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Non-Occupational Risk Factors for Carpal Tunnel Syndrome: A Review

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Abstract

Context: Carpal tunnel syndrome (CTS) is a common neuropathy accounting for up to 90% of all entrapment neuropathies of the upper limb. Identifying potential risk factors might aid in the prevention of this injury. This systematic review aims to identify the current known non-occupational risk factors for CTS as published in three electronic databases.

Evidence Acquisition: Three electronic databases PubMed, Web of Knowledge, and SpringerLink were searched using the keywords "CARPAL TUNNEL SYNDROME RISK" for all published articles up to September 2015. Based on the inclusion and exclusion criteria, 2755 unique titles were independently analyzed and narrowed to a final list of 83 articles. Only articles with a level of evidence of I, II, or III were included, in accordance with robust study design and data analysis methods. The level of certainty for each risk factor was determined using previously defined criteria.

Results: A total of 83 articles were included, which defined 29 individual, non-occupational risk factors. Only sex and previous musculoskeletal disorder/injury were found to have a moderate level of certainty to modify the risk of CTS. All other risk factors were evaluated as having a low level of certainty.

Conclusions: Considering the large number of studies reporting on non-occupational CTS risk factors as well as the differences in reporting between studies, a lack of consistency is observed in the current review. This review does, however, offer a broad outlook on the literature and the current evidence for risk factors commonly believed to be associated with altered CTS risk. Although several risk factors are commonly believed to be associated with altered risk of CTS, the current evidence to support these beliefs is limited. Prospective cohort studies, larger sample sizes, and consistent and robust measures of risk should be used in future research.

Keywords: CTS, Entrapment Neuropathy, Risk, Biological, Medical Condition, Wrist, Injury

1. Context

Carpal tunnel syndrome (CTS) is a common neuropathy, accounting for up to 90% of all entrapment neuropathies of the upper limb (1-4). Although the exact etiology of CTS is not fully understood, it has been suggested that it is multifactorial (5), and researchers have therefore suggested that in addition to the repetitive use of the upper limbs, several other non-occupational risk factors are also associated with CTS (3). Since there is, to our knowledge, no recent comprehensive review of these risk factors in the scientific literature, the objective of this review is to critically assess the published evidence for non-occupational risk factors for CTS.

2. Evidence Acquisition

2.1. Search Strategy

Published articles that examined potential non-occupational risk factors for CTS were reviewed following the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines (6). Three electronic databases PubMed, Web of Knowledge (including biological abstracts, Medline, and Web of Science), and Springerlink were searched using the keywords "CARPAL TUNNEL SYNDROME RISK", search details ("carpal tunnel syndrome"[MeSH terms] or ("carpal"[all fields] and "tunnel"[all fields] and "syndrome"[all fields]) or "carpal tunnel syndrome"[all fields]) and ("risk"[MeSH terms] or "risk"[all fields]). The database search was performed for all articles published up to 1 September 2015. Review articles were initially included in order to include their reference lists. A three-step method was followed to identify the articles that were included in this review. Titles, abstracts, and full texts were screened. Articles were excluded at each step if they met the exclusion criteria as outlined in Box 1. All the references within the included articles were also reviewed using the same criteria to identify any additional articles that were not identified during the initial screening process. All of the identified articles were further appraised and were only included in the review if they met the inclusion and exclusion criteria listed in Box 1.

Box 1. Exclusion and Inclusion Criteria[a]

Criteria
Exclusion criteria
Unrelated to the topic, which is "non-occupational risk factors for CTS"
Commentaries, book chapters, letters, editorials, conference proceedings, case reports, conferences, abstracts, or non-peer-reviewed articles
Studies examining hand/upper limb injuries without reference to CTS/median nerve
Studies of other medical/systemic conditions (e.g., diabetes, amyloidosis) without specific reference to CTS
Considered only self-reported CTS
Animal or cadaver studies
Inclusion criteria
The article must include original data
The article must be published in English
The article must include a minimum of one potential risk factor for CTS
Medically identified/diagnosed (probable or operated) CTS
The article must include a point or risk estimate (e.g., OR), with the 95% CI obtained from χ^2 tests

[a] A three-step method was followed to identify the articles that were included in the systematic review of risk factors associated with carpel tunnel syndrome (CTS). Titles, abstracts, and full texts were screened and excluded at each step if they met the exclusion criteria. The identified articles were included in the systematic review if they met the inclusion criteria.

