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Association between hormone replacement therapy and carpal tunnel syndrome: A nationwide population-based study

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Abstract

Objective: Carpal tunnel syndrome (CTS) is the most common compressive focal mononeuropathy, and the increased incidence in postmenopausal and pregnant women suggests its association with estrogen. The objective of this study is to evaluate the relationship between hormone replacement therapy (HRT) and the occurrence of CTS.

Design: Population-based case-control study

Setting: Nation-wide health insurance program operated by the government with a near 100% coverage rate.

Participants: We identified women ≥45 years old in the Health Insurance Research Database of Taiwan, which contains data on a representative sample of one million enrollees. After exclusion of those who were diagnosed with CTS before the prescription of HRT, a total of 118309 participants were included and followed up for 15 years starting from January 1, 1996. Both HRT and occurrence of CTS were identified using the insurance claims.

Main outcome measures: We identified incident patients of CTS and evaluated the association between HRT and CTS by calculating the odds ratio (OR).

Results: Of the 4535 participants who developed CTS during the study period, 2334 (51.5%) were HRT recipients. In participants without CTS, the proportion of HRT recipients was 28.1%, yielding an OR of 2.72 with a 95% confidence interval (CI) of 2.56 to 2.88. After adjustment for age, diabetes, rheumatoid arthritis, hypothyroidism, gout, and obesity, the OR of CTS associated with HRT was 2.04 (95% CI, 1.91 to 2.17). While HRT, diabetes, rheumatoid arthritis, and gout had similar effects on CTS across all age groups, hypothyroidism and obesity had different effects on different groups.

Conclusion: This study observed an association between HRT and CTS, independent of age,

diabetes, rheumatoid arthritis, hypothyroidism, gout, and obesity. While HRT affected all age groups similarly, modification by age was observed in the effects of hypothyroidism and obesity.

Strengths and limitations of this study

1. The large population enabled us to obtain stable risk estimates and simultaneously adjust for many potential confounding factors.
2. The National Health Insurance Research Database (NHIRD) used in this study is a representative sample of the general population in Taiwan and thus provides an unbiased study population.
3. While the diagnosis coded in the claims may be tentative in some cases, we included cases with at least three claims to ensure the accuracy of the diagnosis.
4. The National Health Insurance of Taiwan has very low co-pay, and so patients are unlikely to be hindered from diagnosis or treatment because of financial consideration, which minimised misclassification of cases.
5. We were unable to adjust for occupational factors such as repetitive hand use because no such data are available in the NHIRD.

Introduction

Carpal tunnel syndrome is the most common compressive focal mononeuropathy, which is mainly caused by an entrapment of the median nerve in the carpal tunnel at the wrist.[1] The estimated annual incidence of carpal tunnel syndrome is about 99 per 100,000.[2] In the U.S., the estimated annual medical cost for carpal tunnel syndrome exceeded 2 billion dollars, mostly paid for surgical releases.[3] The typical symptoms and signs of carpal tunnel syndrome included pain, paresthesia, and weakness in the median nerve distribution.[4]

Both occupational factors and non-occupational factors contribute to the occurrence of carpal tunnel syndrome. Repetitive hand and wrist use, sustained wrist extension and flexion, prolonged wrist or palm pressure, the use of vibratory tools, and working in cold temperature are the most common occupational factors.[5] Common non-occupational factors included female sex, pregnancy, obesity, diabetes, hypothyroidism, and rheumatoid arthritis.[6] A review of literature showed that the most significant medical conditions related to carpal tunnel syndrome were diabetes, hypothyroidism, and rheumatoid arthritis.[7] As both diabetes and hypothyroidism are diseases of the endocrine system and the occurrence of carpal tunnel syndrome was found to be related to pregnancy and menopause,[8] it is reasonable to speculate that there is an association between female reproductive hormones and the occurrence of carpal tunnel syndrome.

Menopause is often associated with irritating vasomotor symptoms such as hot flushes, which are attributable to decreases in estrogen levels,[9] and hormone replacement therapy (HRT) is the most effective treatment for these symptoms. HRT generally includes estrogen preparations,[10] and progesterone regimen should be prescribed to reduce the risk of endometrial hyperplasia and cancer, except in women who have undergone a hysterectomy.[11 12] After evaluating the benefits

and harms of HRT for postmenopausal women, the U.S. Preventive Services Task Force recently released a statement asserting that they do not recommend the use of HRT for the primary prevention of chronic conditions.[13]

If female reproductive hormones can affect the occurrence of carpal tunnel syndrome, HRT should have an effect on carpal tunnel syndrome. However, studies on association between HRT and carpal tunnel syndrome are limited, and carpal tunnel syndrome was not among the conditions evaluated by the U.S. Preventive Services Task Force. A study at a hospital in the U.S. observed a higher risk of carpal tunnel syndrome in women receiving HRT, with an odds ratio (OR) of 2.4.[14] Another study in the U.S. observed a higher risk of carpal tunnel syndrome in women receiving HRT, with an OR of 1.8 after adjusting for other risk factors.[6] However, a study followed six peri-menopausal women who had carpal tunnel syndrome and found improvements in menopausal symptom scores and pain scores after 6 months of HRT.[15] Nonetheless, a study in the U.K. with 3,391 carpal tunnel syndrome patients (including 2,444 women) found that carpal tunnel syndrome was not associated with HRT or oral contraceptive pill use.[16] As the limited number of studies found inconsistent results, we conducted a study to evaluate the association between HRT and carpal tunnel syndrome using data from the National Health Insurance (NHI) in Taiwan.

