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MOHAMMADHOSSEIN POURMEMARI

Risk Factors for Carpal Tunnel Syndrome

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ACADEMIC DISSERTATION
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By three methods we may learn wisdom: First by reflection, which is noblest; second by imitation, which is easiest; and third by experience, which is the bitterest.

Confucius

ABSTRACT

Carpal tunnel syndrome (CTS) is the most common compression neuropathy in the upper limbs. Carpal tunnel release (CTR) is the most commonly performed adult surgical intervention for median nerve decompression. Work-related and individual factors are responsible for the etiology of CTS. The role of some non-occupational factors in CTS are clear, such as age, sex, and obesity. However, the magnitude of the effect of obesity on CTS remains uncertain. At present, the lifetime prevalence of CTR is not known, and the effects of some individual factors, including diabetes mellitus, hypothyroidism, rheumatoid arthritis, and osteoarthritis, on CTS have partly been explained. Furthermore, the effects of type I and type II diabetes and smoking on CTS are not understood.

The overall aim of this study is to estimate the lifetime prevalence of CTR and to identify the risk factors for CTS. Three meta-analyses and one original study were conducted to determine the role of individual factors in CTS and CTR. The meta-analyses were performed using a random-effects model. In the Finnish prospective cohort, a nationwide representative sample (N=6,256 participants) was linked to the Finnish Hospital Discharge Register from 2000 to 2011.

In the meta-analyses, only cross-sectional studies found an association between smoking and CTS. Both type I and type II diabetes were associated with CTS and CTR. Overweight and obesity were associated with CTS with a dose-response relationship. The effects of overweight and obesity on CTS were similar among women and men and were independent of the study design as well as bias and confounding. In the original study, the lifetime prevalence of CTR was 3.1%, and annual incidence was 1.7 per 1,000 person-years. Both prevalence and incidence were twofold higher in women than in men and were higher in individuals with low levels of education than in people with high levels of education. The prevalence peaked at ages 50-59 years, and the incidence peaked at ages 40-49 years. In the final full model,

female sex, ages 40-49 years, education, obesity, and hand osteoarthritis were associated with the incidence of CTR.

The current study suggests that diabetes and obesity increase the risk of CTS and CTR. The basic mechanisms are not fully understood. However, fatty tissue within the carpal canal can gradually increase intracarpal pressure by reducing the carpal tunnel dimension, which leads to impaired peripheral circulation. This causes ischemia, local axonal demyelination, and axon loss. In diabetes, the activation of advanced glycation end-products causes impaired vascular nerve and increases the production of inflammatory cytokines, which resulted in median nerve neuropathy. The findings also indicate that CTR is a common surgical procedure, and 1.9% of men and 4.1% of women experience CTR during their lifetimes. Hand osteoarthritis was associated with CTR. Hand osteoarthritis has been found in severe idiopathic CTS. Therefore, osseous hypertrophy of carpal bones can result in a gradual decrease in carpal tunnel dimension.

TIIVISTELMÄ

Rannekanavaoireyhtymä (karpaalitunnelisyndrooma, CTS) on yleisin hermopinteestä johtuvista neuropatioista yläraajoissa. Rannekanavassa sijaitsevan medianus-hermon vapautusleikkaus (karpaalitunnelin vapautus, engl. carpal tunnel release, CTR) on yleisin toimenpide vaivan helpottamiseksi. CTS:n synnyssä ovat mukana sekä työperäiset että yksilölliset syyt. Ei-työperäiset syyt, kuten ikä, sukupuoli ja ylipaino altistavat selkeästi CTS:lle. Ylipainon vaikutuksen suuruus CTS:n synnyssä on toistaiseksi epäselvä. Tällä hetkellä elinikäistä CTR:n vallitsevuutta ei tunneta. Joidenkin yksilöllisten vaivojen, kuten diabeteksen, kilpirauhasen vajaatoiminnan, nivelreuman sekä nivelrikon yhteyttä CTS:n muodostumiseen on osittain havaittavissa. Ykkös- ja kakkostyypin diabeteksen sekä tupakoinnin vaikutuksia CTS:ään ei toistaiseksi ymmärretä.

Tämän tutkimuksen tarkoituksena oli arvioida CTR:n elinikäistä prevalenssia ja tunnistaa CTS:n riskitekijät. Kolme meta-analyysiä sekä yksi alkuperäinen tutkimus suoritettiin yksilöllisten tekijöiden merkitysten määrittämiseksi sekä CTS:ssä että leikkaushoidossa (CTR). Meta-analyysit suoritettiin hyödyntämällä satunnaisten vaikutusten mallia. Suomalaisessa joukkotutkimuksessa N = 6256 henkilön satunnaisotanta linkitettiin suomalaisiin potilasrekistereihin vuodesta 2000 vuoteen 2011.

Meta-analyyseissä vain poikkileikkaustutkimuksissa löydettiin yhteys tupakoinnin ja CTS:n välillä. Sekä ykkös- että kakkostyypin diabetes olivat yhteydessä CTS:ään sekä CTR:ään. Ylipaino sekä vaikea ylipaino olivat yhteydessä CTS:ään annos-vastesuhteen kautta. Ylipainon sekä vaikean ylipainon vaikutukset CTS:ään olivat samankaltaiset sekä naisilla että miehillä. Vaikutukset olivat riippumattomia tutkimuksen laadusta sekä puolueettomuudesta. Alkuperäisessä tutkimuksessa CTR:n elinkäinen prevalenssi oli 3,1 % ja vuosittainen esiintyvyys 1,7 per 1000 henkilöä. Sekä prevalenssi että esiintyvyys olivat naisilla kaksi kertaa niin suuria kuin

miehillä, ja myös matala koulutustaso nosti lukuja. CTR:n prevalenssi saavutti huippunsa 50–59-vuotiaiden keskuudessa ja esiintyvyys saavutti huippunsa jo 40–49-vuotiaiden keskuudessa. Täydessä, lopullisessa mallissa naissukupuoli, 40–49 vuoden ikä, koulutus, ylipaino sekä nivelrikko olivat yhteydessä CTR:n esiintyvyyteen.

Tämänhetkisen tutkimuksen valossa näyttää siltä, että diabetes ja ylipaino lisäävät CTS:n ja CTR:n riskiä. Syntymekanismeja ei täysin ymmärretä. Kuitenkin tiedetään, että rannekanavassa sijaitseva rasvakudos voi vähitellen lisätä kanavan sisäistä painetta vähentämällä rannekanavan tilavuutta, mikä rajoittaa ääreisverenkiertoa. Tämä aiheuttaa iskemiaa, paikallista aksonaalista demyelinaatiota eli viejähaarakkeen myeliinituhoa sekä aksonin täydellistä menetystä. Diabeteksessa kehittyneet glykaation lopputuotteet heikentävät verisuonihermotusta ja lisäävät tulehduksellisten sytokiinien tuotantoa, mikä johti mediaanihermoneuropatiaan. Löydökset indikoivat myös, että CTR on yleinen leikkaustoimenpide, joka suoritetaan 1,9 %:lle miehistä ja 4,1 %:lle naisista heidän elinikänsä aikana. Käden nivelrikko oli myös yhteydessä CTR:ään. Käden nivelrikkoa esiintyy vaikeassa idiopaattisessa CTS:ssä. Tämän vuoksi karpaaliluiden luuhypertrofia voi ajan kanssa johtaa rannekanavan tilavuuden pienenemiseen.

CONTENTS

ABSTRACT

TIIVISTELMÄ

ABBREVIATIONS

LIST OF PUBLICATIONS

1 INTRODUCTION 1

2 REVIEW OF THE LITERATURE 3
2.1 CLINICAL FEATURES 3
2.1.1 ANATOMY 3
2.1.2 CLINICAL SYMPTOMS AND SIGNNS 3
2.2 PREVALENCE 4
2.3 INCIDENCE 4
2.4 RISK FACTORS 6
2.4.1 Age 6
2.4.2 Sex 7
2.4.3 Smoking 8
2.4.4 Overweight and obesity 9
2.4.5 Physical inactivity 10
2.4.6 Diabetes 11
2.4.7 Hypothyroidism 13
2.4.8 Rheumatoid arthritis 14
2.4.9 Osteoarthritis 15
2.4.10 Other personal risk factors 16
2.4.10.1 Dyslipidemia 16
2.4.10.2 Pregnancy 16
2.4.11 Occupational risk factors 17
2.5 DIAGNOSIS 19
2.6 TREATMENT 20
2.6.1 Non-surgical treatment 21
2.6.2 Surgical treatment 22

3 AIMS OF THE STUDY 24

4 METHODS AND MATERIALS 25
4.1 Reviews and meta-analysis 25
4.1.1 Literature search 25
4.1.2 Inclusion and exclusion criteria 27
4.1.3 Quality assessment 27
4.2 Health 2000 Follow-up study 29
4.2.1 Population 29
4.2.2 Outcome 29
4.2.3 Exposure 30
4.2.4 Statistical analysis 31
4.2.4.1 Meta-analysis 31
4.2.4.2 Original study (Health 2000 follow-up study) 32

5 RESULTS 33
5.1 Review and meta-analysis 33
5.1.1 Smoking 33
5.1.2 Diabetes 37
5.1.3 Overweight and obesity 39
5.2 Original study (Health 2000 Follow-up Study) 41
5.2.1 Incidence rate lifetime prevalence of CTR 41
5.2.2 Risk factors of CTR 45

6 DISCUSSION 47
6.1 Main findings 47
6.2 Prevalence and incidence of carpal tunnel release 47
6.3 Risk factors for CTS and CTR 48
6.3.1 Age 48
6.3.2 Sex 49
6.3.3 Smoking 49
6.3.4 Diabetes 50
6.3.5 Overweight and obesity 52
6.3.6 Arthritis 53
6.3.7 Hypothyroidism 54
6.3.8 Occupational factors 55
6.4 Study strengths 56
6.5 Study limitations 57
6.6 Conclusions 59

7 ACKNOWLEDGMENTS 61

8 REFERENCES 62

ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
CTS	Carpal tunnel syndrome
CTR	Carpal tunnel release
OR	Odds ratio
PR	Prevalence ratio
RR	Risk ratio

LIST OF PUBLICATIONS

This dissertation is based on the following articles referred to throughout the text using Roman numerals (I-IV).

I Pourmemari M.H., Viikari-Juntura E, Shiri R. Smoking and carpal tunnel syndrome: a meta-analysis. Muscle Nerve. 2014; 49(3):345-50.

II Pourmemari M.H., Shiri R. Diabetes as a risk factor for carpal tunnel syndrome: a systematic review and meta-analysis. Diabet Med. 2016; 33(1): 10-16.

III Shiri R, Pourmemari M.H., Falah-Hassani K, Viikari-Juntura E. The effect of excess body mass on the risk of carpal tunnel syndrome: a meta-analysis of 58 studies. Obes Rev. 2015; 16(12):1094-1104.

IV Pourmemari M.H., Heliövaara M, Viikari-Juntura E., Shiri R., Carpal tunnel release: Lifetime prevalence, annual incidence and risk factors. Muscle Nerve. 2018; 58(4): 497-502

1 INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common nerve compression neuropathy in upper extremities (Atroshi et al., 1999), and carpal tunnel release (CTR) is the most commonly performed surgical treatment for upper extremity musculoskeletal disorders (Jain et al., 2014). Of the general population, 1% to 4% suffer from CTS (Atroshi et al., 1999; R. Shiri, Varonen, Heliövaara, & Viikari-Juntura, 2007; Walker-Bone, Palmer, Reading, Coggon, & Cooper, 2004) and 1.3% to 2.0% undergo surgery for CTS (Atroshi, Gummesson, Johnsson, McCabe, & Ornstein, 2003; R. Shiri et al., 2007). CTS is more common in women than in men (English & Gwynne-Jones, 2015; Ha et al., 2009; R. Shiri et al., 2007), and is associated with considerable healthcare costs (Stapleton, 2006), time loss, and lost productivity (Daniell, Fulton-Kehoe, & Franklin, 2009). The economic loss is not limited to direct medical costs; it also includes indirect costs such as the hidden cost of changing one's job and the inability to fulfill family and social roles (Foley, Silverstein, & Polissar, 2007).

The etiology of CTS is multifactorial. Some physical workload factors predict CTS (Kozak et al., 2015). However, the role of some personal factors in CTS is partly clear. There is evidence that CTS is more likely to affect women and people aged 40 years old or over (Tseng et al., 2012). Obesity is a well-known risk factor for CTS (Hendriks et al., 2014). However, the magnitude of the effect of overweight/obesity on CTS is not well known. It is also unclear whether sex modifies the effect of obesity on CTS. Only a few studies investigated the role of waist circumference in CTS (Mondelli, Aretini, Ginanneschi, Greco, & Mattioli, 2014; Plastino et al., 2011; R. Shiri et al., 2011; Uzar, Ilhan, & Ersoy, 2010), which reported inconsistent results. It still remains unclear whether exposure to workload factors modifies the effect of obesity on CTS. The effects of smoking (Atroshi, Gummesson, Ornstein, Johnsson, & Ranstam, 2007; Geoghegan, Clark, Bainbridge, Smith, & Hubbard, 2004) and physical inactivity (Goodson, DeBerard, Wheeler, & Colledge, 2014; R. Shiri et al., 2011) on CTS are

uncertain. To date, no meta-analysis has been conducted on the link between smoking and CTS.

Diabetes mellitus, hypothyroidism, rheumatoid arthritis, and osteoarthritis have been suggested as risk factors for CTS (R. Shiri, 2014a, 2016; van Dijk, Reitsma, Fischer, & Sanders, 2003). Diabetes was associated with CTS (van Dijk et al., 2003). However, the magnitude of the effect of type I and type II diabetes on CTS is unknown. Very few studies have examined the association of osteoarthritis with CTS focusing on different joints being affected by osteoarthritis (R. Shiri, 2016).

The overall aim of this study was to determine the role of personal and occupational risk factors in CTS and CTR. The specific aims of the study were 1) to conduct systematic reviews and meta-analyses of the relationships between smoking, diabetes, and excess body mass index (BMI) with CTS and CTR, and 2) to estimate incidence and lifetime prevalence of CTR in the Finnish general population and to determine risk factors for CTR.

2 REVIEW OF THE LITERATURE

2.1 CLINICAL FEATURES

2.1.1 ANATOMY

The base of the carpal tunnel arch is built medially by pisiform and the hook of the hamate and radially by tubercles of the scaphoid and trapezium. The roof of the carpal tunnel is covered by fibrous flexor retinaculum or transverse carpal ligament (Katz & Simmons, 2002). The carpal canal contains all the finger and thumb flexor tendons, along with the median nerve (Katz & Simmons, 2002). Median nerve branches provide motor innervation to the thenar eminence muscles as well as sensory supply to the palmar cutaneous of the thumb, index, middle, and radial side of the ring finger (Sluiter, Rest, & Frings-Dresen, 2001).

2.1.2 CLINICAL SYMPTOMS AND SIGNS

Clinical symptoms of CTS include pain, tingling, and numbness in the sensory branch of the median nerve of the palmar side of the hand and the three radial digits (Sluiter et al., 2001). There is often nocturnal pain (nocturnal awakening), unpleasant feeling of weakness in the affected hand and radiation in the affected arm. The clinical sign of the thenar muscles atrophy can occur when the disease activity is not under control (Sluiter et al., 2001).

2.2 PREVALENCE

Previous studies in general populations have shown that the prevalence of CTS ranges from 1% to 4% among adults 25 years or older (Atroshi et al., 1999; R. Shiri et al., 2007; Walker-Bone et al., 2004). According to different CTS diagnostic criteria, 2.4% of the general population experienced clinically and electrophysiologically confirmed CTS (Atroshi et al., 1999) as compared to 3.8% (Atroshi et al., 1999; R. Shiri et al., 2007) and 0.9% (Walker-Bone et al., 2004) of the individuals who experienced clinically diagnosed CTS. Moreover, the age distribution of CTS is bimodal, including two peaks in the age groups of 50-59 years and 70 years or over (J. D. P. Bland & Rudolfer, 2003; Mondelli, Giannini, & Giacchi, 2002; R. Shiri et al., 2007). Walker-Bone (Walker-Bone et al., 2004) reported that prevalence rises somewhat with age. Another study showed a high number of prevalent cases in women aged 55-64 and in men aged 45-54 (Atroshi et al., 1999).

The prevalence of undiagnosed CTS was estimated at 0.7% in the Swedish population in which the severity of the condition was similar to that of patients who underwent surgery for CTS (Atroshi, Gummesson, Johnsson, McCabe, et al., 2003). In general, it is believed that one out of ten people with undiagnosed CTS tends to advance clinically towards CTS in some locations (Padua et al., 2016).

Studies conducted in working populations have shown that the point or period of prevalence of clinically and electrophysiologically diagnosed CTS ranges from 4.5% to 15% (Burt et al., 2011; A. M. Dale et al., 2013; Evanoff, Zeringue, Franzblau, & Dale, 2014; Garg et al., 2012; Gell, Werner, Franzblau, Ulin, & Armstrong, 2005; Maghsoudipour, Moghimi, Dehghaan, & Rahimpanah, 2008; B. Silverstein et al., 2009).

2.3 INCIDENCE

In the population-based studies that defined CTS based on symptoms and nerve conduction study, the incidence of CTS ranges from 1.0 to 3.8 per 1,000 person-

years (J. D. P. Bland & Rudolfer, 2003; Bongers, Schellevis, van den Bosch, & van der Zee, 2007; Gelfman et al., 2009; Latinovic, Gulliford, & Hughes, 2006; Mondelli et al., 2002; Nordstrom, DeStefano, Vierkant, & Layde, 1998; Roh et al., 2010; Roquelaure et al., 2008; Stevens, Sun, Beard, O'Fallon, & Kurland, 1988). The incidence rate of CTS has a bimodal age distribution: the first peak occurs between ages 50-54 and a second peak occurs between ages 75-84 (J. D. P. Bland & Rudolfer, 2003).

In the prospective working population studies in which CTS was confirmed by nerve conduction study, the annual incidence rate of CTS ranged from 2.3 to 78 per 1,000 person-years among young adults performing job tasks manually (Burt et al., 2013; A. M. Dale et al., 2013; Evanoff et al., 2014; Garg et al., 2012; Gell et al., 2005; Ricco, Cattani, & Signorelli, 2016; Roquelaure et al., 2017; B. A. Silverstein et al., 2010). The highest rate of CTS occurrence was observed in food processing plants and the lowest in workers involved in several different production processing, such as poultry, manufacturing and assembly, and construction workers (Roquelaure et al., 2017).

The incidence of CTS has a wide range and proves to be higher in occupational populations than in the general populations (Bongers et al., 2007; Ricco et al., 2016). Although a large number of studies on CTS have been conducted in occupational populations, they have not recruited a representative sample of the working population. Moreover, these studies have frequently utilized different case definitions for CTS, and their study populations have been small. Based on the high rate of worker compensation owing to injuries and the rate of primary care consultations, CTS seems to be a painful, ever-present condition (Burton, Chen, Chesterton, & van der Windt, 2018; Dunn et al., 2018).

2.4 RISK FACTORS

2.4.1 Age

In general, age as an individual risk factor tends to have a relationship with CTS, but the results of the studies are contradictory. It has been shown that the risk for CTS is high after the age of 40 years and over (Aboonq, 2015). When age is measured on a continuous scale, the occurrence of CTS increases linearly with age in working populations (Bonfiglioli et al., 2013; Harris-Adamson et al., 2013; Petit et al., 2015; Roquelaure et al., 2008), suggesting that aging may cause a gradual deterioration and loss of the function of the nerve fibers of the median nerve. When age is measured on a categorical scale, the risk of CTS is reported to be notably higher among people aged 40-59 (Harris-Adamson et al., 2013; Roquelaure et al., 2008; Tseng et al., 2012).

In some studies, age was not an independent risk factor for CTS (Burt et al., 2011; Ann Marie Dale et al., 2014; Evanoff et al., 2014; Garg et al., 2012; R. Shiri et al., 2011; Werner et al., 2005), indicating that there may be low statistical power for detecting a significant relationship between age and CTS because of the small study population (Evanoff et al., 2014; Garg et al., 2012). Further population-based prospective cohort studies are needed to re-assess the link between age and CTS.

As aging occurs in people, changes happen to the vasculature system, connective tissue, and inflammatory process, which causes the subjects to be continuously vulnerable to injury. For example, aging is believed to be related to impaired microvascular circulation (Scioli, Bielli, Arcuri, Ferlosio, & Orlandi, 2014); reduction of metabolism in connective tissue (Lindner & Grasedyck, 1982); and, prolonged healing process after the trauma, which may increase the degree of thickening of the fibrocytes and fibrous connective tissue in radial and ulnar bursa and the median nerve (Armstrong, Castelli, Evans, & Diaz-Perez, 1984). These mechanisms may play a role in the onset of CTS symptoms in older adults.

2.4.2 Sex

Sex is a known determinant of CTS. Women present 1.3 to 2.5 times higher prevalence of CTS than men in the general populations (Atroshi et al., 1999; R. Shiri et al., 2007; Walker-Bone et al., 2004), while women show 1.6 to 2.8 times higher prevalence and incidence than men in the working populations (Burt et al., 2011; A. M. Dale et al., 2013; Garg et al., 2012; Gorsche et al., 1999; Harris-Adamson et al., 2013; Melchior et al., 2006; Roquelaure et al., 2008; Roquelaure et al., 2009; B. Silverstein et al., 2009). Moreover, population-based incidence studies detect a 1.2- to 3.6-fold higher risk of CTS in women than in men (Bongers et al., 2007; Gelfman et al., 2009; Latinovic et al., 2006; Mondelli et al., 2002; Nordstrom et al., 1998; Roh et al., 2010; Stevens et al., 1988).

In general, women are more likely to experience a high risk of CTS than men. Sex differences in CTS may be due to several factors; for example, women may complain more often of pain or other symptoms than men because of low threshold and tolerance levels (Barsky, Peekna, & Borus, 2001). The link between sex and CTS may partly be confounded with several factors, but some studies demonstrate that the link does not disappear after the adjustment for the known confounders (Bonfiglioli et al., 2013; Nathan, Meadows, & Istvan, 2002). Furthermore, the differences between sexes may be due to hormonal effects. There is some evidence connecting the risk of the condition to women because of the fluctuations in hormones during pregnancy, menopause, and breastfeeding (Padua et al., 2010). Women are more likely to have a square-shaped wrist as compared to men, which may predispose women to the development of CTS (R. Shiri, 2015). However, a meta-analysis reported that there is no significant difference in mean wrist ratio between men and women (R. Shiri, 2015).

2.4.3 Smoking

Smoking is associated with a number of health concerns. In 2015, the worldwide prevalence of current smoking was 21% in men and 6.2% in women, and smoking resulted in 149 million disability-adjusted life years, was responsible for 640 million premature deaths (GBD 2015 Risk Factors, 2016), and contributes to lost productivity and high healthcare expenditure every year (Ekpu & Brown, 2015). To date, little is known about the role of smoking in CTS. A few studies found an association between smoking and CTS (Atroshi et al., 2007; Eleftheriou et al., 2012; Maghsoudipour et al., 2008; R. Shiri et al., 2011), while some other studies did not find such a relationship. (Geoghegan et al., 2004). One study found an even lower risk of CTS among smokers as compared to nonsmokers (Estirado de Cabo et al., 2003). Moreover, smoking has been defined variously by studies on CTS risk factors. Some investigators have employed the term "currently smoking" in their investigations (Atroshi et al., 2007; Maghsoudipour et al., 2008), while others have defined participants' smoking behaviour as "having ever smoked a cigarette" (Eleftheriou et al., 2012; Frost, Andersen, & Nielsen, 1998). On the other hand, the magnitude of the effect of either current or ever smoking on the condition is unknown. In some studies, the association of smoking habits with the condition was not controlled for known confounders such as physical workload factors and obesity (Karpitskaya, Novak, & Mackinnon, 2002; Wieslander, Norback, Gothe, & Juhlin, 1989). The link between smoking and CTS can be confounded by exposure to physical workload and psychosocial factors, because people who are involved in heavily physical jobs are more likely to smoke than those who are not (Palmer, Syddall, Cooper, & Coggon, 2003).

Smoking may cause harmful effects on the median nerve, which is not fully understood. Palmer and his associates showed that tobacco use decreases pain tolerance in the wrists/hands, shoulders, neck, elbows, hips, and knees (Palmer et al., 2003). Furthermore, cigarette smoking partially suppresses or obstructs the healing process in soft tissues (Ng. et al., 2015) or even in bone tissues (Truntzer, Vopat, Feldstein, & Matityahu, 2015). Smoking may also predispose people to complain more often about musculoskeletal problems (Määttä et al., 2017).

2.4.4 Overweight and obesity

Obesity is an important health issue associated with sizeable non-communicable health problems such as diabetes, cardiovascular and kidney diseases globally. In 2015, a high level of body mass index (BMI) caused four millions premature deaths worldwide (GBD 2015 Obesity, 2017). Overweight and obesity are well-documented determinants of CTS. However, few studies have assessed the role of worker participation in weight-loss programs in the primary prevention of CTS; most of them have focused on ergonomic programs including engineering, administrative, personal interventions, and the use of supporting materials in the working populations (Lincoln et al., 2000; Welcome, Dong, Xu, Warren, & McDowell, 2014). The reason is that they considered work-related factors as the primary cause of CTS.

Obesity defined by earlier cross-sectional studies as BMI $\geqslant$30was associated with CTS in working populations (Atcheson, Ward, & Lowe, 1998; Bonfiglioli et al., 2007). This was later confirmed by cohort studies in the working populations in which the high BMI values were the independent risk factor for the incidence of CTS or CTR (Burt et al., 2013; Harris-Adamson et al., 2013; Reeves, Balkwill, Cairns, Green, & Beral, 2014). Several studies, however, did not find the significant relationship of high BMI with CTS and CTR (Ali & Sathiyasekaran, 2006; Eleftheriou et al., 2012; Farmer & Davis, 2008; Frost et al., 1998; Gell et al., 2005; Gorsche et al., 1999; Melchior et al., 2006). Furthermore, some studies have not defined overweight and obesity using the World Health Organization (WHO) classification (Bonfiglioli et al., 2007; Eleftheriou et al., 2012; Rosecrance, Cook, Anton, & Merlino, 2002), which may have played a role in inconsistent results. CTS is 1.7 to 2.5 times more common in women than in men (R. Shiri et al., 2007; B. Silverstein et al., 2009); however, it is unknown whether sex modifies the effect of overweight or obesity on CTS. Some studies found that the effect of obesity on CTS is about 1.5 times higher in men than in women (Melchior et al., 2006; B. Silverstein et al., 2009), while some other studies reported the effect of obesity on CTS as similar between men and women (Seror & Seror, 2013; Tseng et al., 2012).