2.2. Data Extraction

Study design, study population, and the results of each identified article were reviewed in the appraisal step. Studies reporting risk estimates were identified. These included relative risk (RR), odds ratio (OR), incidence rate ratio (IRR) and hazard ratio (HR). These risk estimates are routinely used as measures of injury risk (7, 8). In order to avoid Type I and II errors made by rounding, the upper and lower 95% confidence interval cut-off values to indicate decreased and increased risk were set at 0.9 and 1.1, respectively. Studies reporting a P value were included only if they were accompanied by a risk estimate, since P values are considered a measure of statistical significance but have limited value in the interpretation and estimation of risk. However, P values were reported if provided. Where studies using pooled data were reported, all risk factors from the first published study were reported and overlapping risk factors in later studies were excluded to avoid bias.

2.3. Level of Evidence and Certainty

Each risk factor was classified using two established methods: 1) level of evidence and 2) level of certainty. Level of evidence, a ranking system for research articles, was determined using previously described definitions (9-11). High-quality prospective cohort studies are considered level I; retrospective studies and lesser-quality prospective studies are level II; case-control studies are level III; case series are level IV; and expert opinions are level V (9, 11). Only articles with a level of evidence of I, II, or III were included in this review.

For each risk factor, the level of evidence of the included studies was used to determine the level of certainty low, moderate, or high for that risk factor. This classification system was based on previously published definitions by the US preventative services task force. The levels of certainty were defined as follows: 1) high certainty is "the available evidence includes consistent results from level I studies. These studies provide a good estimate of risk and are unlikely to be strongly affected by future studies (12)." 2) moderate certainty is "the available evidence includes sufficient evidence to determine that there is risk associated with the injury, but confidence in the estimate is constrained by factors such as the sample size and quality of studies, as well as inconsistency of findings across individual studies. As more information becomes available, the magnitude of risk could change or even alter the conclusion (12)." 3) low certainty is "The available evidence is insufficient to assess risk. Evidence is insufficient because of the limited number or size of studies and inconsistency of findings across individual studies. More information may allow an estimation of risk (12).

In various sections, different variables were grouped under one umbrella risk factor. Although this is not ideal and could cause a potential bias, it was done for simplicity purposes to avoid having an excessive amount of single risk factors investigated in only one study. Furthermore, groupings in this systematic review were based on the risk factor's effect on risk, that is, increased, decreased, or no effect on risk. Although there are several methods of grouping risk factors, this simplified method was chosen to increase the understanding of the effect of a particular risk factor on risk.

3. Results

Initially, 2755 unique titles (duplicates excluded) were identified from the three electronic databases. After applying the inclusion and exclusion criteria, the number of articles was reduced to 1208 abstracts and, finally, 622 full text articles. A total of 75 articles were included. When all the references of the articles that fit the inclusion criteria were analyzed using the same inclusion and exclusion criteria and three-step method as in round one, an additional 8 articles were identified and included in the systematic review. A final selection of 83 articles was therefore included

in this review (Appendix 1). The risk factors were divided into the following categories (1) biological, (2) behavioral and social, (3) medication, (4) medical conditions and injuries, and (5) other.

3.1. Biological Risk Factors

Nine of the risk factors were classified as biological risk factors (Table 1 Appendix 2).

3.2. Ethnicity

Three cross-sectional studies identified different ethnic groups as a risk factor for CTS (13-15). However, none of the prospective cohort (level I and II) studies identified ethnicity as a risk factor (16-18). Although these studies included several ethnic groups, the group composition within each study was different. Ethnicity, as a risk factor for CTS, was assigned a low level of certainty in the context of this review.

3.3. Sex

Female sex was reported to be associated with increased CTS risk in six high quality, prospective (two level I and four level II) studies (16, 18-22), one retrospective study (23), and 16 level III (13, 14, 24-36) studies, with 288 CTS cases in a combined study population of 6148 in the two level I prospective studies (16, 19). In contrast, six prospective studies (17, 37-41), including one level I study, one retrospective study (42), and nine level III (34, 43-50) studies, reported that female sex has no effect. The single level I prospective study only included 35 CTS cases in a study population of 536 (37). All of these studies included several univariate and multivariate analyses. Since only one level I prospective study with a small sample size did not identify sex as a risk factor, and future prospective studies with larger sample sizes could support this finding, sex was assigned a moderate level of certainty. A meta-analysis on sex as a risk factor for CTS is warranted.

