risk factors for CTS will lead to better prevention of the disease. In this study, two-sample MR analysis was used to explore the causal relationship between potential risk factors and CTS.

Methods

MR Design:

Our study was conducted in accordance with the Declaration of Helsinki revised in 2013, and the methods followed the *STROBE-MR checklist* [23,24]. As our MR study was based on publicly available summary statistics, no IRB approval or informed consent was necessary. A total of 88 possible risk factors were enrolled and categorized into the following 14 groups: T2D-related factor, Obesity-related factor, Psychiatric factor, Hormone-related factor, Lifestyle factor, Socioeconomic status, lipids, Mineral, Amino acid, Inflammatory biomarker, Autoimmune disorder, Plasma fatty acid, Vitamin, and Other 14 factors.

Data Sources:

Genetic associations with CTS were obtained from the publicly available GWAS among individuals of European ancestry (n_case = 48,843 and n_control = 1,190,837) from Iceland, the UK, Denmark, and Finland (**Suppl. Table-S1**, data available at https://www.decode.com/summarydata/) [25]. Instrumental variables for the 88 exposures were identified from genome-wide association studies (GWASs) and are detailed in **Table-1**.

*Selection and Validation of SNPs***:**

SNPs that met a significance threshold of P < 5e-08 were selected as instrumental variables (IVs). To ensure variable independence and account for LD effects, an LD parameter (r^2) of 0.001 and a genetic distance of 10,000 kb were utilized. We removed palindromic SNPs from the instrumental SNPs that were chosen for analysis. The F statistic ($F = beta^2/se^2$) was employed to exclude weak instrumental biases, with SNPs having an F statistic < 10 being excluded [26]. Variance estimation was based on the formula $R^2 = 2 \times MAF \times (1 - MAF) \times (beta/SD)$ (MAF indicates minor allele frequency; beta estimation was based on MAF). Due to the limited number of SNPs associated with CTS at the p < 5e-08 significance level for Acromegaly and pituitary gigantism, the genetic instruments were adjusted to p < 1e-05.

Table-1: Data Sources and Instrumental Variables used for Exposures Included in the MR Analyses

Exposure	GWAS ID	PubMed ID	Trait name	Unit	Sample size	Population	SNPs	Used SNPs*
T2D-related factor								
Type 2 diabetes	ebi-a-GCST006867	30297969	Type 2 diabetes	log(OR)	655666	European	118	103
Fasting glucose	ebi-a-GCST90002232	34059833	Fasting glucose	SD	200622	European	65	56
Fasting insulin	ebi-a-GCST90002238	34059833	Fasting insulin	SD	151013	European	38	32
Hemoglobin A1c	ebi-a-GCST90002244	34059833	Hemoglobin A1c	SD	146806	European	73	59
Obesity-related factor								
Birth weight	ukb-b-13378		Birth weight	SD	261932	European	138	109
Body mass index	ukb-b-19953	30124842	Body mass index	SD	461460	European	439	340
Standing height	ukb-b-10787	NA	Standing height	SD	461950	European	723	580
Sitting height	ukb-b-16881	NA	Sitting height	SD	461536	European	576	466
Waist circumference	ukb-b-9405	NA	Waist circumference	SD	462166	European	356	290
Arm fat-free mass (right)	ukb-b-19520	NA	Arm fat-free mass (right)	SD	454753	European	499	409
Arm fat-free mass (left)	ukb-b-19925	NA	Arm fat-free mass (left)	SD	454672	European	496	407
Arm fat mass (right)	ukb-b-6704	NA	Arm fat mass (right)	SD	454757	European	409	322
Arm fat mass (left)	ukb-b-8338	NA	Arm fat mass (left)	SD	454684	European	408	321
Trunk fat mass	ukb-b-20044	NA	Trunk fat mass	SD	454588	European	413	332
Lean body mass	GCST007063	30593698	Lean body mass	SD	155961	European	397	352
Whole body fat mass	ukb-b-19393	NA	Whole body fat mass	SD	454137	European	417	330
Circulating adiponectin	ieu-a-1	22479202	Circulating adiponectin	SD	39883	European	14	10
Psychiatric factor								
Lifetime Anxiety Disorder	GCST009575	31748690	Lifetime anxiety disorder	log(OR)	83566	European	5	3
Depression	GCST007342	30718901	Depression	log(OR)	807553	European	79	66
Sleep duration	GCST007561	30846698	Sleep duration	SD	446118	European	70	52
Short sleep duration	GCST007559	30846698	Short sleep (< 7 h)	log(OR)	446118	European	26	21
Sleeplessness / insomnia	ukb-b-3957	NA	Sleeplessness / insomnia	log(OR)	462341	European	42	29
Morning/evening person	ukb-b-4956	NA	Morning/evening person (chronotype)	log(OR)	413343	European	156	128
Narcolepsy	ukb-b-5776	NA	Daytime dozing / sleeping (narcolepsy)	log(OR)	460913	European	31	29
Frequency of tenseness / restlessness	ukb-b-5664	NA	Frequency of tenseness / restlessness in last 2 weeks	log(OR)	445194	European	16	12
Restless leg syndrome	GCST011995	33239738	Restless leg syndrome	log(OR)	480982	European	16	12
Hormone-related factor								
Age when periods started	ukb-b-3768	NA	Age when periods started (menarche)	SD	243944	European	190	159
Age at menopause	ukb-b-17422	NA	Age at menopause (last menstrual period)	SD	143819	European	112	87
SHBG levels	ebi-a-GCST90012110	32042192	Sex hormone-binding globulin levels adjusted for BMI	SD	368929	European	421	311
SHBG levels adjusted for BMI	ebi-a-GCST90012111	32042192	Sex hormone-binding globulin levels	SD	370125	European	396	275
Estradiol levels	ebi-a-GCST90012105	32042192	Estradiol levels	SD	206927	European	13	8
Total testosterone levels	ebi-a-GCST90012114	32042192	Total testosterone levels	SD	425097	European	163	125