Waist circumference, as a surrogate marker of visceral obesity, was found to be linked to CTS or CTR in some studies (Mondelli et al., 2014; R. Shiri et al., 2011). However, there is no longitudinal study to confirm the results drawn from these case-control and cross-sectional studies. So far, only one meta-analytic review has been published on the association between excess body mass and CTS. However, it was published in German with English abstract only and reported pooled odds ratio of 1.5 (95% CI 1.1-1.9) for overweight or obesity (Spahn, Wollny, Hartmann, Schiele, & Hofmann, 2012). That study did not provide the pooled estimates for overweight and obesity separately. Moreover, the publication bias has not been assessed in the studies reporting the link between overweight or obesity and CTS.

Several possible mechanisms have been proposed for the role of obesity in the onset of CTS. Median nerve compression may be related to the accumulation of adipose tissue in the carpal tunnel (J. D. Bland, 2005), and by the activation of deleterious inflammation mechanisms in soft tissues around tunnel area, such as tenosynovitis through metabolic syndrome (Rechardt, Viikari-Juntura, & Shiri, 2014).

In summary, although most of the studies on the association of excess body mass with CTS or CTR have highlighted the role of overweight and obesity in the condition, not all studies have shown such an association. The findings of different studies have also shown that the size of obesity and overweight effects on CTS or CTR are not well specified. Moreover, the effect size of overweight and obesity on CTS and CTR are not well known in men and women.

2.4.5 Physical inactivity

To date, there is no conclusive evidence on the effect of exercise and other leisure-time physical activities on CTS. It has been reported that physical activity may prevent the prolongation of median nerve conduction time (Nathan, Keniston, Myers, Meadows, & Lockwood, 1998). The role of aerobic exercise or other leisure-time physical activity has not been remarkable in the prevention of CTS. It has been

shown that hand exercises may especially affect the secondary and tertiary prevention of CTS (Unver & Akyolcu, 2018). Moreover, previous studies assessing the link between physical inactivity and the risk of CTS have yielded contradictory results. Some types of sports participation and any regular physical activities, as well as exercise that takes place three times per week, have been associated with a reduction in the risk of CTS (Eleftheriou et al., 2012; Goodson et al., 2014; Nordstrom, Vierkant, DeStefano, & Layde, 1997; Raman, Al-Halabi, Hamdan, & Landry, 2012), while some studies did not confirm such an association between physical activities and CTS (Garg et al., 2012; Harris-Adamson et al., 2013; Nathan et al., 2002; R. Shiri et al., 2011).

In summary, the number of studies concerning the effect of physical activity on CTS is limited, and most of them have been conducted in small working populations. Physical activity should be taken into consideration in further prospective epidemiological studies, owing to its potential influential role in preventing the development of CTS.

2.4.6 Diabetes

Diabetes mellitus is a major contributing factor of morbidity and mortality (Global Burden of Metabolic Risk Factors for Chronic Diseases, 2014) and has a considerable impact on health services use and costs globally (Seuring, Archangelidi, & Suhrcke, 2015). There has been an increase in the worldwide prevalence of diabetes since 1980, doubling from 4.7% to 8.5% (Roglic, 2016). The same trend was seen in both sexes, estimated to rise from 4.3% to 9% in men and from 5% to 7.9% in women, suggesting that this could be due to an increase in the prevalence of well-recognized risk factors such as overweight and obesity in those with type II diabetes only (NCD Risk factor Collaboration, 2016). Although CTS is common in patients with diabetes (Musolin, Ramsey, Wassell, & Hard, 2014), epidemiological studies on diabetes have presented contradictory results.

An earlier meta-analytic review found an association between diabetes and CTS (van Dijk et al., 2003). However, it is not clear which type of diabetes contributes to the development of CTS. That review had some limitations. The number of the studies included in that meta-analysis was small. Some of the included studies did not recruit a control group. Furthermore, only a few studies adjusted their estimates for known confounding factors (van Dijk et al., 2003). Since then, some studies have found that diabetes and both types of diabetes are associated with CTS and CTR (Geoghegan et al., 2004; Kidwai et al., 2013; Musolin et al., 2014; Raigani, Mokhtarirad, Bahrami, Eliaspoor, & valaie, 2009; Tseng et al., 2012; Tuppin, Blotiere, Weill, Ricordeau, & Allemand, 2011; Werner et al., 2005; Wessel, Fufa, Boyer, & Calfee, 2013), while some studies did not detect any association between diabetes and CTS or CTR (Ardic, Soyupek, Kahraman, & Yorgancioglu, 2003; Eleftheriou et al., 2012; Evanoff et al., 2014; Harris-Adamson et al., 2013; Mattioli et al., 2009; R. Shiri et al., 2011). Moreover, a few studies adjusted their estimates for all known confounding factors (Harris-Adamson et al., 2013; Mattioli et al., 2009; Tseng et al., 2012; Werner et al., 2005; Wessel et al., 2013).

Patients with diabetes are more likely to experience median nerve neuropathy than individuals without diabetes. There are several mechanisms for the increased risk. A decrease in myelinated nerve fibers and endoneurial capillary density of the median nerve has been detected in individuals with diabetes who are not subject to nerve compression. A decrease in axonal density is believed to result in median nerve neuropathy (Dahlin et al., 2014). Advanced glycation end-products (AGEs) have been observed to provoke the immune response and lead to high production of inflammatory cytokines (Esposito et al., 2002; Goldin, Beckman, Schmidt, & Creager, 2006), and vascular endothelial growth factor may result in impaired microvascular circulation and leads to demyelination and axonal degeneration in the median nerve (Mojaddidi et al., 2014).

In conclusion, the deleterious effect of diabetes on the median nerve has been confirmed by several studies. However, it should be stated that some studies examining the link between diabetes and CTS or CTR were not high-quality studies. Moreover, some of the observed findings are inconsistent. Therefore, a further meta-analysis on diabetes is needed to clarify the role of diabetes in CTS and estimate the

effect size of type I and type II diabetes. There is also a lack of cohort studies examining the effect of diabetes on CTS in the general population.

2.4.7 Hypothyroidism

Van Dijk and associates reported that the prevalence of hypothyroidism in patients with CTS ranges from 1.3% to 10.3% and showed a relationship between hypothyroidism and CTS. However, this study had some limitations. The number of the studies included in the meta-analytic review was small, and some of the studies did not recruit a control group (van Dijk et al., 2003). The finding was later supported by another meta-analysis in which hypothyroidism was introduced as a possible risk factor for CTS (R. Shiri, 2014a). The observed association between hypothyroidism and CTS or CTR was based on a large number of studies compared to the previous meta-analysis. Nevertheless, this study identified a substantial risk of publication bias. Furthermore, some of the included studies did not control the observed association for the potential confounding factors, such as overweight or obesity. It has been shown that excess body mass is associated with CTS among people with hypothyroidism (Karne & Bhalerao, 2016). This suggests that the excess risk of CTS in patients with hypothyroidism has partly been attributed to publication bias and confounding factors. In addition, the link between hypothyroidism and CTS or CTR has not been prospectively assessed in a large representative sample of the general population.

The onset of median nerve symptoms (acroparaesthesia) in those with uncontrolled hypothyroidism may be attributed to a large amount of deposition of pseudomucinous material in tendon sheaths (Karne & Bhalerao, 2016). It activates an inflammatory pathway, which could result in inflammation and thickening of the synovial sheets of the tendons in the carpal tunnel and subsequently median never compression (Karne & Bhalerao, 2016). However, patients with hypothyroidism experience CTS symptoms if they are euthyroid (Kasem, Fathy, Shahin, & Fikry, 2014) or if they are under thyroid replacement therapy (Geoghegan et al., 2004). Moreover, Kasem et al. have reported that the CTS symptoms can be eliminated after three months of hormone replacement therapy. Therefore, hormone replacement therapy can be performed before surgical intervention for CTS (Kasem et al., 2014). Patients

with subclinical hypothyroidism are less likely to report symptoms of CTS (Cakir, Samanci, Balci, & Balci, 2003).

2.4.8 Rheumatoid arthritis

Rheumatoid arthritis is one of the known chronic systematic autoimmune disorders that is characterized by symmetrical persistent synovitis, resulting in swelling, pain, morning stiffness, and limited range of motion in joints (Grassi, De Angelis, Lamanna, & Cervini, 1998). The prevalence of rheumatoid arthritis is observed to be high in CTS patients (van Dijk et al., 2003). The role of rheumatoid arthritis in CTS or CTR etiology is unclear. One meta-analytic review investigated the link between rheumatoid arthritis and CTS and found a two-fold increase in the risk of CTS (van Dijk et al., 2003). The review suffered from the low quality of the primary studies included in the meta-analysis. Some studies in the review were carried out among CTS patients and lacked a control group. Other studies were focusing merely on the effect of arthritis. Since then, some recent studies have revealed that the role of rheumatoid arthritis in CTS is inconsistent. A national-insurance-based population case-control study found a link between rheumatoid arthritis and CTS (Tseng et al., 2012), while working population cohort studies reported a non-significant relationship (Harris-Adamson et al., 2013; Werner et al., 2005). A recent meta-analysis found that rheumatoid arthritis is associated with an increased risk of CTS and CTR (R. Shiri, 2016). In the meta-analyses on the effect of rheumatoid arthritis on CTS or CTR, only a few prospective cohort studies were included (Gell et al., 2005; Harris-Adamson et al., 2013; Werner et al., 2005); two of those studies did not provide any adjusted risk estimates (Gell et al., 2005; Werner et al., 2005).

Furthermore, obesity is believed to affect CTS. However, a few studies attempted to eliminate this role in their analyses. Thus, the observed association between rheumatoid arthritis and CTS may have been overestimated. Median nerve compression observed in patients with rheumatoid arthritis is thought to be the after-effect of tenosynovitis, which is the swelling of the synovial sheaths of the flexor tendons in the carpal tunnel (R. Shiri, 2016).

In conclusion, the meta-analytic estimates imply that rheumatoid arthritis plays a role in CTS. A few high-quality studies prospectively examined the link between rheumatoid arthritis and CTS. Thus, further high-quality, population-based, prospective studies are required to evaluate the effects of rheumatoid arthritis on CTS and CTR.

2.4.9 Osteoarthritis

Osteoarthritis is the most common chronic degenerative joint disease in the aging population, causing pain, loss of motion, and stiffness, mostly in the knees, hips, and hands (Lawrence et al., 2008; Lawrence et al., 1998). The role of hand osteoarthritis in CTS and CTR is unclear. A systematic review and meta-analysis found a relationship between osteoarthritis and CTS in a few epidemiological studies that investigated different affected joints (R. Shiri, 2016). Previously, Florack et al. (Florack, Miller, Pellegrini, Burton, & Dunn, 1992) found that the prevalence of basal joint osteoarthritis of the thumb is higher in those in the working population with electrophysiologically confirmed CTS. Later, other researchers found a positive relationship between hand osteoarthritis and CTS (Geoghegan et al., 2004). Moreover, another investigator found that basal joint arthritis was common in those with idiopathic CTS who undergo CTR (Kim et al., 2013). However, two case-control studies did not find a significant relationship between basal thumb osteoarthritis and CTS (Bacle, Marteau, Corcia, Garaud, & Laulan, 2018; Shin et al., 2012), whereas hand osteoarthritis was associated with CTS (Bacle et al., 2018).

The effect of hand osteoarthritis, as a subgroup of degenerative osteoarthritis, on CTS has not been extensively studied. Moreover, most of the studies on hand osteoarthritis were cross-sectional in nature, as they could not present a cause-and-effect link between hand/wrist osteoarthritis and CTS. Therefore, cohort studies should assess hand osteoarthritis and ascertain its effect on CTS or CTR risk. Subgroup analysis should be conducted to determine the difference among the sexes in the relationship between hand/wrist osteoarthritis and CTS. Severe idiopathic CTS has been observed in patients with hand osteoarthritis caused by osseous hypertrophy in the carpal tunnel (Kim et al., 2013). Osseous hypertrophy can reduce carpal tunnel size (R. Shiri, 2016).

2.4.10 Other personal risk factors

2.4.10.1 Dyslipidemia

To date, the association between dyslipidemia and CTS is uncertain. Higher serum cholesterol is linked to tendon xanthomas and has been emphasized in people with familial hypercholesterolemia, who may develop tendon xanthomas in the carpal tunnel, resulting in suggestive CTS symptoms (Yensel & Karalezli, 2006). Epidemiological studies on dyslipidemia and CTS have reported inconsistent results. Nakamichi et al. (Nakamichi & Tachibana, 2005) have suggested that a high LDL level may be one of the causes of increased median nerve size, which results from changes in collagen production. However, a recent study found that a high level of serum triglyceride, rather than LDL, is a risk factor for idiopathic CTS (Hong, Yeo, & Joo, 2010). Moreover, a study assessing general population health data has not detected any association between hyperlipidemia and the condition, whereas stratified analyses have revealed that low-density lipoprotein cholesterol and triglycerides were linked to clinically diagnosed CTS among the individuals aged 30-44 (R. Shiri et al., 2011).

2.4.10.2 Pregnancy

Women at gestational age may experience the onset of CTS. The prevalence of pregnancy-related CTS has been reported to peak at 62% (Ablove & Ablove, 2009), suggesting that parental healthcare services may not succeed at preventing the occurrence of such a rare condition in pregnancy, particularly in women at the third trimester (Ablove & Ablove, 2009; Khosrawi & Maghrouri, 2012). Moreover, a systematic review reported that the incidence of CTS-related pregnancy ranges from 0.8% to 70%. It seems that this review had some limitations. Most of the reviewed studies recruited small samples and were at risk of selection bias. Moreover, the

studies included in the review were mostly cross-sectional and case-control studies (Padua et al., 2010).

Several factors may be linked to CTS occurrence during pregnancy. However, a few reports have scrutinized the risk factors of pregnancy-related CTS. A large study conducted in the maternal population has recognized that the age of 29 versus 26, pre-pregnancy obesity versus typical maternal weight, and maternal weight gain of 18.4 kg versus 15.5 kg are all responsible for the increase in the risk of CTS. Moreover, the condition was more likely to occur at the first and second trimesters (Wright et al., 2014), although it has been prevalently reported in the third trimester (Finsen & Zeitlmann, 2006). Furthermore, high prevalence, especially in patients with persistent symptoms, may imply further use of invasive management. However, it has been shown that symptoms of CTS diminish during pregnancy through mostly conservative treatments, such as a splint, and disappear relatively soon after delivery. It could also persist during breastfeeding and even subsequently. However, the utilization of surgery has rarely been reported during pregnancy (Atzmon et al., 2014). One hypothesis has been proposed to explain the related mechanism of the occurrence of CTS in pregnant women: the hormone relaxin plays a modulatory role in stress response and breastfeeding, and it may trigger the inflammation of flexor retinaculum, resulting in median nerve compression (Wright et al., 2014).

2.4.11 Occupational risk factors

A review by Palmer and his associates (Palmer, Harris, & Coggon, 2007) concluded that the risk of CTS is associated not only with the regular and extended use of vibrating hand tools but with long-term repetition, high-force gripping, and combination of both. The associations between workplace factors and CTS were observed to be identical between a direct assessment of exposure and self-reported exposure. There was no evidence to support the link between keyboard and computer use and CTS (Palmer et al., 2007).

A more recent review (van Rijn, Huisstede, Koes, & Burdorf, 2009) found that job activities including food processing, packaging, and assembly work; jobs involving repetitive movements at wrist level, high handgrip force, and wrist posture; and a

combination of repetition with force and hand-arm vibrations using vibrating tools were associated with CTS. However, most of the studies had cross-sectional and case-control nature and a few were prospective cohort studies.

A meta-analysis further evaluated the effect of wrist posture on CTS. Wrist extension/flexion activities in workplaces were found to play a role in CTS (You, Smith, & Rempel, 2014). However, most of the included cross-sectional and case-control studies did not adjust their estimates for potential confounding factors. The study also found several reports with negative results missing, indicating that confounding and publication bias could partly lead to excess risk. Several recent reviews focusing on the association between physical work factors and CTS have been scrutinized by Kozak et al. (Kozak et al., 2015). Their assessment indicates that repetition, high-force grip, and especially combined exposure result in CTS, whereas their evidence for vibration was of moderate quality and that for wrist posture at the workplace was of low quality.

Computer work presented no apparent association with CTS. Nonetheless, as the number of studies on this topic has increased, several systematic reviews or meta-analyses concluded that the use of a computer, mouse, and keyboard is an insignificant work-related risk factor for the condition (Mediouni et al., 2014; R. Shiri & Falah-Hassani, 2015; Thomsen, Gerr, & Atroshi, 2008).

The role of work-related psychosocial factors in CTS is uncertain. Psychosocial risk factors included low social support, low job control, high job demands, and low job satisfaction, some of which were positively associated with CTS after the adjustment for known confounders (Goodson et al., 2014; Harris-Adamson et al., 2013; Leclerc et al., 1998). On the other hand, the results of some other studies indicated no association between psychosocial risk factors and CTS (Coggon et al., 2013; Nordstrom et al., 1997; Roquelaure, Mariel, Dano, Fanello, & Penneau-Fontbonne, 2001; Werner et al., 2005). One report found a marginal association due to low statistical power (Andersen et al., 2003). A recent study reviewed the relevant primary reports and stated that there is insufficient evidence of the positive effect of the psychosocial factors on CTS (Mansfield, Thacker, & Sandford, 2018).

2.5 DIAGNOSIS

Clinical examination and nerve conduction study

Phalen's and Tinel's tests are the most commonly used diagnostic tests for clinical examination and should be combined with hand/wrist symptoms for the clinical diagnosis of CTS. Although these provocative tests are simple and low-cost methods, the sensitivity and specificity of these clinical tests offers significant variations as well as different degrees of negative or positive predictive values (Bruske, Bednarski, Grzelec, & Zyluk, 2002; Gerr & Letz, 1998; Wiesman, Novak, Mackinnon, & Winograd, 2003). The probability of diagnosing CTS cases can be 79% when examiners used a classic or probable hand diagram along with either positive Tinel's or Phalen's test (O'Gradaigh & Merry, 2000). Of the general population, 3.8% suffered from clinically diagnosed CTS and 4.9% experienced symptoms and electrophysiologically confirmed CTS (Atroshi et al., 1999). A combination of symptoms and nerve study findings can provide more accurate diagnostic information (Rempel et al., 1998). The sensitivity of nerve conduction studies is between 60% and 84%, and its specificity is more than 95% (The American Association of Electrodiagnostic Medicine, The American Academy of Neurology, & Rehabilitation., 2002). However, nerve conduction testing itself has well-documented high false negatives and positives (Alrawashdeh, 2016; Atroshi, Gummesson, Johnsson, & Ornstein, 2003) and cannot be deemed an optimal test by itself. The findings may also vary, owing to the lack of normalization of factors such as age, sex, skin and room temperature, and finger diameter (Massy-Westropp, Grimmer, & Bain, 2000).

Ultrasound

Ultrasonography can show and measure the internal anatomy of the carpal tunnel, including the thickness of the median nerve, flattening of the nerve within the carpal canal, bowing of the flexor retinaculum, and the cross-sectional area. Moreover, it is believed that the cross-sectional area is the most predictive value, especially when the cross-sectional area is measured at the level of the pisiform bone or tunnel inlet,

but there is not much agreement on the cut-off for the cross-sectional area (range from 6.5 to 15 mm2) (McDonagh, Alexander, & Kane, 2015).

A meta-analytic review pooled some data on the sensitivity and specificity of the ultrasound and found that its sensitivity and specificity were comparable to those of the nerve conduction studies (80% and 79%, respectively). This suggests that ultrasonography could play an important role in CTS diagnosis (Fowler, Gaughan, & Ilyas, 2011). Ultrasound is inexpensive with high acceptability and, although it is not considered a routine diagnostic test, can demonstrate unsuspected structural abnormalities such as space-occupying lesions and bifid median nerves in the tunnel (Sucher & Schreiber, 2014). However, these abnormalities rarely occur.

Magnetic Resonance Imaging (MRI)

MRI depicts the soft tissue when the carpal tunnel should be studied precisely (Onen et al., 2015). Several disadvantages of MRI have been reported, including high cost, an excessive requirement of time, and not being readily available (Ghasemi-Rad et al., 2014). The primary role of MRI is to provide precise information about the rarest CTS cases, such as severe symptoms due to blunt trauma, arthritis, failure of a surgical procedure, undetectable median nerve compression, and changes in median nerve connective tissue (Ghasemi-Rad et al., 2014). Its diagnostic sensitivity is as high as 98%, and the specificity as low as 38% (Cudlip, Howe, Clifton, Schwartz, & Bell, 2002). One review (Pasternack, Malmivaara, Tervahartiala, Forsberg, & Vehmas, 2003) was unable to study the sensitivity and specificity because of the limited quality of primary studies and high heterogeneity among individual studies.

2.6 TREATMENT

The treatment of CTS can be operationally classified into conservative and surgical. However, specialists routinely recommend a nonsurgical option for initiating treatment in mild and moderate cases when there is no muscle weakness or atrophy and electrophysiological parameters indicate a mild abnormality in the median nerve. Moreover, several conservative treatments have been used to alleviate clinical symptoms, such as local and systemic corticosteroids, wrist splinting, non-steroidal

anti-inflammatory drugs (NSAIDs), ultrasound, and diuretics (Newington, Harris, & Walker-Bone, 2015).

2.6.1 Non-surgical treatment

Wrist splinting: A nocturnal splint is more often recommended for people with CTS (J. D. Bland, 2007). However, existing evidence for splint usage is not sufficient. This treatment method, explored in the previous Cochrane review in 2012 (Page, Massy-Westropp, O'Connor, & Pitt, 2012), concluded that the use of a nocturnal splint did not offer a greater benefit than no treatment in the short term (Page et al., 2012). There is also not sufficient evidence regarding the effectiveness of a splint as compared with other non-surgical interventions for CTS (Page et al., 2012).

Oral steroids: A recent review by Huisstede and associates (Huisstede et al., 2018) found strong evidence that oral steroids are more effective than a placebo in improving CTS symptoms after two weeks and moderate evidence after four weeks (Huisstede et al., 2018). Moreover, moderate evidence exists to support that an oral steroid is more effective than wearing a splint in the short term (Huisstede et al., 2018).

Local corticosteroid injection: The local steroid injection is considered a safe and successful treatment for CTS in primary care and is regularly prescribed along with a splint (J. D. Bland, 2007). A review by Huisstede and associates (Huisstede et al., 2018) showed that a local steroid injection adequately improves the clinical symptoms of CTS in the short term. Furthermore, a local steroid injection was found to be more effective than oral steroids in the short-term (Huisstede et al., 2018).

Therapeutic ultrasound: Ultrasound may be prescribed for some patients with mild or moderate CTS. However, the evidence of the role of therapeutic ultrasound in CTS treatment is of low-quality: it demonstrated that ultrasound was more effective than placebo (Page, O'Connor, Pitt, & Massy-Westropp, 2013). There is limited evidence that one type of therapeutic ultrasound regimen is superior to another, and the use of ultrasound had greater effectiveness than other non-surgical interventions such as splinting, exercises, and oral drugs (Page et al., 2013).

Non-steroidal anti-inflammation drugs: The short-term use of non-steroidal anti-inflammation drugs has been shown to be ineffective in the treatment of CTS as compared to a placebo during a four-week follow-up (Huisstede et al., 2018). Furthermore, no significant CTS symptoms relief was found for non-steroidal anti-inflammation drugs as compared to diuretics within four weeks (Huisstede et al., 2018).

2.6.2 Surgical treatment

CTR is carried out to divide the flexor retinaculum either in an open surgical procedure or closed endoscopic procedure aiming to reduce pressure on the median nerve by enlarging the carpal tunnel, and it is usually carried out for patients with severe symptoms along with abnormal electrodiagnostic findings and who do not respond to conservative interventions (Baker & Livengood, 2014). CTR, which has been a common hand procedure since the 1950s (Boskovski & Thomson, 2014), is associated with lost productivity and a high cost of health services (Atroshi et al., 2006; Stapleton, 2006).

Between 1.3% and 2.0% of people aged 25 or older in the general population undergo surgery due to CTS (Atroshi, Gummesson, Johnsson, McCabe, et al., 2003; R. Shiri et al., 2007). The incidence of CTR has been estimated at between 0.3 and 3.3 per 1,000 person-years in the working or other populations among people aged 20 or older (Atroshi, Englund, Turkiewicz, Tagil, & Petersson, 2011; Ebskov, Boeckstyns, & Sorensen, 1997; English & Gwynne-Jones, 2015; Fajardo, Kim, & Szabo, 2012; Fnais, Gomes, Mahoney, Alissa, & Mamdani, 2014; Gelfman et al., 2009; Hobby & Dias, 2006; Jain et al., 2014; Keller, Largay, Soule, & Katz, 1998; Latinovic et al., 2006; Mattioli et al., 2008; Rodriguez-Martinez et al., 2013; Roh et al., 2010; Roquelaure et al., 2017; Tepper et al., 2006; Tuppin et al., 2011).

A recent meta-analysis (Shi, Bobos, Lalone, Warren, & MacDermid, 2018) found that surgical interventions offer clear superiority over splint or corticosteroid injection. The pooled estimates indicate better functional status as well as improvement in nerve conduction outcomes in the surgery group, compared to splint or steroid

injection at 6 months. However, no significant difference between the two groups was found at long-term follow-up (Shi et al., 2018).

Various techniques have been introduced, excluding the conventional technique of open CTR, such as endoscopic CTR with one-portal or two-portal approaches, and a modified incision in open release surgery. Investigators found that patients undergoing endoscopic surgery for CTS had less pain resulting from the scar tissue, and they were more restricted in terms of after-surgery activities than in open surgery for CTS (Atroshi et al., 2006). On the other hand, another study found that there is no conclusive evidence suggesting which techniques would lead to a better improvement of symptoms in the short or long term (Scholten, Mink van der Molen, Uitdehaag, Bouter, & de Vet, 2007). Furthermore, some studies provide evidence of an earlier return to work in patients who undergo endoscopic surgery than in individuals with open CTR (Scholten et al., 2007; Vasiliadis, Georgoulas, Shrier, Salanti, & Scholten, 2014).

3 AIMS OF THE STUDY

The overall aim of the current study is to determine the associations of personal risk factors with CTS and CTR.

The specific aims of this study are as follows:

To determine the effect of smoking on CTS and CTR (publication I).