Methods

Data sources

The NHI was implemented in Taiwan on March 1, 1995 and covers almost all of the 23 million residents. We obtained data on one million randomly selected enrollees from the National Health Insurance Research Database (NHIRD). The data covers a period of 15 years, starting from

January 1, 1996, and there were 483,147 (48.3%) females in the dataset.

Study design

Because the median and mean ages of menopause are both around 51 years old,[17 18] we included women ≥ 45 years old and divided them into five groups: 45-49, 50-54, 55-59, 60-64, and ≥ 65 years old.

We used the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 354.0 to identify patients with carpal tunnel syndrome. We defined patients who were diagnosed with carpal tunnel syndrome in at least three ambulatory care visits as cases of carpal tunnel syndrome and others as controls. Likewise, we identified patients with the prescription of estrogen or estradiol in at least three ambulatory care visits as HRT recipients. Patients with a diagnosis of carpal tunnel syndrome before receiving HRT were excluded from the analyses (Figure 1).

The potential risk factors for carpal tunnel syndrome we evaluated in this study included diabetes (ICD-9 code 250 and A-code A181), rheumatoid arthritis (ICD-9 code 714 and A-code A430), gout (ICD-9 code 274 and A-code A189), hypothyroidism (ICD-9 codes 243 and 244, and A-code A180), and obesity (ICD-9 code 278 and A-code A183). Again, patients with the diagnosis in at least three ambulatory care visits were defined as having the risk factor.

Statistical analysis

We used chi-square tests to evaluate the differences in the proportion of HRT recipients in both carpal tunnel syndrome cases and controls across different age groups. Univariate and

multivariate logistic regressions were performed to calculate the OR and the associated 95% confidence interval (CI) for each risk factor and to evaluate its effects. We used the Cochran–Armitage trend test to evaluate the trends of risks across age groups. All the data analyses were performed using SAS Enterprise Guide and SPSS Version 17.0.

Results

A total of 15,617 participants were identified as case of carpal tunnel syndrome from the one million randomly selected enrollees, yielding an estimated prevalence of 1.6% among all ages and genders. Of the 118,309 women ≥ 45 years old, 5,156 were identified as cases of carpal tunnel syndrome, yielding an estimated prevalence of 4.34%. A total of 102,374 participants were identified as HRT recipients, yielding an estimated prevalence of 10.3%. After excluding those who had been diagnosed with carpal tunnel syndrome before being prescribed estrogen, we included 4,535 cases of carpal tunnel syndrome in the data analyses.

Overall, the proportion of HRT recipients among carpal tunnel syndrome cases ≥ 45 years old was 51.5%, and it was 28.1% in the controls. This yielded an OR of 2.72 (95% CI, 2.56 to 2.88). When broken down by age, the OR increased with age. Specifically, the OR was 2.01 (95% CI, 1.82 to 2.21) in women 45 to 49 years old, 2.04 (95% CI, 1.79 to 2.33) in women 50 to 54 years old, 2.07 (95% CI, 1.78 to 2.39) in women 55 to 59 years old, 2.13 (95% CI, 1.78 to 2.56) in women 60 to 64 years old, and 2.35 (95% CI, 1.92 to 2.88) in women ≥ 65 years old (Table 1).

In the univariate logistic regression analysis, we also identified obesity (OR = 2.56), rheumatoid arthritis (OR = 1.90), gout (OR = 1.64), hypothyroidism (OR = 1.50), and diabetes (OR = 1.21) as potential risk factors for carpal tunnel syndrome. Results of multivariate logistic regression

analyses showed that HRT was an independent risk factor, with an OR of 2.04 (95% CI, 1.91 to 2.17) after adjusting for other potential risk factors, including age, diabetes, rheumatoid arthritis, hypothyroidism, gout, and obesity (Table 2). The adjusted OR associated with other independent risk factors for carpal tunnel syndrome was 1.21 for diabetes (95% CI, 1.13 to 1.29), 1.85 for rheumatoid arthritis (95% CI, 1.70 to 2.00), 1.76 for obesity (95% CI, 1.41 to 2.18), 1.52 for gout (95% CI, 1.40 to 1.64), and 1.19 for hypothyroidism (95% CI, 1.04 to 1.37). An age ≥ 55 years appeared to be a protective factor, with an adjusted OR of 0.45 (95% CI, 0.43 to 0.48).

When we performed stratified analyses by age, we found that HRT was an independent risk factor for carpal tunnel syndrome in all age groups and that the risk increased with age. Specifically, the adjusted OR was 1.83 (95% CI, 1.66 to 2.02) in women 45 to 49 years old, 1.84 (95% CI, 1.60 to 2.10) in women 50 to 54 years old, 1.88 (95% CI, 1.62 to 2.19) in women 55 to 59 years old, 1.90 (95% CI, 1.58 to 2.29) in women 60 to 64 years old, and 1.93 (95% CI, 1.57 to 2.37) in women ≥ 65 years old. (Table 3) Rheumatoid arthritis and gout were independent risk factors in all age groups. While diabetes was associated with an increased risk of carpal tunnel syndrome in all age groups, the increase did not reach statistical significance in the age group 60 to 64 years old. Likewise, obesity was associated with an increased risk of carpal tunnel syndrome in all age groups, but the increase in the risk decreased with age and did not reach statistical significance in the two age groups above 59 years old. Hypothyroidism was not a significant independent risk factor for carpal tunnel syndrome in women between 50 and 64 years of age. The Cochran–Armitage trend test showed a significant trend ($p < 0.001$) in the increases of risks for carpal tunnel syndrome associated with HRT with increases in age.