Lifestyle factor								
Alcohol intake frequency	ukb-b-5779	NA	Alcohol intake frequency	SD	462346	European	95	79
Alcohol consumption	GCST007461	30643251	Alcohol consumption (drinks per week)	SD	941280	European	37	29
Coffee intake	ukb-b-5237	NA	Coffee consumption	SD	428860	European	40	34
Age of smoking initiation	ieu-b-4877	30643251	Age of smoking initiation	SD	607291	European	91	70
Current tobacco smoking	ukb-b-223	NA	Current tobacco smoking	log(OR)	462434	European	35	30
Ever smoked	ukb-b-20261	30643251	Ever smoked	log(OR)	461066	European	83	64
Time spent using computer	ukb-b-4522	NA	Time spent using computer	SD	360895	European	83	66
Plays computer games	ukb-b-4779	NA	Plays computer games	log(OR)	462433	European	49	42
Sedentary behaviour	GCST006913	30531941	Sedentary behaviour	SD	91105	European	5	3
Moderate to vigorous physical activity duration	NA	35320144	Moderate to vigorous physical activity duration	SD	377234	European	19	19
Vigorous physical activity duration	NA	35320144	Vigorous physical activity duration	SD	261055	European	7	7
Socioeconomic status								
Years of schooling	ieu-a-1239	30038396	Years of schooling	SD	766345	European	310	241
Qualifications	ukb-b-16489	30038396	Qualifications: College or University degree	SD	458079	European	251	192
Intelligence	ebi-a-GCST006250	29942086	Intelligence	SD	269867	European	163	138
Serum lipids								
HDL cholesterol	ieu-b-109	24097068	HDL cholesterol	SD	403943	European	325	254
LDL cholesterol	ieu-a-300	24097068	LDL cholesterol	SD	173082	European	79	72
Total cholesterol	ieu-a-301	24097068	Total cholesterol	SD	187365	European	85	77
Triglycerides	ieu-a-302	24097068	Triglycerides	SD	177861	European	55	51
Apolipoprotein A1	met-d-ApoA1	NA	Apolipoprotein A1	SD	115078	European	74	57
Apolipoprotein B	met-d-ApoB	NA	Apolipoprotein B	SD	115078	European	53	39
Mineral								
Calcium in serum	ukb-d-30680_irnt	24068962	Calciuma in serum	SD	39400	European	195	158
Sodium in urine	ukb-a-335	31409800	Sodium in urine	SD	326831	European	34	27
Magnesium in serum	GCST000756	20700443	Magnesiuma in serum	SD	15366	European	5	3
Potassium in urine	ukb-a-334	31409800	Potassium in urine	SD	326816	European	9	8
Iron in serum	ieu-a-1049	25352340	Irona in serum	SD	23986	European	3	3
Amino acid								
Carnitine	met-a-379	24816252	Carnitine	SD	7797	European	17	15
Cysteine	met-a-455	23824729	Cysteine	SD	7692	European	13	7
Isoleucine	met-d-Ile	27898682	Isoleucine	SD	115075	European	8	7
Inflammatory biomarker								
Interleukin-6 levels	ebi-a-GCST90012005	33067605	Interleukin-6 levels	SD	21758	European	2	2
C-reactive protein	ieu-b-35	30388399	C-Reactive protein level	SD	204402	European	55	45
Immunoglobulin E	GCST001316	22075330	Immunoglobulin E	SD	6819	European	5	3
Autoimmune disorder								
Type 1 diabetes	ebi-a-GCST005536	21980299	Type 1 diabetes	log(OR)	29652	European	36	31
Allergic disease	ebi-a-GCST005038	30013184	Doctor diagnosed hayfever or allergic rhinitis	log(OR)	360838	European	72	54