To investigate the association of diabetes mellitus with CTS and CTR (publication II).

To assess the associations of overweight and obesity with CTS and CTR (publication III).

To estimate incidence rate and lifetime prevalence of CTR and to identify risk factors for CTR (publication IV).

4 METHODS AND MATERIALS

4.1 Review and meta-analysis

4.1.1 Literature review

The literature search comprised six online databases, which were used to identify all relevant primary studies that reported associations of smoking, diabetes, and excess body mass with CTS or CTR. Key terms were defined in advance for smoking, diabetes, obesity, and CTS and presented in Table 1. When possible, the keywords were searched in both medical subject heading (MeSH) terms and text words and in both Emtree terms and text words. We searched for studies on smoking in PubMed, Embase, and Scopus until October 2012. We searched PubMed, Embase, Scopus, and Web of Sciences from their inception until January 2015 for studies on diabetes, and from their inception until February 2015 for studies on excess body mass. We additionally searched Google Scholar and ResearchGate. We also screened the reference list of relevant studies and contacted the authors of some reports for further information.

Table 1. Key items used in literature searches for each systematic review

Main item	Keywords for exposure and outcome
Smoking	Smoke, smok*, smoking, tobacco, cigar, cigarettes, lifestyle, life-style, life style
Diabetes	Diabetes mellitus, diabetes, glucose, "hemoglobin A, glycosylated", HbA1c, hypoglycemic agents, hypoglycemi*, insulin, diabetes complications, "diabetes mellitus, type I", "diabetes mellitus, type II", risk factors, metformin, insulin resistance
Excess body mass	Body mass index, obesity, overweight, body weight, body height, thinness, underweight, Quetelet index, waist circumference, body weight, hip circumference, waist-hip ratio, life style, risk factors
Carpal tunnel syndrome	Carpal tunnel syndrome, carpal tunnel, median nerve, median neuropathy, CTS, carpal canal

4.1.2 Inclusion and exclusion criteria

Two reviewers independently screened the title and abstract of the studies to identify relevant studies on smoking, excess BMI, and diabetes. The studies that were not particularly designed to assess the associations of obesity, smoking, and diabetes with CTS were also included in the reviews. The observational studies were eligible for meta-analysis if they reported relative measurements of the effects (e.g., OR, RR, hazard ratio [HR], or prevalence ratio [PR]) on CTS or CTR for diabetes, smoking, overweight or obesity or reported raw data for estimation of the relative measures. Both population-based and hospital-based case-control studies were included in the review. The corresponding authors were contacted for more information. The studies that defined CTS on the basis of a combination of symptoms and nerve conduction study or clinical diagnosis and CTS confirmed by surgery were included. Moreover, we excluded studies that recruited self-selected volunteers, conducted among patients with CTS as defined by self-report or by only symptoms or by only nerve conduction studies. The studies that did not recruit a control group or were rated as having strong selection bias were excluded from the meta-analysis. Lastly, we excluded studies that did not provide quantitative results to estimate the effect size.

4.1.3 Quality assessment

Two reviewers separately appraised the risk of bias using criteria adapted from the Effective Public Health Practice Project tool for observational studies (Armijo-Olivo, Stiles, Hagen, Biondo, & Cummings, 2012). For each study, we appraised and rated the quality of evidence by several sources of bias, including selection, detection, performance, attrition, and confounding (Table 2). Through discussion, two reviewers resolved their disagreement concerning the quality assessment.

Table 2. Summary showing five bias domains for quality assessment of studies

Type of bias	Criteria description	Category (potential for bias)
Selection bias	Sampling method and representativeness of the study population; response rate; the difference between responders and non-responders; assessment and control variables in case of difference between responders and non-responders	**Weak**: The study population was representative of the general population, subgroup of the general population (specific age group, women, men, specific geographic area, and specific occupational group) with a response rate of over 80% **Moderate**: The study population was slightly representative of the general population (a limited subgroup of the general population) with a response rate of 60% to 79%. **Strong**: The study population was self-referred volunteers with a response rate of under 60%.
Performance bias	Validity and reliability of assessment of exposure The blindness of the appraiser to the outcome of the interest	**Weak:** **Smoking**: The following definition of exposure status was reported: never, former, and currently smoking, as well as information on the number of cigarettes smoked per day or the number of the packs per year. **Diabetes**: Information on the exposure status was based on high-fasting blood glucose and/or a high two-hour impaired glucose tolerance test and/or a known previous diagnosis of diabetes using oral hypoglycemic drugs or insulin. **Excess body mass**: The definition of the exposure status was based on the measurement of weight and height. **Moderate**: **Smoking**: The following definition of exposure status was provided to include never, former, and currently smoking. The number of the cigarettes smoked per day or number of packs smoked per year was not reported. Diabetes: Self-reported exposure status or assessment method was not provided. **Excess body mass**: The definition of exposure status was based on self-reported weight and height data, or the assessment method was not available. **Strong**: **Smoking**: Exposure status was based on a dichotomous question. Never and current smoking could not be distinguished from formerly smoking.
Detection bias	Apparent definition of the outcome The standard technique of the outcome evaluation The blindness of appraiser to the exposure	**Weak**: The outcome was defined by the standard method. **Moderate**: The outcome was defined based on somewhat limited diagnostic tests. **Strong**: Self-reported outcome, the appraiser was not blinded to exposure status.
Confounding	No differences between groups, matching, stratification, statistical analysis	**Weak**: The confounders were considered and were controlled from 80% to 100% of the confounders. **Moderate**: The confounders were considered and were controlled from 60% to 79% of the confounders. **Strong**: The confounders were considered and were controlled for less than 60% of the confounders.
Attrition bias	Withdrawals and dropout rates, the size of missing data	**Weak**: Follow up or participation rate was reported from 80% to 100%, and missing data was less than 20%. **Moderate**: Follow up or participation rate was reported from 60% to 79%, and missing data was 20% to 40%. **Strong**: Follow up or participation rate was reported to be less than 60%, and missing data was more than 40%.

4.2 Health 2000 Follow-up Study

4.2.1 Population

The Health 2000 Survey aimed to investigate most public health concerns. The survey consisted of all men and women aged 30 years or older living in Finland from autumn 2000 to spring 2001. To obtain a representative sample of the Finnish population, the population was divided into subgroups based on five hospital districts and congregated into 16 healthcare regions, amounting to 80 healthcare regions across the country (Aromaa & Koskinen, 2004). The Health 2000 Survey provides current information about disease determinants and treatments such as respiratory, cardiovascular diseases, musculoskeletal, and mental health disorders as well as different disabilities.

The participants in the Health 2000 Survey consisted of 8,028 people linked to the Finnish Hospital Discharge Register from 2000 to 2011. Of these, 6,354 (79.7%) subjects underwent home interviews and health examinations. Individuals whose data about CTR (n=98) at baseline was missing were excluded from the study, and 6,256 (78.4%) individuals qualified for the lifetime prevalence analyses. In this study, the patients with surgical release of carpal tunnel at baseline (n=79) were excluded, and thus 6,177 (77.4%) individuals were included in the incidence analyses. The Finnish Hospital Discharge Register provides information on inpatient medical services and has been reported to identify 80% to 90% of the standard discharge diagnoses (Sund, 2012).

4.2.2 Outcome

In the face-to-face interview, those who had any history of CTR at baseline in 2000/ 2001 were identified. The study population was followed up for 11 years (between 2001 and 2011), and the incident cases of CTR were derived from the Hospital Discharge Register using ICD-10 codes. When the G56.0 codes ended in ACC51 and ACC59, they were considered events of interest. We assessed the reliability of

self-reported CTRs based on the information provided by the register data from 1997-2000. Twenty-three out of 79 subjects with self-reported surgical treatment for CTS were recognized by the Hospital Discharge Register from 1997 to 2000. During these years, we found no further registered CTRs among those who did not report their CTR. The remaining 56 self-reported cases underwent CTR in 1996 or earlier.

4.2.3 Exposure

In addition to age and sex as individual factors, the home interview was used to collect information regarding education levels of the study population at baseline. People with a basic comprehensive school certificate were considered to have a low level of education, people with upper secondary or vocational school diploma were considered to have a medium level of education, and individuals with a university degree were considered to have high level of education. Waist and hip circumference, weight, and height were measured. The study population was grouped into three BMI classes: normal weight (BMI 18.5-24.9 kg/m2), overweight (BMI 25-29.9 kg/m2), and obesity (BMI ≥30 kg/m 2). Waist circumference was grouped into three classes: for men <94 cm, 94-101.9 cm, and ≥102 cm , and for women <80 cm , 80-87.9 cm and ≥88 cm (R. Shiri et al., 2011). Wais-to-hip ratio was calculated and individuals were then classified into three groups: for men <0.9, 0.9-1.0, and >1.0, and for women <0.8, 0.8-0.9, and >0.9 (R. Shiri et al., 2011). Information regarding smoking status was obtained through home interviews and participants were grouped into four levels: 1) current smokers; smoked cigarettes, cigar or a pipe at any time during the survey, 2) former smokers; smoked for at least one year previously, 3) occasional smokers, and 4) non-smokers. A single question was used to assess the frequency of leisure-time physical activity: "How often do you exercise in your leisure time so that you are slightly out of breath and sweating?" This variable was classified into three levels: ≤1; 2-3; and ≥4 tim es per week .

Six physical workload factors (frequency or duration per day) in the interviewees' most recent jobs were assessed at the time of interview, including 1) manual material handling of loads heavier than 5 kg at least two times per minute at the minimum of two hours per day; 2) manual material handling of loads heavier than 20 kg at least 10 times every day; 3) heavy physical work such as lifting, digging by shovel, or

chopping wood; 4) high handgrip force, e.g., holding burdensome material or tools, twisting, squeezing at minimum one hour daily on average; 5) the repetitive activity of the hands/wrists, such as sorting out and packing no less than 120 minutes daily on average; and 6) the use of vibrating tools during work at minimum two hours daily on average.

For defining diabetes, the history of the use of anti-diabetic medicines or high fasting blood glucose and/or a previous history of diabetes were used. For defining hypothyroidism, rheumatoid arthritis, and knee or hip osteoarthritis, interview and physical examination were used. The information on hand osteoarthritis was obtained through face-to-face interviews. Serum rheumatoid factor was drawn by blood samples for analysis and grouped into normal value <15 IU/ml and high value ≥15 IU/ml.

4.2.4 Statistical analysis

4.2.4.1 Meta-analysis

We used a fixed-effect model to pool the estimates of different subgroups of one study, for example men and women, and individuals with type I and type II diabetes. The effects of smoking, diabetes, and excess body mass on CTS can be different from study to study because of the variations in individuals' characteristics as well as methodological issues. We used the random-effects model for pooling the estimates of individual studies. We estimated the heterogeneity across studies using chi-square and I-squared statistics (J. P. Higgins & Thompson, 2002). The I2 statistics derived from (Q - degrees of freedom)/Q x 100, where Q has chi-square distribution, presenting the exact inconsistency of the association between the risk factor (smoking, diabetes, or obesity) and CTS that is beyond chance. The value of <25% and >50% indicates small and high inconsistency, respectively. For the Q test, the statistical significance was shown using a P-value of <0.10. (J. P. T. Higgins & Green, 2011). A funnel plot was used to assess publication bias and consists of the size of smoking, diabetes, or obesity effect against standard error (SE) (J. P. T. Higgins &

Green, 2011). Moreover, Egger's test was used to assess the presence of asymmetry in the funnel plot, where a P value of <0.10 showed the statistical significance for publication bias. The trim and fill method was used to estimate the number of missing studies due to publication bias (J. P. T. Higgins & Green, 2011). We used meta-regression to determine whether study-level covariates explain the heterogeneity. The meta-analyses were performed using Stata software, version 10 or 13.

4.2.4.2 Original study (Health 2000 follow-up study)

We used weighting for calculating lifetime prevalence, incidence rate, PR, and HR and their 95% confidence intervals to adjust for the unbalanced selection of persons in population subgroups such as language, sex, age, and residential area in order to make the study population a representative sample of the Finnish general population.

We conducted a survey log-binomial regression to estimate adjusted PR for prevalence data and a survey Cox proportional hazards regression model to obtain adjusted HR for incidence data. Age was considered at the follow-up for lifetime prevalence and at the baseline for incidence rate. To calculate age at follow-up for each participant, we summed age at baseline with the individual's follow-up time. The main analysis was run to identify risk factors for CTR using survey Cox proportional hazards regression models. In addition to a combined analysis of both sexes, we ran sex-specific subgroup analysis. Variables with P-value $\leqslant 0.3$ were included in models where the estimates also adjusted for both age and sex. The final full model included age, sex, education, high handgrip force, heavy physical work, obesity, and hand osteoarthritis. A P-value of <0.05 was considered as statistically significant. Version 13 of Stata software was used for the survey analyses.

5 RESULTS

5.1 Review and meta-analysis

5.1.1 Smoking

The search initially identified 1,045 potential reports; of those, 843 were primarily excluded through screening the titles and abstracts. Furthermore, 17 studies were identified through a hand search of the reference list. After screening 219 full-text reports, 24 relevant studies were identified. Eleven studies were excluded from the meta-analysis. Two cross-sectional studies and one cohort study recruited volunteers; of those studies, one also used self-reported CTS and reported estimates that were not adjusted for the confounders. Two reports had used self-reported CTS as an outcome of interest. Two studies defined CTS based on symptoms, and one study defined cases and controls based on nerve conduction study only. One study did not provide quantitative data to estimate an odds ratio. A case-control study carried out on outpatients referring to specialized hospitals was rated as having strong selection bias and reported unadjusted estimates. Finally, one study was conducted on a non-random sample of patients with toxic oil syndrome. Finally, 13 studies qualified for the meta-analysis (Figure 1).

The cross-sectional studies controlled their estimates for the confounders better than case-control and cohort studies. A pooled analysis of three cross-sectional studies showed that current smoking was associated with CTS while ever smoking was not. Case-control studies did not find any significant association between smoking and CTS. The pooled estimate of the three small, low-quality cohort studies was also not statistically significant. Moreover, a meta-analysis of all 13 included studies showed a 1.2 times higher risk of CTS in smokers than in non-smokers (pooled OR=1.22, 95% CI 0.99-1.50), although there was considerable heterogeneity (Figure 2). The funnel plot of 13 included studies was symmetrical (Egger test=0.25),

indicating absence of publication bias. Furthermore, only one missing study due to publication bias was imputed by the trim and fill method.

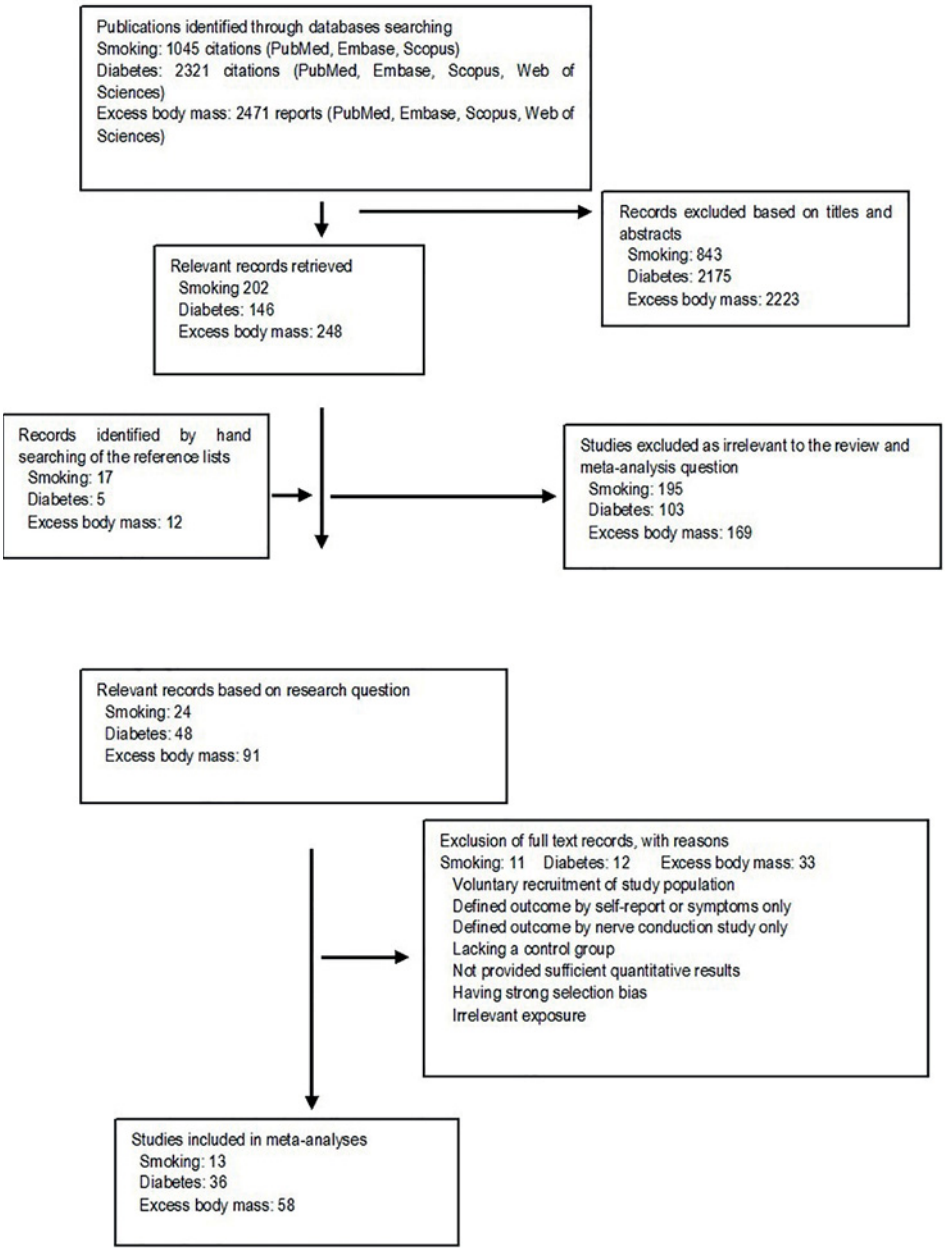

Figure 1. Flowchart of search strategy and selection of studies for the three systematic reviews and meta-analyses.

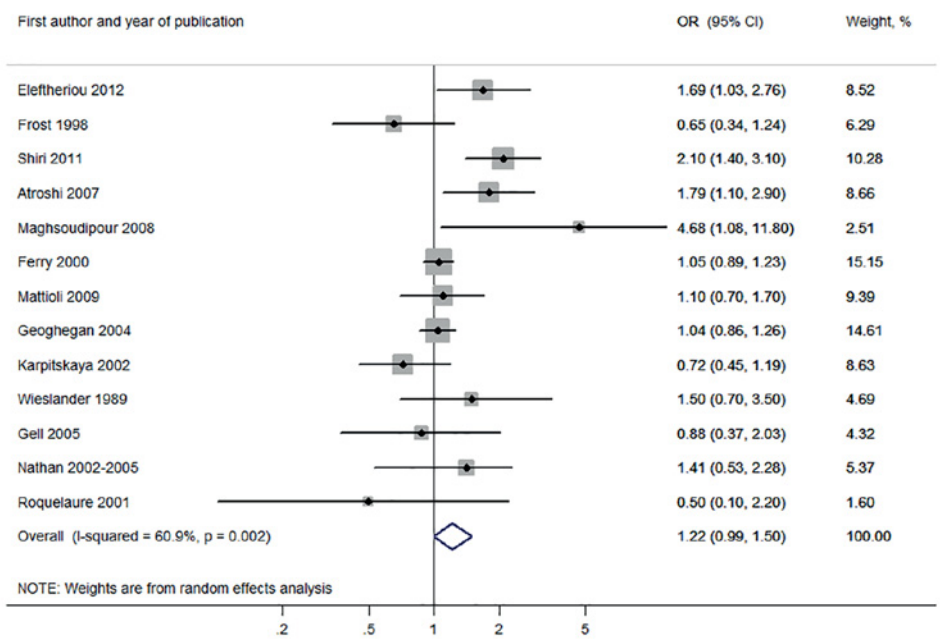

Figure 2. Forest plot for a meta-analysis of 13 included studies on the relationship between smoking and carpal tunnel syndrome.

5.1.2 Diabetes

Study selection

Our searches retrieved 2,321 potential publications; of those we excluded 2,175 reports by screening the titles and abstracts. We reviewed the full text of 146 publications and identified 48 relevant reports. Twelve of these studies were not appropriate for meta-analysis because they suffered from some systematic biases. Three studies recruited volunteers as the study population. Two studies used only symptoms for diagnosing CTS, and two used only nerve conduction study for diagnosing CTS. Two studies recruited people with CTS but without recruiting a control group. Two studies did not provide adequate quantitative data, and one was conducted in patients with prediabetic status. Finally, 36 studies were included in the meta-analysis (Figure 1).

Quality assessment of included studies

Based on the quality assessment of the included studies, five reports did not have selection bias, 22 had moderate selection bias, and nine were assessed as having high selection bias. Age and sex were controlled in 19 studies.

Diabetes and CTS

Pooling of unadjusted PR of eight cross-sectional studies showed a pooled PR of 1.84, (95% CI 1.43-2.36, I2=0.0%, N=13,576) for the association between diabetes and CTS. Pooled OR of 13 case-control and cohort studies reported unadjusted estimates was 2.03 (95% CI 1.45-2.84, I2=72.7%, N=72,546). The pooled OR of 14 case-control and cohort studies provided adjusted estimates was 1.91 (95% CI 1.45-2.53, I2=70.5%, N=75,218).

Diabetes and CTR

The pooled OR of four case-control studies on CTR that provided unadjusted estimates was 1.95 (95% CI 1.23-3.10, I2=43.9%, N=6,442). The pooled OR of five

case-control studies reported adjusted OR was 1.60 (95% CI 1.56-1.63, I2=0.0%, N=37, 140,225), indicating that adjustment for confounding factors slightly attenuated the association between diabetes and CTR.

A meta-analysis of 25 reports on CTS or CTR with unadjusted estimates revealed a pooled OR of 1.97 (95% CI 1.56-2.49, I2=71.2%, N=92,564). The pooled OR of 18 case-control or cohort studies on CTS or CTR with adjusted estimates was 1.69 (95% CI 1.45-1.96, I2=63.1%, N=37,207,483).

Type I or type II diabetes

Both type I and type II diabetes were associated with CTS or CTR. The effect of diabetes on CTS or CTR did not statistically differ significantly between type I (OR=3.21) and type II diabetes (OR=2.33).

Publication bias

The funnel plot of 36 studies was symmetrical (P for Egger's test=0.16). However, six missing studies were imputed by the trim and fill method, showing publication bias. After adjusting for funnel plot asymmetry, the adjusted pooled risk estimate decreased from 1.69 to 1.55.

Sensitivity analysis

The sensitivity analyses were conducted to investigate the role of confounding factors and selection bias in the association between diabetes and CTS. The confounding role of BMI was investigated by four case-control and two cohort studies only. A meta-analysis of four case-control studies showed a pooled OR of 1.68, which decreased to 1.56 after including two cohort studies. The studies appraised to have high risk of selection bias were excluded from the analysis. Thus, the pooled adjusted estimate of the relationship between diabetes and CTS dropped from 1.91 to 1.76 and that of CTS or CTR dropped from 1.69 to 1.64.

5.1.3 Overweight and obesity

Study selection

A total of 2,471 publications were identified through several online databases. After screening the abstracts, 2,223 reports were excluded. The full texts of the remaining 248 reports were scrutinized, resulting in 91 studies; of those, 58 studies were qualified for the systematic review and meta-analysis. With regard to study designs, 22 were cross-sectional, 26 were case-control, and 10 were prospective cohort studies. Overall, 49 studies were on CTS and 9 on CTR. Two studies provided OR estimates for both CTS and CTR. The sex-specific results of the relationship of BMI with CTS were available in 23 studies (Figure 1).

Studies excluded from meta-analysis

Thirty-three studies were ineligible for meta-analysis. Volunteers were sampled in the 10 studies. In two of these investigations, CTS was defined based on symptoms only or nerve conduction study only. Two studies were conducted among patients with CTS but did not enlist a group of the subjects as a control group. Six studies used only symptoms for diagnosing CTS, six used only nerve conduction study, and four studies defined CTS based on self-report. Two reports did not supply the estimations of the relationship between BMI and CTS. Ultimately, we did not include one of the reports, as it examined the role of weight gain in CTS (Figure 1).

Quality of included studies

Eighteen studies had high risk of selection bias, leaving 40 reports that had either low or moderate selection bias. More than half of the reports (38 studies) defined BMI based on self-report, while 20 studies measured height and weight. Forty studies used a nerve conduction study to confirm the CTS diagnosis, and 18 studies either clinically diagnosed CTS or used medical records. Finally, most of the studies (51

studies) were assessed as having low attrition bias, three reports were assessed having moderate risk, and only four were found to have high attrition bias.

Association between body mass index and CTS

A higher mean BMI was observed among people with CTS or CTR, compared to those without CTS or CTR when the estimates were controlled for age and sex (mean difference 2.5, 95% CI 0.69-4.5, N=1,002, four studies). A similar trend was seen in those studies (13 studies) that provided unadjusted estimate (mean difference=2.2, 95% CI 1.41-2.89, N=4,429).

Overweight and obesity were associated with CTS and CTR. The pooled adjusted-estimate of 17 studies showed that overweight increases the risk of CTS by 1.5-fold (pooled adjusted OR=1.48, 95% CI 1.40-1.56, I2=0%, N=26,642), overweight or obesity by 1.8-fold, and obesity by twofold (OR=1.97, 95% CI 1.84-2.10, I2=0.70%, N=109,126). Moreover, a meta-analysis of 11 studies on CTR revealed that overweight increased the risk of CTR by 1.5-fold and obesity by over twofold.

For each one-unit increase in BMI, the risk of CTS increased by 7.4% (pooled adjusted OR=1.074, 95% CI 1.701-1.077, I2=0.0%, N=1,258,578, 13 studies). Increased central obesity, measured as waist circumference, was associated with an increased risk of CTS (pooled OR for overweight or obesity=2.21, 95% CI 1.26-3.89 I2=80.7%, N=7,691, four studies). In subgroup analysis, the relationships of overweight and obesity with CTS were similar in men and women.

Publication bias and sensitivity analysis

The funnel plot of 58 studies was asymmetrical (Eager's test=0.077), which was drawn by 40 studies on obesity and 18 reports on overweight/obesity. Eleven missing studies were imputed by the trim and fill method. After adjustment for publication bias, the pooled OR of 58 reports dropped from 2.20 to 1.98.

