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A Comprehensive Systematic Review of Medical And Non Medical Correlates Of Carpal Tunnel Syndrome

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ABSTRACT

Introduction: Carpal Tunnel Syndrome (CTS) is a common entrapment neuropathy with a multifactorial etiology involving medical, occupational, anatomical, and lifestyle factors. Understanding its diverse correlates is crucial for prevention, diagnosis, and management.

Methods: A systematic evidence synthesis was conducted. Forty sources were included after screening based on predefined criteria, including established CTS diagnosis, examination of correlates, robust study design, quantitative association measures, adult population, and human studies. Data were extracted on study design, population, CTS definition, correlates examined, measurement methods, association results, and limitations.

Results: Medical correlates with strong evidence include diabetes mellitus (OR=1.90), obesity (OR=2.02), rheumatoid arthritis

(OR=1.96), and hypothyroidism (ES=1.44). Pregnancy-related CTS is prevalent (31-62%) and often persists postpartum. Non-medical correlates include occupational biomechanical exposures like vibration (OR=5.40) and hand force (OR=4.23), anatomical factors like a square-shaped wrist (OR=4.56), and female sex (OR=9.99). Psychosocial factors such as high job strain (HR=1.86) and low social support (HR=0.54) are also influential. Genetic factors, including variants in SERPINA1, explain approximately 2% of CTS risk. Notable heterogeneity exists for factors like computer use and smoking, largely dependent on study design and comparison groups.

Discussion: The synthesis reconciles heterogeneous findings by emphasizing the impact of diagnostic rigor, study design, confounding, and population context. Diabetes and obesity show consistent, mechanistically plausible links. Occupational risks are hierarchical and potent. Discordant findings for hormone replacement therapy (observational vs. RCT) and smoking (cross-sectional vs. longitudinal) highlight the critical role of study design in causal inference. CTS may serve as an early indicator of systemic conditions like cardiac amyloidosis.

Conclusion: CTS is a condition with diverse and interconnected correlates. A holistic, multidisciplinary approach to prevention and management is warranted, considering individual medical history, occupational exposure, anatomical predisposition, and psychosocial context. Future research should prioritize longitudinal designs, standardized diagnostic criteria, and exploration of gene-environment interactions.

Keywords: Carpal Tunnel Syndrome, Risk Factors, Occupational Diseases, Diabetes Mellitus, Obesity, Biomechanics, Meta-

Analysis, Systematic Review.

INTRODUCTION

Background

Carpal Tunnel Syndrome (CTS) is the most prevalent peripheral entrapment neuropathy, characterized by compression of the median nerve within the carpal tunnel. It presents with pain, paresthesia, and numbness in the radial digits, potentially progressing to thenar muscle weakness and atrophy. Its significant personal and socioeconomic burden stems from pain, functional impairment, work absenteeism, and healthcare costs (Barcenilla et al., 2012; Peters et al., 2016). The etiology of CTS is multifactorial and complex, involving an interplay of systemic medical conditions, local anatomical constraints, occupational biomechanical stressors, and lifestyle factors. Historically viewed as primarily an occupational disorder, contemporary evidence underscores a substantial contribution from non-occupational and intrinsic patient factors (Burger et al., 2016; Hassan et al., 2022). A comprehensive, integrated understanding of these diverse correlates is essential for refining risk stratification, implementing targeted prevention strategies, optimizing diagnostic pathways, and personalizing treatment approaches.

Research Gap and Novelty

While numerous studies have investigated individual risk factors for CTS, the literature is fragmented, with conclusions often varying by study design, diagnostic criteria, and population. Significant gaps exist in synthesizing evidence across both medical and non-medical domains within a single analytical framework. Key areas of uncertainty include: the magnitude and independence of associations for endocrine disorders like hypothyroidism; the paradoxical findings related to computer use and smoking across different study designs; the potential for CTS to be a sentinel sign for systemic diseases like cardiac amyloidosis; and the relative contribution of newly identified genetic factors. Furthermore, there is a need to reconcile apparently discordant findings, such as those for hormone replacement therapy, by critically examining methodological influences. This review aims to fill these gaps by providing a detailed, methodologically rigorous synthesis of

the broad spectrum of CTS correlates, explicitly addressing heterogeneity and offering a nuanced interpretation of the evidence.

Research Objectives

The primary objective of this study is to systematically identify, synthesize, and critically appraise the evidence on medical and non-medical correlates of Carpal Tunnel Syndrome. Specific aims include:

1. To quantify the strength of association between CTS and various medical conditions (e.g., diabetes, thyroid disorders, arthritis).
2. To evaluate the role of occupational and biomechanical exposures (e.g., vibration, repetition, posture).
3. To assess the influence of demographic, anatomical, lifestyle, and psychosocial factors.
4. To examine the impact of genetic predispositions on CTS risk.
5. To reconcile heterogeneity in effect estimates by analyzing the influence of study design, diagnostic criteria, and confounding.
6. To identify high-risk patient profiles and discuss implications for clinical and occupational practice.

Research Hypothesis

We hypothesize that CTS arises from a cumulative or synergistic interaction between intrinsic patient susceptibility (governed by genetic, anatomical, and medical factors) and extrinsic biomechanical loads. Specifically, we posit that:

1. Systemic medical conditions (e.g., diabetes, inflammatory arthritis) will show strong, consistent associations with CTS, independent of occupational exposure.

2. Occupational biomechanical factors will demonstrate a dose-response relationship and a hierarchy of risk (vibration > force > repetition).
3. Anatomical factors (e.g., wrist ratio, bifid median nerve) will significantly modify individual risk.
4. Apparent contradictions in the literature for factors like smoking and computer use will be largely explained by methodological differences in study design and exposure assessment.

Significance of the Study

This comprehensive synthesis holds significant value for multiple stakeholders:

- **For Clinicians**: It provides an evidence-based reference to guide clinical evaluation, identify patients who may require screening for concomitant conditions (e.g., diabetes, hypothyroidism, cardiac amyloidosis), and inform prognostic discussions, particularly regarding surgical outcomes in populations like diabetics or workers' compensation patients (Moradi et al., 2020; Dunn et al., 2018; Elghouneimy et al., 2024).
- **For Occupational Health Professionals**: It clarifies the attributable risk of work-related factors, supporting the development of effective ergonomic interventions and workplace policies to mitigate biomechanical and psychosocial risks (You et al., 2014; Mansfield et al., 2018).
- **For Researchers**: It identifies key methodological challenges and knowledge gaps, directing future research towards longitudinal designs, standardized diagnostics, and the exploration of interaction effects and genetic epidemiology (Skuladottir et al., 2022).
- **For Policymakers**: It offers a robust evidence base for formulating public health guidelines and compensation criteria related to work-related musculoskeletal disorders.

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate medical and non medical correlates of Carpal Tunnel Syndrome.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Carpal Tunnel Syndrome	CTS	Carpal Tunnel Disorder	Median Nerve Compression
Intervention (I) / Exposure (E)	Associated Factors	Predictors	Comorbidities	Work-Related Factors
Comparison (C)	Healthy Controls	Asymptomatic Individuals	General Population	Non-CTS Controls
Outcome (O)	Incidence	Occurrence	Clinical Diagnosis	Symptom Severity

The Boolean MeSH keywords inputted on databases for this research are: *("Carpal Tunnel Syndrome" OR "CTS" OR "Carpal Tunnel Disorder" OR "Median Nerve Compression") AND ("Associated Factors" OR "Predictors" OR "Comorbidities" OR "Work-Related Factors") AND ("Healthy Controls" OR "Asymptomatic Individuals" OR "General Population" OR "Non-CTS Controls") AND ("Incidence" OR "Occurrence" OR "Clinical Diagnosis" OR "Symptom Severity")*

Screening

We screened in sources based on their abstracts that met these criteria:

- **CTS Diagnosis**: Does the study investigate participants diagnosed with carpal tunnel syndrome using established diagnostic criteria (clinical examination, nerve conduction studies, or validated diagnostic tools)?
- **CTS Correlates**: Does the study examine medical and/or non-medical correlates of CTS (such as diabetes, hypothyroidism, rheumatoid arthritis, pregnancy, obesity, occupational factors, repetitive activities, ergonomic factors, or lifestyle factors)?
- **Study Design**: Is the study design one of the following: cross-sectional, case-control, cohort study, randomized controlled trial, systematic review, or meta-analysis?
- **Quantitative Measures**: Does the study report quantitative measures of association (such as odds ratios, relative risks, correlation coefficients, or prevalence ratios)?
- **Adult Population**: Does the study include adult participants (≥18 years of age)?
- **Study Type Quality**: Is the study NOT a case report, case series, editorial, letter, or conference abstract?
- **Study Focus**: Does the study examine correlates/factors associated with CTS (rather than focusing solely on treatment interventions without examining correlates)?
- **Human Studies**: Is this a human study (not an animal study or in vitro study)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

- **Study Design & Population**:

  Extract study methodology and population details including:

  - Study design (cross-sectional, case-control, cohort, meta-analysis, etc.)