Rheumatoid arthritis	ieu-a-833	NA	Rheumatoid arthritis	log(OR)	80799	European	57	47
Hypothyroidism/myxoedema	ukb-b-19732	NA	Non-cancer illness code, self-reported: hypothyroidism/myxoedema	log(OR)	462933	European	119	93
Plasma fatty acid								
Docosahexaenoic acid	met-d-DHA	21829377	Docosahexaenoic acid	SD	114999	European	46	35
Linoleic acid	met-d-LA	24823311	Linoleic acid	SD	114999	European	53	39
Palmitoleic acid	GCST001841	23362303	Palmitoleate (16:1n7)	SD	8961	European	5	5
Stearic acid	GCST001840	23362303	Stearate (18:0)	SD	8961	European	3	2
Vitamin								
Folate (vitamin B9)	NA	23754956	Folate (vitamin B9) in serum	SD	37341	European	2	2
Vitamin B12	NA	23754956	Vitamin B12 in serum	SD	45576	European	4	4
Vitamin D	ebi-a-GCST90000618	29343764	Serum 25-Hydroxyvitamin D levels in serum	SD	496946	European	177	92
Other factors								
Osteoarthritis	ebi-a-GCST007092	30664745	Osteoarthritis of the hip or knee	log(OR)	417596	European	25	20
Acromegaly and pituitary gigantism	E4_ACROMEG	NA	Acromegaly and pituitary gigantism	log(OR)	329258	European	6	5
Fractured bone site(s): Wrist	ukb-b-9571	NA	Fractured bone site(s): Wrist	log(OR)	460340	European	7	6
Glomerular filtration rate	ebi-a-GCST003375	26831199	Glomerular filtration rate	SD	32834	European	4	4
Hemoglobin concentration	ebi-a-GCST004615	27863252	Hemoglobin concentration	SD	172925	European	120	96
Hypertension	ukb-b-14057	NA	Hypertension	log(OR)	462933	European	216	166
Diastolic blood pressure	ieu-b-39	30224653	Diastolic blood pressure	SD	757601	European	441	365
Systolic blood pressure	ieu-b-38	30224653	Systolic blood pressure	SD	757601	European	436	358
Coronary artery disease	ebi-a-GCST005195	26343387	Coronary artery disease	log(OR)	547261	European	73	57
Peripheral artery disease	GCST008474	31285632	Peripheral artery disease	log(OR)	394408	European	18	13
Total body bone mineral density (age 45-60)	ebi-a-GCST005350	29304378	Total body bone mineral density (age 45-60)	SD	18805	European	21	18
Total body bone mineral density (age over 60)	ebi-a-GCST005349	29304378	Total body bone mineral density (age over 60)	SD	22504	European	22	18
Overall health rating	ukb-b-6306	NA	Overall health rating	SD	460844	European	109	92
Urate	GCST008971	31578528	Urate levels	SD	288649	European	178	145

*NA not available; SNP single nucleotide polymorphism;*Numbers of SNPs used in the present Mendelian randomization analyses*

MR Analysis:

The primary analysis method employed was the inverse variance-weighted (IVW) approach [27]. Additionally, MR Egger, weighted median, simple mode, and weighted mode methods were utilized. The estimates were reported as odds ratios (ORs) along with their corresponding 95% confidence intervals (CIs). A Bonferroni-corrected significance level of $p < 5.68e-04$ (0.05 divided by 88 risk factors) was applied. To balance Type I and II error rates, P-values ranging from 5.68e-04 to 0.05 were considered indicative of suggestive associations (**Suppl. Table-S2**).