In sensitivity analyses, we assessed the role of study design, study quality, and confounding factors. The findings indicated that the relationship between obesity and CTS was independent of study design, study quality, and confounding factors.

A meta-analysis of nine cohort studies on CTS with adjusted estimates showed similar findings for overweight, overweight/obesity, and obesity. Furthermore, excluding the studies reported the estimate for a one-unit increase in BMI, as well as excluding the study with a large study population (N=1,251,619) (Reeves et al., 2014), did not change the effect size for overweight, overweight/obesity, and obesity. Moreover, exclusion of the largest study and the inclusion of the studies with low or moderate selection bias, low attrition bias, and those well-controlled for confounders did not lead to a considerable change in the results.

5.2 Original study (Health 2000 follow-up study)

The mean age of the Health 2000 population was 52 ± 14 years, mean BMI was 27 ± 4.6, and more than one-fourth of the participants held a university degree. Fewer than one-fourth of the participants were current smokers, and more than one-fourth engaged in exercise four times or more per week. During the 11-year follow-up, 867 subjects (13.9%) died. Among all participants, 192 cases of CTR were identified; 79 cases self-reported their surgery at baseline in 2000/2001, and 113 cases who underwent surgery for CTS between 2000 and 2011 were recognized from the Hospital Discharge Register.

5.2.1 Incidence rate lifetime prevalence of CTR

The lifetime prevalence of CTR was 3.1% (95% CI 2.7%-3.5%), and the annual incidence rate was 1.73 (95% CI 1.44-2.09) per 1,000 person-years. The prevalence and incidence of CTR were about twofold higher in women than in men. The peak prevalence occurred between ages 50-59 (4.0%, 95% CI 3.0%-4.9%, Figure 3), and the peak incidence rate occurred between ages 40-49 years (2.8, 95% CI 2.1-3.8 per 1,000 person-years, Figure 4). In highly educated people, the prevalence of CTR was about half that of the low-educated individuals (1.6% vs. 3.6%), and the incidence rate was 37% lower (1.2 vs. 1.9 per 1,000 person-years).

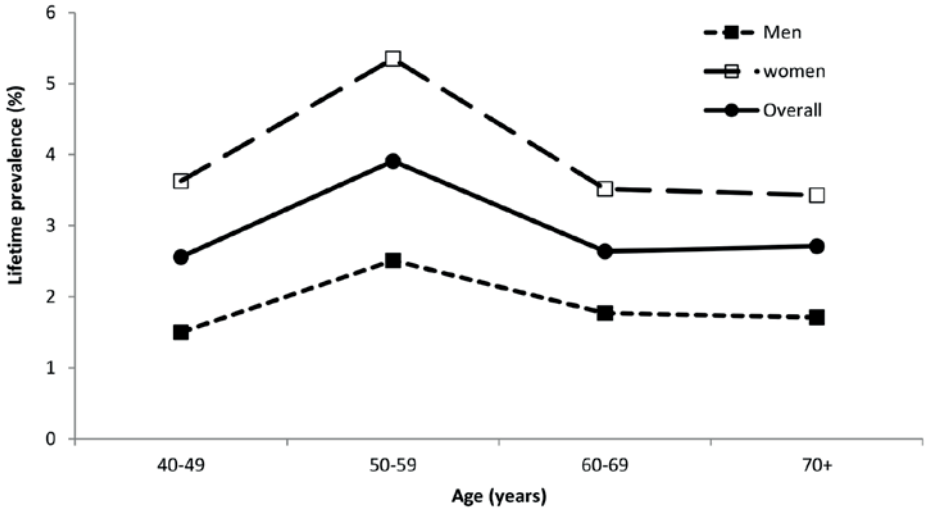

Figure 3. Age-specific lifetime prevalence of carpal tunnel release, age at follow-up.

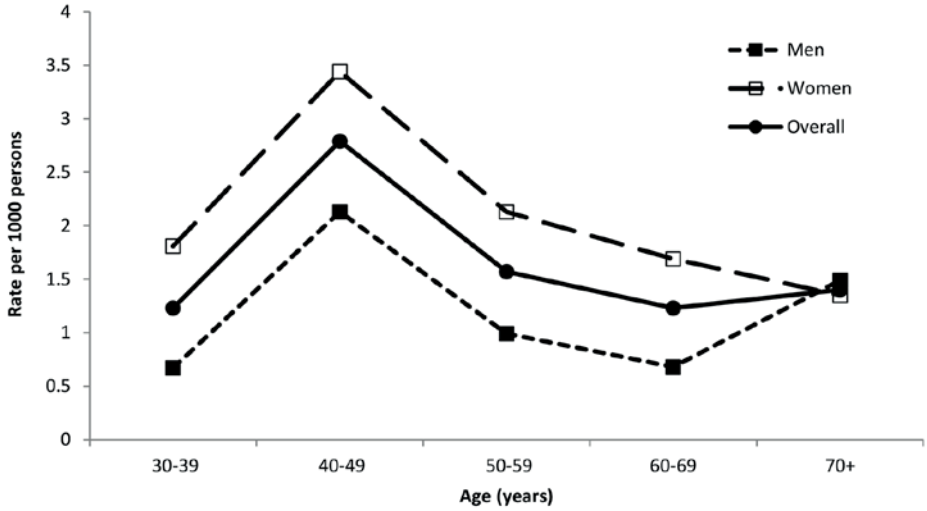

Figure 4. Age-specific annual incidence of carpal tunnel release, age at baseline.

5.2.2 Risk factors of CTR

Age- and sex-adjusted results

The age-adjusted incidence of CTR was about two times higher in women than in men (HR=1.9, 95% CI 1.3-2.7), and the sex-adjusted incidence of CTR was twice as common in the age group of 40-49 years than in the other age groups (HR=2.3, 95% CI 1.3-3.9). Moreover, BMI ≥30 kg/m 2 (HR=1.8, 95% CI 1.2-2.7), high waist-to-hip ratio (HR=2.3, 95% CI 1.1-4.8), and hand osteoarthritis (HR=2.8, 95% CI 1.6-4.8) were linked to high occurrence of surgical treatment for CTS. Highly educated individuals were less likely to experience surgical intervention for CTS as compared to those with low level of education (HR=0.5, 95% CI 0.3-0.9). Smoking, leisure-time physical activity, waist circumference, diabetes, rheumatoid arthritis, hypothyroidism, knee or hip osteoarthritis, and workload factors were not associated with CTR.

Sex-specific results

In age-adjusted analyses, obesity measured by BMI (HR=1.6, 95% CI 1.6-2.6), hand osteoarthritis (HR=3.0, 95% 1.6-5.9), heavy physical work (HR=2.1, 95% CI 1.2-3.5), and work requiring high handgrip force (HR=2.4, 95% CI 1.4-4.0) were associated with high risk of CTR in women. Furthermore, highly educated women were less likely to undergo CTR surgery than poorly educated women (HR=0.5, 95% CI 0.2-0.9). Similar tendencies were observed in those with a high level of education, obesity, and hand osteoarthritis in men; however, the differences between the groups were not statistically significant. We found that knee or hip osteoarthritis was related to high occurrence of surgical intervention for CTS in men (HR= 6.0, 95% CI 2.30-16.1).

Final full model results

The female (HR=1.8, 95% CI 1.2-2.8) age group of 40-49 years versus other age groups (HR=2.5, 95% CI 1.7-3.8), high versus low or moderate education (HR=0.6, 95% CI 0.4-0.9), obesity defined by BMI ≥30 vs. ≤30 kg/m 2 (HR=1.7, 95% CI 1.2-2.5) and hand osteoarthritis (HR=2.4, 95% CI 1.4-3.9) were associated with the risk of CTR. Waist-to-hip ratio did not show any significant association with CTR in the

full model. In further subgroup analyses, the relationships of heavy physical work and work requiring high handgrip force with CTR did not change after removing education from the model. Moreover, the association between obesity and CTR was independent of exposure to heavy physical work and work requiring high handgrip force.

6 DISCUSSION

6.1 Main findings

Three systematic reviews and meta-analyses suggest that diabetes (both type I and type II) and excess BMI (both overweight and obesity) are risk factors for CTS and CTR. For excess BMI, the effect size is large, with a dose-response relationship, and does not differ between women and men. For diabetes, the excess risk is modest and was similar among type I and type II diabetes. A limited number of cross-sectional studies found that current smoking is associated with CTS. However, case-control and cohort studies did not find such a relationship.

Our original prospective cohort study showed an incidence rate of 1.73 per 1,000 person-years and a lifetime prevalence of 3.1% for CTR. The incidence and prevalence were about twofold higher in women than in men and were higher in people with a low level of education than in individuals with a high level of education. The incidence was higher in those aged 40-49 and the prevalence was higher in people aged 50-59. Female sex, ages 40-49, hand osteoarthritis, and obesity were related to a higher rate of CTR.

6.2 Prevalence and incidence of carpal tunnel release

CTR prevalence ranged from 0.9% to 2.0% in the general population (Atroshi, Gummesson, Johnsson, McCabe, et al., 2003; A. M. Dale et al., 2013; R. Shiri et al., 2007). It ranges from 1.8% to 2.6% in women and from 0.7% to 1.2% in men (Atroshi, Gummesson, Johnsson, McCabe, et al., 2003; R. Shiri et al., 2007). Our study was the first to estimate the lifetime prevalence of CTR. Women had a higher lifetime prevalence as compared to men. The peak prevalence was among people between ages 50-59. It is plausible that the survivorship and recall biases in this study resulted in lower CTR lifetime prevalence in participants aged 60 or older. Some of the people who

died during the follow-up period might have experienced surgery for CTS had they survived longer.

Our incidence rate is within the range of the previous epidemiological studies. The incidence in these studies ranged from 0.3 to 3.3 per 1,000 person-years (Atroshi et al., 2011; Ebskov et al., 1997; English & Gwynne-Jones, 2015; Fajardo et al., 2012; Fnais et al., 2014; Gelfman et al., 2009; Hobby & Dias, 2006; Jain et al., 2014; Keller et al., 1998; Latinovic et al., 2006; Mattioli et al., 2008; Rodriguez-Martinez et al., 2013; Roquelaure et al., 2017; Tepper et al., 2006; Tuppin et al., 2011). The reasons for this variation among studies can be attributed to some factors. The majority of the preceding studies did not draw a representative sample from the general population. The discrepancy also exists among nations in terms of the utilization of traditional and surgical treatments for CTS. Moreover, our sex-specific CTR incidence rates appear to be similar to earlier studies. The incidence ranged from 0.5 to 4.8 per 1,000 person-years in women and from 0.1 to 1.9 per 1,000 person-years in men (Atroshi et al., 2011; English & Gwynne-Jones, 2015; Fajardo et al., 2012; Fnais et al., 2014; Gelfman et al., 2009; Jain et al., 2014; Latinovic et al., 2006; Mattioli et al., 2008; Rodriguez-Martinez et al., 2013; Roh et al., 2010; Roquelaure et al., 2017; Tuppin et al., 2011).

6.3 Risk factors for CTS and CTR

6.3.1 Age

In the current study, participants aged 40-49, in comparison to other age groups, had an increased risk of CTR after adjustment for sex, BMI, educational level, hand osteoarthritis, and workload factors. This finding is consistent with other studies (Evanoff et al., 2014; Tseng et al., 2012). Moreover, some investigators also found that the risk of CTS increases with age (Bonfiglioli et al., 2013; Harris-Adamson et al., 2013; Petit et al., 2015; Roquelaure et al., 2008). On the other hand, a few studies suggested that the age distribution of CTS is bimodal, with a peak in the age group of 50-59 and a second peak in people aged 70 or older (J. D. P. Bland & Rudolfer, 2003; Mondelli et al., 2002; R. Shiri et al., 2007). Some other studies in which work-related and personal risk factors were examined did not show that age is an independent risk factor for CTS (Burt et al., 2011; Garg et al., 2012; Werner et al., 2005).

6.3.2 Sex

According to our final multivariable model, women were about two times more likely to undergo CTR than men, a finding that has been reported by previous studies (English & Gwynne-Jones, 2015; Fajardo et al., 2012), while another study did not report sex difference in CTR because of its study design (Mattioli et al., 2009). Moreover, consistent findings of sex difference in CTS exist to support that CTS prevalence and incidence are higher in women than in men (Atroshi et al., 1999; A. M. Dale et al., 2013; Garg et al., 2012; R. Shiri et al., 2007). Some investigators have showed that the existence of the risk associated with women among patients with CTS in their multivariable analyses is not owing to confounding factors (Bonfiglioli et al., 2013; Nathan et al., 2002). However, others found a statistically insignificant relationship (Evanoff et al., 2014; Harris-Adamson et al., 2013; Werner et al., 2005). A lack of association in these studies may be due to a small number of participants. Furthermore, the risk factors contributing to an increased risk of CTS in women are not well-recognized. However, there is some evidence of the hormonal effect on CTS, which may put women at risk for CTS more often than men (Padua et al., 2010). Women mainly present a low threshold and tolerance levels of reported pain (Barsky et al., 2001). Women may be less likely than men to have a square-shaped wrist, which leads to the development of CTS. However, a meta-analysis found no significant difference in mean wrist ratio between men and women (R. Shiri, 2015). In the current study, obesity and hand osteoarthritis were related to high rate of CTR in women only.

6.3.3 Smoking

Cross-sectional studies showed an association between smoking and CTS. Workload or psychosocial factors might confound the relationship between smoking and CTS, since people with physically stressful jobs are more likely to use more tobacco than those with less stressful jobs (Palmer et al., 2003). However, the associations adjusted for some work-related factors in nearly all of the cross-sectional studies and pooled estimates exhibited low variations. The same trend was observed for the associations between ever smoking and CTS but was not statistically significant.

There is no study to suggest that CTS would predict smoking, so the observed associations are not due to reverse causation. Moreover, most of the case-control studies included in our analysis, which used hospital-based controls, did not show an association. One case-control study (Wieslander et al., 1989) reported a distinctly higher proportion of current smokers in hospital-based controls than in population-based controls (29% vs. 19%). For different control groups, a separate risk estimate has not been provided, suggesting that the studies with case-control design have underestimated the association between smoking and CTS.

Cross-sectional studies have found smoking to be a risk factor for CTS. However, cross sectional studies do not employ a valid design for exploring causal relationship. Therefore, there is no reliable evidence to confirm the role of smoking in CTS. However, case-control and cohort studies did not present any significant relationship between smoking and CTS. These studies, especially cohort studies, may be dependent on the history of past exposures and may thus suffer from unreliable data and bias. Three cohort studies on smoking were included in our analyses. Nonetheless, it seems that they lacked internal validity such as presence of attrition bias (Gell et al., 2005; Nathan, Istvan, & Meadows, 2005; Nathan et al., 2002; Roquelaure et al., 2001). People lost to follow-up may smoke more than individuals who remained in a follow-up study. Furthermore, the sample size of these studies was small, and the included cohort studies did not have statistical power to determine the effect of smoking on CTS. Further large and high-quality cohort studies are necessary to scrutinize the link between smoking and CTS. However, large cohort studies are highly expensive and time consuming. In earlier case-control studies, the controls may not have comprised a representative sample of the reference population. The prevalence of smoking was higher in controls as compared with the general population, leading to a determination of no relationship between smoking and CTS.

6.3.4 Diabetes

Our meta-analysis confirmed the association between diabetes and CTS, but the relationship is modest. Both type I and type II diabetes were associated with CTS

and CTR. Moreover, the relationship between diabetes and CTS was stronger than the relationship between diabetes and CTR although statistically non-significant. The possible reason is that the surgical release of the carpal tunnel is less often recommended in patients with diabetes. In patients with diabetes, CTS is likely to coexist with Dupuytren's contracture, limited joint mobility, or flexor tenosynovitis (Ramchurn et al., 2009), whereas surgery may not help to improve hand function and alleviate hand symptoms.

Furthermore, the observed link between diabetes and CTS was partly due to confounding effects. In our assessment of the risk of confounding, it appears that all studies adjusted their estimates for age and sex. Therefore, the association of diabetes with CTS or CTR has not been confounded by these risk factors. On the other hand, obesity is a risk factor for CTS (Tseng et al., 2012) and may affect the association of diabetes with CTS. Although six studies on diabetes controlled their estimates for BMI and subgroup analyses of four case-control studies showed a similar effect size (Geoghegan et al., 2004; Harris-Adamson et al., 2013; Hendriks et al., 2014; Mattioli et al., 2009; Tseng et al., 2012; Werner et al., 2005), adding two prospective studies to this analysis attenuated the risk of CTS among patients with diabetes by 18%. Of these cohort studies (Harris-Adamson et al., 2013; Werner et al., 2005), one (Werner et al., 2005) was assessed as having high risk of selection bias and another (Harris-Adamson et al., 2013) pooled six prospective studies and found an adjusted lower risk of CTS among people with diabetes as compared to their counterparts without diabetes. The protective effect of diabetes on CTS is unexpected and can be due to lack of adjustment for between-study variations (R. Shiri, 2014b). Moreover, obesity is a well-recognized risk factor for type II diabetes, but our analyses found that both type I and type II diabetes were significantly linked with an increased risk of CTS.

In the assessment of the publication bias, a funnel plot was not asymmetrical, and Eager's test was not significant. After adjusting for publication bias, the trim and fill method, however, imputed six missing studies and the pooled adjusted estimate was reduced. The results suggest that when there is heterogeneity among studies, the trim and fill method over-imputed missing studies in which publication bias does not exist (Peters, Sutton, Jones, Abrams, & Rushton, 2007).

The prevalence of obesity (GBD 2015 Obesity, 2017) and diabetes (NCD Risk factor Collaboration, 2016) is increasing globally. The increased prevalence of obesity and diabetes may cause a high rate of CTS occurrence. In patients with diabetes, advanced glycation end-products provoke the median nerve neuropathy. High production of circulating inflammatory cytokines is also caused by advanced glycation end-products (Goldin et al., 2006). The vascular endothelial growth factor may be the responsible factor for microvascular ischemia and axonal degeneration in the median nerve (Mojaddidi et al., 2014).

6.3.5 Overweight and obesity

We found that overweight and obesity are associated with the risk of CTS and CTR. The link between inactivity and CTS is considerably controversial. It is not known whether physical activity modifies the effect of obesity on CTS. Despite the extensive investigations on obesity, there is no general agreement on the pathophysiological pathway leading to CTS. Two proposed hypotheses, however, explain the possible mechanisms of median nerve compression. One indicates peripheral axonal loss of median nerve, or fibrosis, the thickening of synovial connective tissue in the tunnel caused by intermittent or sustained increase in intracarpal pressure owing to the accumulation of fatty tissues in the carpal tunnel (J. D. Bland, 2005, 2007). The other hypothesis involves a systemic process of inflammation activated by adiposity (Rechardt et al., 2014).

Obesity is a primary specific stimulus of some circulating biomarkers causing inflammation such as cytokines, e.g., interleukin-1, interleukin-6, and tumor necrosis factor-α (Lago, Dieguez, Gómez-R, & Gualillo, 2007), which are associated with pain in people who have musculoskeletal disorders (Carp, Barbe, Winter, Amin, & Barr, 2007). There is no considerable evidence regarding the role of adipose-tissue-derived cytokines in the symptoms of CTS. On the other hand, the high levels of free oxygen radicals like malondialdehyde bis (diethyl acetate) and interleukin-6 with normal levels of interleukin-1 are associated with the symptoms of CTS through local ischemia-induced reperfusion injury (Sud & Freeland, 2005).

Furthermore, central obesity measured by waist circumference in comparison to BMI has been found to be a leading metabolic risk factor, which also increases the risk of diabetes and atherosclerosis by a systemic process of pro-inflammation biomarkers. Regarding the link between waist circumference and CTS, our meta-analysis of the four studies (Mondelli et al., 2014; Plastino et al., 2011; R. Shiri et al., 2011; Uzar et al., 2010) concluded that overweight or obesity is over two times more likely to increase the risk of CTS than normal waist circumference.

Excess body mass is an independent risk factor for CTS and CTR. Obesity prevention is an important public health priority. Future epidemiological studies should investigate whether a healthy lifestyle, such as diet low in fat and sugar along with leisure-time physical activity, decreases the burden of CTS in the working population.

6.3.6 Arthritis

An association between hand osteoarthritis and the risk of CTR was found in our 11-year follow-up study. Moreover, in a subgroup analysis, excluding the participants who were exposed to heavy workload factors, did not change the association of hand osteoarthritis with CTR. As far as we know, one case-control study recognized hand osteoarthritis as a risk factor for CTS (Geoghegan et al., 2004). However, the unconfounded association may not be estimated, since their estimate was controlled for a limited number of confounders such as age and sex. The underlying mechanisms for the observed association are not fully known. On the other hand, wrist osteoarthritis can be responsible for severe idiopathic CTS by osseous hypertrophy in the carpal tunnel. Osseous hypertrophy can tighten carpal tunnel dimension (R. Shiri, 2016).

Moreover, a meta-analysis (R. Shiri, 2016) reported that the pooled adjusted estimate for rheumatoid arthritis is approximately twofold, suggesting that rheumatoid arthritis is a possible risk factor for CTS. That review suffers from some limitations. The majority of the studies included in that meta-analysis were case-control and cross-sectional studies, and a few included cohort studies did not control their risk estimates for the confounding factors (R. Shiri, 2016). Our longitudinal

study did not demonstrate a statistically significant relationship between rheumatoid arthritis and the incidence of CTR after adjustment for age and sex. This could be due to a number of reasons. Rheumatoid arthritis is a rare autoimmune disease: only 2.4% of the study population had physician-diagnosed rheumatoid arthritis. A full representative sample of the general population had not been recruited by the previous studies. In our 11-year follow-up study, the annual CTR incidence was estimated at 1.5 per 1,000 person-years in those with rheumatoid arthritis and 1.7 per 1,000 person-years in those without this medical condition (age-and-sex-adjusted HR=0.9). The symptoms of CTS may be eliminated in patients with rheumatoid arthritis within one year (Chamberlain & Corbett, 1970). Thus, when transient, the symptoms may reduce the number of patients who experience surgery for CTS. Moreover, our study did not have the statistical power to detect the link between rheumatoid arthritis and CTR.

6.3.7 Hypothyroidism

In patients with CTS, hypothyroidism is more prevalent in comparison to individuals without the condition (van Dijk et al., 2003). In our cohort study, this medical condition was not associated with the risk of CTR. The recent meta-analysis (R. Shiri, 2014a) detected a modest association between hypothyroidism and CTS. The observed effect size was based on cross-sectional and case-control studies. The studies with a cohort design have not been included in the meta-analysis. The causal relationship, then, is unclear. Most of the case-control studies were conducted among the selected populations.

Patients with hypothyroidism complain of CTS symptoms when they are euthyroid (Kasem et al., 2014). Patients with hypothyroidism also suffer from symptoms of CTS during thyroid therapy (Geoghegan et al., 2004). On the other hand, one investigator reported that the symptoms of CTS in patients with the condition were eliminated after three months of hormone therapy replacement (Kasem et al., 2014). If the hypothyroidism treatment fails, the patient can be a candidate for CTR. Hypothyroidism was observed in 3% of our study population in which the occurrence of CTR in patients with the condition was 1.3 per 1,000 person-years as compared to 1.7 per 1,000 person-years in those without the condition. So the

patients seemed to have controlled their symptoms. Ultimately, we did not have the statistical power to detect a statistically significant association.

6.3.8 Occupational factors

In the current study, we found a non-significant association between workload factors and CTR. Heavy physical work and high handgrip force were associated with the risk of CTR in women after adjustment for age but not after adjustment for other confounding factors. These findings are not consistent with earlier studies that found significant associations between workload risk factors and CTR (Mattioli et al., 2009; Rossignol, Stock, Patry, & Armstrong, 1997). According to recent reviews, the role of workplace factors in CTS was presented more often through cross-sectional studies than case-control and cohort studies (Palmer et al., 2007; van Rijn et al., 2009). The cohort studies have priority over other types of observational studies because they also concentrate on the temporal sequence between workload factors and CTS. In the cohort studies, information on occupational exposures was collected once at the baseline using self-reports, which can lead to biased estimates (Palmer, 2011; van Rijn et al., 2009). The previous prospective cohort studies reported a modest incidence of CTS in occupational populations with a long-term follow-up. With regard to the low incidence, cohort studies with a low exposure prevalence are not able to show significant relationships between some workload risk factors and CTS (van Rijn et al., 2009).

A few other studies scrutinized the risk of CTR in people engaged in physical workload factors (Mattioli et al., 2009; Rossignol et al., 1997; R Shiri, Miranda, Heliövaara, & Viikari-Juntura, 2009). Two of the studies were case-control studies that utilized the self-reported history of past workplace exposures (Mattioli et al., 2009; Rossignol et al., 1997). The investigators reported that manual or blue-collar workers had a higher risk of CTR as compared to white-collar or non-manual workers (Mattioli et al., 2009; Rossignol et al., 1997). Our study was not statistically powerful enough to show the link between workload factors and CTR.

6.4 Study strength

Meta-analyses

We attempted to limit detection bias in our meta-analyses. We included the studies that used case definitions for CTS based on clinical diagnosis or CTS symptoms confirmed by nerve conduction study and excluded those studies that used case definitions for CTS based on symptoms only or nerve conduction studies only.

Several sensitivity analyses allowed us to obtain the reliable pooled estimates of the associations between diabetes and CTS or CTR by taking into account the possible risk of selection bias, adjustment for confounding factors, as well as selective publication. However, these associations were independent of performance bias, attrition bias, and publication bias. Moreover, a meta-analysis of 18 case-control and cohort studies with adjusted estimates yielded a pooled OR of 1.69, which was obtained from over 37 million subjects. To the best of our knowledge, this is the first study to pool the estimates of the observational studies on the associations of type I and type II diabetes with CTS and CTR.

A meta-analysis of 58 observational studies consisting of 1,379,372 people on the role of excess body mass in CTS/CTR enabled us to conduct the subgroup analyses by study design, adjustment for confounding factors and other study quality.

Original study

In the Health 2000 Survey, the study population was relatively large and a representative sample of the general population. Participation rate was high, and specially trained nurses performed the data collection for lifestyle factors, work-related factors, and medical conditions. The data was linked to the Finnish Hospital Discharge register from 2000 to 2011. Therefore, information regarding the surgery cases of CTS is reliable, and the findings can be more widely applicable to the adult Finnish population.

6.5 Study limitations

Meta-analyses

A limitation of the present meta-analysis on smoking was the limited number and low quality of the included prospective cohort studies. Moreover, the primary studies did not provide results on the associations of the number of the cigarettes smoked per day, the length of smoking, or pack-years with CTS.