Discussion

Prevalence of carpal tunnel syndrome

The prevalence of carpal tunnel syndrome in the general population varies substantially across studies, depending on factors including the diagnostic tool, survey method, population, etc. For example, in a study on 2,466 subjects in southern Sweden, the prevalence of clinically confirmed patients of carpal tunnel syndrome was 3.8%, electrophysiologically confirmed patients was 4.9%, and both clinically and electrophysiologically confirmed patients was 2.7%.[19] The 1988 National Health Interview Survey in the U.S. found that the prevalence of self-reported cases of carpal tunnel syndrome was 1.55%.[20] A study using various methods on 715 subjects in the Netherlands found that the prevalence was 5.8% in women and 0.6% in men.[21]

In this study, we identified patients with a diagnosis of carpal tunnel syndrome for at least three ambulatory visits as confirmed cases. Of the 118,309 women ≥ 45 years old, 5,156 such patients were identified, yielding an estimated prevalence of 4.34%, which is close to the reported prevalence of clinically confirmed patients of carpal tunnel syndrome, 3.8%, of a study in southern Sweden.

Possible pathogenesis of carpal tunnel syndrome associated with HRT

While most cases of carpal tunnel syndrome are idiopathic, the pathogenesis of such cases is known to be related to the decreased size of the carpal canal (the container) or the increased volume of the contents within the canal (contents).[22 23 24] For example, joint abnormalities caused by inflammatory arthritis and abnormalities of the shape or position of the bones caused by fractures are both abnormalities of the container that may lead to carpal tunnel syndrome. Metabolic tenosynovitis caused by diabetes, abnormalities of fluid distribution caused by pregnancy or hypothyroidism, and hematoma caused by trauma are examples of abnormalities of

content that may lead to carpal tunnel syndrome.[23]

We found that HRT was an independent risk factor for carpal tunnel syndrome, which was observed in all women ≥ 45 years old. In carpal tunnel syndrome patients, the most common histological finding is non-inflammatory fibrosis of the subsynovial connective tissue. [25 26] Hormonal fluctuations and fluid accumulation are generally believed to be the pathogenesis of the development of carpal tunnel syndrome symptoms in pregnant women.[27] In postmenopausal women, some studies demonstrated that fluctuation of the estrogen level was associated with idiopathic carpal tunnel syndrome, although the pathogenesis remains unclear.[8]

Estrogens have some anti-inflammatory properties, and increased levels of some inflammatory cytokines such as IL-1, IL-6, and TNF-alpha are noted after menopause.[28] Therefore, decreases in the estrogen level, as in menopausal women who require HRT, may lead to high levels of cytokines, which may in turn cause cellular proliferation, angiogenesis, increased capillary permeability, edematous changes and then fibrosis.[29] When these changes occur in the carpal tunnel, they might contribute to the development of carpal tunnel syndrome.

It was also postulated that the stimulations of tenosynovial tissue may cause carpal tunnel syndrome. Receptors of estrogen (ER) and progesterone (PR) have been found in the transverse carpal ligament and flexor tenosynovium.[30] A study found an increase of the expressions of ER in tenosynovial tissue histologically and immunohistochemically in patients with carpal tunnel syndrome.[31] Fibroblasts and synovial lining cells in the tenosynovial tissue may thus increase. HRT might play a role in this up-regulation pathway and lead to carpal tunnel syndrome in postmenopausal women (Figure 2).

Other potential risk factors for carpal tunnel syndrome

Diabetes mellitus is one of the most common risk factors for carpal tunnel syndrome. A recent study proposed that the ischemic damage and neoangiogenesis in diabetes patients contribute to the occurrence of carpal tunnel syndrome. The increased VEGF expression and neovascularisation within the subsynovial connective tissue are also believed to be contributing factors, as in diabetic nephropathy and retinopathy.[32] In multivariate analyses, we found that diabetes was associated with an increased risk of carpal tunnel syndrome in women ≥ 45 years old (OR = 1.21, $p < 0.001$). When we divided the participants into five age groups, the ORs were similar across all age groups (fluctuating between 1.18 and 1.36), although the OR did not reach statistical significance in the 60 to 64 year-old group, most likely because of the smaller case number (the smallest of all groups).

Rheumatoid arthritis has also been identified as a risk factor for carpal tunnel syndrome.[6] The pathogenesis of carpal tunnel syndrome in rheumatoid arthritis patients is believed to be a result of increasing intra-carpal-tunnel pressure caused by tenosynovitis around the transverse carpal ligament and flexor tendons.[33] In multivariate analyses, we found that rheumatoid arthritis was associated with an increased risk of carpal tunnel syndrome in women ≥ 45 years old (OR = 1.85, $p < 0.001$). When we divided the participants into five age groups, the ORs were similar across all age groups (fluctuating between 1.67 and 2.25), and all reached statistical significance.

The mechanism of neuropathy in patients with hypothyroidism is unclear. Abnormalities of fluid distribution is a likely etiology carpal tunnel syndrome.[23] The deposition of mucopolysaccharides or mucinous material on the median nerve might also contribute to its occurrence.[34] In

multivariate analyses, we found that hypothyroidism was associated with an overall OR of 1.19 ($p = 0.013$) for carpal tunnel syndrome in women ≥ 45 years old. When we divided the participants into five age groups, the OR showed a U shape dose-response relationship with age and reached statistical significance only in the youngest and the oldest groups. This implies that multiple factors are involved.