Pleiotropy and Heterogeneity Analysis:

Cochran's Q test was performed to assess heterogeneity among individual causal effects, with significance defined as a Q_P-value < 0.05, or I^2 statistics > 25% indicating heterogeneity. We utilized MR-Egger regression to evaluate whether there is a presence of directional pleiotropy of instrumental variables [28] (**Suppl. Table-S3**). We identified exposures with horizontal pleiotropy for MR-Egger regression, performed Mendelian randomization pleiotropic residual and outlier (MR-PRESSO) analysis, and leave-one-out analysis to identify any outlier

instrumental variables [29]. If outlier SNPs were found to impact the MR estimates, they were removed and MR analysis was performed again to confirm the stability of results (**Suppl. Table-S4** and **Suppl. Table-S5**).

Results

Among 88 possible risk factors, 19 traits, including Type 2 diabetes, body mass index, standing height, sitting height, waist circumference, arm fat mass (right), arm fat mass (left), trunk fat mass, whole body fat mass, short sleep duration, insomnia, age when periods started, sex hormone-binding globulin levels (SHBG), SHBG levels adjusted for BMI, coffee intake, years of schooling, qualifications, intelligence, and overall health rating, were robustly associated with the risk of CTS. There were suggestive associations with 17 factors, including fasting glucose, hemoglobin A1c, arm fat-free mass (left), arm fat-free mass (right), depression, sleep duration, frequency of tenseness/restlessness, alcohol intake frequency, smoking initiation, current tobacco smoking, ever smoked, plays computer games, HDL cholesterol, sodium in urine, osteoarthritis, hypertension, and diastolic blood pressure (**Fig-1**).

T2D-Related Factor and Obesity-Related Factor:

Liability to Type 2 diabetes was significantly associated with an increased risk of CTS. Additionally, fasting glucose and hemoglobin A1c showed suggestive associations with an increased risk of CTS. Among the 13 obesity-related risk factors examined, eight demonstrated significant associations with CTS. Positive associations were found between CTS risk and BMI, waist circumference, arm fat mass right and left, trunk fat mass, and wholebody fat mass. In contrast, standing height and sitting height showed inverse and significant associations with CTS risk. Moreover, arm fat-free mass right and left exhibited suggestive associations with CTS risk, while birth weight, lean body mass, and adiponectin did not show any associations with CTS risk.

Psychiatric Factor:

Among the 9 psychiatric risk factors examined, five showed associations with CTS. Depression, short sleep duration, sleeplessness/insomnia, and frequency of tenseness/restlessness were positively associated with CTS risk, while sleep duration exhibited an inverse association with the risk.

Hormone-Related Factor:

Age when periods started, SHBG, and SHBG levels adjusted for BMI demonstrated a significantly inverse association with CTS risk. However, other hormone-related factors did not show any significant associations with CTS risk.

Lifestyle Factor and Socioeconomic Status:

Coffee intake was significantly associated with an increased risk of CTS. Alcohol intake frequency, age of smoking initiation, current tobacco smoking, ever smoked, and playing computer games showed suggestive associations with an increased risk of CTS. On the other hand, higher years of schooling, qualifications, and intelligence were all significantly associated with a lower risk of CTS.

Serum Lipids, Mineral, Amino Acid, Plasma Fatty Acid, and Vitamin:

Genetic predisposition to higher levels of high-density lipoprotein cholesterol was suggestively associated with a lower risk of CTS, whereas cysteine and sodium in urine were suggestively associated with a higher risk of CTS. There was limited evidence supporting causal associations of other factors with CTS.

Inflammatory Biomarker and Autoimmune Disorder:

There was no evidence of a causal association between autoimmune diseases (including Type 1 diabetes, allergic diseases, rheumatoid arthritis, and hypothyroidism/myxedema) or inflammatory biomarkers (including interleukin-6 levels, C-reactive protein, immunoglobulin E) and CTS risk.

Other Factors:

Among 14 other potential factors related to CTS, only overall health rating exhibited a statistically significant association with CTS. Three factors (osteoarthritis, hypertension, and diastolic blood pressure) were shown to be associated with CTS.