3.4. Age

Age as a whole, as a risk factor for CTS, was investigated in this review. Most studies, however, reported age in different age groupings. Three prospective studies reported that the risk for CTS increased with increasing age (> 20 years in intervals of 5 or 10 years) (16, 20, 21), with a fourth reporting increased risk for individuals 50 years old or older (18). Similarly, a single retrospective study found that only workers between 35 and 49 years were at increased risk (42). The single prospective study and the retrospective studies that reported an age-related decreased risk of CTS only included breast cancer patients older than 60 years old who were not specifically defined as industrial workers, and should therefore be considered with caution (51, 52). In contrast, ten prospective (17-19, 21, 22, 37, 38, 40, 41, 53) studies and one retrospective (42) study investigating industrial workers reported that age or age group is not associated with risk of CTS. Age, as investigated as a group risk factor in the present systematic review, was therefore assigned a low level of certainty.

Since all different age groups were investigated together in this review, and the information revealed was contradictory, a more in-depth investigation on the different age groups could potentially yield different results and is thus warranted. Future research in the form of prospective studies should aim to investigate different consensus age groups instead of considering age as a whole.

3.5. Anthropometric Measurements

Three studies investigating height, including one level II (21) and two level III (54, 55) studies, have reported that tall stature decreases the risk of CTS in both men and women, while short stature is not associated with risk. Due to the low number of available studies, height/stature was assigned a low level of certainty. Only one level III study reported several variations of weight together with other anthropometric measurements, such as increased waist-to-hip ratio, to be associated with increased CTS risk (56). In contrast, other variations of these measurements were shown not to alter risk. Additionally, one retrospective study (52), two case-control studies (55, 57) and one cross-sectional (47) study reported that weight has no effect on CTS risk. Considering the different groupings across studies as well as the lack of good quality prospective studies, weight was assigned a low level of certainty as a modifier of CTS risk.

Four higher quality (levels I and II) studies have reported that obesity (BMI $\geq$ 30) is associated with an increased risk of CTS (16, 22, 38, 58). In contrast, 12 high quality studies found that increased BMI is not a risk factor (17-19, 21, 37-40, 42, 53, 59). Similarly, 26 and 23 level III studies have reported that BMI or obesity is associated with increased or no effect on CTS risk, respectively. A single level III study found decreased risk for CTS in orthopedic patients with a BMI of less than 18.5 kg/m^2 (60). Although different BMI groups were investigated together in this review and revealed contradictory information, a more in-depth investigation on the BMI groups could potentially yield different results and is thus warranted. Future research in the form of prospective studies should aim to investigate different BMI intervals instead of considering BMI as a whole. Even though obesity and overweight were often mentioned and readily accepted as risk factors for CTS, due to the conflicting evidence and large number of studies that found no effect, this risk factor was assigned a

Table 1. The Number of Studies Reporting Increased, Decreased, or no Effect on Carpel Tunnel Syndrome (CTS) for Each Biological Risk Factor

Biological Risk Factor	Level I			Level II			Level III			Appendix 2
	I	N	D	I	N	D	I	N	D	
Ethnicity	-	1	-	-	2	-	3	-	-	1.1
Sex	2	1	-	6	16	-	16	9	-	1.2
Age	1	2	-	4	9	2	12	19	-	1.3
Height	-	-	-	-	1	1	-	1	1	1.4
Weight	-	-	-	-	1	-	1	3	-	1.5
BMI or obesity	1	2	-	3	10	-	26	24	1	1.6
Waist measurements	-	-	-	-	-	-	2	2	-	1.7
Hand/wrist structure/dimension	-	-	-	-	-	-	4	6	1	1.8
Familial history and genetic markers	-	1	-	1	1	-	7	4	4	1.9

low level of certainty. Although this finding might change as research progresses, it is interesting to note that the data generated in the investigated studies suggest that increased BMI or obesity has no effect on CTS risk. Future work should investigate this possibility.

Increased waist circumference was reported to increase CTS risk in two level III studies (56, 61). Interestingly, only a very high waist circumference (> 102 cm) was associated with increased risk in males, whereas any increase (> 80 cm) was associated with increased CTS risk in females. Waist-to-hip ratio was reported to either increase or have no effect on CTS risk. Waist measurements were assigned a low level of certainty.