The limitation of the meta-analysis on diabetes was that few studies had presented separate risk estimates for CTS among the patients with type I and type II diabetes. Furthermore, 18 of the included studies did not control for common confounders such as age and sex in their analysis. Only six studies controlled for obesity. The primary studies did not evaluate the associations of the length of diabetes and the glycaemic control with CTS and CTR.

Several limitations of the meta-analysis on excess body mass should be mentioned. Nearly one-third of the included studies reported unadjusted estimates of associations between excess BMI and CTS or CTR. Almost two-thirds of the studies used self-reported data on weight and height, and weight and height were measured in one-third of the studies. Women are more likely to underreport their weight and men are more likely to over-report their height (Ng et al., 2014). Our sub-group analyses suggest that the utilization of self-reported data on weight and height may contribute to the underestimation of the association of excess body mass with CTS.

Furthermore, the majority of the case-control studies included in our pooling analysis used hospital-based controls. One study recruited hospital-based and also population-based controls and estimated a higher prevalence of overweight/obesity in hospital-based controls in comparison with population-based controls (22% vs. 9%) (Wieslander et al., 1989). However, this study did not report the risk of CTS for both types of control groups. In this respect, the underestimation of the association between obesity and CTS has probably occurred in the hospital-based case-control studies.

Original study (Health 2000 Survey)

A limitation of this study was the use of the self-reported information on hand osteoarthritis. The agreement between self-reported osteoarthritis and physician-diagnosed osteoarthritis is low (Heliövaara et al., 1993), which could lead to exposure misclassification and possibly weaken the relationship between hand osteoarthritis and the occurrence of CTR. Moreover, this study had limited statistical power to determine the effects of diabetes, rheumatoid arthritis, and hypothyroidism on the risk of CTR. Although the incidence of CTR was about 1.5-fold higher among those with diabetes than individuals without diabetes, the difference between the two groups did not reach statistical significance.

The data on CTR before 1996 was collected using self-reports. It is likely that some of the participants might not have recalled their CTR. Furthermore, the hospital discharge register does not include inpatient/outpatient discharges in nearly all private clinics. The Finnish hospital discharge register has generally identified over 80% of diseases discharges and improved to over 95% in more recent years only (Sund, 2012). According to these limitations, it seems that CTR lifetime prevalence is likely to be more than 3.1%.

We assessed exposure to workload factors by self-reports. The symptomatic individuals are likely to over-report their exposures (Viikari-Juntura et al., 1996). Moreover, exposure to physical workload factors may have been modified by CTS symptoms.

6.6 Conclusions

This study found convincing associations of diabetes and excess body mass with CTS and CTR. Diabetes appears to be a modest risk factor for CTS and CTR when controlling for confounding factors. Type I and type II diabetes are associated with CTS and CTR, and the effect size does not differ between type I and type II. Overweight and obesity are independent risk factors for CTS and CTR in both women and men. This study is the first to investigate the relationship between smoking and CTS. Although some cross-sectional studies found an association between smoking and CTS, smoking is not associated with CTS in case control and cohort studies. In Finland, CTR is a commonly performed surgical procedure, and more than 3% of adult people undergo CTR in their lifetimes. With regard to other factors in our original study, the age group 40-49, a low level of education, female sex, obesity, and hand osteoarthritis were linked to a high occurrence of surgery for CTS.

Globally, the growing numbers of people with obesity and diabetes are public health concerns. Burden of these medical conditions can increase the occurrence of CTS and CTR. Obesity and diabetes are multifactorial medical conditions that involve a complicated interaction between genetics, environment, and individual behavior. Changes in one's food environment, such as a diet low in fat and with low-sugar foods, along with changing one's physical activity environment to promote higher levels of physical activities during leisure time, are key to obesity prevention, which can also prevent type II diabetes. However, there is no consistent finding surrounding the role of a healthy lifestyle such as leisure time physical activity in CTS. Few studies focused on the role of a low-fat and low-sugar diet in CTS. It appears that primary prevention of CTS has not yet been extensively studied, and most studies focus on secondary prevention. Future epidemiological studies should explore whether physical activity and healthy diet modify the effects of obesity and diabetes on CTS.

The links between other individual factors such as hand osteoarthritis, rheumatoid arthritis, hypothyroidism, and waist circumference with CTS and CTR need to be further examined regarding the possible biases and residual confounding. Future high-quality prospective studies employing a large representative sample of

the general population are recommended. Furthermore, future studies should investigate whether exposure to occupational factors such as repetition and high handgrip force, and a combination of both, modify the effect of individual factors on CTS and CTR.

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PUBLICATION

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SMOKING AND CARPAL TUNNEL SYNDROME: A META-ANALYSIS

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ABSTRACT: *Introduction:* We assessed the association between smoking and carpal tunnel syndrome (CTS) and estimated the magnitude of the association with meta-analysis. *Methods:* The PubMed, Embase, Scopus, and SciVerse databases were searched through December 2012. Thirteen studies were included in the meta-analysis. *Results:* Cross-sectional studies reported an association between current smoking and CTS (pooled odds ratio (OR) = 1.99, 95% confidence interval (CI) 1.38–2.60, I-squared = 0%). Meta-analyses of case–control studies did not, however, show an association between smoking and CTS (pooled OR = 1.04, 95% CI 0.95–1.12, I-squared = 0.0%) or surgery due to CTS (pooled OR = 0.99, 95% CI 0.82–1.15, I-squared = 0%). Moreover, smoking was not associated with CTS in the meta-analysis of cohort studies (pooled OR = 0.97, 95% CI 0.45–1.50, I-squared = 0%). *Conclusions:* We found an association between smoking and CTS in cross-sectional studies. This association should be further explored in appropriately designed case–control and cohort studies.

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Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in the upper extremity.[1] Its prevalence in the general population ranges between 1% and 5%.[2,3] The etiology of CTS is multifactorial, involving both occupational and non-occupational risk factors.[4–6]

The findings of the role of smoking in CTS are inconsistent. Some studies have shown an association between smoking and increased occurrence of CTS,[6,7] while others have reported no association[8] or even a lower risk of CTS in smokers compared with non-smokers.[9] However, few studies have been designed specifically to assess the association between smoking and CTS.

So far, the role of smoking in CTS has not been addressed with a systematic review and meta-analysis. Our aim was to carry out a systematic review to assess the association between smoking and CTS and to estimate the magnitude of the association with a meta-analysis.

METHODS

Search Strategy. A comprehensive literature search was conducted in PubMed, Embase, Scopus, and SciVerse, using predefined keywords [carpal tunnel syndrome OR median nerve OR median neuropathy OR carpal tunnel (text word only)] AND (smoke OR smok* OR smoking OR tobacco OR cigar OR cigarettes OR lifestyle OR life-style OR life style). We used both MeSH terms and text words in PubMed, and we used Emtree terms and text words in Embase. We included all languages and excluded case reports, reviews, guidelines, editorials, and letters. We checked the reference lists of included articles for additional studies. We also looked at the full text of studies on the association between body mass index and CTS for additional studies on smoking.

Selection of the Studies. Two reviewers (M.H.P. and R.S.) assessed independently the titles and abstracts of the studies and investigated whether the studies looked at the association between smoking and CTS. We included cross-sectional, case–control, and cohort studies. We included both population-based and hospital-based case–control studies in the review. To be included in the meta-analysis, the studies had to report quantitative data on the association between smoking and CTS. We have contacted a few authors for additional results. None of them, however, provided new results or data.

Quality Assessment. Two reviewers (M.H.P. and R.S.) assessed independently the quality of the studies using the Effective Public Health Practice Project tool for observational studies.[10] Summary quality scores may provide a useful overall assessment. However, the scales are not recommended for assessment of the quality of studies in systematic reviews.[11] Therefore, we assessed 5 main domains: selection bias; performance bias; detection bias; confounding; and attrition bias (see table A1 in the appendix). Studies conducted among volunteers, studies on self-reported CTS, and those assessed as having strong selection bias or not reporting quantitative results to estimate odds ratios were excluded from the meta-analysis. Disagreements between the 2 reviewers were resolved by consensus.

Meta-Analysis. We used random-effects meta-analysis. A small study in a random-effects model usually obtains more weight than in a fixed-effect

Abbreviation: CTS, carpal tunnel syndrome
Key words: carpal tunnel syndrome; cigarettes; median nerve; median neuropathy; smoking
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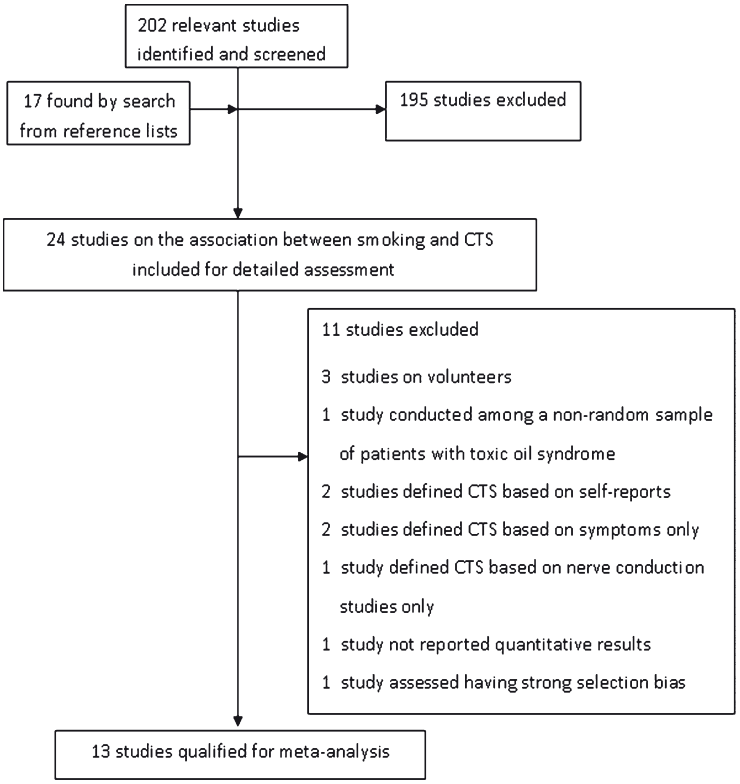

FIGURE 1. Flowchart of the search strategy and selection of studies.

model, and the estimates are more conservative.[12] One cohort study reported the results for 11-year[13] as well as for 17-year[14] follow-ups. The confidence interval (CI) for the estimate was not reported for the 17-year follow-up. We calculated the standard error (SE) for the estimate of this study using the following formula: SE = log (odds ratio)/*Z*-value.[12] We pooled the 2 estimates of this study using the fixed-effect model.

The presence of heterogeneity across the studies was assessed by chi-square and I-squared statistics.[15] The I-squared statistic shows the total variation across studies, which is not due to chance. I-squared statistics <25% and >50% indicate small and large inconsistency, respectively.[16] A funnel plot was used to inspect potential publication bias and comprised the size of smoking effect against SE. The Egger regression test was used to examine funnel plot asymmetry.[17] The trim-and-fill method was used to assess the number of missing studies due to publication bias.[18] Statistical significance was based on a P value ≤ 0.05 for an effect and <0.10 for publication bias. Stata version 10 (StataCorp, College Station, TX) was used for meta-analysis.

RESULTS

We identified 219 relevant reports for detailed assessment (Fig. 1). Of them, 24 were included in the review and, finally 13 were qualified for meta-analysis. There were 5 cross-sectional studies,[6,7,19–21] 5 case–control studies,[8,22–25] and 3 cohort studies.[13,14,26,27] The characteristics of the studies included in the meta-analysis are listed in the Appendix (Table A2).

The methodological quality was in general higher in cross-sectional studies than in case–control or cohort studies. Cross-sectional studies controlled better for confounders than were case–control or cohort studies.

Studies Excluded from Meta-Analysis. Eleven studies were excluded from the meta-analysis (Fig. 1 and Table A3 in the Appendix). Two cross-sectional studies[28,29] and one cohort study[30] were conducted among volunteers. Among those

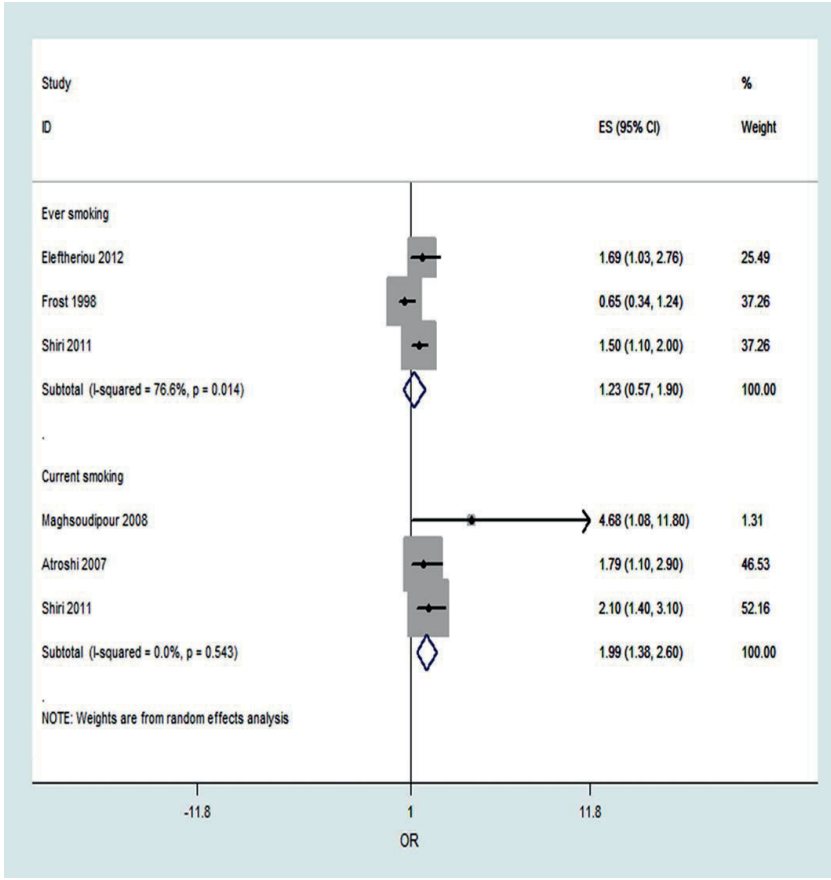

FIGURE 2. Forest plot for the meta-analysis of cross-sectional studies on the association between smoking and carpal tunnel syndrome. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

studies, one[28] also defined CTS based on self-report and reported estimates that were not controlled for confounders. A cross-sectional study[31] defined CTS by self-report, and another[32] reported unadjusted estimate without quantitative results to estimate an odds ratio. One case–control study[33] defined cases and controls based on nerve conduction studies only, and another[34] defined CTS by self-report for outpatients and excluded women using the contraceptive pill for <8 years. A case–control study[35] had strong selection bias, and its estimate was not controlled for confounders. The other[9] was conducted among a non-random sample of patients with toxic oil syndrome. Two cohort studies[36,37] defined CTS based on symptoms only.

Cross-Sectional Studies. In the meta-analysis of cross-sectional studies (Fig. 2), current smoking was associated with CTS (pooled OR = 1.99, 95% CI 1.38–2.60, I-squared = 0%). There was no association between ever smoking and CTS (pooled OR = 1.23, 95% CI; 0.57–1.90, I-squared = 76.6%).

Case–Control Studies. The meta-analysis of case–control studies (Fig. 3) did not show an association between current smoking and CTS (pooled OR = 1.04, 95% CI 0.95–1.12, I-squared = 0.0%) or surgery due to CTS (OR = 0.99, 95% CI 0.82–1.15, I-squared = 0%).

Cohort Studies. The meta-analysis of cohort studies (Fig. 3) showed no association between current smoking and CTS (pooled OR = 0.97, 95% CI 0.45–1.50, I-squared = 0%).

Publication Bias. The funnel plot of 13 studies included in the meta-analysis was symmetrical (Fig. 4). The *P*-value for the Egger test was 0.25.

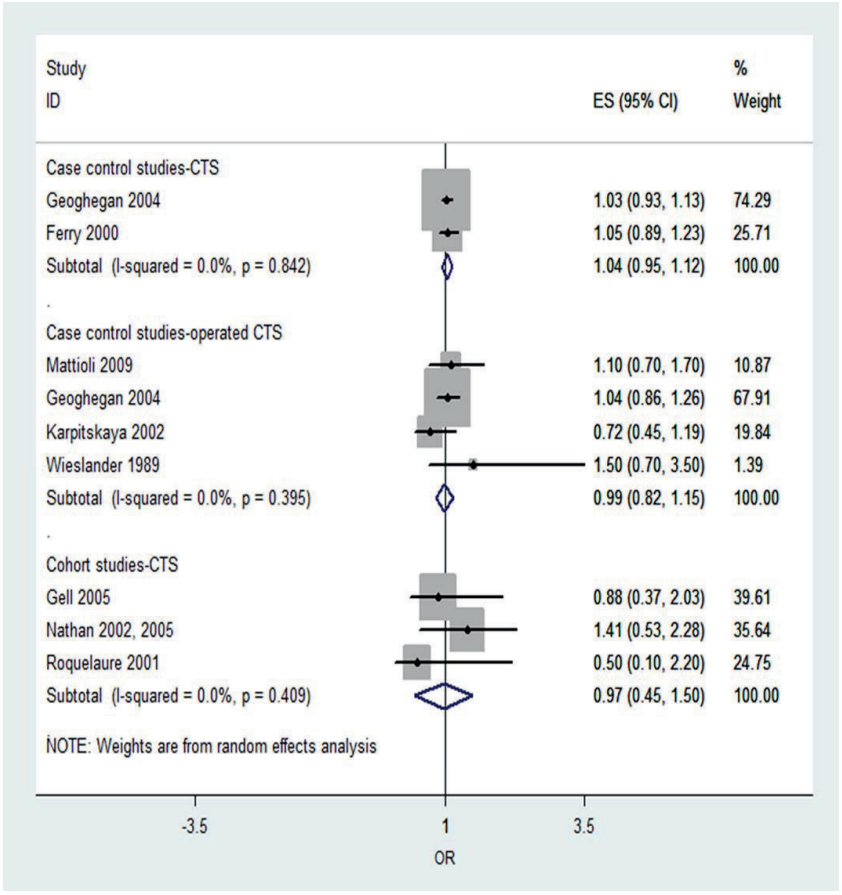

FIGURE 3. Forest plot for the meta-analysis of case–control and cohort studies on the association between smoking and carpal tunnel syndrome. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

Only 1 missing study was imputed using the trim-and-fill method.

DISCUSSION

Our meta-analysis showed an association between current smoking and CTS in cross-sectional studies. However, the case–control and cohort studies showed no association between current smoking and CTS.

The observed association in cross-sectional studies may be related to confounding factors. Individuals with physically stressful jobs are more likely to smoke than those with less stressful jobs. The association between smoking and CTS could therefore be confounded by work-related physical or psychosocial factors. However, most of the cross-sectional studies included in the meta-analysis controlled their estimates for some physical load factors.

The observed association between smoking and CTS may also be due to comorbid diseases.[38] Of the comorbid conditions associated with CTS, smoking is a risk factor for rheumatoid arthritis only.[39] The relationship between smoking and CTS might also be due to reverse causation, if individuals with CTS are more likely to smoke than people free from CTS. However, CTS is an unlikely reason for initiation of smoking.

The observed association between smoking and CTS in cross-sectional studies is insufficient to conclude that there is a link between smoking and CTS. In case of a possible association between smoking and CTS, smoking can impair the vascular supply of the median nerve and thereby may increase the susceptibility of the nerve to physical workloads. Prolonged tissue ischemia may lead to median nerve degeneration and fibrosis. Smoking may cause

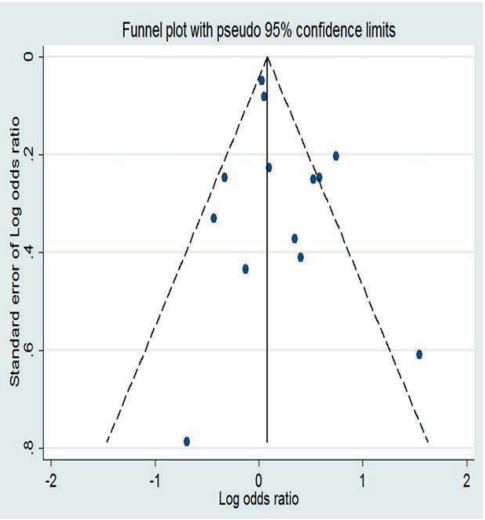

FIGURE 4. Funnel plot for publication bias in studies on the association between smoking and carpal tunnel syndrome. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

peripheral neuropathy through toxic effects,[40] or it may impair recovery following peripheral nerve injury.[41] More recent studies suggested that smoking may cause CTS through atherosclerosis.[7,42]

The absence of an association in case–control studies may be due to the fact that all case–control studies included in this meta-analysis used hospital-based controls. Smokers are more likely to seek medical care due to health problems other than CTS. One case–control study[22] included in the meta-analysis used hospital-based as well as population-based controls. This study showed a clearly higher prevalence of current smoking for hospital-based controls than population-based controls (29% vs. 19%).[22] A separate risk estimate, however, was not provided for the different control groups. It seems that case–control studies have underestimated the association between smoking and CTS.

We included only 3 prospective studies on the association between smoking and CTS, and none of them were very high quality. The case definition of CTS should be based on symptoms and electrodiagnostic testing in an epidemiological study.[43] The latter requires expertise and is costly when performed in a large study. An incidence study would also require a very large population.

The studies included in this review had some methodological limitations. They used a variety of case definitions. We included CTS defined by clinical diagnosis in our meta-analysis and excluded self-reported CTS and CTS defined by only symptoms or nerve conduction studies. Yet, the estimates of the associations between smoking and CTS in the included studies showed low variation and were independent of the methodological quality of case definition. On the other hand, 2 cohort studies that were excluded from the meta-analysis due to relying on only symptom-based case definition reported a strong association between smoking and CTS (pooled OR = 1.70, 95% CI 1.33–2.17). Most of the studies included in the meta-analysis did not assess the number of cigarettes smoked per day or length of smoking (pack-years). The number of prospective studies was also limited.

CONCLUSIONS

In conclusion, we found an association between smoking and CTS in cross-sectional studies only. This evidence is insufficient to conclude that there is an association between smoking and CTS. This association should be further explored in appropriately designed case–control and cohort studies. It is recommended that the control population for case–control studies be drawn from the normal population.

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Diabetes as a risk factor for carpal tunnel syndrome: a systematic review and meta-analysis

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Systematic Review or Meta-analysis

Diabetes as a risk factor for carpal tunnel syndrome: a systematic review and meta-analysis

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Abstract

Aims To assess whether diabetes increases the risk of carpal tunnel syndrome and to estimate the magnitude of the association with Type 1 and Type 2 diabetes.

Methods We conducted a systematic search of PubMed, Embase, Web of Science, Scopus, Google Scholar and ResearchGate for articles published between 1950 and January 2015. A total of 36 studies (eight cross-sectional, 21 case–control and seven cohort studies) qualified for meta-analysis. We used a random-effects meta-analysis and assessed heterogeneity and publication bias.

Results The pooled odds ratio of 25 studies (including a total of 92 564 individuals) that reported unadjusted estimates for the association between diabetes and carpal tunnel syndrome or carpal tunnel release was 1.97 (95% CI 1.56–2.49). The pooled odds ratio of 18 case–control or cohort studies consisting of >37 million individuals that reported estimates after controlling for potential confounders was 1.69 (95% CI 1.45–1.96). The association did not differ for Type 1 and Type 2 diabetes. Furthermore, there was no publication bias.

Conclusion This meta-analysis suggests that both Type 1 and Type 2 diabetes are risk factors for carpal tunnel syndrome.

Diabet. Med. 00, 000–000 (2015)

Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in the upper extremities, and it is a cause of sick leave and work disability [1]. Personal risk factors for CTS are not well known. Obesity [2,3], diabetes [4], hypothyroidism [5] and rheumatoid arthritis [4] have been suggested as possible risk factors for CTS.

Diabetes is one of the leading causes of disability globally [6]. Its incidence has been increasing because of population growth, population ageing and lifestyle changes [7]. Previous studies have reported inconsistent results on the association between diabetes and CTS [8–10]. Some studies found an increased risk of CTS in individuals with diabetes [11,12], a finding that was not confirmed by other studies [13–15]. Moreover, it is unclear whether both Type 1 and Type 2 diabetes increase the risk of CTS.

To date, only a single meta-analysis on the association between diabetes and CTS has been published [4]. That meta-analysis included five cross-sectional and four case–control studies published between 1985 and 2002, and found a more than twofold increased risk of CTS in patients with diabetes; however, of the included studies in that meta-analysis, three were conducted in patients with CTS without a control group, and four other studies did not control for any potential confounding factor in their risk estimates.

The aim of the present systematic review and meta-analysis was to assess whether diabetes increases the risk of CTS, and to estimate the magnitude of the effect for Type 1 and Type 2 diabetes.

Methods

Search strategy

We conducted systematic searches in PubMed, Embase, Scopus, Web of Sciences, Google Scholar, and ResearchGate for articles published between 1950 and January 2015 using the following predefined keywords: [carpal tunnel syndrome OR carpal tunnel (text word) OR median neuropathy OR median nerve OR CTS (text word only) OR carpal canal (text word only)] AND (diabetes mellitus OR diabetes (text word) OR diabetic (text word) OR glucose OR 'hemoglobin

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A, glycosylated' OR HbA1c (text word) OR hypoglycemic agents OR hypoglycemi* (text word) OR insulin OR diabetes complications OR 'diabetes mellitus, Type 1' OR 'diabetes mellitus, Type 2' OR risk factors OR metformin OR insulin resistance]. The search strategy conducted in PubMed is shown in Table S1. We used Medical Subject Headings (MeSH) terms, Emtree terms and text words. We then examined the reference lists of eligible reports and the full-text of studies on the associations of smoking [16], obesity, thyroid disease [5], arthritis, hand anthropometric measurements and computer use with CTS for additional studies on the relationship between diabetes and CTS.

Inclusion and exclusion criteria

There was no language restriction. Cross-sectional studies, both population-based and hospital-based case–control studies and cohort studies were eligible to be included in the meta-analysis. We contacted the corresponding authors of five studies for additional information; two of these [8,17] provided additional results.

Studies conducted among volunteers, studies that defined CTS by self-report, or by symptoms only or by a nerve conduction study only, were excluded from the meta-analysis. We also excluded studies that were conducted in patients with CTS without a control group. Lastly, we excluded studies that did not report sufficient quantitative results to estimate an effect size for diabetes.