Gouty tophi can lead to the non-traumatic compression of the median nerve in the carpal tunnel, causing mechanical or neurological symptoms. carpal tunnel syndrome secondary to gout is uncommon except in the cases with space-occupying lesions caused by tophi.[35] Except for the median nerve, tophi may also involve the flexor tendons inside the carpal tunnel.[36] In multivariate analyses, we found that gout was associated with an increased risk of carpal tunnel syndrome in women ≥ 45 years old (OR = 1.52, $p < 0.001$). When we divided the participants into five age groups, the ORs were similar across all age groups (fluctuating between 1.33 and 1.91), all reaching statistical significance.

Our findings confirm that obesity is an independent risk factor for carpal tunnel syndrome.[6] It may due to the increased fat tissue within the carpal tunnel and increased hydrostatic pressure throughout the carpal tunnel.[37] In multivariate analyses, we found that obesity was associated with an increased risk in women ≥ 45 years old (OR = 1.76, $p < 0.001$). When we divided the participants into five age groups, the OR showed an inversed U shape dose-response relationship with age and did not reach statistical significance in the two oldest groups. This implies that multiple factors are involved, although the smaller case numbers in the two oldest age groups might also contribute to the results.

Strength and limitations

The large population in this study enabled us to obtain stable risk estimates and simultaneously adjust for many potential confounding factors. We were also able to conduct stratified analyses. In addition, the near 100% coverage of the NHIRD provides an unbiased study population, and therefore the results are representative of the whole country. Because we used the claim data from an insurance program with a 500-fold fine on treatment deemed to be unnecessary, both over-diagnosis of carpal tunnel syndrome and over-use of HRT are unlikely. While the diagnosis coded in the claims may be tentative in some cases, we included cases with at least three claims. On the other hand, the NHI has a nearly 100% coverage and a very low co-pay, less than 20 U.S. Dollars. Therefore, patients are unlikely to be hindered from diagnosis or treatment because of financial consideration, and so misclassification of cases was minimum in our study.

Nonetheless, our study had some limitations. In particular, carpal tunnel syndrome is a common occupational disease, but no data on occupation risk factors such as repetitive hand use are available in the NHIRD. Although we were unable to adjust for occupational factors, we did observe the association in women more than 60 years old, and most women in Taiwan have retired by this age, not to mention that the association was also observed in the oldest age group (≥ 65 years).

Conclusion

The previous studies on the association between HRT and carpal tunnel syndrome were mostly conducted in Western countries and had insistent findings. We observed an approximately two-fold increase in the prevalence of carpal tunnel syndrome in female HRT recipient ≥ 45 year old. In addition, we observed the increase in all age groups and found that it was independent of

most risk factors that have been recognized, including diabetes, rheumatoid arthritis, hypothyroidism, gout, and obesity. While these factors were also found to be associated with carpal tunnel syndrome in our study, we found that hypothyroidism and obesity had different effects on different age groups, which should be a novel finding. Further studies are needed to identify the underlying mechanism, so that this side effect of HRT can be minimised.

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Contributors

All authors contributed to the study design (H-CT, Y-YC, and H-RG). H-RG led all aspects of the study. H-CT was responsible for the first draft of the manuscript. H-CT and Y-YC conducted the analysis. All authors (H-CT, Y-YC, and H-RG) participated in critical revisions of the manuscript, read and approved the final manuscript.

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Competing interests

None declared.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not required.

Ethics approval

This study has been reviewed and approved by the Institutional Review Boards of the Ditmanson Medical Foundation Chia-Yi Christian Hospital (approval No. 104068).

Data availability statement

All the data used in this study are available from the Taiwanese government after approval of the application.

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Figure legends

Figure 1. Flow chart of the study of the association between hormone replacement therapy (HRT) and carpal tunnel syndrome (CTS)

Figure 2. Possible mechanisms of estrogen causing carpal tunnel syndrome (CTS)

Table 1. The relationship of carpal tunnel syndrome and hormone replacement therapy (HRT) in women in different age groups.

	Carpal Tunnel Syndrome		
Age (year)	**No (N=113774)**	**Yes (N=4535)**	**Odds Ratio (95% CI*)**
45-49			
No HRT	15998 (58.7%)	740 (41.4%)	1.00
HRT	11266 (41.3%)	1046 (58.6%)	2.01 (1.82-2.21)
50-54			
No HRT	9490 (57.0%)	378 (39.3%)	1.00
HRT	7173 (43.1%)	583 (60.7%)	2.04 (1.79-2.33)
55-59			
No HRT	11377 (66.6%)	369 (49.2%)	1.00
HRT	5686 (33.3%)	381 (50.8%)	2.07 (1.78-2.39)
60-64			
No HRT	11462 (76.4%)	306 (60.4%)	1.00
HRT	3536 (23.6%)	201 (39.6%)	2.13 (1.78-2.56)
≥65			
No HRT	33489 (88.6%)	408 (76.8%)	1.00
HRT	4297 (11.4%)	123 (23.2%)	2.35 (1.92-2.88)

*confidence interval

Table 2. Logistic regression analyses of potential risk factors for carpal tunnel syndrome.