3.6. Hand/Wrist Structure/Dimension

Altered wrist ratio is believed to alter CTS risk (62). Researchers have reasoned that the structure of the wrist, in particular any parameter that will result in narrowing of the carpal tunnel, which reduces the available space for the median and flexor tendons, will increase the risk for CTS (63). Four level III studies reported an increased risk with a difference in hand/wrist structure; specifically, a wrist index (wrist depth/wrist width) of greater than 0.695 (64) or 0.7 (28, 56), respectively, or an increase in digit index (digit 3 length $\times$ 100/hand length) or shape index (hand width $\times$ 100/hand length) (65). Six level III studies reported no effect or various hand/wrist dimensions (24, 43, 64-67), including a wrist ratio of 0.73 or greater (43) as well as no effect with the presence of flexor muscle bellies in the carpal tunnel (67). In contrast, a single low-level study reported that increased wrist circumference led to decreased risk (24). Considering the low quality and conflicting results of the studies, it is clear that more research in the form of high quality prospective studies needs to be performed to get a better impression of whether hand/wrist shape and dimensions influence the risk of developing CTS. Therefore, wrist/hand structure or dimensions were assigned a low level of certainty.

3.7. Familial History and Genetic Markers

One retrospective study (68) and three level III studies found an increase in risk if a family member suffers from CTS (54, 69, 70). In addition, these studies found that familial factors influence CTS risk, with the number of siblings or a family history of this condition significantly increasing the risk of developing CTS. Similarly, four case control studies found that various genetic variants and gene variant combinations were associated with increased, decreased, and no effect on CTS risk (71-74). In contrast, a single case-control study that investigated 520 female twin pairs found a decreased risk of CTS with regard to a genetic component or heritability (75). Three of the case-control studies also found different genetic variants and variant combinations that decrease CTS risk (71-73). Although these are the same studies, different variants were associated with increased and decreased risk. In contrast, two prospective studies reported that a positive family history has no effect on risk of CTS (21, 37). Similarly, four level III studies reported no effect of family history on CTS risk (46, 54, 72, 74). Considering the limited information available on this specific risk factor, it was assigned a low level of certainty.

3.8. Behavioral and Social Risk Factors

Six factors were classified as behavioral and social risk factors for CTS (Table 2, Appendix 3).

3.9. Smoking and Alcohol Use

All the high quality studies, two level I studies (37,16, five level II studies (18, 21, 38, 42, 51), and most of the level III studies investigating smoking as a risk factor reported no association between current and former smoking status and risk of CTS. Only a single cross-sectional study (30) reported an increased risk in industrial workers even after multivariate analysis, while a decreased CTS risk with smoking was reported in three level III studies (35, 46, 76).

Table 2. The Number of Studies Reporting Increased, Decreased, or no Effect on Carpel Tunnel Syndrome (CTS) for Each Behavioral and Social Risk Factor

Behavioral and Social Risk Factor	Level I			Level II			Level III			Appendix 3
	I	N	D	I	N	D	I	N	D	
Smoking	-	2	-	-	5	-	1	11	3	2.1
Alcohol Use	-	1	-	-	1	-	1	2	-	2.2
Socio-Demographic	-	1	-	-	-	-	1	8	2	2.3
Geographical Location	-	-	-	2	2	-	-	-	-	2.4
Hobbies	1	2	-	-	-	-	-	2	-	2.5
Exercise	-	2	-	-	1	-	-	4	3	2.6

However, upon multivariate analyses, the effect of smoking in one of the studies was lost (46). The low level of evidence and low number of studies (n = 3) that found an effect of smoking on CTS risk, together with the fact that multivariate analyses further decreased this to only two studies compared to the large number of studies finding no evidence of smoking being a risk factor were considered contradictory. Smoking was therefore assigned a low level of certainty as a risk factor of CTS.

Two prospective studies (21, 37) as well as two level III studies reported that light, moderate, and/or excessive alcohol use had no effect on CTS risk (54, 61). Since all of the high quality studies reported no effect, with only a single cross-sectional study reporting an increase in risk with increased alcohol consumption (77), this factor was assigned a low level of certainty.

3.10. Socio-Demographic Factors and Geographical Location

Considering that there are few studies investigating education, income, and other socio-economic variables as CTS risk factors, they were all considered together as socio-demographic factors. Only one level III study reported an increase in risk with a higher income level; however, considering the criteria of this review, the effect was lost during multivariate analysis (26). In contrast, two level III studies reported a decreased risk of CTS with a higher education level (30, 54). A single prospective study reported no effect of educational level on CTS risk (16), with several other level III studies also reporting no effect of level of education (13, 69, 78, 79), income (13, 70), social class (57), urbanization (26), or home/leisure activity (75). All of these factors, which are considered a proxy for broad socio-demographic groupings (54), were assigned a low level of certainty.