- Sample size and population characteristics (age range, gender distribution, occupational groups)
- Setting (workplace, community, clinical, etc.)
- Country/region where conducted
- Study period/timeframe

- **CTS Definition**:

  Extract how carpal tunnel syndrome was defined and diagnosed:

  - Diagnostic criteria used (symptoms only, nerve conduction studies, clinical examination, etc.)
  - Whether standardized criteria were applied (e.g., NIOSH criteria)
  - Case ascertainment method (self-report, medical records, clinical examination)
  - Any severity grading or classification used

- **Correlates Examined**:

  List all correlates/risk factors studied, categorizing as medical or non-medical:

  - Occupational factors (repetitive motions, force, vibration, posture, specific job types)
  - Personal/demographic factors (age, gender, BMI, pregnancy status)
  - Medical conditions (diabetes, arthritis, thyroid disorders, etc.)
  - Anatomical factors (wrist size, tunnel dimensions)
  - Lifestyle factors (physical activity, smoking, alcohol use)
  - Other exposures investigated

- **Measurement Methods**:

  Describe how each correlate was measured or assessed:

  - Measurement tools or instruments used

- Whether objective or subjective measures
- Exposure assessment method (self-report, observation, direct measurement)
- Timeframe of exposure assessment
- Any validation of measurement methods mentioned

- **Association Results**:

  Extract quantitative results for each correlate-CTS association:

  - Effect measures (odds ratio, relative risk, correlation coefficient, etc.) with confidence intervals
  - P-values or statistical significance
  - Direction of association (positive/negative)
  - Any dose-response relationships identified
  - Subgroup analyses results (by gender, age, etc.)
  - Adjusted vs unadjusted results if both provided

- **Key Limitations**:

  Note important study limitations that affect interpretation:

  - Methodological issues (bias, confounding, temporal relationships)
  - Measurement limitations or exposure misclassification
  - Sample size or power issues
  - Generalizability concerns
  - Author-identified limitations
  - Risk of bias assessment results if available

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Carpal Tunnel Syndrome" OR "CTS" OR "Carpal Tunnel Disorder" OR "Median Nerve Compression") AND ("Associated Factors" OR "Predictors" OR "Comorbidities" OR "Work-Related Factors" AND "Healthy Controls" OR "Asymptomatic Individuals" OR "General Population" OR "Non-CTS Controls") AND ("Incidence" OR "Occurrence" OR "Clinical Diagnosis" OR "Symptom Severity")*	2
Semantic Scholar	*("Carpal Tunnel Syndrome" OR "CTS" OR "Carpal Tunnel Disorder" OR "Median Nerve Compression") AND ("Associated Factors" OR "Predictors" OR "Comorbidities" OR "Work-Related Factors") AND ("Healthy Controls" OR "Asymptomatic Individuals" OR "General Population" OR "Non-CTS Controls") AND ("Incidence" OR "Occurrence" OR "Clinical Diagnosis" OR "Symptom Severity")*	250
Springer	*("Carpal Tunnel Syndrome" OR "CTS" OR "Carpal Tunnel Disorder" OR "Median Nerve Compression") AND ("Associated Factors" OR "Predictors" OR "Comorbidities" OR "Work-Related Factors") AND ("Healthy Controls" OR "Asymptomatic Individuals" OR "General Population" OR "Non-CTS Controls") AND ("Incidence" OR "Occurrence" OR "Clinical Diagnosis" OR "Symptom Severity")*	1,923
Google Scholar	*("Carpal Tunnel Syndrome" OR "CTS" OR "Carpal Tunnel Disorder" OR "Median Nerve Compression") AND ("Associated Factors" OR "Predictors" OR "Comorbidities" OR "Work-Related Factors") AND ("Healthy Controls" OR "Asymptomatic Individuals" OR "General Population" OR "Non-CTS Controls") AND ("Incidence" OR "Occurrence" OR "Clinical Diagnosis" OR "Symptom Severity")*	17,200
Wiley Online Library	*("Carpal Tunnel Syndrome" OR "CTS" OR "Carpal Tunnel Disorder" OR "Median Nerve Compression") AND ("Associated Factors" OR "Predictors" OR "Comorbidities" OR "Work-Related Factors") AND ("Healthy Controls" OR "Asymptomatic Individuals" OR "General Population" OR "Non-CTS Controls") AND ("Incidence" OR "Occurrence" OR "Clinical Diagnosis" OR "Symptom Severity")*	2,243