Quality assessment

We independently appraised the quality of the included studies using criteria adapted from the Effective Public Health Practice Project tool [18]. We assessed five possible sources of bias; selection bias, performance bias, detection bias, confounding and attrition bias (Table S2). Discrepancies in the quality assessments between two reviewers were solved through discussion.

Meta-analysis

We calculated a prevalence ratio for four cross-sectional studies [1,19–21], an odds ratio (OR) for 11 case–control studies [8,9,11,12,22–28] and a risk ratio for two cohort studies [29,30]. We calculated Woolf's CIs for estimated ORs.

We used a fixed-effects meta-analysis to combine the subgroups of a single study, such as men and women [13], people with Type 1 diabetes and those with Type 2 diabetes [14], or different anti-hyperglycaemic agent subgroups [3]. We used a random-effects meta-analysis [31] to combine the estimates of different studies. Zero-cell correction was used for two studies [19,32] with a zero-cell count using the Mantel–Haenszel fixed effect.

The I^2 statistic was used to assess the presence of heterogeneity [31]. The I^2 statistic shows the true inconsistency of the association between diabetes and CTS that is not attributable to chance. An I^2 statistic < 25% indicates low heterogeneity and an I^2 statistic > 50% indicates high heterogeneity [31]. A funnel plot was used to assess publication bias. Egger's test was used to assess asymmetry in the funnel plot. We also estimated the number of missing studies attributable to publication bias by the trim and fill method [31]. A P value ≤ 0.10 was considered to indicate statistical significance for publication bias [31]. We used STATA, version 13 (Stata Corp, College Station, TX, USA) to perform our meta-analyses.

Results

Study selection

Our initial searches identified 2321 publications (Figure S1). We excluded 2175 publications by scrutinizing the titles and abstracts. After assessing the full text of 146 reports, a total of 36 studies qualified for meta-analysis. Of those, 28 studies were on CTS [1,2,8–13,15,19–25,28–30,32–40], six were on carpal tunnel release [17,26,27,41–43], and two studies were on both CTS and carpal tunnel release [3,14]. There were eight cross-sectional studies, 21 case–control studies and seven cohort studies. The characteristics of included studies are shown in Tables S3 and S4.

We excluded 12 studies from the meta-analysis. Detailed information is shown in Table S5 and Fig. S1. Three studies on volunteers, two studies that defined CTS by self-report or symptoms only, and two studies that defined CTS by a nerve conduction study only were excluded from the meta-analysis. In addition, we excluded two studies that were conducted among patients with CTS with no control group. Lastly, we excluded one study on individuals with prediabetic status, and two not reporting quantitative data to estimate an OR.

Quality assessment

The majority of included studies used pain, numbness, burning and/or tingling in the thumb, index or middle finger as the symptoms of CTS. Nineteen studies confirmed CTS symptoms by a nerve conduction study and 17 by a clinical diagnosis. Tinel's sign, positive Phalen's test, and/or weakness or atrophy of the thenar muscles were the most commonly used clinical tests. Five studies were rated as having low risk of selection bias, 22 as having moderate risk of selection bias, and nine as having high risk of selection bias. Nineteen studies controlled for potential confounders such as age and sex.

Diabetes and carpal tunnel syndrome

All cross-sectional studies, except one [14] reported only unadjusted estimates on the association between diabetes and CTS (Table S3). The pooled unadjusted prevalence ratio of eight cross-sectional studies was 1.84 [95% CI 1.43–2.36; I^2 = 0%, N = 13 576 (Fig. 1)].

The pooled OR of 13 case–control and cohort studies that reported unadjusted estimates was 2.03 (95% CI 1.45–2.84; I^2 = 72.7%, *N*=72 546 (Fig. 1; Table S3)]. Six cohort studies reported unadjusted estimates and their pooled estimate was 2.10 (95% CI 0.98–4.49; I^2 = 45.1%, *N*= 5305).

Fourteen case–control and cohort studies controlled their estimates for potential confounders and their pooled OR was 1.91 [95% CI 1.45–2.53; I^2 = 70.5%, *N* = 75 218 (Fig. 2)]. Only three cohort studies controlled for potential confounding factors. The pooled estimate of the three studies was 1.59 (95% CI 0.57–4.45; I^2 = 74.6%, *N* = 3686).

Diabetes and carpal tunnel release

There were eight studies on the association between diabetes and carpal tunnel release (Table S4). The pooled OR of four case–control studies that reported unadjusted estimates was 1.95 [95% CI 1.23-3.10; I^2 = 43.9%, *N* = 6442 (Fig. 1)]. Five case–control studies controlled their estimates for potential confounders and their pooled OR was 1.60 [95% CI 1.56–1.63, I^2 = 0%, *N* = 37 140 225 (Fig. 2)].

Diabetes and carpal tunnel syndrome or carpal tunnel release

The pooled unadjusted OR of 25 studies for the association between diabetes and CTS or carpal tunnel release was 1.97 [95% CI 1.56–2.49; I^2=71.2%, *N*=92 564 (Fig. 1)] and the pooled OR of 18 case–control or cohort studies that controlled for potential confounders was 1.69 [95% CI 1.45–1.96, I^2 =63.1%, *N*= 37 207 483 (Fig. 2)].

Eleven studies reported an estimate for Type 1 and/or Type 2 diabetes [3, 8, 9, 11, 12, 14, 22, 23, 25, 26, 34]. The association between diabetes and CTS or carpal tunnel release was similar for Type 1 and Type 2 diabetes. For Type 1 diabetes the pooled unadjusted OR of four studies was 2.22 [95% CI 1.62–3.05; I^2 = 0%, *N* = 24 048 (Fig. 3)] and the pooled OR of four studies that controlled for confounders in their estimates was 3.21 (95% CI 1.24–8.28; I^2 = 70.4%, *N* = 23 645). For Type 2 diabetes, the pooled unadjusted OR of six studies was 1.90 (95% CI 1.57–2.28; I^2 = 0%, *N* = 25 754 (Fig. 3)] and the pooled OR of eight studies that controlled for potential confounders was 2.33 (95% CI 1.44–3.79; I^2 = 73.1%, *N* = 26 458).

Publication bias

A funnel plot of 36 studies on the association between diabetes and CTS or carpal tunnel release was symmetrical (*P* for Egger's test = 0.164; Fig. 4); however, the trim and fill method imputed six missing studies. The pooled unadjusted estimate did not change after adjustment for publication

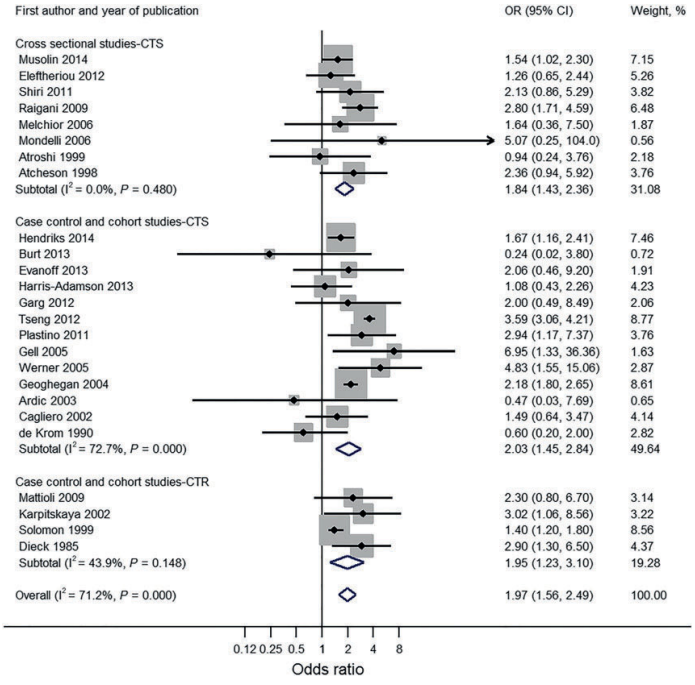

FIGURE 1 Pooled unadjusted estimates of eight cross-sectional studies on the association between diabetes and carpal tunnel syndrome (CTS), and 17 case–control and cohort studies on the association between diabetes and CTS or carpal tunnel release (CTR). The size of the grey shaded area indicates the weight of each study. Horizontal lines show the 95% CIs. OR, odds ratio.

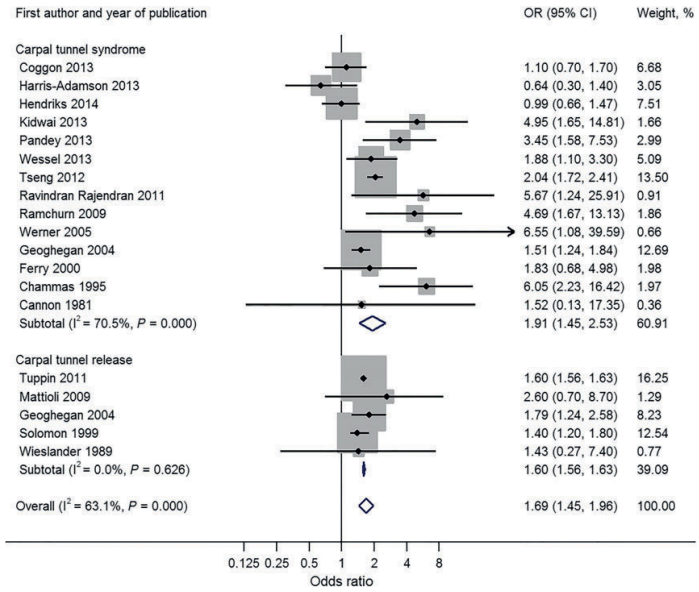

FIGURE 2 A meta-analysis of 19 case–control and cohort studies that reported estimates controlled for potential confounders on the association between diabetes and carpal tunnel syndrome or carpal tunnel release. The size of the grey shaded area indicates the weight of each study. Horizontal lines show the 95% CIs. OR, odds ratio.

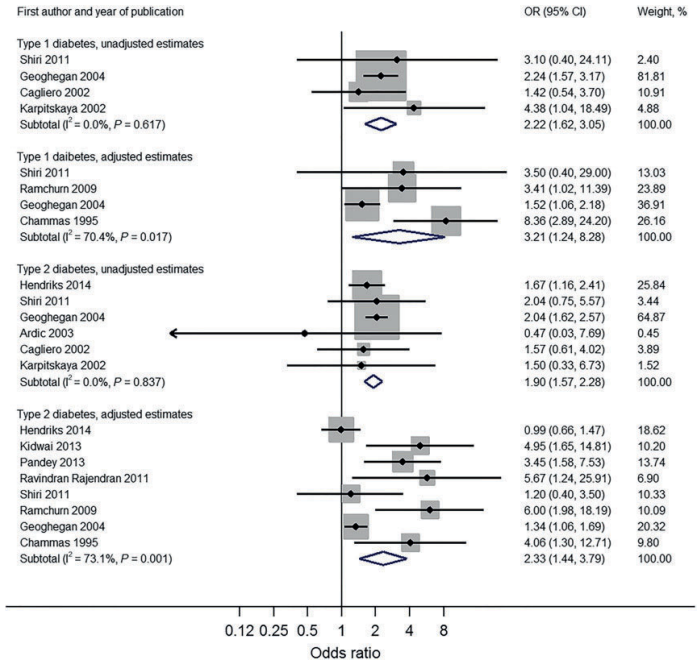

FIGURE 3 A meta-analysis of 11 studies on the association between Type 1 or Type 2 diabetes and carpal tunnel syndrome or carpal tunnel release. The size of the grey shaded area indicates the weight of each study. Horizontal lines show the 95% CIs. OR, odds ratio.

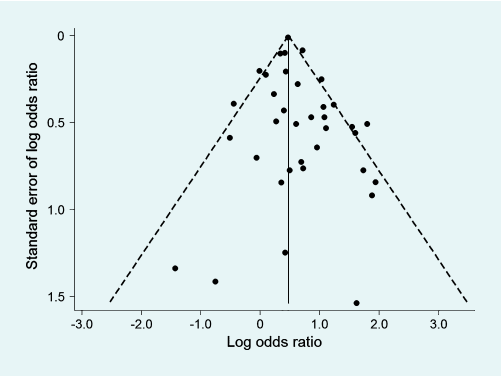

FIGURE 4 A funnel plot of 36 studies on the association between diabetes and carpal tunnel syndrome or carpal tunnel release. Seventeen studies reported estimates that were not adjusted for any confounder and 19 studies reported estimates adjusted for some potential confounders.

bias, while the pooled confounder-adjusted estimate dropped from 1.69 (95% CI 1.45–1.96) to 1.55 (95% CI 1.32–1.82).

Sensitivity analysis

Only four case–control [2,3,34,41] and two cohort studies [15,30] adjusted their estimates for BMI. A pooled OR of four case–control studies was 1.68 (95% CI 1.12–2.53, I^2 = 72.8%, N = 66 528). The pooled estimate decreased somewhat after adding two cohort studies [pooled OR 1.56 (95% CI 1.00–2.43); I^2 = 75.1%, N=69 914].

Excluding the studies that were rated as having a high risk of selection bias decreased the magnitude of the association between diabetes and CTS. The confounder-adjusted pooled OR of CTS dropped from 1.91 (95% CI 1.45–2.53) to 1.76 (95% CI 1.28–2.43) and that of CTS or carpal tunnel release dropped from 1.69 (95% CI 1.45–1.96) to 1.64 (95% CI 1.41–1.90). The observed association between diabetes and CTS or carpal tunnel release was independent of performance and detection bias.

Discussion

The present meta-analysis suggests that diabetes is a risk factor for CTS. The magnitude of the association is modest, and does not differ between Type 1 and Type 2 diabetes.

The association between diabetes and carpal tunnel release was weaker than the association between diabetes and CTS. CTS is a complication of diabetes, therefore, carpal tunnel release may be recommended less often for patients with diabetes than for those without. The outcome of carpal tunnel release may be less favourable in patients with diabetes. In addition, in patients with diabetes, CTS coexists with Dupuytren's contracture, limited joint mobility or flexor tenosynovitis [8].

The observed association between diabetes and CTS may partly be attributable to confounding factors. All case–control and cohort studies that were included in the present meta-analysis controlled their estimates for age and sex; thus, the observed association between diabetes and CTS was not confounded by age and sex. As obesity is a risk factor for CTS [2,3], the observed association between diabetes and CTS may be confounded by obesity. Of studies included in the present meta-analysis, six [2,3,15,30,34,41] controlled for BMI in their risk estimates. The meta-analysis of four case–control studies showed a similar effect size; however, after adding two cohort studies [15,30] the pooled estimate decreased by 18%. One [30] of these two cohort studies was rated as having high risk of selection bias and the other study [15] pooled six prospective studies and found a lower risk of CTS in patients with diabetes, albeit not statistically significant, after controlling for age, sex and BMI. This finding was unexpected and can be attributable to not controlling for between-study variation [44]. Furthermore, obesity is a risk factor for Type 2 diabetes, but this meta-analysis found an increased risk of CTS for both Type 1 and Type 2 diabetes.

In the present meta-analysis, the funnel plot was symmetrical and Egger's test was not significant. The trim and fill method, however, imputed six missing studies and the pooled adjusted estimate decreased slightly after controlling for publication bias. In the presence of high between-study heterogeneity and absence of significant test for publication bias, the trim and fill method may impute more missing studies [45]. It is unlikely that the observed association between diabetes and CTS is attributable to publication bias.

It has been shown that CTS does not predict diabetes [46], whereas diabetes predicts CTS. The adverse effects of diabetes on peripheral nerves have been studied extensively, but the mechanism by which diabetes increases the risk of CTS is still being investigated. Median nerve neuropathy is a complication of diabetes. A reduction in myelinated nerve fibre and endoneurial capillary densities is found in patients with diabetes who are not exposed to nerve compression [47]. A low axonal density may lead to median nerve neuropathy [47]. Moreover, in patients with diabetes, advanced glycation end-products [48] have been found to increase production of circulating inflammatory cytokines [49], and vascular endothelial growth factor [50] may cause impaired microvascular circulation and result in demyelination and axonal degeneration in the median nerve.

The studies included in the present review had some limitations. Few studies reported the risk of CTS among patients with Type 1 and Type 2 diabetes separately. Half of the included studies did not control for age and sex, and only six studies adjusted their risk estimates for obesity. Furthermore, the included studies did not assess the effect of diabetes duration and poor glycaemic control on CTS.

Conclusions

Diabetes is a modest risk factor for CTS. The magnitude of the association does not differ between Type 1 and Type 2 diabetes. Future studies should explore whether occupational physical workload factors potentiate the adverse effects of diabetes on the median nerve.

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Competing interests

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow chart of search study and study selection.
Table S1. Strategy for PubMed search conducted on 22 January 2015.
Table S2. Quality assessment of the included studies.
Table S3. Studies included in the meta-analysis on carpal tunnel syndrome.
Table S4. Studies included in the meta-analysis on carpal tunnel release.
Table S5. Studies excluded from the meta-analysis.

The effect of excess body mass on the risk of carpal tunnel syndrome: a meta-analysis of 58 studies

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Obesity Comorbidity

The effect of excess body mass on the risk of carpal tunnel syndrome: a meta-analysis of 58 studies

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Summary

We aimed to estimate the effects of overweight and obesity on carpal tunnel syndrome (CTS), and to assess whether sex modifies the associations. Literature searches were conducted in PubMed, Embase, Web of Science, Scopus, Google Scholar and ResearchGate databases from 1953 to February 2015. Fifty-eight studies consisting of 1,379,372 individuals qualified for a meta-analysis. We used a random-effects meta-analysis, assessed heterogeneity and publication bias, and performed sensitivity analyses. Overweight increased the risk of CTS or carpal tunnel release 1.5-fold (pooled confounder-adjusted odds ratio [OR] = 1.47, 95% CI 1.37–1.57, N = 1,279,546) and obesity twofold (adjusted OR = 2.02, 95% CI 1.92–2.13, N = 1,362,207). Each one-unit increase in body mass index increased the risk of CTS by 7.4% (adjusted OR = 1.074, 95% CI 1.071–1.077, N = 1,258,578). Overweight and obesity had stronger effects on carpal tunnel release than CTS. The associations did not differ between men and women, and they were independent of study design. Moreover, the associations were not due to bias or confounding. Excess body mass markedly increases the risk of CTS. As the prevalence of overweight and obesity is increasing globally, overweight-related CTS is expected to increase. Future studies should investigate whether a square-shaped wrist and exposure to physical workload factors potentiate the adverse effect of obesity on the median nerve.

Keywords: Body mass index, carpal tunnel syndrome, median neuropathy, obesity.

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Introduction

Carpal tunnel syndrome (CTS) is the most common upper extremity entrapment neuropathy (1). The prevalence of CTS ranges between 1 and 5% (1,2) and that of carpal tunnel release ranges between 1 and 2% (2,3) in the general population. CTS is a common cause of work disability and high healthcare costs (4,5).

The role of lifestyle risk factors in CTS is not well known. Previous studies reported inconsistent results on the effects of leisure time physical activity on CTS (6–8). In our earlier meta-analysis (9), we found an association between smoking and CTS in cross-sectional studies, but not in case–control or cohort studies. Although obesity has been consistently found as a risk factor for CTS, the results regarding overweight have been inconsistent. An association has been seen in some studies (10,11) but not in others (2,12).

Obesity is a major global health problem (13). Worldwide, 37% of men and 38% of women were overweight or obese in 2013 (13). Despite the fact that obesity has been consistently found as a risk factor for CTS, the size of its

effect on CTS is not well known. Moreover, CTS is two to four times more common in women than men (14,15). It is however unclear whether sex modifies the effect of obesity on CTS.

To date, only a single systematic review and meta-analysis (16) on the effects of overweight or obesity on CTS have been conducted. However, that meta-analysis was published in German. The aims of this systematic review and meta-analysis were twofold: (i) to estimate the magnitude of the effects of overweight and obesity on CTS and (ii) to assess whether sex modifies the association between obesity and CTS.

Materials and methods

Search strategy

The protocol and reporting of the results of this systematic review were based on the PRISMA statement (17). We conducted comprehensive literature searches in PubMed, Embase, Web of Science, Scopus, Google Scholar and ResearchGate databases from 1953 to February 2015 using predefined keywords (Supplementary Table S1). We used both Mesh terms and text words in PubMed, and we used Emtree terms and text words in Embase. We also looked at the reference lists of included reports, and the full text of studies on other risk factors associated with CTS including smoking (9), thyroid disease (18), computer use (19), diabetes (20), anthropometric measurements of the hand (21), rheumatoid arthritis and osteoarthritis for additional studies on the relationship between body mass index (BMI) and CTS.

Inclusion and exclusion criteria

Two reviewers (RS and MHP) independently screened the title and abstract of the studies to identify eligible studies on the association between BMI and CTS. We also looked at the full text of studies that had not been designed particularly to assess the relationship between BMI and CTS. All relevant observational studies were considered, including cross-sectional, case–control or cohort studies. We included both population-based and hospital-based case–control studies. The requirement for case definition of CTS was either a diagnosis of CTS (based on symptoms and nerve conduction studies or physical examination) or having undergone carpal tunnel release. We used the World Health Organization (WHO) cut-off to define overweight (BMI 25–29.99 kg/m^2), overweight or obesity (BMI > 25 kg/m^2), and obesity (BMI ≥30 kg/m^2) (13). We contacted the corresponding authors of several studies for additional results; however, only one (22) provided new information.

We excluded studies that were conducted among self-selected volunteers. Volunteers are generally healthier than the general population, and particularly volunteers who serve as a control group are more likely to be non-overweight participants. Furthermore, we excluded studies that defined CTS based on a self-report or a nerve conduction study only, or symptoms of CTS only. Lastly, we excluded studies that were conducted among CTS patients with no control group, and studies that did not provide quantitative results to estimate an effect size.

Quality assessment

Two reviewers (RS, and MHP or KFH) independently rated the quality of the included reports using the criteria adopted from the Effective Public Health Practice Project tool (23). We assessed five sources of bias: selection bias, performance bias, detection bias, attrition bias and confounding (Supplementary Table S2). Attrition bias refers to systematic differences between groups in withdrawals from a study, or missing outcome data. Discrepancies in the quality assessments between two reviewers were resolved through discussion.

Meta-analysis

We estimated a prevalence ratio for cross-sectional studies, an odds ratio (OR) for case–control studies and a risk ratio for cohort studies. We calculated Woolf confidence intervals (24) for the estimated ORs.

For studies that did not report a confidence interval for their risk estimates, we estimated a standard error (SE) for their estimates using the following formula: *se = log (odds ratio) / z value* (25). For studies that reported mean BMI in participants with or without CTS, we calculated the standardized mean difference by dividing the difference between the two means by their pooled standard deviation. We then converted the standardized mean difference into OR (26).

For studies that reported an OR or a risk ratio for one-unit increase in BMI, we calculated the effect sizes for overweight and obesity. First, we transformed the effect size and its confidence interval into natural logarithm, and then multiplied each value by 5 to get an estimate for overweight and by 10 to get an estimate for obesity. We pooled the estimates for overweight and obesity to obtain an estimate for overweight/obesity using a fixed-effect meta-analysis. This assumes that on average people who are overweight have a BMI five units higher (e.g. an average BMI 27 or 28) than normal weight people (e.g. an average BMI 22 or 23), and that for people who are obese (e.g. an average BMI 32 or 33), BMI is on average 10 units higher. We performed a sensitivity analysis and excluded these studies from the meta-analyses (Table 1).

We used a fixed-effect meta-analysis to combine the subgroups of a single study and a random-effects meta-analysis to combine the estimates of different studies (25). We

Table 1 A sensitivity analysis of 39 studies that reported estimates for overweight or obesity adjusted at least for age and sex according to study design, methodological quality of included studies and adjustment for publication bias

Characteristic	Overweight				Overweight or obesity				Obesity			
	Sample	OR	95% CI	*P*	Sample	OR	95% CI	*P*	Sample	OR	95% CI	*P*
Overall	1,279,546	1.47	1.37–1.57		1,284,231	1.79	1.63–1.96		1,362,207	2.02	1.92–2.13	
Adjustment for publication bias		1.35	1.26–1.44			1.60	1.45–1.76			2.01	1.90–2.14	
Excluding studies where estimates were derived from one-unit increase in BMI	1,272,587	1.53	1.32–1.78		1,277,272	1.99	1.72–2.31		1,355,248	2.02	1.87–2.17	
Excluding the largest study	27,927	1.50	1.43–1.58		32,612	1.82	1.63–2.04		110,588	2.04	1.90–2.19	
Study design												
Cross-sectional	10,644	1.45	1.31–1.59		12,792	1.71	1.49–1.97		13,947	2.07	1.76–2.44	
Case–control	15,533	1.55	1.45–1.65		17,382	1.96	1.65–2.32		90,895	2.07	1.88–2.29	
Cohort	1,253,369	1.32	1.30–1.35	0.25	1,254,057	1.58	1.36–1.83	0.99	1,257,365	2.00	1.93–2.08	0.58
Selection bias												
Low	8,218	1.55	1.18–2.03		10,221	1.74	1.46–2.07		58,280	2.07	1.73–2.46	
Moderate	1,264,535	1.43	1.28–1.60		1,267,217	1.87	1.59–2.20		1,296,837	1.98	1.82–2.15	
High	6,793	1.48	1.38–1.59	0.69	6,793	1.66	1.50–1.82	0.78	7,090	2.20	1.94–2.49	0.32
Confounding												
Low	1,266,069	1.35	1.29–1.42		1,266,470	1.65	1.52–1.79		1,316,487	2.01	1.96–2.06	
Moderate	13,477	1.52	1.40–1.64	0.13	17,761	1.95	1.60–2.37	0.41	45,720	2.04	1.82–2.30	0.86
Performance bias												
Low	10,476	1.49	1.36–1.63		11,526	2.03	1.55–2.66		10,823	2.22	1.89–2.61	
Moderate	1,269,070	1.45	1.33–1.59	0.57	1,272,705	1.69	1.54–1.85	0.28	1,351,384	2.00	1.87–2.14	0.25
Detection bias												
Low	9,322	1.45	1.36–1.55		12,824	1.93	1.65–2.26		38,842	1.95	1.78–2.13	
Moderate	1,270,224	1.49	1.30–1.71	0.92	1,271,407	1.65	1.44–1.88	0.22	1,323,365	2.07	1.92–2.22	0.45
Attrition bias												
Low	1,269,256	1.44	1.35–1.53		1,273,253	1.81	1.63–2.02		1,351,917	2.00	1.89–2.12	
Moderate/high	10,290	1.48	1.21–1.82	0.33	10,978	1.70	1.33–2.18	0.73	10,290	2.17	1.93–2.44	0.42
Excluding the largest study and including studies with low or moderate selection bias, low attrition bias and low confounding	10,569	1.41	1.25–1.60		10,714	1.64	1.43–1.89		60,987	2.03	1.77–2.34	

A meta-regression was used to test for the differences between subgroups. Sample indicates the total population of the study and not the number of participants with overweight or obesity. Twenty studies contributed data for overweight, 28 for overweight or obesity, and 31 for obesity.

examined the presence of heterogeneity using I^2 statistic (25). An I^2 statistic shows the total variation across the studies, which is beyond chance. A value less than 25% indicates small inconsistency and a value more than 50% indicates large inconsistency (25).