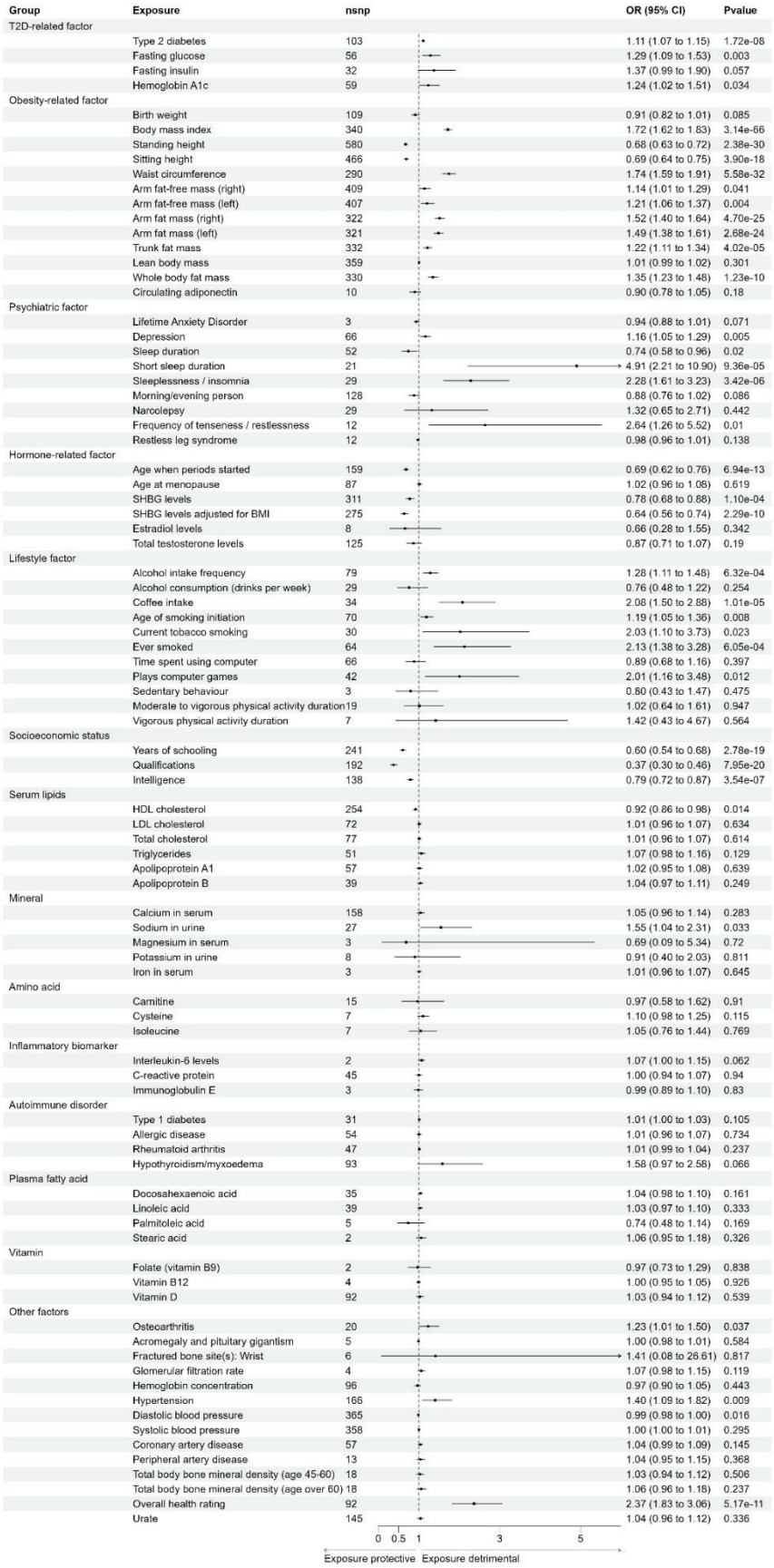

Fig-1:

Forest Plot Depicting the Summary Causal Effects of Risk Factors on Carpal Tunnel Syndrome (CTS) Using IVW MR Methods

Discussion

This study utilized MR analysis to investigate the associations between a wide range of potential factors and CTS. After analyzing 88 possible risk factors, we found 19 traits significantly associated with CTS risk. Additionally, suggestive associations were observed between CTS risk and 17 other factors.

The robust associations between CTS risk and Type 2 diabetes and BMI are consistent with prior literature, supporting the role of metabolic factors in the development of CTS. Our study further explored additional factors related to these two variables. We found significant correlations between fasting glucose, HbA1c, and CTS risk, indicating that glucose dysregulation might play a role in CTS pathogenesis. Diabetes and obesity may increase pressure within the carpal tunnel, resulting in compression of the median nerve. Additionally, increased waist circumference, arm fat mass, and whole body fat mass may raise carpal tunnel pressure, leading to an elevated risk of CTS. Conversely, taller height, sitting height, and higher arm fat-free mass showed a negative correlation with CTS risk. Higher standing height and sitting height may lead to reduced pressure inside the carpal tunnel, thereby decreasing the likelihood of compression on the median nerve. Additionally, the correlation with upper limb fat-free mass suggests that muscle tissue might play a protective role in the development of CTS.