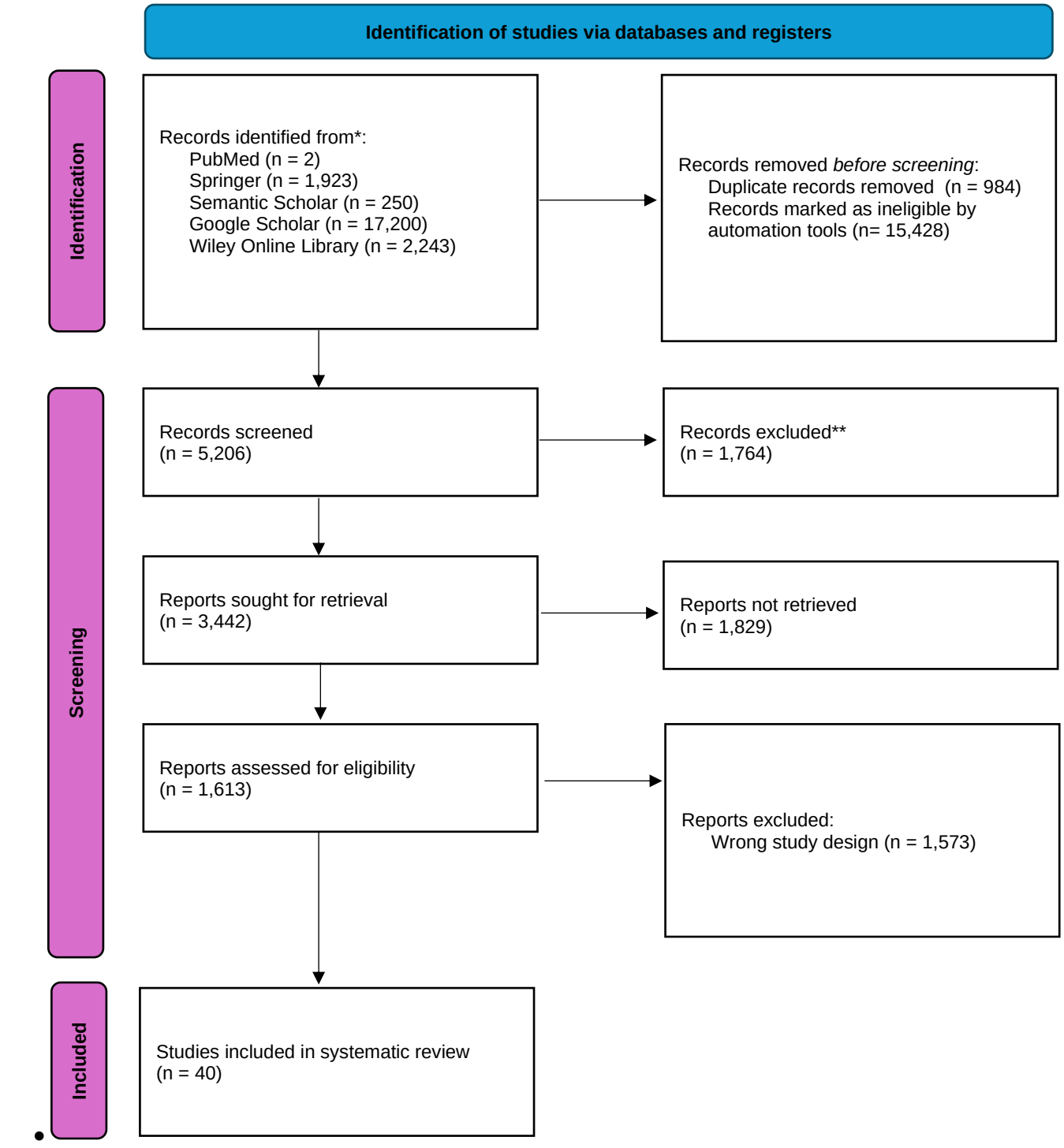

Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	**Bias related to temporal precedence** Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	**Bias related to selection and allocation** Was there a control group?	**Bias related to confounding factors** Were participants included in any comparisons similar?	**Bias related to administration of intervention/exposure** Were the participants included in any comparisons receiving similar treatment/ care, other than the exposure or intervention of interest?	**Were there multiple measurements of the outcome, both pre and post the intervention/exposure?**	**Were the outcomes of participants included in any comparisons measured in the same way?**	**Were outcomes measured in a reliable way?**	**Bias related to participant retention** Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	**Statistical conclusion validity** Was appropriate statistical analysis used?
A. Barcenilla et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Islam et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Peters et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓

R. Shiri et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Deepika Chenna et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Sesek et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
Y. Kim et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kaisa Lampainen et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Manosroi et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ş. Deveci et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. D. Gökharman et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Shiri et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Meems et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Manosroi et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓

M. S. Dawod et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Weronika Nowak et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Mansfield et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Awatif Hassan et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Doohee You et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Peters et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
Z. Mediouni et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Shiri et al., 2015a	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Padua et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Dunn et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. J. Van Dijk et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓

R. Shiri et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
M.R Dsouza et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Burger et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Pourmemari et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Skuladottir et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Elaheh Sanjari et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Nathan et al., 2001	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Moradi et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Šestak et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mohamed A Elghouneimy et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Spagnolo et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓

M. Mondelli et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Kasem et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Shiri et al., 2015b	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Asghar et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULT

Characteristics of Included Studies

The 40 sources included in this review comprise a diverse range of study designs examining medical and non-medical correlates of carpal tunnel syndrome (CTS). The majority were meta-analyses and systematic reviews synthesizing evidence from multiple primary studies, supplemented by case-control, cohort, cross-sectional, and prospective studies.

Study	Population/Sample Size	Geographic Region	Key Correlates Examined
A. Barcenilla et al., 2012	37 studies	Not specified	Hand force, repetition, vibration, wrist posture
M. Islam et al., 2013	80 participants	Bangladesh	Hypothyroidism, DM, RA, obesity, pregnancy
S. Peters et al., 2016	4,187 participants	Not specified	Occupational, psychosocial, demographic factors

Study	Population/Sample Size	Geographic Region	Key Correlates Examined
R. Shiri et al., 2016	23 studies	Multiple countries	Rheumatoid arthritis, osteoarthritis
Deepika Chenna et al., 2023	17,152 dental personnel	North America, Asia, Europe	Occupational factors, age, gender
R. Sesek et al., 2007	70 subjects	Not specified	Prolonged wrist flexion
Y. Kim et al., 2017	230 participants	Korea	Diabetes mellitus
Kaisa Lampainen et al., 2022	31 studies	International	Smoking
W. Manosroi et al., 2022	Not specified	Not specified	Hormone replacement therapy
Ş. Deveci et al., 2023	246 participants	Not specified	Anemia, vitamin deficiencies
F. D. Gökharman et al., 2017	48 female participants	Not specified	Interosseous muscle, carpal tunnel dimensions
R. Shiri et al., 2015	12 studies	Not specified	Computer and mouse use
M. Meems et al., 2017	1,044 pregnant women	Not specified	Pregnancy-related factors, depression
W. Manosroi et	270,764 women	International	Hormone replacement therapy

Study	Population/Sample Size	Geographic Region	Key Correlates Examined
al., 2023			
M. S. Dawod et al., 2024	681 patients	Not specified	Age, diabetes, nocturnal symptoms
Weronika Nowak et al., 2023	14 studies	Not specified	Occupational factors, medical conditions
M. Mansfield et al., 2018	12,773 participants	France, USA	Psychosocial factors
Awatif Hassan et al., 2022	Not specified	Not specified	Physical work-related factors
Doohee You et al., 2014	9 studies	Not specified	Wrist posture
S. Peters et al., 2011	Not specified	Not specified	Prognostic factors for return to work
Z. Mediouni et al., 2014	6 studies	Multiple continents	Computer work
R. Shiri et al., 2015a	1,379,372 individuals	Not specified	Overweight, obesity
L. Padua et al., 2010	6 studies	Not specified	Pregnancy
J. Dunn et al., 2018	4,367 wrists	Not specified	Workers' compensation status
M. J. Van Dijk et al., 2003	12,579 participants	Not specified	DM, hypothyroidism, RA

Study	Population/Sample Size	Geographic Region	Key Correlates Examined
R. Shiri et al., 2014	18 studies	Not specified	Hypothyroidism
M.R Dsouza et al., 2023	752 participants	Not specified	Carpal tunnel cross-sectional area
M. Burger et al., 2016	83 articles	International	Multiple non-occupational factors
M. Pourmemari et al., 2014	13 studies	Not specified	Smoking
A. Skuladottir et al., 2022	1,239,680 participants	Iceland, UK, Denmark, Finland	Genetic factors, BMI, height
Elaheh Sanjari et al., 2024	3,377,816 participants	America, Europe, Asia	Diabetes mellitus
P. Nathan et al., 2001	30 volunteers	Not specified	BMI, physical activity
A. Moradi et al., 2020	2,869 subjects	Not specified	Diabetes mellitus (surgical outcomes)
I. Šestak et al., 2009	6,186 women	Not specified	Aromatase inhibitors, HRT
Mohamed A Elghouneimy et al., 2024	1,416 patients	Multiple countries	Cardiac amyloidosis
F. Spagnolo et	96 CTS cases	Not specified	Anastrozole, BMI

Study	Population/Sample Size	Geographic Region	Key Correlates Examined
al., 2016			
M. Mondelli et al., 2004	282 patients	Not specified	Age, diabetes, thyroid disease
A. Kasem et al., 2014	57 patients	Not specified	Hypothyroidism
R. Shiri et al., 2015b	16 studies	Not specified	Wrist ratio
A. Asghar et al., 2022	Not specified	Not specified	Bifid median nerve

The included studies used varied diagnostic criteria for CTS, ranging from self-reported symptoms to nerve conduction studies and clinical examination . Several meta-analyses employed standardized criteria such as NIOSH definitions or ICD codes . This diagnostic heterogeneity represents an important consideration when interpreting pooled estimates.