We used meta-regression (27) to determine whether a study-level covariate accounted for the observed heterogeneity and to test for differences in the effect sizes between two or more subgroups. We used a funnel plot to assess publication bias, and Egger regression test to explore an asymmetry in the funnel plot (25). We estimated the number of missing studies attributed to publication bias using the trim-and-fill method (28). We used a random-effects trim-and-fill method to adjust the pooled estimates for publication bias. We used Stata, version 13 (Stata Corp, College Station, TX, USA) for meta-analyses.

Results

We identified 2,471 potentially relevant publications by searching multiple large electronic bibliographic databases (Fig. 1). We screened 248 full-text articles. Ninety-one studies assessed the effect of BMI on CTS (Supplementary Tables S3–S6). Of those, we excluded 33 studies (Supplementary Table S6) and included 58 studies (Supplementary Tables S3–S5) in the meta-analyses.

There were 22 cross-sectional, 26 case–control and 10 (11 reports) cohort studies (Supplementary Tables S3 and S4). Two studies reported results for both CTS and carpal tunnel release (2,10). Thus, there were 49 studies on CTS and 11 on carpal tunnel release. More than half of the included case–control studies recruited hospital-based controls. Twenty-three studies reported sex-specific results for

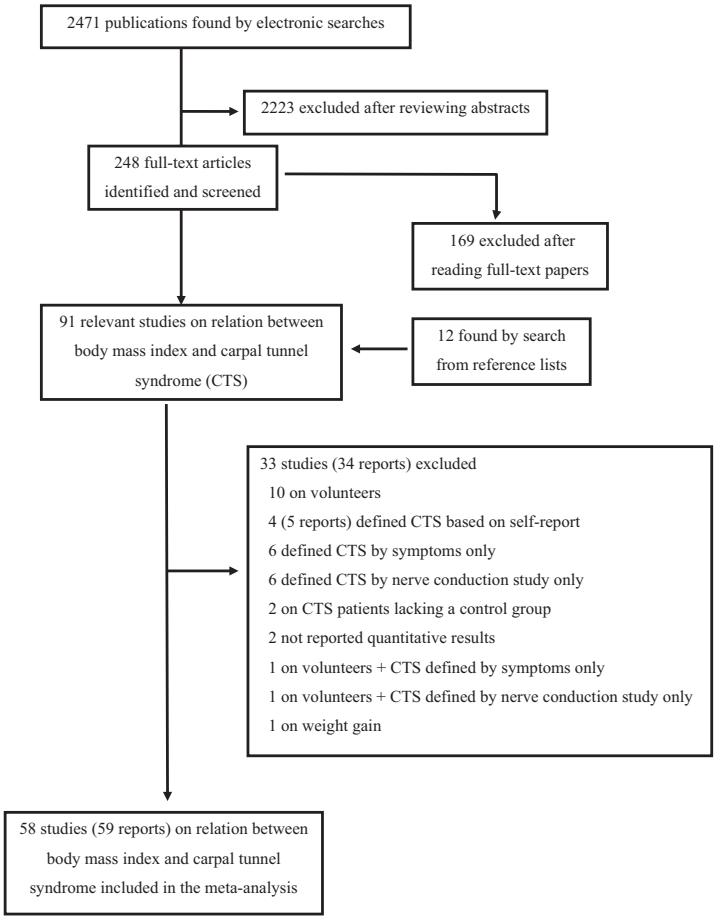

Figure 1 Flow chart of the search strategy and selection of studies.

the association between BMI and CTS (Supplementary Table S5).

Studies excluded from the meta-analysis

We excluded 33 studies (34 reports) from the meta-analysis (Fig. 1 and Supplementary Table S6). Ten studies were conducted among self-selected volunteers, and two studies were conducted among self-selected volunteers and also defined CTS by symptoms only, or nerve conduction study only. Two studies recruited CTS patients and lacked a control group, and four studies (five reports) used self-reported CTS. Six studies defined CTS using symptoms only and six studies defined CTS using nerve conduction study only. Two studies did not provide quantitative results to estimate an effect size. Lastly, we excluded one study that assessed the effect of weight gain on CTS.

Methodological quality of included studies

Seven studies were rated as having low risk of selection bias, 33 studies as having moderate risk and 18 as having high risk of selection bias (Supplementary Tables S4 and S5). Twenty studies measured weight and height whereas 38 studies used self-reported measures. The diagnosis of CTS was confirmed by a nerve conduction study in 40 studies. The assessment of CTS was based on a clinical diagnosis or a medical record in 18 studies. Fifty-one studies were rated as having low risk of attrition bias, three as having moderate risk and four studies as having high risk of attrition bias.

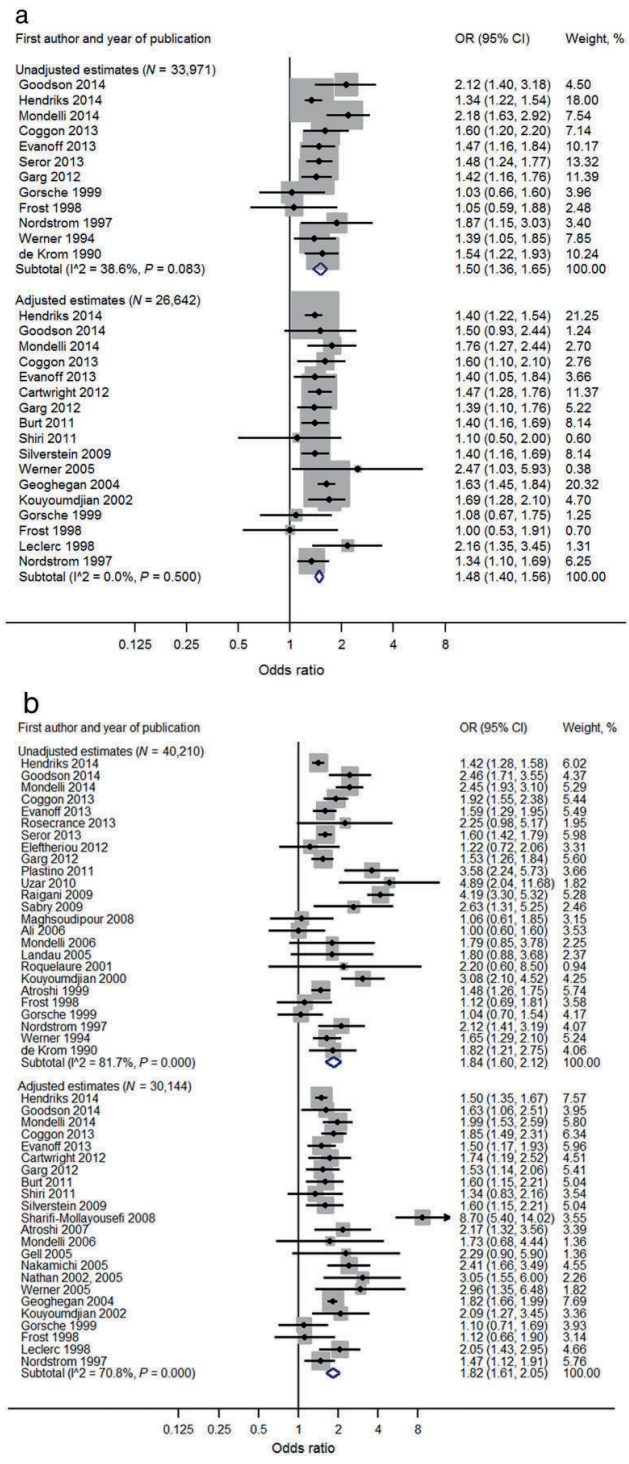

Figure 2 A meta-analysis of 49 studies on the association between excess body mass and carpal tunnel syndrome. (a) Overweight. (b) Overweight or obesity. (c) Obesity. The size of the grey shaded area indicates the weight of each study. Horizontal lines show the 95% confidence intervals (CI). OR, odds ratio.

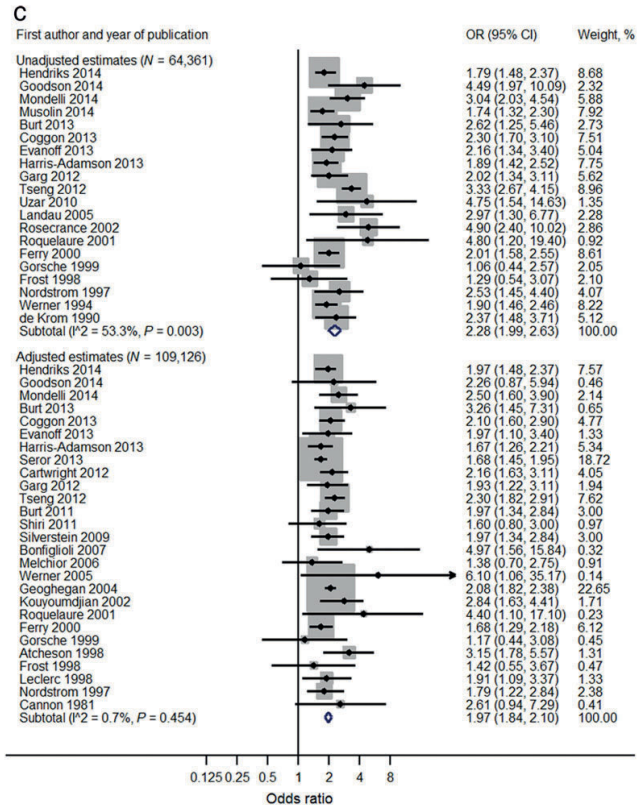

Figure 2 *Continued*

Excess body mass and carpal tunnel syndrome

Mean body mass index difference

Seventeen studies reported mean difference in BMI between individuals with and without CTS or carpal tunnel release (Supplementary Fig. S1). Individuals with CTS or carpal tunnel release had higher mean BMI than those without CTS. Pooled unadjusted mean difference was 2.150 (95% CI 1.408–2.892, 13 studies, $N = 4{,}429$ individuals) and pooled age- and sex-matched mean difference was 2.518 (95% CI 0.699–4.463, 4 studies, $N = 1{,}002$ individuals).

Overweight or obesity

A meta-analysis of 49 studies on CTS is presented in Fig. 2. Pooled adjusted OR was 1.48 (95% CI 1.40–1.56, $I^2 = 0\%$, $N = 26{,}642$, Fig. 2a) for overweight, 1.82 (95% CI 1.61–2.05, $I^2 = 70.8\%$, $N = 30{,}144$, Fig. 2b) for overweight or obesity, and 1.97 (95% CI 1.84–2.10, $I^2 = 0.7\%$, $N = 109{,}126$, Fig. 2c) for obesity.

A meta-analysis of 11 studies on carpal tunnel release is shown in Fig. 3. Pooled adjusted OR was 1.54 (95% CI 1.29–1.84, $I^2 = 69.7\%$, $N = 1{,}267{,}118$) for overweight, 1.80 (95% CI 1.46–2.23, $I^2 = 75\%$, $N = 1{,}268{,}301$) for overweight or obesity, and 2.40 (95% CI 1.96–2.93, $I^2 = 51.2\%$, $N = 1{,}267{,}295$) for obesity.

A unit increase in body mass index

A one-unit increase in BMI was associated with a 7.4% increased risk of CTS (pooled adjusted OR = 1.074, 95% CI 1.071–1.077, $I^2 = 0\%$, 13 studies, $N = 1{,}258{,}578$, Fig. 4). Excluding the largest study (sample size 1,251,619) (29) did not change the size of the effect (pooled adjusted OR = 1.076, 95% CI 1.063–1.089, $I^2 = 0\%$, 12 studies, $N = 6{,}959$).

Waist circumference

Of studies included in this meta-analysis, only four (2,30–32) explored the association between waist circumference and CTS. A meta-analysis was possible for overweight/obesity only. The pooled estimate of four studies was 2.21 (95% CI 1.26–3.89, $I^2 = 80.7\%$, $N = 7{,}691$) for overweight or obesity.

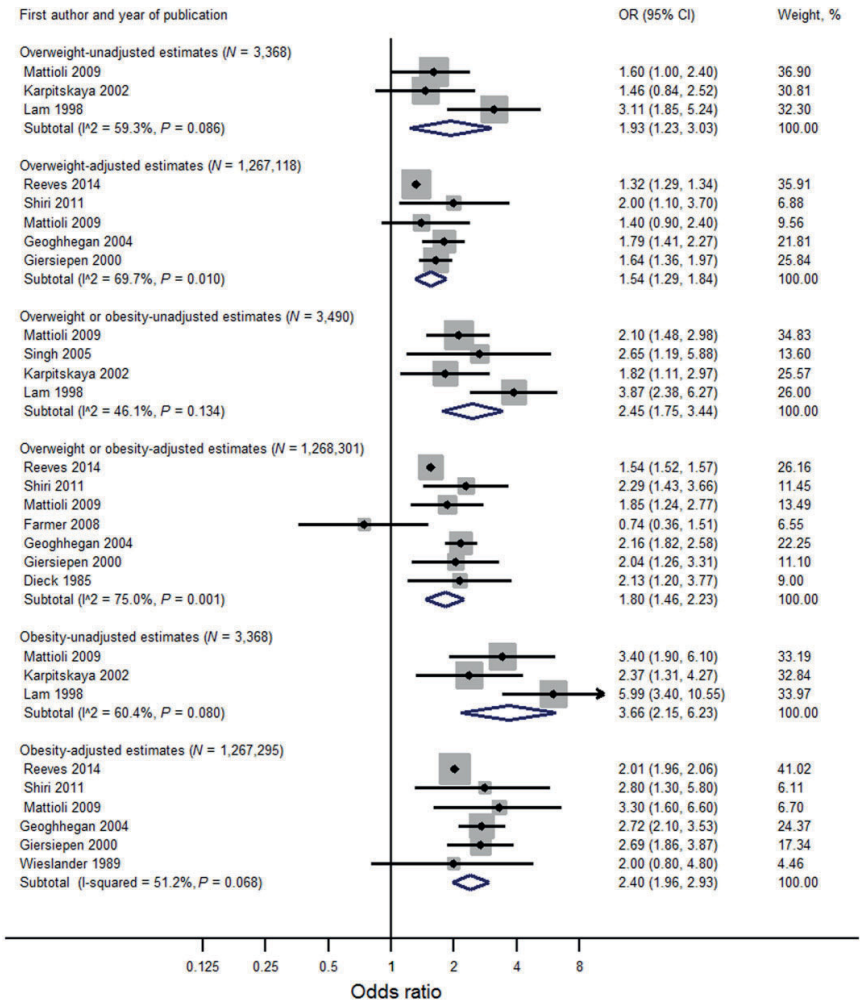

Figure 3 A meta-analysis of 11 studies on the association between overweight or obesity and carpal tunnel release. The size of the grey shaded area indicates the weight of each study. Horizontal lines show the 95% confidence intervals (CI). OR, odds ratio.

Sex-specific results

The effects of overweight and obesity on CTS or carpal tunnel release did not differ significantly between men and women (Fig. 5). The pooled adjusted OR for overweight was 1.61 (95% CI 1.31–1.99, $I^2 = 0\%$, $N = 4{,}100$, Fig. 5a) in men and 1.38 (95% CI 1.24–1.54, $I^2 = 28.7\%$, $N = 1{,}256{,}908$, Fig. 5b) in women. For obesity, the pooled adjusted OR was 2.16 (95% CI 1.78–2.62, $I^2 = 0\%$, $N = 39{,}604$) in men and 1.91 (95% CI 1.67–2.19, $I^2 = 50.9\%$, $N = 1{,}299{,}652$) in women.

Publication bias

The pooled estimate of 18 studies on the association of overweight/obesity and 40 studies on the association of obesity with CTS or carpal tunnel release was 2.20 (95% CI 2.02–2.39). The funnel plot of these 58 studies was asymmetrical (Supplementary Fig. S2). *P* value for Egger test was 0.077 and the trim-and-fill method imputed 11 missing studies. The pooled OR reduced by only 10% (random model OR = 1.98, 95% CI 1.81–2.17) after adjustment for publication bias.

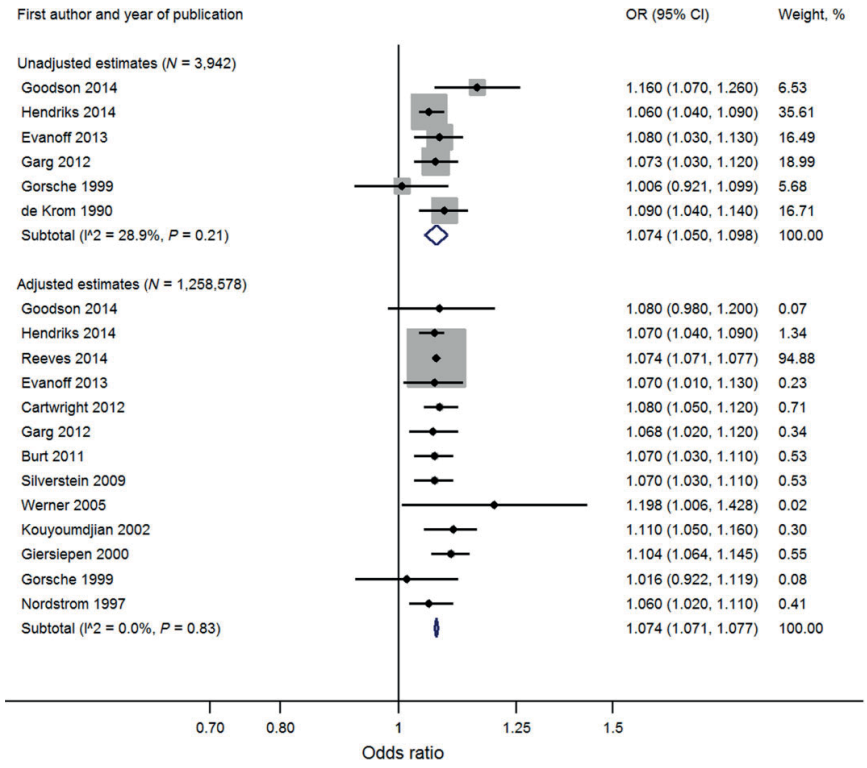

Figure 4 A meta-analysis of 14 studies on the association between one-unit increase in BMI and carpal tunnel syndrome or carpal tunnel release. The size of the grey shaded area indicates the weight of each study. Horizontal lines show the 95% confidence intervals (CI). OR, odds ratio.

Sensitivity analysis

Sensitivity analyses showed that the effect of obesity on CTS or carpal tunnel release was independent of study design, study quality, confounding and adjustment for publication bias (Table 1). A meta-analysis of nine cohort studies on CTS that reported a confounder-adjusted estimate showed similar results for overweight, overweight/obesity, and obesity (Supplementary Fig. S3). The pooled estimate was 1.38 (CI 1.17–1.63, $I^2 = 0\%$, 4 studies) for overweight, 1.67 (CI 1.29–2.17, $I^2 = 47.8\%$, 6 studies) for overweight or obesity, and 1.92 (CI 1.52–2.42, $I^2 = 9.4\%$, 7 studies) for obesity. Moreover, excluding the studies where the estimates for overweight or obesity were derived from an estimate for one-unit increase in BMI as well as excluding the largest study (sample size 1,251,619) (29) did not change the magnitude of the associations for overweight, overweight/obesity, or obesity (Table 1). Furthermore, excluding the largest study and including studies with low or moderate selection bias and low attrition bias that controlled their risk estimates for all known confounding factors did not affect the estimates markedly (Table 1 and Supplementary Fig. S4). The pooled estimate was 1.41 (CI 1.25–1.60, $I^2 = 0\%$, 6 studies, $N = 10{,}569$) for overweight, 1.64 (CI 1.43–1.89, $I^2 = 0\%$, 7 studies, $N = 10{,}714$) for overweight or obesity, and 2.03 (CI 1.77–2.34, $I^2 = 3.9\%$, 10 studies, $N = 60{,}987$) for obesity.

Discussion

This meta-analysis suggests that both overweight and obesity are risk factors for CTS with a dose–response relationship. The effect of excess body mass on CTS does not differ between men and women. Moreover, the effects of overweight and obesity on CTS are similar across different study designs, and they are not due to bias or confounding.

The mechanisms by which excess body mass increases the risk of CTS are not known. Adipose tissue within the carpal tunnel may gradually tighten the tunnel and lead to high intracarpal pressure (33). Sustained high intracarpal pressure impairs blood circulation of the median nerve and leads to median nerve ischemia, local demyelination and, ultimately, axonal loss (34). Moreover, high carpal tunnel pressure may lead to fibrosis and thickening of the

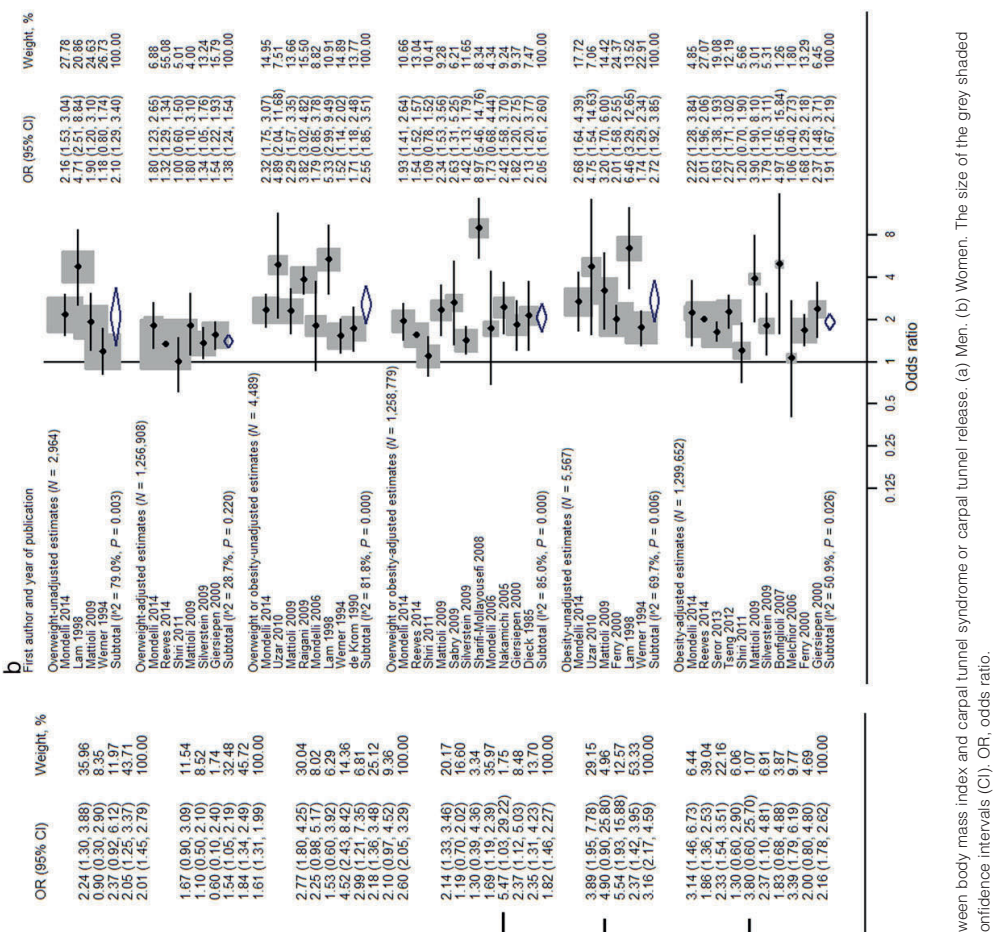

Figure 5 Sex-specific meta-analysis of 23 studies on the association between body mass index and carpal tunnel syndrome or carpal tunnel release. (a) Men. (b) Women. The size of the grey shaded area indicates the weight of each study. Horizontal lines show the 95% confidence intervals (CI). OR, odds ratio.

subsynovial connective tissue in the canal (34). Furthermore, obesity is one component of the metabolic syndrome that is often associated with peripheral neuropathy (35). Mechanisms by which metabolic syndrome and obesity cause nerve injury include fatty deposition in nerves, extracellular protein glycation, mitochondrial dysfunction and oxidative stress (35). Neuropathy can render the median nerve more vulnerable for compression within the carpal tunnel and against the volar ligament.

CTS is more common in individuals with short and wide hands than in those with long hands (21). A square-shaped wrist may increase the vulnerability of the median nerve to adverse effects of obesity. Furthermore, regular and prolonged use of handheld vibratory tools, and prolonged and highly repetitious flexion and extension of the wrist increase the risk of CTS (36). The tissue ischemia caused by sustained high intracarpal pressure may increase the vulnerability of the median nerve to the adverse effects of occupational physical workload factors (33).

The current study has some strengths. The current review took into account possible confounding by sex, and the possibility of bias from differences in study design, study quality and selective publication. The studies included in the present meta-analysis had, however, some limitations. A third of them did not adjust their risk estimates for age and sex. Nearly two-thirds used self-reported weight and height and only one-third measured weight and height. Women may underreport their weight and men may overreport their height (13). Our sensitivity analyses indicated that the use of self-reported weight and height results in an underestimation of the associations of overweight and obesity with CTS.

The majority of the case–control studies used hospital-based controls. Obese individuals are more likely to seek care for health problems associated with obesity than healthy individuals. A case–control study (37) used hospital-based as well as population-based controls and reported a higher prevalence of overweight/obesity for hospital-based controls compared with population-based controls (22% vs. 9%) (37). This study did not however estimate a separate CTS risk for the two types of control group. It seems that hospital-based case–control studies have likely underestimated the relationship between obesity and CTS.

Of 58 studies included in this meta-analysis, only four (2,30–32) measured waist circumference. These studies showed that BMI is as good as waist circumference for predicting the effects of excess fat mass on CTS.