We have also identified the involvement of psychological factors, hormones, lifestyle, and socioeconomic status in the development of CTS. Research has shown a positive correlation between CTS risk and major depressive disorders, sleep duration, frequency of stress/anxiety, and hypertension. Interestingly, these psychological factors are often associated with stress and disrupted sleep patterns, which may affect neural function and contribute to the development of CTS. Conversely, the negative correlation between sleep duration and CTS risk could be attributed to the role of sufficient sleep in neural repair and recovery, thereby reducing the risk of CTS. Age at menarche, levels of SHBG, and SHBG levels adjusted for BMI show a significant negative correlation with CTS risk. However, menopausal age, estradiol levels, and total testosterone levels do not exhibit a significant association with CTS. Previous observational studies consistently indicate a higher risk of CTS in females, especially during pregnancy and lactation. Gender and life-stage differences in CTS risk may partially be attributed to variations in SHBG levels, providing theoretical support for hormone replacement therapy. These findings may be related to the protective and reparative effects of hormones in the nervous system and their regulatory role in inflammation responses.

Moreover, the research reveals a significant positive correlation between coffee consumption and CTS risk, while higher education level, academic qualifications, and intelligence exhibit a significant negative correlation with CTS risk. The positive correlation with coffee consumption may be due to the stimulating effect of caffeine on the nervous system, leading to an increased risk of CTS. On the other hand, higher education and intelligence levels may be associated with healthier lifestyles and better self-management, thereby reducing the risk of CTS. These findings offer new insights into understanding the underlying mechanisms of CTS. However, apart from the association with osteoarthritis, our analysis did not find causal evidence linking autoimmune diseases (such as rheumatoid arthritis, hypothyroidism/myxedema), inflammatory biomarkers, acromegaly and pituitary gigantism, and wrist fractures to CTS risk. Although these factors were previously considered to be related to CTS, further research is needed to determine their causal relationship with CTS.

One of the strengths of this study is the utilization of Mendelian randomization analysis to assess causal relationships. By simulating randomized trials through the random distribution of genotypes, this method reduces confounding bias and reverses causality issues commonly associated with observational study designs, thus enhancing the credibility of causal inference. Additionally, the study benefits from a large sample size, comprehensively investigating 88 potential factors. The research results encompass 19 factors significantly associated with CTS risk and 17 factors with suggestive associations, providing a rich dataset for gaining deeper insights into the underlying mechanisms of CTS. However, there are limitations to the Mendelian randomization analysis method. The assumption that genotypes do not directly affect the causal variable may

not hold true in certain cases. Moreover, the reliance on known genetic associations with risk factors may be limited, potentially impacting the accuracy of the study's findings. Furthermore, the study did not cover all factors related to CTS risk, despite exploring multiple potential factors. Unconsidered genetic and environmental factors may still play a role in the development of CTS.

Conclusion

This study employed Mendelian randomization analysis to identify several potential factors significantly associated with the risk of CTS. Factors such as short sleep duration, insomnia, Type 2 diabetes, obesity, psychiatric factors, hormone-related factors, coffee intake, lifestyle, and socioeconomic status were found to be potentially related to CTS development. These findings contribute to a deeper understanding of the pathogenesis of CTS and offer novel insights for its prevention and intervention. However, it is important to acknowledge that Mendelian randomization analysis has its limitations and should be complemented by other research methods for further validation. Future studies could delve into the biological mechanisms underlying the association with CTS risk, aiming to provide more robust evidence for the prevention and management of CTS.

Ethics Approval and Consent to Participate

As our MR study was based on publicly available summary statistics, no IRB approval or informed consent was necessary.

Consent for Publication

All authors have read and agreed to the final version of the manuscript.

Availability of Data and Materials

All data utilized were sourced from publicly available databases, as detailed in Supplementary Table 1.

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Authors' Contributions

Yi Zhang: Conceptualization, Visualization, Project administration, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

Jianhong Ren: Visualization, Project administration, Data curation, Formal analysis, Methodology, Writing – review & editing.

Rurong Wang: Project administration, Data curation, Formal analysis, Methodology, Writing – review & editing.

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Disclosure

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

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