Medical Correlates

Metabolic and Endocrine Conditions

Correlate	Effect Measure	95% CI	Study Type	Source
Diabetes mellitus	OR = 1.90	1.64–2.21	Meta-analysis (42 studies)	Sanjari et al., 2024
Diabetes mellitus (adjusted)	OR = 1.68	1.45–1.94	Meta-analysis	Sanjari et al., 2024

Correlate	Effect Measure	95% CI	Study Type	Source
Diabetes mellitus	OR = 2.2	0.91–11.81	Case-control	Islam et al., 2013
Diabetes mellitus	OR = 2.31	2.17–2.46	Systematic review	Nowak et al., 2023
Hypothyroidism (unadjusted)	ES = 2.15	1.64–2.83	Meta-analysis	Shiri et al., 2014
Hypothyroidism (adjusted)	ES = 1.44	1.27–1.63	Meta-analysis	Shiri et al., 2014
Hypothyroidism	OR = 1.4	1.0–2.0	Systematic review	Van Dijk et al., 2003
Hypothyroidism	OR = 1.28	0.91–11.81	Case-control	Islam et al., 2013
Obesity	OR = 2.02	1.92–2.13	Meta-analysis (58 studies)	Shiri et al., 2015a
Overweight	OR = 1.47	1.37–1.57	Meta-analysis	Shiri et al., 2015a
BMI (per unit increase)	OR = 1.074	1.071–1.077	Meta-analysis	Shiri et al., 2015a
Obesity	OR = 5.90	1.54–22.61	Case-control	Islam et al., 2013

Diabetes mellitus demonstrates a consistent positive association with CTS across multiple large-scale studies. The most comprehensive meta-analysis of 42 studies including 3,377,816 participants found that diabetic patients have 90% higher odds of developing CTS compared to non-diabetic individuals (OR = 1.90) , with the adjusted estimate remaining

significant at OR = 1.68 . Nerve conduction studies in diabetic patients showed longer latency, smaller amplitude, and lower conduction velocity regardless of CTS presence , suggesting that diabetes affects median nerve function even in the absence of clinical CTS. Surgical outcomes analysis revealed that diabetic patients showed significantly poorer improvement in sensory conduction velocities after carpal tunnel release (MD = -4.31, P < 0.001 for wrist-palm segment) , though symptomatic and functional improvements were comparable to non-diabetic patients .

Hypothyroidism shows a modest but consistent association with CTS, though the magnitude attenuates substantially after adjustment for confounders. The unadjusted effect size of 2.15 decreased to 1.44 after controlling for potential confounders , with evidence of publication bias noted . Importantly, hormone replacement therapy in hypothyroid patients showed significant improvement in median nerve function parameters (P = 0.001) , with 84% of patients normalizing after treatment .

Obesity represents one of the strongest metabolic risk factors for CTS. Each one-unit increase in BMI increases CTS risk by 7.4% , demonstrating a clear dose-response relationship. The association did not differ between men and women and was independent of study design .

Inflammatory and Rheumatologic Conditions

Correlate	Effect Measure	95% CI	Study Type	Source
Rheumatoid arthritis (unadjusted)	OR = 2.91	2.33–3.62	Meta-analysis	Shiri et al., 2016
Rheumatoid arthritis (adjusted)	OR = 1.96	1.57–2.44	Meta-analysis	Shiri et al., 2016

Correlate	Effect Measure	95% CI	Study Type	Source
Rheumatoid arthritis	OR = 2.2	1.4–3.4	Systematic review	Van Dijk et al., 2003
Rheumatoid arthritis	OR = 3.84	1.29–47.61	Case-control	Islam et al., 2013
Osteoarthritis (any joint)	OR = 2.13	1.65–2.76	Meta-analysis	Shiri et al., 2016
Osteoarthritis (adjusted)	OR = 1.87	1.64–2.13	Meta-analysis	Shiri et al., 2016
Arthritis (any type, adjusted)	OR = 1.96	1.21–3.18	Meta-analysis	Shiri et al., 2016

Both inflammatory (rheumatoid arthritis) and degenerative (osteoarthritis) arthritis consistently increase CTS risk. The meta-analysis of 23 studies found approximately two-fold increased risk for both conditions after adjustment . No evidence of publication bias was detected, and sensitivity analyses excluding cross-sectional studies or those with high selection bias did not change the magnitude of associations .

Pregnancy-Related CTS

Outcome	Prevalence/Effect	95% CI	Source
Neurophysiologically confirmed PRCTS	7–43%	Not reported	Padua et al., 2010
Clinically diagnosed PRCTS	31–62%	Not reported	Padua et al., 2010
Symptoms at 1 year postpartum	>50%	Not reported	Padua et al., 2010

Outcome	Prevalence/Effect	95% CI	Source
Symptoms at 3 years postpartum	~30%	Not reported	Padua et al., 2010
CTS during pregnancy	34%	Not reported	Meems et al., 2017
Persistent symptoms at 12 months	15%	Not reported	Meems et al., 2017
Higher BCTQ scores → persistence	OR = 1.93	1.08–3.45	Meems et al., 2017
Early symptom onset → persistence	OR = 2.88	1.45–5.72	Meems et al., 2017
Postpartum depression → persistence	OR = 1.11	1.03–1.19	Meems et al., 2017

Pregnancy-related CTS shows considerable variation in reported incidence depending on diagnostic methods . The prospective cohort of 1,044 pregnant women found 34% prevalence during pregnancy , decreasing to 5% by 12 months postpartum . Predictors of persistent symptoms included earlier onset during pregnancy (OR = 2.88) , more severe symptoms during pregnancy (OR = 1.93) , and higher postpartum depression scores (OR = 1.11) .

Hormonal Factors and Medication Effects

Correlate	Effect Measure	95% CI	P-value	Source

Correlate	Effect Measure	95% CI	P-value	Source
HRT use (overall)	OR = 1.49	0.99–2.23	0.06	Manosroi et al., 2023
HRT (non-RCT studies)	OR = 1.87	1.24–2.83	<0.001	Manosroi et al., 2023
HRT (RCT studies)	OR = 0.79	0.69–0.92	<0.001	Manosroi et al., 2023
Anastrozole vs. tamoxifen	2.6% vs. 0.7%	Not reported	<0.0001	Šestak et al., 2009
Anastrozole vs. placebo	OR = 2.16	1.40–3.33	<0.001	Spagnolo et al., 2016
Anastrozole (surgical intervention)	OR = 3.06	1.21–7.72	0.018	Spagnolo et al., 2016

The association between hormone replacement therapy and CTS demonstrates notable discordance between observational and randomized studies. While non-randomized studies showed increased CTS risk with HRT (OR = 1.87) , randomized controlled trials showed a protective effect (OR = 0.79) , suggesting that observational findings may be confounded . Aromatase inhibitors, which suppress estrogen in postmenopausal women, consistently increased CTS risk in both the ATAC trial (anastrozole 2.6% vs. tamoxifen 0.7%, P < 0.0001) and the IBIS-II trial (OR = 2.16) . Prior HRT use (P = 0.007) and prior chemotherapy (P = 0.01) were additional risk factors for CTS in aromatase inhibitor users .

Other Medical Conditions

Correlate	Effect Measure	95% CI	Source

Correlate	Effect Measure	95% CI	Source
Cardiac amyloidosis in CTS patients	13%	4–35%	Elghouneimy et al., 2024
CTS history in cardiac amyloidosis patients	38%	35–41%	Elghouneimy et al., 2024
Time from CTS to cardiac amyloidosis	6.02 years	3.76–8.36	Elghouneimy et al., 2024
Lower hemoglobin (EP+ vs EP-)	P = 0.001	Not reported	Deveci et al., 2023
Lower ferritin (EP+ vs control)	P = 0.045	Not reported	Deveci et al., 2023

CTS may serve as an early indicator of cardiac amyloidosis, with 38% of cardiac amyloidosis patients having a prior history of CTS and symptoms preceding cardiac diagnosis by an average of 6 years . Anemia and lower ferritin levels were more common in CTS patients with electrophysiological abnormalities, though these did not correlate with symptom severity . No associations were found between CTS symptoms and vitamin D, B12, calcium, or magnesium levels .

Non-Medical Correlates

Occupational Biomechanical Factors

Exposure	Effect Measure	95% CI	Source
Vibration	OR = 5.40	3.14–9.31	Barcenilla et al., 2012
Hand force	OR = 4.23	1.53–11.68	Barcenilla et al.,

Exposure	Effect Measure	95% CI	Source
			2012
Repetition	OR = 2.26	1.73–2.94	Barcenilla et al., 2012
Force + repetition combined	OR = 1.85	0.99–3.45	Barcenilla et al., 2012
Wrist posture	OR = 4.73	0.42–53.32	Barcenilla et al., 2012
Non-neutral wrist posture	RR = 2.01	1.65–2.43	You et al., 2014
Mouse use	OR = 1.93	1.43–2.61	Shiri et al., 2015
Frequent mouse use	OR = 1.84	1.18–2.87	Shiri et al., 2015
Years of computer work	OR = 1.92	1.17–3.17	Shiri et al., 2015
Computer use (vs. general population)	OR = 0.72	0.58–0.90	Shiri et al., 2015

Occupational biomechanical factors demonstrate the strongest associations with CTS among non-medical correlates. Vibration exposure showed the highest risk (OR = 5.40) , followed by hand force (OR = 4.23) and repetition (OR = 2.26) , when using conservative CTS definitions requiring nerve conduction abnormality with symptoms . Significant heterogeneity was observed across studies, with CTS case definition, study design, country, and risk of bias score identified as significant determinants .