	Carpal Tunnel Syndrome		Odds Ratio (95% CI*)	
	No (N=113774)	Yes (N=4535)	Uni-variate	Multi-variate
Age (year)				
45-54	43827 (38.6%)	2747 (60.6%)	1.00	1.00
≥55	69847 (61.4%)	1788 (39.4%)	0.41 (0.39-0.44)	0.45 (0.43-0.48)
Hormone Replacement Therapy				
No	81816 (71.9%)	2201 (48.5%)	1.00	1.00
Yes	31958 (28.1%)	2334 (51.5%)	2.72 (2.56-2.88)	2.04 (1.91-2.17)
Diabetes Mellitus				
No	79117 (71.1%)	3044 (67.1%)	1.00	1.00
Yes	32159 (28.9%)	1491 (32.9%)	1.21 (1.13-1.28)	1.21 (1.13-1.29)
Rheumatoid Arthritis				
No	99946 (89.8%)	3730 (82.3%)	1.00	1.00
Yes	11330 (10.2%)	805 (17.8%)	1.90 (1.76-2.06)	1.85 (1.70-2.00)
Hypothyroidism				
No	107365 (96.5%)	4300 (94.8%)	1.00	1.00
Yes	3911 (3.5%)	235 (5.2%)	1.50 (1.31-1.72)	1.19 (1.04-1.37)
Gout				
No	96481 (86.7%)	3626 (80.0%)	1.00	1.00
Yes	14795 (13.3%)	909 (20.0%)	1.64 (1.52-1.76)	1.52 (1.40-1.64)
Obesity				
No	110342 (99.2%)	4439 (97.9%)	1.00	1.00
Yes	934 (0.8%)	96 (2.1%)	2.56 (2.07-3.16)	1.76 (1.41-2.18)

*CI: confidence interval

Table 3. Stratified multivariate logistic regression analyses of potential risk factors for carpal tunnel syndrome (CTS) by age.

	Non-CTS	CTS	Odds Ratio (95% CI*)
45 to 49 years old			
HRT	11266 (41.3%)	1046 (58.6%)	1.83 (1.66-2.02)
Diabetes Mellitus	5069 (18.9%)	433 (24.2%)	1.21 (1.08-1.36)
Rheumatoid Arthritis	1621 (6.0%)	221 (12.4%)	1.86 (1.60-2.17)
Hypothyroidism	1005 (3.7%)	95 (5.3%)	1.24 (1.00-1.55)
Gout	2261 (8.4%)	259 (14.5%)	1.52 (1.32-1.76)
Obesity	318 (1.2%)	41 (2.3%)	1.55 (1.10-2.17)
50 to 54 years old			
HRT	7173 (43.1%)	583 (60.7%)	1.84 (1.60-2.10)
Diabetes Mellitus	4446 (27.0%)	313 (32.6%)	1.18 (1.02-1.36)
Rheumatoid Arthritis	1402 (8.5%)	188 (19.6%)	2.25 (1.89-2.67)
Hypothyroidism	740 (4.5%)	51 (5.3%)	0.97 (0.73-1.31)
Gout	2003 (12.2%)	186 (19.4%)	1.40 (1.18-1.67)
Obesity	201 (1.2%)	28 (2.9%)	2.08 (1.38-3.13)
55 to 59 years old			
HRT	5686 (33.3%)	381 (50.8%)	1.88 (1.62-2.19)
Diabetes Mellitus	5457 (32.3%)	296 (39.5%)	1.23 (1.05-1.43)
Rheumatoid Arthritis	1794 (10.6%)	158 (21.1%)	1.93 (1.60-2.32)
Hypothyroidism	2449 (14.5%)	162 (21.6%)	0.96 (0.67-1.36)
Gout	695 (4.1%)	34 (4.5%)	1.33 (1.10-1.60)
Obesity	171 (1.0%)	17 (2.3%)	1.81 (1.08-3.02)
60 to 64 years old			
HRT	3536 (23.6%)	201 (39.6%)	1.90 (1.58-2.29)
Diabetes Mellitus	5293 (35.8%)	218 (43.0%)	1.18 (0.98-1.42)
Rheumatoid Arthritis	1749 (11.8%)	107 (21.1%)	1.67 (1.33-2.08)
Hypothyroidism	522 (3.5%)	26 (5.1%)	1.27 (0.85-1.91)
Gout	2400 (16.2%)	151 (29.8%)	1.91 (1.57-2.34)
Obesity	126 (0.9%)	7 (1.4%)	1.22 (0.56-2.65)
≥ 65 years old			
HRT	4297 (11.4%)	123 (23.2%)	1.93 (1.57-2.37)

Diabetes Mellitus	11894 (32.8%)	231 (43.5%)	1.36 (1.14-1.63)
Rheumatoid Arthritis	4764 (13.1%)	131 (24.7%)	1.82 (1.48-2.23)
Hypothyroidism	949 (2.6%)	29 (5.5%)	1.82 (1.24-2.67)
Gout	5682 (15.7%)	151 (28.4%)	1.78 (1.46-2.16)
Obesity	118 (0.3%)	3 (0.6%)	1.19 (0.37-3.80)

*CI: confidence interval; HRT: [b]hormone replacement therapy

Figure 1. Flow chart of the study of the association between hormone replacement therapy (HRT) and carpal tunnel syndrome (CTS)