Both of the level II studies investigating geographical location found that living in the USA leads to increased risk compared to the living in the UK, the southern Hemisphere, and Hong Kong (51, 52). Both of these studies considered only female breast cancer patients, and the results should therefore be interpreted with caution. This factor was assigned a low level of certainty.

3.11. Hobbies

Of the four studies that investigated different hobbies or recreational activities as possible modifiers of CTS risk, only one high quality prospective study reported that knitting and gardening, both activities that involve repetitive hand movements (37), were associated with increased CTS risk. The same prospective study reported no effect for computer work and maintenance hobbies. A second high quality prospective study (16), as well as one level II study and one level III study (18, 80), reported no effect on risk for hobbies in general. Two cross-sectional studies also reported no effect of knitting (69) and other hobbies (80) with regard to CTS risk. Hobbies, as a risk factor for CTS, were assigned a low level of certainty.

3.12. Exercise

Three level III studies reported a decreased risk for CTS with exercise, which included sports participation, any physical activity as well as frequency of exercise (27, 32, 70). In contrast, three prospective studies reported no effect on risk in industrial workers who exercised by means of walking (37), general avocational physical activity (18), or aerobic, non-hand-intensive activity for more than 3 hours per week (16). Similarly, four level III studies reported no effect of various forms and amounts of exercise per week on the risk of CTS (27, 32, 47, 61). Exercise as a modifier for risk of CTS was also assigned a low level of certainty.

3.13. Medication

The role of six specific treatment(s)/medication use as risk factors for CTS was classified under medication (Table 3, Appendix 4).

3.14. Corticosteroid Use

Only two level III studies (29, 81) have reported that the use of corticosteroids increases CTS risk. Upon multivariate analysis and in the case of operated CTS, there was no effect on risk (81). This treatment is therefore assigned a low level of certainty.

Table 3. The Number of Studies Reporting Increased, Decreased, or no Effect on Carpel Tunnel Syndrome (CTS) for Different Medication/Treatments

Medication	Level I			Level II			Level III			Appendix 4
	I	N	D	I	N	D	I	N	D	
Corticosteroid use	-	-	-	-	-	-	2	-	-	3.1
Contraceptive use	-	-	-	-	1	-	2	5	-	3.2
HRT	-	-	-	2	3	-	4	5	-	3.3
Chemotherapy	-	-	-	1	1	-	-	-	-	3.4
Radiotherapy	-	-	-	-	2	-	-	-	-	3.5
Other	-	-	-	2	1	-	3	2	-	3.6

3.15. Contraceptive Use and Hormone Replacement Therapy

A single level II study (38) and five level III studies found former and current use, as well as number of years of contraceptive use to have no effect on risk (55, 57, 80-82). Two level III studies, on the other hand, reported that former or current contraceptive use increased risk (25, 57), and it was assigned a low level of certainty.

Although the focus is primarily on hormone replacement therapy (HRT) as a risk factor for CTS, several other hormone-related statuses have also been included. Although there was no effect after multiple regression or adjustment, two level II studies (51, 52) reported that current or previous use of HTR is associated with increased risk. An additional three level II studies reported that hormonal factors have no effect on risk when hormone receptor status, defined as the receptor status of estrogen and progesterone (i.e., positive or negative) and used in the diagnosis and treatment of breast cancer (51); and hormone use (18); time since menopause; and previous oophorectomy (52) were considered. Four (29, 55, 57, 81) and five (30, 55, 57, 75, 82) lower quality (level III) studies also reported increased risk or no effect on risk, respectively. The lack of studies with a high level of evidence led to HRT and other hormonal factors being assigned a low level of certainty; however, future research should aim to investigate all the mentioned risk factors individually to assess their potential effect on CTS risk.

3.16. Chemotherapy and Radiotherapy

One level II study reported that chemotherapy increases CTS risk (51), while another found that it has no effect (52). These studies both reported that radiotherapy has no effect on CTS risk. Chemotherapy as well as radiotherapy were assigned a low level of certainty.