Computer use findings are notably context-dependent. When comparing computer workers to the general population, computer use appeared protective (OR = 0.72) , but this comparison failed to control for occupational risk factors . Within office worker populations, mouse use (OR = 1.93) , frequent computer use (OR = 1.89) , and duration of computer work (OR = 1.92) were all significantly associated with CTS. A separate meta-analysis

found no overall association between computer use and CTS (meta-OR = 1.67, 95% CI 0.79–3.55) , though the authors noted heterogeneous work exposures across studies .

Prolonged wrist flexion provokes both increased tactile threshold and discomfort ratings in symptomatic patients, with conduction latency correlating significantly with tactile threshold at baseline ($r = 0.52$, $P < 0.0001$) and after 15 minutes of flexion ($r = 0.67$, $P < 0.0001$) . Patients with abnormal conduction latency showed significantly elevated baseline thresholds and slower recovery after flexion .

Anatomical Factors

Anatomical Factor	Effect Measure	95% CI	Source
Wrist ratio (mean OR)	OR = 4.56	2.97–6.99	Shiri et al., 2015b
Wrist ratio ≥0.70 vs. <0.70	OR = 2.73	1.49–5.01	Shiri et al., 2015b
Wrist ratio (per 0.01 increase)	OR = 1.12	1.09–1.16	Shiri et al., 2015b
Bifid median nerve	OR = 1.50	1.17–1.93	Asghar et al., 2022
Bifid median nerve CSA difference	+1.50 mm^2	0.56–2.45	Asghar et al., 2022
Carpal tunnel CSA (proximal)	MD = 0.79	0.63–0.96	Dsouza et al., 2023
Carpal tunnel CSA (distal)	MD = 0.54	0.32–0.76	Dsouza et al., 2023

A square-shaped wrist (higher wrist thickness/width ratio) is a robust predictor of CTS, with risk increasing by 12% for each 0.01 increase in wrist ratio . The association did not differ between men and women , and no publication bias was detected . Bifid

median nerve increased CTS risk by 50% , with the cross-sectional area being 1.5 mm^2 greater than solitary median nerves . Increased carpal tunnel cross-sectional area at both proximal (P = 0.003) and distal (P = 0.32) levels was associated with CTS .

In CTS patients, interosseous muscle and intermetacarpal space dimensions were significantly lower than controls (P < 0.01) , with grip strength correlating positively with these dimensions in both groups . This suggests muscular atrophy may be detectable sonographically earlier than by physical examination .

Demographic and Personal Factors

Factor	Effect Measure	95% CI/P-value	Source
Female sex	OR = 9.99	3.64–27.44	Nowak et al., 2023
Age 40-49 (vs. younger)	HR = 2.5	1.7–3.8	Nowak et al., 2023
Blue-collar vs. white-collar	OR = 1.67	Not reported	Nowak et al., 2023
Working in pain	OR = 3.94–4.73	1.06–19.29	Nowak et al., 2023
Age ≥60 years (protective in AI users)	P = 0.002	Not reported	Šestak et al., 2009

Female sex is strongly associated with CTS risk, with women 10 times more likely to have symptoms than men . Age shows a non-linear relationship, with risk more than doubling in the 40-49 age group but older age (≥60) being protective in aromatase inhibitor users . Blue-collar workers had 67% higher risk than white-collar workers , and working while in pain substantially increased risk (OR = 3.94–4.73) .

Psychosocial Factors

Psychosocial Factor	Effect Measure	95% CI	Direction	Source
High psychological distress	OR = 4.3	1.0–18.6	Positive	Mansfield et al., 2018
Psychological problems	OR = 2.34	1.42–3.85	Positive	Mansfield et al., 2018
High job strain	HR = 1.86	1.11–3.14	Positive	Mansfield et al., 2018
High psychological work demand	HR = 1.57	1.06–2.33	Positive	Mansfield et al., 2018
Least influence over work	OR = 2.86	1.10–7.14	Positive	Mansfield et al., 2018
High social support	HR = 0.54	0.31–0.95	Protective	Mansfield et al., 2018
More coworker support	OR = 0.69	0.48–0.99	Protective	Mansfield et al., 2018

Psychosocial factors demonstrate both positive and negative associations with CTS. High psychological distress (OR = 4.3) , job strain (HR = 1.86) , and low job control (OR = 2.86) were associated with increased risk, while high social support (HR = 0.54) and coworker support (OR = 0.69) were protective. However, the systematic review noted high heterogeneity across studies, variability in measurement tools preventing meta-analysis, and inconsistent diagnostic criteria .

Lifestyle Factors

Factor	Effect Measure	95% CI	Source
Current smoking (cross-sectional)	OR = 1.52	1.11–2.09	Lampainen et al., 2022
Current smoking (cohort)	HR = 1.09	0.84–1.43	Lampainen et al., 2022
Current smoking (case-control)	OR = 0.92	0.56–1.53	Lampainen et al., 2022
Current smoking (cross-sectional)	OR = 1.99	1.38–2.60	Pourmemari et al., 2014
Smoking (case-control)	OR = 1.04	0.95–1.12	Pourmemari et al., 2014
Aerobic exercise → median latency	r = 0.52	P = 0.004	Nathan et al., 2001

Smoking associations with CTS vary markedly by study design. Cross-sectional studies consistently show positive associations (OR = 1.52–1.99) , but cohort and case-control studies find no association . These discrepancies suggest the cross-sectional findings may reflect biases, confounding by work-related factors, or reverse causation . Associations attenuated or disappeared when limiting analyses to higher-quality studies or adjusting for publication bias .

A small cohort study found that aerobic exercise improved median nerve conduction, with decreased 14-cm sensory latency correlating with decreased body fat percentage (r = 0.52, P = 0.004) and BMI (partial r = 0.47, P = 0.014) .

Genetic Factors

A genome-wide association study of 48,843 cases and 1,190,837 controls identified 53 sequence variants at 50 loci associated with CTS . The most significant association was a missense variant (p.Glu366Lys) in SERPINA1 that protects against CTS ($P = 2.9 \times 10^{-24}$, OR = 0.76) . At least 22 genes were implicated in mediating CTS risk, with 19 variants highlighting the role of extracellular matrix biology in CTS pathogenesis . The polygenic risk score explained approximately 2% of variance , and bilateral, recurrent, or persistent cases showed higher genetic risk scores than nonrecurrent cases .

Workers' Compensation and Return-to-Work Factors

Factor	Finding	P-value	Source
Return to work time (WC vs. non-WC)	+5 weeks longer	<0.0005	Dunn et al., 2018
Return to preinjury vocation	16% less likely	<0.0005	Dunn et al., 2018
Complication rate (WC vs. non-WC)	3× higher	<0.0001	Dunn et al., 2018
Persistent pain rate	2× higher	Not reported	Dunn et al., 2018
Reoperation odds ratio	>5.0	Not reported	Dunn et al., 2018

Workers' compensation patients demonstrate markedly poorer outcomes after carpal tunnel release, with nearly 5 weeks longer return-to-work times, 16% lower likelihood of returning to preinjury vocation, approximately 3 times the complication rate, and twice the rate of persistent pain . These patients were also younger, less likely to have appropriate

preoperative workup (Phalen test P < 0.0001) , and more often involved the dominant extremity .

Prognostic factors for delayed return-to-work after carpal tunnel surgery included older age, lower household income, greater upper extremity functional limitation, multiple musculoskeletal pain sites, worse mental health status, high job strain, poor coworker relationships, and less-supportive workplace policies . Factors associated with earlier return-to-work included lower expected days off work, lower pain anxiety, and occupation.

Synthesis

Reconciling Heterogeneity in Effect Estimates

The included studies demonstrate substantial heterogeneity in effect estimates for many correlates, requiring careful interpretation based on study design, diagnostic criteria, and population characteristics.