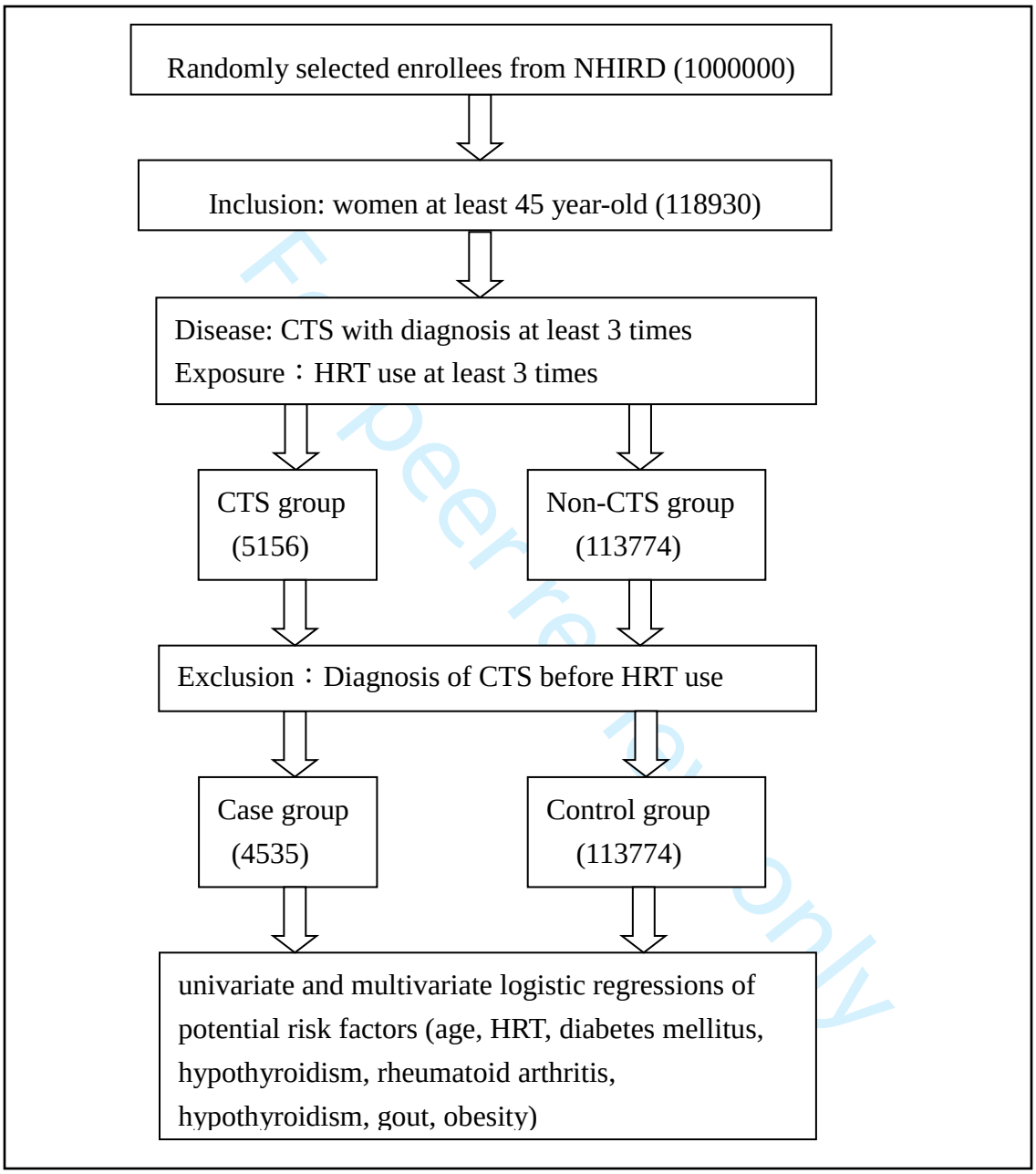
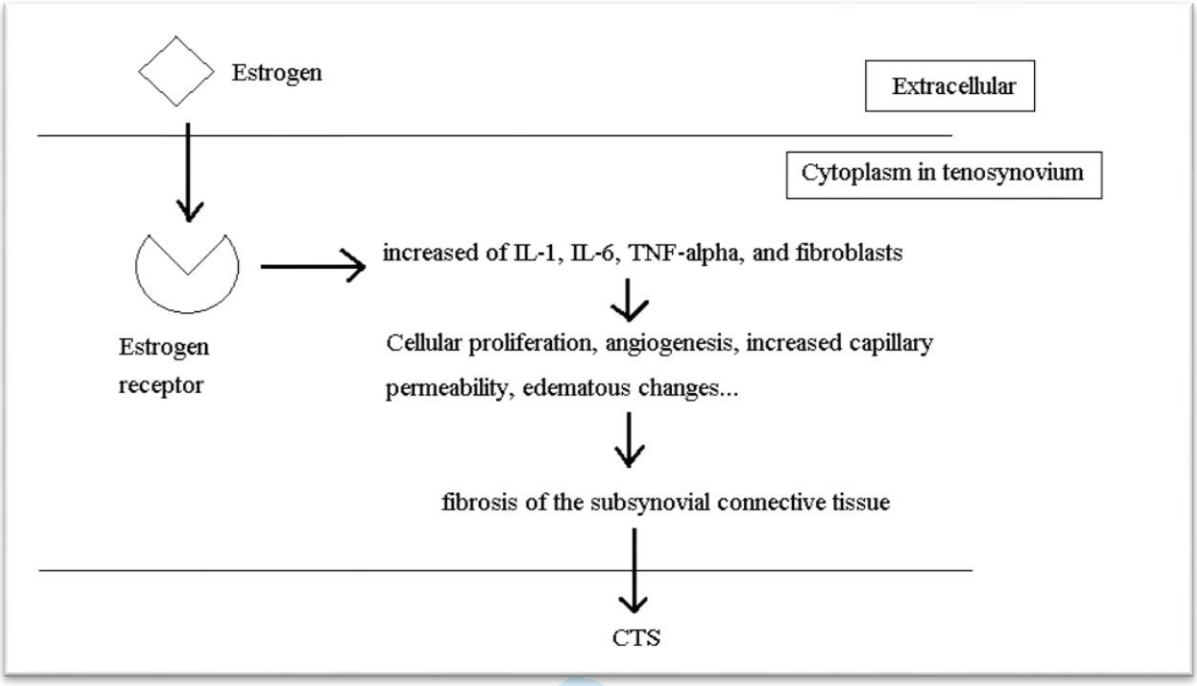