In conclusion, excess body mass markedly increases the risk of CTS. As the prevalence of overweight and obesity is increasing globally, weight-related CTS is expected to increase. Reduction of obesity is likely to reduce the occurrence of CTS. Future studies should investigate whether a square-shaped wrist and exposure to physical workload factors potentiate the adverse effect of obesity on the median nerve.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Author contributions

RS developed the review protocol. RS and MHP conducted the literature searches and extracted data. RS updated searches and extracted additional data. RS, MHP and KFH rated the quality of included studies. RS performed the meta-analyses, interpreted the results and drafted the manuscript. KFH and EVJ contributed to the editing of the manuscript. All authors have approved the final manuscript to be submitted.

Supporting information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12324

Figure S1. Forest plot of 17 studies on mean difference (MD) in body mass index between individuals with and without carpal tunnel syndrome (15 studies) or carpal tunnel release (two studies).
Figure S2. Funnel plot of 58 studies on the effects of obesity (40 studies) or overweight/obesity (18 studies) on carpal tunnel syndrome or carpal tunnel release (*P* for Egger's test = 0.077).
Figure S3. A meta-analysis of nine cohort studies on carpal tunnel syndrome that controlled their risk estimates for some confounding factors. The largest study (Reeves *et al*. 2014) on carpal tunnel release was excluded from this analysis.
Figure S4. A meta-analysis of 11 studies with low or moderate selection bias and low attrition bias that controlled their risk estimates for all known confounding factors. The largest study (Reeves *et al*. 2014) was excluded from this analysis.
Table S1. PubMed search strategy made on February 26, 2015.
Table S2. Quality assessment of the included studies.
Table S3. Studies included in the meta-analysis on carpal tunnel syndrome.
Table S4. Studies included in the meta-analysis on carpal tunnel release.

Table S5. Sex-specific results of the studies included in the meta-analysis.
Table S6. Studies excluded from the meta-analysis.

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Carpal tunnel release: Lifetime prevalence, annual incidence and risk factors

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CARPAL TUNNEL RELEASE: LIFETIME PREVALENCE, ANNUAL INCIDENCE, AND RISK FACTORS

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ABSTRACT: *Introduction*: We estimated the lifetime prevalence and incidence of carpal tunnel release (CTR) and identified risk factors for CTR. *Methods*: The study population consisted of individuals aged ≥30 years living in Finland during 2000–2001 ($N = 6,256$) and was linked to the Finnish Hospital Discharge Register from 2000 to 2011. *Results*: Lifetime prevalence of CTR was 3.1%, and incidence rate was 1.73 per 1,000 person-years. Female sex (adjusted hazard ratio [HR] = 1.8, 95% confidence interval [CI] 1.2–2.8), age of 40–49 years (HR = 2.5, CI 1.7–3.8 compared with other age groups), education (HR = 0.6, CI 0.4–0.9 for high level vs. low/medium level), obesity (HR = 1.7, CI 1.2–2.5 for body mass index ≥30 vs. < 30 kg/m^2), and hand osteoarthritis (HR = 2.4, CI 1.4–3.9) were associated with incidence of CTR. *Discussion*: CTR is a common surgical procedure, performed on 1.9% of men and 4.1% of women during their lifetimes. Obesity and hand osteoarthritis are associated with an increased risk of CTR.

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Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in the upper extremities,[1,2] and carpal tunnel release (CTR) is one of the most common upper extremity surgical procedures.[3] CTS is associated with high healthcare costs,[4] absence from work, and changes in job duties.[5] Surgical interventions for CTS may be more effective than conservative treatments in reducing symptoms and improving hand function,[6] particularly in patients with severe CTS.[7]

The prevalence of CTR ranges between 1.3% and 2.0% in the general population among persons aged 25 years or older,[2,8] and its incidence ranges between 0.3 and 3.3 per 1,000 person-years.[3,9–22] Both prevalence[2,8] and incidence[3,11–15,17,19–23] of CTR are higher in women than in men. Currently, the lifetime prevalence of CTR is unknown. Furthermore, only a few studies have estimated the incidence of CTR in a representative sample of the general population.

The etiology of CTS is multifactorial and includes occupational and personal factors.[24,25] Physical workload factors play an important role in CTS,[24,26] but the role of some personal factors is less clear. Obesity is a well-documented risk factor for CTS.[27] Hypothyroidism,[28,29] diabetes mellitus,[29,30] rheumatoid arthritis,[29,31] and osteoarthritis[31] are possible risk factors for CTS. However, less is known about the effects of different types of obesity because only 4 studies[27] have explored the association between waist circumference and CTS. Moreover, the association between osteoarthritis and CTS is based on relatively few studies with varying joints affected by osteoarthritis.[31] It is also unclear whether exposure to workload factors modifies the effect of obesity on CTS. Finally, the role of smoking in CTS is uncertain. Cross-sectional studies, but not case-control or cohort studies, have found an association between smoking and CTS.[32] In this study, we sought to estimate the lifetime prevalence and annual incidence of CTR with regard to age, sex, and level of education and to identify risk factors for CTR.

MATERIALS AND METHODS

Population. The study sample consisted of the population of the Health 2000 Survey, which was linked to the Finnish Hospital Discharge Register for specialist medical care. The main objective of the Health 2000 Survey was to obtain up-to-date information on cardiovascular, musculoskeletal, respiratory, and mental health and disability risk factors and treatments. In the Health 2000 Survey, a representative sample of men and women aged 30 years or older living in Finland between the fall of 2000 and spring of 2001 was recruited by using a two-stage cluster sampling design. The sample was stratified according to 5 university hospital regions. Each region contained roughly 1 million residents. From each university hospital region, 16 healthcare districts were sampled as clusters (altogether, $N = 80$).[33]

The Finnish Hospital Discharge Register includes data on inpatient care and identifies 80%–99% of common discharge diagnoses.[34] The Health 2000 Survey sample included 7,977 individuals aged 30 years or older. Among these, 6,986 (87.6%) individuals were interviewed, and 6,354 (79.7%) participated in the health examination. Individuals with missing information on CTR ($n = 98$) at baseline were excluded, leaving 6,256 (78.4%) persons eligible

Additional supporting information may be found in the online version of this article.

Abbreviations: BMI, body mass index; CI, confidence interval; CTR, carpal tunnel release; CTS, carpal tunnel syndrome; HR, hazard ratio

Key words: carpal tunnel syndrome; incidence; prevalence; obesity; osteoarthritis

Conflict of interest: None of the authors have any conflicts of interest to disclose.

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Table 1. Incidence rate per 1,000 person-years and lifetime prevalence of CTR by sex, age, and education

	Incidence				Lifetime prevalence			
Characteristic	*n*	Cases, *n*	Rate	95% CI	*n*	Cases, *n*	%	95% CI
Sex								
Men	2,824	38	1.1	0.9–1.7	2,844	55	1.9	1.5–2.4
Women	3,353	75	2.2	1.8–2.8	3,412	137	4.1	3.4–4.8
Age								
30–39	1,416	19	1.2	0.8–1.9	14	9	62	36–88
40–49	1,510	47	2.8	2.1–3.8	1,304	33	2.5	1.7–3.3
50–59	1,348	25	1.6	1.1–2.4	1,552	62	4.0	3.0–4.9
60–69	934	12	1.2	0.7–2.3	1,417	40	2.8	1.9–3.6
70+	969	10	1.4	0.8–2.8	1,969	48	2.5	1.8–3.2
Level of education								
Low	2,401	45	1.9	1.4–2.6	2,443	88	3.6	2.9–4.3
Medium	1,973	46	2.1	1.6–2.9	2,003	75	3.7	2.8–4.6
High	1,783	22	1.2	0.8–1.8	1,789	28	1.6	0.9–2.2
Overall	6,177	113	1.7	1.4–2.1	6,256	192	3.1	2.7–3.5

CTR, carpal tunnel release.

for the analyses. For the analyses of the incidence rate and the risk factors of CTR, persons with CTR at baseline (n=79) were excluded (Supp. Info. Fig. 1).

Outcome. Persons with any history of prior CTR at baseline in 2000–2001 were identified through face-to-face interviews. Incident CTR cases during the follow-up period between 2001 and 2011 were identified from the Hospital Discharge Register by using ICD-10 codes. ACC51 and ACC59 codes (in the presence of G56.0 code) were considered the events of interest. Only first hospital admission for CTR was considered as a case. We had register data available from 1997 to 2000, and we checked the reliability of self-reported CTR. Among those 79 individuals who self-reported their CTR surgery in 2000–2001, we identified 23 cases in the Hospital Discharge Register between 1997 and 2000. During these years, no CTR was registered among those who did not report CTR. The remaining 56 CTR were carried out in 1996 or earlier.

Determinants. Information on level of education was collected by home interviews at baseline. Low level of education was defined as having a basic comprehensive school certificate, medium level of education was defined as having upper secondary or vocational school diploma, and high level of education was defined as having a university degree. Weight, height, waist circumference, and hip circumference were measured. Participants were categorized into 3 body mass index (BMI) groups: normal weight (BMI $< 25\,kg/m^2$), overweight (BMI $25–29.9\,kg/m^2$), and obese (BMI $\geq 30\,kg/m^2$). Waist circumference was classified into 3 categories (per sex): for men, < 94 cm, 94–101.9 cm, and ≥ 102 cm and for women, <80 cm, 80–87.9 cm, and ≥ 88 cm.[35] Waist-to-hip ratio was estimated and categorized into 3 groups (per sex): for men < 0.9, 0.9–1.0, and >1.0 and for women, < 0.8, 0.8–0.9, and >0.9.[35] Home interviews were used to obtain information on smoking status, with participants grouped into 4 levels: current smokers smoking cigarettes, cigars, or a pipe at the time of interview; former smokers who had smoked for at least 1 year previously; occasional smokers; and non-smokers. Frequency of leisure time physical activity was based on a single question, "How often do you exercise in your leisure time so that you are slightly out of breath and sweating," and was grouped into 3 levels: ≤ 1, 2 or 3, and ≥ 4 times per week.

The information on the following 6 workplace physical exposures (frequency or duration per day) in the most recent jobs was obtained through an interview: heavy physical work (manually lifting, carrying heavy items, and manually digging by shovel or chopping wood); manual handling of loads heavier than 5 kg at least 2 times per min for a minimum of 2 h daily; manual handling of loads heavier than 20 kg at least 10 times per day; work demanding high handgrip forces (e.g., squeezing, twisting, holding loads or tools) at least 1 h per day on average; repetitive movements of the hands or wrists (e.g., packing and sorting) at least 2 h per day on average; and work with a vibrating tool at least 2 h per day on average.

Diagnosis of diabetes was based on a person's use of antidiabetic medicines, or high fasting blood glucose level, and/or a previous history of diabetes. Information on hypothyroidism, rheumatoid arthritis, and knee or hip osteoarthritis was elicited through interviews and physical examinations. Hand osteoarthritis was assessed through home interviews. A blood sample was drawn for the analysis of serum rheumatoid factor and was grouped into normal value (<15 IU/ml) or high value (≥ 15 IU/ml) for the current analysis.

Statistical Analysis. Population weighting was used for estimating lifetime prevalence, annual incidence rate, and hazard ratio (HR) to correct the distribution of age, sex, residential area, and language of study sample to correspond to those of the Finnish general population. For incidence data we used age at baseline, and for lifetime prevalence we used age at follow-up. We ran sex-specific and both-sexes-combined Cox proportional hazard models to identify risk factors for CTR. Variables with *P*-values ≤ 0.3 in the age or age- and sex-adjusted models were included in the multivariable model. Age, sex, education, high handgrip forces, heavy physical work, obesity, and hand osteoarthritis were included in the final model. Analyses were performed in Stata version 13 (StataCorp, College Station, Texas, USA).

Table 2. Sex-specific age-adjusted HR of CTR by personal factors

	Men			Women			All*		
Characteristic	*n*	Cases, *n*	HR (95%CI)	*N*	Cases, *n*	HR (95%CI)	*n*	Cases, *n*	HR (95%CI)
Sex									
Men							2,824	35	1
Women							3,353	78	1.9 (1.3–2.7)
Age									
30–39	669	5	1	747	15	1	1,416	20	1
40–49	718	16	3.2 (1.2–8.3)	792	30	1.9 (0.9–3.7)	1,510	46	2.3 (1.3–3.9)
50–59	660	7	1.5 (0.5–4.8)	688	16	1.2 (0.6–2.4)	1,348	23	1.3 (0.8–2.3)
60–69	431	3	1.0 (0.2–4.2)	503	9	0.9 (0.4–2.1)	934	12	0.9 (0.5–1.9)
70+	346	4	2.3 (0.6–9.1)	623	8	0.75 (0.3–1.9)	969	12	1.1 (0.5–2.3)
Level of education									
Low	1,070	13	1	1,331	33	1	2,401	46	1
Medium	1,059	17	1.2 (0.5–2.8)	914	28	0.9 (0.5–1.6)	1,973	45	1.04 (0.7–1.6)
High	685	5	0.5 (0.2–1.7)	1,098	17	0.5 (0.2–0.9)	1,783	22	0.5 (0.3–0.9)
BMI									
<25	923	6	1	1,390	34	1	2,313	40	1
25–29.9	1,324	19	2.1 (0.7–6.2)	1,164	16	0.6 (0.3–1.12)	2,488	35	0.9 (0.6–1.5)
≥30	576	10	2.7 (0.8–8.6)	794	28	1.6 (1.0–2.6)	1,370	38	1.8 (1.2–2.7)
Waist circumference									
Normal	1,072	12	1	940	26	1	2,012	38	1
Increased	805	10	1.1 (0.5–2.8)	807	11	0.5 (0.2–1.2)	1,612	21	0.7 (0.4–1.3)
Obese	936	13	1.2 (0.5–2.9)	1,573	40	1.1 (0.7–1.8)	2,509	53	1.2 (0.8–1.8)
Waist-to-hip ratio									
Normal	329	2	1	592	10	1	921	12	1
Increased	1,504	15	1.8 (0.2–8.2)	1,902	45	1.5 (0.7–3.1)	3,406	60	1.5 (0.8–2.9)
Obese	980	18	3.3 (0.8–14.4)	825	22	2.0 (0.9–4.7)	1,805	40	2.3 (1.1–4.8)
Smoking status									
No	1,015	12	1	2,160	47	1	3,175	59	1
Occasional	130	1	0.6 (0.1–4.8)	118	1	0.3 (0.04–2.2)	248	2	0.4 (0.1–1.8)
Former	881	11	1.1 (0.5–2.7)	471	15	1.3 (0.7–2.3)	1,352	26	1.2 (0.8–1.9)
Current	788	11	1.2 (0.5–2.9)	592	15	1.0 (0.6–1.7)	1,380	26	1.1 (0.7–1.7)
Physical activity, times/wk									
≤1	1,178	14	1	1,289	33	1	2,467	47	1
2–3	883	14	1.4 (0.7–2.7)	1,065	26	0.9 (0.5–1.5)	1,948	40	1.0 (0.76–1.6)
≥4	705	7	0.8 (0.3–1.9)	893	17	0.7 (0.4–1.3)	1,598	24	0.8 (0.5–1.2)
Diabetes mellitus									
No	2,662	33	1	3,166	72	1	5,828	105	1
Yes	162	2	1.2 (0.3–5.0)	187	6	1.9 (0.8–4.7)	349	8	1.6 (0.8–3.4)
Rheumatoid arthritis									
No	2,766	34	1	3,266	77	1	6,032	111	1
Yes	58	1	1.7 (0.2–13.7)	87	1	0.6 (0.1–4.1)	145	2	0.9 (0.2–3.8)
Knee or hip osteoarthritis									
No	2,577	26	1	2,987	73	1	5,564	99	1
Yes	247	9	6.0 (2.3–16.1)	366	5	0.7 (0.3–1.9)	613	14	1.8 (0.9–3.8)
Hand osteoarthritis									
No	2707	32	1	2,998	62	1	5,705	94	1
Yes	117	3	2.4 (0.7– 8.5)	355	16	3.0 (1.6– 5.9)	472	19	2.8 (1.6– 4.8)
Hypothyroidism									
No	2,805	35	1	3,151	75	1	5,956	110	1
Yes	19	0	--	202	3	0.7 (0.2–2.1)	221	3	0.7 (0.2–1.9)
Rheumatoid factor (IU/ml)									
<15	1,282	17	1	1,452	56	1	2,734	85	1
≥15	1,512	18	0.9 (0.4–1.8)	1,855	22	0.9 (0.6–1.5)	3,367	28	0.9 (0.6–1.3)

BMI, body mass index; CI, confidence interval; CTR, carpel tunnel release; HR, hazard ratio.

**Adjustment for age and sex.*

RESULTS

The mean age of the study population was 52 ± 14 years at baseline and 62 ± 13 years at follow-up. During the 11-year follow-up period, 867 participants (13.9%) died. Twenty-eight percent of the participants had a university degree. In total, 192 cases of CTR were identified: 79 individuals self-reported their CTR at baseline in 2000–2001, and 113 individuals who underwent CTR surgery between 2001 and 2011 were identified from the Hospital Discharge Register (Supp. Info. Fig. 1).

Table 3. Sex-specific age-adjusted HR of CTR by occupational factors

	Men			Women			All*		
Characteristic	*n*	Cases	HR (95%CI)	*n*	Cases	HR (95%CI)	*n*	Cases	HR (95%CI)
Heavy physical work									
No	1,705	22	1	2,207	43	1	3,912	65	1
Yes	1,089	13	0.9 (0.5–1.9)	1,077	35	2.1 (1.2–3.5)	2,166	48	1.4 (0.9–2.2)
Manual handling of loads >5 kg									
No	2,049	27	1	2,673	59	1	4,722	86	1
Yes	741	7	0.8 (0.3–1.8)	605	19	1.8 (0.9–3.2)	1,346	26	1.2 (0.7–1.9)
Manual handling of loads >20 kg									
No	1,968	29	1	2,734	62	1	4,702	91	1
Yes	825	6	0.5 (0.2–1.2)	547	16	1.6 (0.9–2.6)	1,372	22	0.9 (0.6–1.4)
High handgrip forces									
No	1,723	25	1	2,582	51	1	4,305	76	1
Yes	1,072	10	0.7 (0.3–1.4)	695	27	2.4 (1.4–4.0)	1,767	37	1.2 (0.8–1.9)
Repetitive movements of hands or wrists									
No	1,452	20	1	1,766	34	1	3,218	54	1
Yes	1,343	15	0.8 (0.4–1.6)	1,516	44	1.6 (0.9–2.6)	2,859	59	1.3 (0.8–1.9)
Using a vibrating tool									
No	2,312	29	1	3,177	74	1	5,489	103	1
Yes	484	6	1.1 (0.5–2.6)	105	4	1.8 (0.7–4.8)	589	10	0.9 (0.5–1.9)

CI, confidence interval; CTR, carpel tunnel release; HR, hazard ratio.

**Adjustment for age and sex.*

Lifetime Prevalence. The prevalence of self-reported CTR at baseline was 1.3% (95% confidence interval [CI] 1.0-1.6%). The prevalence of CTR at the end of follow-up was 3.1% (95% CI 2.7–3.5%; Table 1). The prevalence was about 2.1-fold higher in women than in men and peaked in those aged 50–59 years (Table 1, Supp. Info. Fig. 2). The lifetime prevalence of CTR in participants with high level of education was half that of participants with low level of education (Table 1).

Incidence Rate. The incidence rate of CTR was 1.73 (95% CI 1.44–2.09) per 1,000 person-years. The rate was almost twofold higher in women than in men (Table 1) and peaked in those aged 40–49 years (Table 1, Supp. Info. Fig. 3). Moreover, the incidence rate of CTR in participants with high level of education was about 60% of that of participants with low-level of education.

Risk Factors. After adjustment for age, women were twice as likely as men to undergo surgery for CTS (Table 2). The risk of CTR in the 40–49-year-old age group was more than twice that in the other age groups after adjustment for sex. Furthermore, the risk of CTR was significantly higher in participants with BMI $\geq 30\,kg/m^2$, high waist-to-hip ratio, or hand osteoarthritis than in those without such characteristics after adjustment for age and sex. Individuals with a high level of education were about half as likely as those with a low level of education to undergo surgery for CTS. Smoking, leisure time physical activity, waist circumference, diabetes, rheumatoid arthritis, hypothyroidism, and workload factors were not associated with CTR.

In sex-specific analyses, obesity defined by BMI, hand osteoarthritis, heavy physical work, and work requiring high handgrip forces increased the risk of CTR in women after adjustment for age (Tables 2 and 3). Moreover, women with a high level of education were only half as likely as women with a low level of education to undergo CTR. The associations in men were not statistically significant. On the

Table 4. Mutually adjusted HR of CTR by occupational and personal factors ($N = 6{,}064$)

	Men		Women		All	
Independent variables	HR	95% CI	HR	95% CI	HR	95% CI
Female sex					1.8	1.2–2.8
Age, 40–49 years vs. other age groups	2.5	1.4–4.7	2.5	1.5–4.1	2.5	1.7–3.8
Education, high vs. low or medium	0.4	0.2–1.3	0.7	0.4–1.2	0.6	0.4–0.9
Obesity, BMI ≥ 30 vs. $< 30\,kg/m^2$	1.6	0.7–3.7	1.7	1.1–2.6	1.7	1.2–2.5
Hand osteoarthritis	2.7	0.8–8.8	2.2	1.2–3.9	2.4	1.4–3.9
Heavy physical work	1.2	0.5–2.6	1.3	0.7–2.6	1.2	0.7–2.1
High handgrip forces	0.5	0.2–1.2	1.5	0.8–2.9	1.1	0.6–1.8

BMI, body mass index; CI, confidence interval; CTR, carpel tunnel release; HR, hazard ratio.

other hand, knee or hip osteoarthritis was significantly associated with CTR in men only. In the final full model (Table 4), female sex, 40–49-year-old age group, education, obesity, and hand osteoarthritis were associated with the incidence of CTR.

Waist-to-hip ratio did not remain statistically significant in the full model. Excluding education from the full model did not change the associations of heavy physical work and work requiring high handgrip forces with CTR. Moreover, in stratified analyses, the association between obesity and CTR was similar in individuals with or without exposure to heavy physical work or work requiring high handgrip forces.

DISCUSSION

This study shows that CTR is a common upper extremity surgical procedure and about 1.9% of men and 4.1% of women undergo surgery for CTS during their lifetime. CTR is more common in women than in men and in individuals with lower levels of education than in those with higher levels of education. Moreover, it is more common in individuals aged 40–49 years, people who are obese, and in those who have hand osteoarthritis.

Previous epidemiological studies in the general and occupational populations[2,8,36] reported point or period prevalence estimates for CTR ranging from 0.9% to 2.0%. The current study is the first to report the lifetime prevalence of CTR. The incidence rates reported in previous studies ranged from 0.3 to 3.3 per 1,000 person-years, and our estimated incidence rate was within this range.[3,9–22] Variations between studies can result from several factors. Most of the previous studies did not recruit a representative sample of the general population. There are also variations between nations in the use of conservative and surgical treatments for CTS.

We found a higher prevalence and incidence of CTR in women than in men, which is in line with previous studies. The Prevalence of CTR has ranged between 1.8% and 2.6% in women[2,8] and between 0.7% and 1.2% in men.[2,8] The Incidence of CTR has ranged between 0.5 and 4.8 per 1,000 person–years in women and between 0.1 and 1.9 per 1,000 person-years in men.[3,11–15,17,19–23] The risk factors responsible for higher risk of CTS in women than in men are not well known. In the current study, we found obesity and hand osteoarthritis to increase the risk of CTR significantly in women.

In the current study, the incidence of CTR peaked at ages 40–49 years, and the lifetime prevalence of CTR peaked at ages 50–59 years. Previous studies also reported an increase in the incidence of CTR with advancing age.[3,11,13,14,20–23,26] It is likely that the drop in the lifetime prevalence of CTR in individuals aged 60 or older is the result of survivorship bias and recall bias. In our analysis, CTR at baseline did not predict mortality during the follow-up period. However, some of the participants who died during the follow-up might have undergone surgery for CTS had they lived longer.

Obesity defined by BMI predicted CTR, which is in line with a recent meta-analysis.[27] However, waist circumference as a marker of abdominal obesity did not predict surgical treatment for CTS. This suggests that the accumulation of adipose tissue—also in the carpal tunnel—rather than mechanisms activated by the metabolic syndrome may lead to the development of CTS. Moreover, in line with the findings of our meta-analysis,[32] smoking was not associated with the incidence of CTR. Hand osteoarthritis has only infrequently been studied in patients with CTS.[31] The mechanism by which hand osteoarthritis contributes to CTS is not fully understood. Hand/wrist osteoarthritis can account for severe idiopathic CTS by osseous hypertrophy of carpal bones.[31] Osseous hypertrophy can lead to a gradual decrease in carpal tunnel space.

In the current study, 22.2% of the study population had a BMI of 30 kg/m^2 or greater, and 5.6% had diabetes. Obesity[37,38] and diabetes[39] are more prevalent in other countries, such as the United States. With increasing burden of obesity and diabetes, the occurrence of CTS increases. Furthermore, the percentage of patients with CTS who undergo CTR may vary between countries. These factors could potentially explain the higher prevalence and incidence of CTS and CTR in other countries compared with Finland. In Finland, the prevalence of probable CTS is 1%,[35] and for those with progressive symptoms, severe electrodiagnostic findings, or failure of conservative treatments, CTR is recommended. Considering the incidence rate of CTR in the present study, it appears that approximately 1 of 6 patients with CTS undergoes CTR.

The strengths of the current study include a longitudinal design, a large population-based sample with a high participation rate, face-to-face interviews, physical examinations, and laboratory tests. This study also had some limitations. Information on hand osteoarthritis was based on self-reports. The agreement between self-reported osteoarthritis and physician-diagnosed osteoarthritis is low.[40] This type of exposure misclassification is likely to dilute the association between hand osteoarthritis and CTR. Moreover, the current study had low statistical power to explore the effects of diabetes, rheumatoid arthritis, and hypothyroidism on CTR. The incidence of CTR was 2.3 per 1,000 person-years in individuals with diabetes and 1.7 per 1,000 person-years in those

without diabetes (age- and sex-adjusted HR = 1.6). The difference between 2 groups, however, did not reach statistical significance because of low statistical power. We collected the data on CTR until 1996 using self-reports, and not all participants may have recalled their surgery for CTS. Moreover, our hospital discharge register does not include all private clinics. The coverage of the Finnish Hospital Discharge Register has been above 80%,[34] and coverage has improved to above 95% only in more recent years.[34] These limitations indicate that the lifetime prevalence of CTR may even be higher than 3.1%.

In summary, this study shows that CTR is a commonly performed upper extremity surgical procedure. Greater than 3% of people undergo surgery for CTS in their lifetime. Obesity and hand osteoarthritis are associated with an increased incidence of CTR.

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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