Diabetes mellitus shows the most consistent association, with meta-analyses converging on approximately 1.7–2.0-fold increased risk after adjustment . The mechanistic basis appears multifactorial: direct metabolic effects on the median nerve produce altered conduction parameters even in the absence of clinical CTS , while the presence of diabetes does not prevent symptomatic and functional improvement following surgery despite poorer sensory conduction recovery .

Occupational biomechanical factors demonstrate a clear hierarchy of risk when conservative CTS definitions are applied: vibration (OR = 5.40) > hand force (OR = 4.23) > repetition (OR = 2.26) . The meta-regression identified CTS case definition as a key determinant of heterogeneity , with more stringent diagnostic criteria producing more precise effect estimates. Studies using symptoms alone as the outcome likely include false positives, diluting true associations.

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Computer use associations are highly dependent on comparison group selection. The apparent protective effect when comparing computer workers to the general population (OR = 0.72) reflects inadequate control for occupational confounders—general populations include manual laborers with higher biomechanical exposures . Within appropriate comparison groups (office workers with low vs. high computer use), mouse use (OR = 1.93) and prolonged computer work (OR = 1.92) emerge as modest risk factors .

Smoking exemplifies how study design affects conclusions. The positive association observed in cross-sectional studies (OR = 1.52–1.99) disappears in cohort and case-control studies . This pattern suggests that cross-sectional findings reflect confounding by occupational factors or reverse causation rather than a true causal relationship . The association also attenuates when restricting to higher-quality studies or nerve conduction-confirmed CTS .

Hormone replacement therapy demonstrates a striking reversal of effect between observational and randomized studies. Non-randomized studies suggest increased risk (OR = 1.87) , while randomized controlled trials show protection (OR = 0.79) . This discordance likely reflects confounding by indication in observational studies—women who initiate HRT may have underlying characteristics (hormonal changes, menopausal symptoms) that independently increase CTS risk. Conversely, aromatase inhibitors consistently increase CTS risk across studies (OR = 2.16) , with most cases being mild-to-moderate and occurring early in treatment .

Population-Specific Findings

Effect estimates may apply differentially across populations:

- **Sex differences** : While BMI effects were equivalent in men and women , and wrist ratio effects showed no gender modification , the overall burden of CTS is

substantially higher in women (OR = 9.99 compared to men) , suggesting either unmeasured risk factors or different susceptibility thresholds.

- **Age effects** : Risk peaks in the 40-49 age group , but elderly patients (≥70 years) show less improvement after surgical release despite equivalent subjective symptom relief, attributed to greater preoperative nerve damage and reduced repair capacity . Paradoxically, age ≥60 is protective against aromatase inhibitor-induced CTS .

- **Occupational context** : The same exposure may have different effects depending on concurrent factors. Studies suggest that a square-shaped wrist may potentiate adverse effects of obesity and occupational workloads , though this interaction requires further investigation .

Methodological Considerations Affecting Interpretation

Several methodological factors systematically influence effect estimates:

1. **Diagnostic criteria** : CTS defined by nerve conduction studies yields more precise estimates than symptom-based definitions . Studies using NCS-confirmed CTS found smoking associations attenuated , while occupational factor associations strengthened .

2. **Confounding adjustment** : Unadjusted estimates consistently exceed adjusted estimates (e.g., hypothyroidism ES 2.15 unadjusted vs. 1.44 adjusted ; RA OR 2.91 vs. 1.96), indicating that unmeasured confounders inflate crude associations.

3. **Study design hierarchy** : For smoking, the consistent pattern of positive cross-sectional but null cohort/case-control findings suggests that study designs with stronger temporal inference yield more reliable conclusions. For HRT, the discordance between observational and randomized evidence underscores the importance of randomization for isolating causal effects.

4. **Publication bias** : Evidence of publication bias was detected for hypothyroidism and smoking , with associations attenuating after adjustment.

DISCUSSION

This comprehensive synthesis of 40 studies elucidates the complex, multifactorial landscape of Carpal Tunnel Syndrome (CTS) correlates. The findings underscore that CTS is not a disorder with a single cause but rather a common clinical endpoint reached via multiple pathogenic pathways involving medical, occupational, anatomical, and psychosocial domains. A critical interpretation of the evidence requires reconciling heterogeneity and understanding the mechanistic and methodological underpinnings of the observed associations.

Medical Correlates: Systemic Conditions and Local Manifestations

The strong and consistent association between **diabetes mellitus (DM)** and CTS, with a ~90% increased odds, is one of the most robust findings (Sanjari et al., 2024; Kim et al., 2017). This link is supported by a clear biological mechanism: diabetic polyneuropathy and metabolic alterations increase median nerve susceptibility to compression. Nerve conduction studies confirm subclinical dysfunction in diabetics even without CTS, indicating a lowered threshold for symptomatic entrapment (Kim et al., 2017). Importantly, while diabetic patients may have poorer electrophysiological recovery post-surgery, their symptomatic and functional improvements are comparable to non-diabetics, supporting the effectiveness of surgical intervention in this group (Moradi et al., 2020).

Obesity emerges as a potent and independent risk factor, with a clear dose-response relationship (each unit increase in BMI raising risk by 7.4%) (Shiri et al., 2015). The pathophysiology likely involves increased fatty tissue within the carpal canal, elevated hydrostatic pressure, and systemic pro-inflammatory states. Its effect magnitude is comparable across genders, highlighting it as a universal modifiable risk factor.

Inflammatory arthritis, particularly rheumatoid arthritis (RA), doubles the risk of CTS (Shiri, 2016). The mechanism is directly local: synovial proliferation and tenosynovitis within the carpal tunnel physically compress the median nerve. This underscores the importance of evaluating for CTS in RA patients with hand symptoms. The association with osteoarthritis, while slightly weaker, suggests that joint degeneration and related biomechanical changes also contribute to the risk milieu.

Hypothyroidism shows a more modest association that attenuates significantly after adjustment for confounders (Shiri, 2014). This suggests that shared factors (e.g., age, gender, possibly weight) may partly explain the link. However, the demonstrable improvement in nerve conduction with hormone replacement therapy indicates a reversible metabolic component, making thyroid function a relevant check in CTS evaluation (Kasem et al., 2014).

Pregnancy-related CTS (PRCTS) is a classic example of a transient, hormonally mediated state increasing susceptibility. The high prevalence (31-62%) and frequent persistence postpartum, especially with early onset and severe symptoms, indicate that pregnancy can unmask a lasting predisposition (Padua et al., 2010; Meems et al., 2017). The link to postpartum depression further illustrates the intersection of physiological and psychosocial factors in chronicity.

The striking discordance in findings for **hormone replacement therapy (HRT)**—increased risk in observational studies but decreased risk in RCTs—is a pivotal lesson in causal inference (Manosroi et al., 2023). This almost certainly reflects "confounding by indication" in observational settings, where women prescribed HRT differ fundamentally (e.g., in severity of menopausal symptoms, baseline hormonal status) from those who are not. In contrast, the consistent link between **aromatase inhibitors** (which drastically lower estrogen) and CTS provides strong evidence for a protective role of estrogen in maintaining nerve tissue integrity (Šestak et al., 2009; Spagnolo et al., 2016).

The association of CTS with **cardiac amyloidosis** is a novel and clinically significant finding, suggesting CTS can be a early, extra-cardiac manifestation of systemic amyloid deposition, preceding cardiac diagnosis by years (Elghouneimy et al., 2024). This positions CTS not only as a local disorder but occasionally as a red flag for serious systemic disease.

Non-Medical Correlates: The External and Intrinsic Load

Occupational biomechanical factors demonstrate a logical hierarchy of risk: vibration exposure (OR=5.40) is most deleterious, followed by high hand force and repetitive motion (Barcenilla et al., 2012). These exposures cause direct mechanical trauma, ischemic injury, and inflammatory edema. The strength of these associations is magnified when stringent, electrophysiologically confirmed CTS definitions are used, filtering out false positives and highlighting true work-related pathophysiology. The debate around **computer use** exemplifies the importance of the reference group. The apparent "protective" effect versus the general population is an ecological fallacy, as the general population includes high-risk manual laborers. When compared appropriately within office-worker cohorts, prolonged mouse use and computer work show modest but significant risks (Shiri & Falah-Hassani, 2015; Mediouni et al., 2014).