Figure 2. Possible mechanisms of estrogen causing carpal tunnel syndrome (CTS)



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6-7
		(*b*) For matched studies, give matching criteria and the number of controls per case	none
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how matching of cases and controls was addressed	none
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	8-9
		(c) Consider use of a flow diagram	25
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	none
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between hormone replacement therapy and carpal tunnel syndrome: A nationwide population-based study

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Keywords: carpal tunnel syndrome; hormone replacement therapy; risk factors

Abstract

Objective: Carpal tunnel syndrome (CTS) is the most common compressive focal mononeuropathy, and the increased incidence in postmenopausal and pregnant women suggests its association with estrogen. The objective of this study is to evaluate the relationship between hormone replacement therapy (HRT) and the occurrence of CTS.

Design: Population-based case-control study

Setting: Nation-wide health insurance program operated by the government with a near 100% coverage rate.

Participants: We identified women ≥45 years old in the Health Insurance Research Database of Taiwan, which contains data on a representative sample of one million enrollees. After exclusion of those who were diagnosed with CTS before the prescription of HRT, a total of 118309 participants were included and followed up for 15 years starting from January 1, 1996. Both HRT and occurrence of CTS were identified using the insurance claims.

Main outcome measures: We identified incident patients of CTS and evaluated the association between HRT and CTS by calculating the odds ratio (OR).

Results: Of the 4535 participants who developed CTS during the study period, 2334 (51.5%) were HRT recipients. In participants without CTS, the proportion of HRT recipients was 28.1%, yielding an OR of 2.72 with a 95% confidence interval (CI) of 2.56 to 2.88. After adjustment for age, diabetes, rheumatoid arthritis, hypothyroidism, gout, and obesity, the OR of CTS associated with HRT was 2.04 (95% CI, 1.91 to 2.17). While HRT, diabetes, rheumatoid arthritis, and gout had similar effects on CTS across all age groups, hypothyroidism and obesity had different effects on different groups.

Conclusion: This study observed a positive association between HRT and CTS, independent of

age, diabetes, rheumatoid arthritis, hypothyroidism, gout, and obesity. While the ORs of CTS associated with HRT were similar across age groups, those associated with hypothyroidism and obesity were not, indicating effect modifications by age.

Strengths and limitations of this study

1. The large population enabled us to obtain stable risk estimates and simultaneously adjust for many potential confounding factors.
2. The National Health Insurance Research Database (NHIRD) used in this study is a representative sample of the general population in Taiwan and thus provides an unbiased study population.
3. While the diagnosis coded in the claims may be tentative in some cases, we included cases with at least three claims to ensure the accuracy of the diagnosis.
4. The National Health Insurance of Taiwan has very low co-pay, so patients are unlikely to be hindered from diagnosis or treatment because of financial consideration, which minimised misclassification of cases.
5. We were unable to adjust for occupational factors such as repetitive hand use because no such data are available in the NHIRD.

Introduction

Carpal tunnel syndrome is the most common compressive focal mononeuropathy, which is mainly caused by an entrapment of the median nerve in the carpal tunnel at the wrist.[1] The estimated annual incidence of carpal tunnel syndrome is about 99 per 100,000.[2] In the U.S., the estimated annual medical cost for carpal tunnel syndrome exceeded 2 billion dollars, mostly paid for surgical releases.[3] The typical symptoms and signs of carpal tunnel syndrome included pain, paresthesia, and weakness in the median nerve distribution.[4]

Both occupational factors and non-occupational factors contribute to the occurrence of carpal tunnel syndrome. Repetitive hand and wrist use, sustained wrist extension and flexion, prolonged wrist or palm pressure, the use of vibratory tools, and working in cold temperature are the most common occupational factors.[5] Common non-occupational factors included female sex, pregnancy, obesity, diabetes, hypothyroidism, and rheumatoid arthritis.[6] A review of literature showed that the most significant medical conditions related to carpal tunnel syndrome were diabetes, hypothyroidism, and rheumatoid arthritis.[7] As both diabetes and hypothyroidism are diseases of the endocrine system and the occurrence of carpal tunnel syndrome was found to be related to pregnancy and menopause,[8] it is reasonable to speculate that there is an association between female reproductive hormones and the occurrence of carpal tunnel syndrome.

Menopause is often associated with irritating vasomotor symptoms such as hot flushes, which are attributable to decreases in estrogen levels,[9] and hormone replacement therapy (HRT) is the most effective treatment for these symptoms. HRT generally includes estrogen preparations,[10] and progesterone regimen should be prescribed to reduce the risk of endometrial hyperplasia and cancer, except in women who have undergone a hysterectomy.[11,12] After evaluating the benefits

and harms of HRT for postmenopausal women, the U.S. Preventive Services Task Force recently released a statement asserting that they do not recommend the use of HRT for the primary prevention of chronic conditions.[13]