3.17. Other Medication/Treatment

Different types of medication or treatment, each assessed in a single study and not previously evaluated, were investigated in five different studies, of which, two level II (51, 52) studies reported an increase in CTS risk with various treatments, including anastrozole and exemestane medication, medication for hypertension, insulin, metformin, sulphonyl, and hemodialysis (29, 47, 51, 52, 81). Level II and III studies reported that diuretic use had no effect (52, 82). As a result of insufficient research on these different types of medications/treatments as potential risk factors, a low certainty was assigned to each.

3.18. Medical Conditions and Injuries

Seven specific medical conditions and injuries, as well other factors, which included various medical conditions investigated in only one study, were classified under medical conditions and injuries (Table 4, Appendix 5).

3.19. Diabetes

A single retrospective cohort study (83) and five level III studies (26, 29, 50, 57, 84) reported that diabetes is associated with an increased risk for CTS. In contrast, four higher quality (levels I and II) (16, 37, 39, 52) and nine level III studies reported no effect of diabetes (27, 28, 33, 35, 36, 50, 54, 55, 76, 81). Diabetes is widely believed to be a significant risk factor for CTS and although it was assigned a low level of certainty because of the conflicting evidence found, there is a promising trend towards this condition not influencing CTS risk. Future research should investigate this further.

3.20. Thyroid Disorders

Only three level III studies have reported an increased risk of CTS in participants suffering from hypothyroidism or hyperthyroidism (26, 29, 35), whereas three higher quality (level I and II) (16, 37, 52) as well as four level III (27, 35, 54, 55) studies have reported that thyroid disorders have no effect. Thyroid disorders were therefore assigned a low level of certainty.

Table 4. The Number of Studies Reporting Increased, Decreased, or no Effect on Carpel Tunnel Syndrome (CTS) for Different Medical Conditions

Medical conditions	Level I			Level II			Level III			Appendix 5
	I	N	D	I	N	D	I	N	D	
Diabetes	-	2	-	1	2	-	5	10	-	4.1
Thyroid disorders	-	2	-	-	1	-	3	4	-	4.2
Rheumatoid arthritis	1	1	-	-	-	-	4	3	-	4.3
Osteoarthritis	-	1	-	-	1	-	3	3	-	4.4
Hypertension	-	1	-	-	-	-	1	2	-	4.5
Gout	-	1	-	-	-	-	1	-	-	4.6
Previous MSD/injury	2	1	-	3	2	-	4	6	-	4.7
Other	1	-	-	4	1	-	7	6	3	4.8

3.21. Rheumatoid and Osteoarthritis

Rheumatoid arthritis (RA), an autoimmune disorder characterized by joint inflammation, was investigated in nine studies. A single level I (37) and four level III (26, 29, 54, 81) studies reported an increased risk of CTS. In contrast, one level I (16) and three level III studies found RA to have no effect on CTS risk (27, 57, 76). Considering the conflicting evidence presented to determine whether RA is in fact a true risk factor for CTS, it was assigned a low level of certainty.

Only three level III studies (35, 57, 81) found that osteoarthritis (OA) is associated with an increased risk of CTS. Ferry et al. investigated various forms of OA and found that OA of the spine is associated with increased risk of CTS, whereas for participants who did not specify the type of arthritis they were suffering from there was no difference in their risk of developing CTS (57). Besides this, four other studies, including two higher quality studies (37, 52) and two level III studies (34, 76) also reported no effect of OA on CTS risk. As a result, a low level of certainty was assigned to OA as a risk factor for CTS. Prospective studies should, in future, investigate OA to determine its effect on CTS risk.

3.22. Hypertension

A single level III study (26) found that participants in the general population suffering from hypertension were at increased risk, whereas three studies, including one high quality prospective study (37) and two level III studies (34, 57), reported it to have no effect. Hypertension, as a CTS risk factor, was assigned a low level of certainty.

3.23. Gout

A case-control study (26) reported an increased risk of CTS in members of the general population suffering from gout, while a high quality prospective study (16) reported gout to have no effect on CTS risk in industrial workers. Subsequently, gout as a modifier of CTS risk was assigned a low level of certainty.