Anatomical factors represent intrinsic susceptibility. A **square-shaped wrist** (high wrist ratio) is a strong predictor, likely due to a narrower carpal arch configuration that leaves less space for the median nerve (Shiri, 2015). A **bifid median nerve** has a larger cross-sectional area, increasing its vulnerability to compression within the fixed tunnel space (Asghar et al., 2022). Similarly, a smaller **carpal tunnel cross-sectional area** is directly associated with CTS (Dsouza et al., 2023). These immutable factors help explain why individuals exposed to similar occupational loads develop CTS at different rates.

Demographic and psychosocial factors paint a picture of the vulnerable individual. The overwhelming female predominance (OR=9.99) points to hormonal, anatomical (smaller carpal tunnel size), and potentially societal (occupational segregation) factors (Nowak et al.,

2023). **Psychosocial stressors** like high job strain, low control, and low social support are robustly linked to CTS reporting and chronicity (Mansfield et al., 2018). The pathways are likely biopsychosocial: stress can increase muscle tension and pain perception, alter inflammatory responses, and affect health-seeking behaviors and recovery.

The case of **smoking** is a masterclass in how study design dictates conclusions. The positive associations seen in cross-sectional studies vanish in longitudinal designs (Lampainen et al., 2022; Pourmemari et al., 2014). This pattern strongly suggests that the cross-sectional link is not causal but stems from confounding (smokers may have more physically demanding jobs) or reverse causation (CTS-related discomfort may influence smoking behavior).

Genetic factors, identified through large-scale GWAS, now provide a molecular basis for inherited susceptibility (Skuladottir et al., 2022). The implicated genes point toward the biology of the extracellular matrix and connective tissue—the very structure of the carpal tunnel itself. While the individual effect of each variant is small, the polygenic risk score explains a meaningful portion of liability, particularly for bilateral and recurrent cases.

Methodological Synthesis: Reconciling the Evidence

The heterogeneity observed across studies is not merely noise but contains critical information. Key methodological determinants of effect estimates include:

1. **Diagnostic Rigor**: Studies using nerve conduction studies (NCS) yield more biologically precise estimates for occupational and metabolic factors, while symptom-based definitions inflate prevalence and may dilute true associations.
2. **Study Design Hierarchy**: Cross-sectional studies are prone to confounding and reverse causation, as seen with smoking and HRT. Cohort and case-control designs offer better temporal inference, while RCTs provide the gold standard for isolating causal effects.

3. **Confounding Control**: The consistent attenuation of effect sizes from unadjusted to adjusted analyses (e.g., for hypothyroidism, RA) highlights the pervasive influence of confounders like age, sex, and BMI. Inadequate adjustment can lead to spurious conclusions.

4. **Comparison Group Selection**: As demonstrated with computer use, choosing an inappropriate reference group can reverse the apparent direction of risk.

Integrated Pathogenic Model and Clinical Implications

The evidence supports a dynamic, multi-hit model for CTS pathogenesis. An individual's genetic blueprint and anatomical constitution set a baseline susceptibility. Systemic medical conditions (DM, obesity, arthritis) load the "first hit," creating a neuropathy-prone or space-occupying environment within the tunnel. External biomechanical loads from occupation or activity deliver the "second hit," precipitating symptomatic compression. Psychosocial factors act as amplifiers, influencing pain perception, reporting behavior, and recovery trajectories.

This model has direct clinical implications:

- **Evaluation**: A patient with CTS should trigger a holistic assessment, not just of the wrist. Screening for diabetes, thyroid dysfunction, and inflammatory symptoms is prudent, especially in non-manual workers. A history of bilateral, severe, or recurrent CTS, particularly in an older male, should raise consideration of cardiac amyloidosis.

- **Management**: Treatment must be multifocal. While carpal tunnel release addresses the local compression, concomitant management of obesity, diabetes, or thyroid disease, and attention to ergonomic and psychosocial stressors at work, are essential for optimal and durable outcomes.

- **Prevention**: Workplace interventions should prioritize reducing vibration and high-force tasks. Health promotion focusing on weight management and metabolic health is a viable

population-level strategy. Identifying individuals with high-risk anatomy (square wrist) for targeted ergonomic protection may be beneficial.

Limitations of the Evidence Base

This synthesis is constrained by the limitations of the primary studies. Diagnostic heterogeneity remains a major challenge. Exposure assessments, especially for occupational factors, are often based on self-report, leading to misclassification. Many studies lack detailed adjustment for key confounders. There is a paucity of research on interaction effects (e.g., does obesity potentiate the effect of repetitive work?).

CONCLUSION

This detailed synthesis confirms that Carpal Tunnel Syndrome is a condition of multifactorial etiology, where systemic health, occupational exposure, individual anatomy, and psychosocial context converge. Key medical correlates with strong evidence include diabetes mellitus, obesity, rheumatoid arthritis, and hypothyroidism. Among non-medical factors, occupational vibration and force, a square-shaped wrist, and female sex carry significant risk. The evidence clearly demonstrates that study methodology—particularly diagnostic criteria, study design, and control for confounding—profoundly influences the observed strength and even direction of associations, as exemplified by the cases of smoking, computer use, and hormone replacement therapy.

Recommendations

1. **For Clinical Practice**: Adopt a comprehensive evaluation approach for CTS patients that includes assessment for metabolic, endocrine, and rheumatologic conditions. Consider CTS as a potential early sign of systemic disease like cardiac amyloidosis in appropriate clinical contexts.

2. **For Occupational Health**: Implement hierarchical controls targeting vibration, high force, and repetitive motions. Develop workplace policies that address not only ergonomics but also psychosocial factors like job strain and social support.

3. **For Patient Management**: Advocate for and support weight management and glycemic control as part of CTS treatment plans. Provide realistic prognostic counseling, particularly for patients with workers' compensation or significant comorbidities.

4. **For Future Research**: Prioritize prospective cohort studies with standardized, NCS-confirmed CTS definitions and objective exposure measurements. Investigate gene-environment interactions and the predictive utility of polygenic risk scores. Explore the mechanisms linking psychosocial stress to CTS pathophysiology.

REFERENCES

A. Asghar, A. Patra, K. Ravi, R. Tubbs, Ashutosh Kumar, and S. Naaz. “Bifid Median Nerve as an Anatomical Risk Factor for Carpal Tunnel Syndrome: A Meta-analysis.” *Clinical Anatomy (New York, N.Y. Print)*, 2022.

A. Barcenilla, L. March, J. S. Chen, and P. Sambrook. “Carpal Tunnel Syndrome and Its Relationship to Occupation: A Meta-Analysis.” *Rheumatology*, 2012.

A. Kasem, Sabry M. Fathy, D. Shahin, and Amir A. Fikry. “Carpal Tunnel Syndrome in Hypothyroid Patients: The Effect of Hormone Replacement Therapy,” 2014.

A. Moradi, Ata Sadr, M. Ebrahimzadeh, Golnaz Ghayyem Hassankhani, and Hassan Mehrad-Majd. “Does Diabetes Mellitus Change the Carpal Tunnel Release Outcomes? Evidence from a Systematic Review and Meta-Analysis.” *Journal of Hand Therapy*, 2020.

A. Skuladottir, G. Bjornsdottir, E. Ferkingstad, G. Einarsson, L. Stefánsdóttir, M. S. Nawaz, A. Oddsson, et al. “A Genome-Wide Meta-Analysis Identifies 50 Genetic Loci Associated with Carpal Tunnel Syndrome.” *Nature Communications*, 2022.

Awatif Hassan, A. Beumer, P. Kuijer, and Henk F. Molen. “Work-relatedness of Carpal Tunnel Syndrome: Systematic Review Including Meta-analysis and GRADE.” *Health Science Reports*, 2022.

Deepika Chenna, M. Madi, Mathangi Kumar, Vijay Kumar, Sitaram Chopperla, Abhinav Tadikonda, and K. Pentapati. “Worldwide Prevalence of Carpal Tunnel Syndrome Among Dental Health Care Personnel - A Systematic Review and Meta-Analysis.” *F1000Research*, 2023.

Doohee You, Allan H. Smith, and D. Rempel. “Meta-Analysis: Association Between Wrist Posture and Carpal Tunnel Syndrome Among Workers.” *Safety and Health at Work*, 2014.

Elaheh Sanjari, Hadi Raeisi Shahraki, Lusine G. Khachatryan, and A. Mohammadian-Hafshejani. “Investigating the Association Between Diabetes and Carpal Tunnel Syndrome: A Systematic Review and Meta-Analysis Approach.” *PLoS ONE*, 2024.

F. D. Gökharman, S. Ramadan, Sonay Aydın, and P. Koşar. “Can Decrease in Hand Grip Strength in Carpal Tunnel Syndrome Be Explained by Interosseous Muscle and Intermetacarpal Space Dimensions,” 2017.

F. Spagnolo, I. Šestak, A. Howell, J. Forbes, and J. Cuzick. “Anastrozole-Induced Carpal Tunnel Syndrome: Results From the International Breast Cancer Intervention Study II Prevention Trial.” *Journal of Clinical Oncology*, 2016.

I. Šestak, F. Sapunar, and J. Cuzick. “Aromatase Inhibitor-Induced Carpal Tunnel Syndrome: Results from the ATAC Trial.” *Journal of Clinical Oncology*, 2009.

J. Dunn, N. Kusnezov, Logan Koehler, Dennis J. Vanden Berge, Ben Genco, Justin S. Mitchell, J. Orr, and M. Pallis. “Outcomes Following Carpal Tunnel Release in Patients Receiving Workers’ Compensation: A Systematic Review.” *HAND*, 2018.

Kaisa Lampainen, S. Hulkkonen, J. Ryhänen, S. Curti, and R. Shiri. “Is Smoking Associated with Carpal Tunnel Syndrome? A Meta-Analysis.” *Healthcare*, 2022.

L. Padua, A. Pasquale, C. Pazzaglia, G. Liotta, Alessia Librante, and M. Mondelli. “Systematic Review of Pregnancy-related Carpal Tunnel Syndrome.” *Muscle and Nerve*, 2010.

M. Burger, Shameemah Abrahams, and M. Collins. “Non-Occupational Risk Factors for Carpal Tunnel Syndrome: A Review,” 2016.

M. Islam, Mohammad Shah Jahirul Hoque Chowdhury, Md Tauhidul Islam Chowdhury, A. Chowdhury, Mahmudul Islam, Enayet Hossain, M. Baqui, et al. “Identification of Common Risk Factors Associated with Carpal Tunnel Syndrome.” *Bangladesh Journal of Neuroscience*, 2013.

M. J. Van Dijk, J. Reitsma, J. Fischer, and G. Sanders. “Indications for Requesting Laboratory Tests for Concurrent Diseases in Patients with Carpal Tunnel Syndrome: A Systematic Review.” *Clinical Chemistry*, 2003.

M. Mansfield, M. Thacker, and Fiona M Sandford. “Psychosocial Risk Factors and the Association With Carpal Tunnel Syndrome: A Systematic Review.” *HAND*, 2018.

M. Meems, Sophie E. M. Truijens, V. Spek, L. Visser, and V. Pop. “Follow-up of Pregnancy-Related Carpal Tunnel Syndrome Symptoms at 12 Months Postpartum: A Prospective Study.” *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 2017.

M. Mondelli, L. Padua, and F. Reale. “Carpal Tunnel Syndrome in Elderly Patients: Results of Surgical Decompression.” *Journal of the Peripheral Nervous System*, 2004.

M. Pourmemari, E. Viikari-Juntura, and R. Shiri. “Smoking and Carpal Tunnel Syndrome: A Meta-analysis.” *Muscle and Nerve*, 2014.

M. S. Dawod, M. Alswerki, A. Alelaumi, A. E. Hamadeen, A. Sharadga, J. Sharadga, H. Alsamarah, and A. Khanfar. “Risk Factors, Associations, and High-Risk Patient Profiles for Nocturnal Pain in Carpal Tunnel Syndrome: Implications for Patient Care.” *Musculoskeletal Surgery*, 2024.

Mohamed A Elghouneimy, Nagham Bushara, O. A. Abdelwahab, Ayman A Makableh, Doaa M Alnabwy, and Rehab A Diab. “Carpal Tunnel Syndrome as a Potential Indicator of Cardiac Amyloidosis: A Systematic Review and Meta-Analysis.” *Cureus*, 2024.

M.R Dsouza, A.K. Bhat, S. Guruprasad Kalthur, and S. Allwyn Joshua. “Association Between Carpal Tunnel Cross-Sectional Area and Carpal Tunnel Syndrome: A Systematic Review and Meta-Analysis.” *Muscle Ligaments and Tendons Journal*, 2023.

P. Nathan, A. Wilcox, P. Emerick, K. D. Meadows, and A. L. McCormack. “Effects of an Aerobic Exercise Program on Median Nerve Conduction and Symptoms Associated With Carpal Tunnel Syndrome.” *Journal of Occupational and Environmental Medicine*, 2001.

R. Sesek, M. Khalighi, D. Bloswick, M. Anderson, and R. Tuckett. “Effects of Prolonged Wrist Flexion on Transmission of Sensory Information in Carpal Tunnel Syndrome.” *Journal of Pain*, 2007.

R. Shiri. “A Square-shaped Wrist as a Predictor of Carpal Tunnel Syndrome: A Meta-analysis.” *Muscle and Nerve*, 2015.

———. “Arthritis as a Risk Factor for Carpal Tunnel Syndrome: A Meta-Analysis.” *Scandinavian Journal of Rheumatology*, 2016.

———. “Hypothyroidism and Carpal Tunnel Syndrome: A Meta-analysis.” *Muscle and Nerve*, 2014.

R. Shiri, and K. Falah-Hassani. “Computer Use and Carpal Tunnel Syndrome: A Meta-Analysis.” *Journal of Neurological Sciences*, 2015.

R. Shiri, M. Pourmemari, K. Falah-Hassani, and E. Viikari-Juntura. “The Effect of Excess Body Mass on the Risk of Carpal Tunnel Syndrome: A Meta-analysis of 58 Studies.” *Obesity Reviews*, 2015.

S. Peters, V. Johnston, S. Hines, M. Ross, and M. Coppieters. “Prognostic Factors for Return-to-Work Following Surgery for Carpal Tunnel Syndrome: A Systematic Review.” *The JBI Database of Systematic Reviews and Implementation Reports*, 2016.

S. Peters, V. Johnston, S. Hines, M. Ross, and Michel Coppitiers. “Prognostic Factors for Return to Work Following Carpal Tunnel Release: Systematic Review.” *JBI Library of Systematic Reviews*, 2011.

Ş. Deveci, and Z. Matur. “Does the Severity of Carpal Tunnel Syndrome Symptoms Vary Due to Vitamin and Mineral Deficiencies and Anemia?” *Neurological Sciences and Neurophysiology*, 2023.

W. Manosroi, and Pichitchai Atthakomol. “Hormone Replacement Therapy and Risk of Carpal Tunnel Syndrome: A Meta-Analysis,” 2022.

W. Manosroi, Pichitchai Atthakomol, P. Phinyo, and Pojsakorn Danpanichkul. “Hormone Replacement Therapy in Women and Risk of Carpal Tunnel Syndrome: A Systematic Review and Metaanalysis.” *Journal of Orthopaedics and Traumatology*, 2023.

Weronika Nowak, Patrycja Znamirowska, Natalia Szmigielska, Katarzyna Zemsta, Joanna Miśkiewicz, Hanna Plata, Monika Pałatyńska, and B. Kulesza. “Risk Factors for Carpal Tunnel Syndrome.” *Journal of Pre-Clinical and Clinical Research*, 2023.

Y. Kim, Kyung-Sook Yang, Han-Soo Kim, H. Seok, Jung Hun Lee, Myeong Hun Son, and Byung-Jo Kim. “Does Diabetes Mellitus Influence Carpal Tunnel Syndrome?” *Journal of Clinical Neurology*, 2017.

Z. Mediouni, Alexis de Roquemaurel, C. Dumontier, B. Bécour, Hélène Garrabé, Y. Roquelaure, and A. Descatha. “Is Carpal Tunnel Syndrome Related to Computer Exposure at Work? A Review and Meta-Analysis.” *Journal of Occupational and Environmental Medicine*, 2014.