3.24. Previous MSD/Injury

Several different musculoskeletal disorders (MSD) and injuries were combined in this section for simplicity and should, ideally, be investigated individually in future investigations. Five higher quality studies together with four level III studies (32, 54, 57, 81) reported an increased risk of CTS with previous musculoskeletal disorder (MSD) or injury (16, 37, 42, 52, 83). Garg et al. reported that although distal upper extremity musculoskeletal disorder (DUE MSD) increases the risk of CTS, previous wrist fracture has no effect on future risk (37). Similarly, three high quality studies (37, 39, 42) and six lower quality studies (28, 54, 55, 57, 70, 82) reported that wrist trauma or injury at baseline had no effect on risk. Even though it appears that a previous MSD and/or injury could indeed affect the risk for CTS, the fact that several injuries were grouped together constrains this finding. Future research should aim to investigate the injuries separately. For the purposes of this review, previous MSD/injury was assigned a moderate level of certainty to affect CTS risk.

3.25. Other Medical Conditions

Twelve studies found that various medical conditions led to increased risk (18, 19, 21, 26, 32, 35, 42, 52, 55, 57, 61, 85). Only one level I prospective study found an increase in risk with more than one predisposing condition (19). Four level II studies investigated lymphedema, hot flashes, endocrine conditions, and any other medical conditions that predispose to CTS, and found that these conditions increased the risk of developing CTS (18, 21, 42, 52). It should be kept in mind that “hot flashes” are likely to be the effect of a hormonal condition and should therefore be interpreted with caution in relation to the etiology of CTS. In contrast, three level III studies found various different conditions to lead to a decrease in CTS risk (35, 57, 61). Furthermore, seven studies found various other medical conditions were not associated with CTS risk (30, 35, 50, 52, 61, 80, 86). Considering the vast differences in the other medical conditions

that were grouped together for simplicity, a low level of certainty was assigned to each of the above-mentioned medical conditions, considering the lack of adequate good quality studies verifying these associations.

3.26. Other

A total of 19 studies considered various other single risk factors that were not previously investigated (Append 6). The only higher quality study was a single retrospective study (level II) that reported that the type of primary surgery a participant had influenced their future risk of developing CTS (52). Each of these risk factors was assigned a low level of certainty, based on the little evidence available.

An overview of all the results of this study is presented in Table 5.

Table 5. Summary of the Level of Certainty of Carpal Tunnel Syndrome Risk Factors

Risk Factors	Level of Certainty		
	High	Moderate	Low
Biological			
Sex		*	
Ethnicity			*
Height			*
Weight			*
BMI			*
Age			*
Hand/wrist structure/dimension			*
Genetic/Familiar			*
Behavioral and Social			
Education/Social			*
Alcohol use			*
Exercise			*
Hobbies			*
Smoking			*
Geographic location			*
Medication			
Corticosteroids			*
Chemotherapy			*
Contraceptives			*
HRT			*
Radiotherapy			*
Other			*
Medical conditions and injuries			
Previous MSD/injury		*	
Diabetes			*
Thyroid disorders			*
Rheumatoid arthritis			*
Osteoarthritis			*
Hypertension			*
Gout			*
Other medical conditions			*

4. Conclusions

The multifactorial etiology of CTS is poorly understood, and there are several risk factors commonly believed to be associated with increased risk for this condition (5). Female sex, commonly believed to be associated with increased risk, was shown to have a moderate level of certainty as a true modifier of CTS risk. In addition, a previous musculoskeletal disorder (MSD) or injury was shown to have a moderate level of certainty to truly modify risk. It is possible, however, that future research will reveal more information that could change these findings, especially because "previous MSD/injury" has a broad definition in this review. Interestingly, various other risk factors that have been widely believed to alter risk, including increased age, diabetes, BMI, and wrist dimensions, had only a low level of certainty with regard to risk. However, there is a lack of high quality studies providing evidence for this hypothesis. It is therefore clear that although there is a trend towards wrist dimensions being associated with a higher risk for CTS, more research in the form of high quality, prospective studies needs to be performed to gain a better understanding of the effect of hand/wrist shape and dimensions on the risk of developing CTS.

Future, prospective studies with large sample sizes should aim to investigate these and other risk factors in order to create a better understanding of the role these factors play in the etiology of CTS. Furthermore, a meta-analysis to investigate the combination and/or interaction of different studies would provide more information on the effect of different risk factors in this multifactorial condition.

Supplements

Supplementary material(s) is available at below link: http://womenshealthbulletin.com/?page=download&file_id=56237.

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Footnotes

Authors' Contribution: Marilize C. Burger, data acquisition, analysis, interpretation; manuscript preparation and editing; Shameemah Abrahams, data acquisition, analysis, interpretation; editing of manuscript; Malcolm Collins, study concept and design; editing of manuscript; overall supervision.

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