If female reproductive hormones can affect the occurrence of carpal tunnel syndrome, HRT should have an effect on carpal tunnel syndrome. However, studies on association between HRT and carpal tunnel syndrome are limited, and carpal tunnel syndrome was not among the conditions evaluated by the U.S. Preventive Services Task Force. A study at a hospital in the U.S. observed a higher risk of carpal tunnel syndrome in women receiving HRT, with an odds ratio (OR) of 2.4.[14] Another study in the U.S. observed a higher risk of carpal tunnel syndrome in women receiving HRT, with an OR of 1.8 after adjusting for other risk factors.[6] However, a study followed six peri-menopausal women who had carpal tunnel syndrome and found improvements in menopausal symptom scores and pain scores after 6 months of HRT.[15] Nonetheless, a study in the U.K. with 3,391 carpal tunnel syndrome patients (including 2,444 women) found that carpal tunnel syndrome was not associated with HRT or oral contraceptive pill use.[16] There were limited number of studies, and the results were inconsistent. Three of the four previous studies used cross-sectional data and thus could not determine the temporal relationship between HRT and carpal tunnel syndrome. The study that could determine the temporal relationship included six peri-menopausal women only and examined the effects of HRT on existing carpal tunnel syndrome, not the effects of HRT on the occurrence of carpal tunnel syndrome. Therefore, we conducted a study to evaluate the association between HRT and the occurrence of carpal tunnel syndrome using data from the National Health Insurance (NHI) in Taiwan.

Methods

Data sources

The NHI was implemented in Taiwan on March 1, 1995 and covers almost all of the 23 million residents. We obtained data on one million randomly selected enrollees from the National Health Insurance Research Database (NHIRD). The data covers a period of 15 years, starting from January 1, 1996, and there were 483,147 (48.3%) females in the dataset.

Study design

Because the median and mean ages of menopause are both around 51 years old,[17, 18] we included women ≥ 45 years old and divided them into five groups: 45-49, 50-54, 55-59, 60-64, and ≥ 65 years old.

We used the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 354.0 to identify patients with carpal tunnel syndrome. We defined patients who were diagnosed with carpal tunnel syndrome in at least three ambulatory care visits as cases of carpal tunnel syndrome and others as controls. Likewise, we identified patients with the prescription of estrogen or estradiol in at least three ambulatory care visits as HRT recipients. Patients with a diagnosis of carpal tunnel syndrome before receiving HRT were excluded from the analyses (Figure 1).

The potential risk factors for carpal tunnel syndrome we evaluated in this study included diabetes (ICD-9 code 250 and A-code A181), rheumatoid arthritis (ICD-9 code 714 and A-code A430), gout (ICD-9 code 274 and A-code A189), hypothyroidism (ICD-9 codes 243 and 244, and A-code A180), and obesity (ICD-9 code 278 and A-code A183). Again, patients with the diagnosis

in at least three ambulatory care visits were defined as having the risk factor.

Statistical analysis

We used chi-square tests to evaluate the differences in the proportion of HRT recipients in both carpal tunnel syndrome cases and controls across different age groups. To identify independent risk factors for carpal tunnel syndrome, we first applied univariate logistic regressions to calculate the OR and the associated 95% confidence interval (CI) for each risk factor and to evaluate its effects. Then, we constructed a multivariate logistic model that included all the potential risk factors identified in the univariate regressions. The goodness of fit of models was evaluated by the Hosmer-Lemeshow test. Because HRT is related to age, we conducted stratified analyses to evaluate potential effect modifications by age, using multivariate regression models that include all potential risk factors other than age. We used the Cochran–Armitage trend test to evaluate the trends of risks across age groups. All the data analyses were performed using SAS Version 9.3 (SAS Inc., Raleigh, NC, USA) and SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA), and all statistical tests were performed at a two-sided significance level of 0.05.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results

A total of 15,617 participants were identified as cases of carpal tunnel syndrome from the one million randomly selected enrollees, yielding an estimated prevalence of 1.6% among all ages and genders. Of the 118,309 women ≥ 45 years old, 5,156 were identified as cases of carpal

tunnel syndrome, yielding an estimated prevalence of 4.34%. A total of 102,374 participants were identified as HRT recipients, yielding an estimated prevalence of 10.3%. After excluding those who had been diagnosed with carpal tunnel syndrome before being prescribed estrogen, we included 4,535 cases of carpal tunnel syndrome in the data analyses.

Overall, the proportion of HRT recipients among carpal tunnel syndrome cases ≥ 45 years old was 51.5%, and it was 28.1% in the controls. This yielded an OR of 2.72 (95% CI, 2.56 to 2.88). When broken down by age, the OR increased with age. Specifically, the OR was 2.01 (95% CI, 1.82 to 2.21) in women 45 to 49 years old, 2.04 (95% CI, 1.79 to 2.33) in women 50 to 54 years old, 2.07 (95% CI, 1.78 to 2.39) in women 55 to 59 years old, 2.13 (95% CI, 1.78 to 2.56) in women 60 to 64 years old, and 2.35 (95% CI, 1.92 to 2.88) in women ≥ 65 years old (Table 1).

In the univariate logistic regression analysis, we also identified obesity (OR = 2.56), rheumatoid arthritis (OR = 1.90), gout (OR = 1.64), hypothyroidism (OR = 1.50), and diabetes (OR = 1.21) as potential risk factors for carpal tunnel syndrome. Results of multivariate logistic regression analyses showed that HRT was an independent risk factor, with an OR of 2.04 (95% CI, 1.91 to 2.17) after adjusting for other potential risk factors, including age, diabetes, rheumatoid arthritis, hypothyroidism, gout, and obesity (Table 2). The adjusted OR associated with other independent risk factors for carpal tunnel syndrome was 1.21 for diabetes (95% CI, 1.13 to 1.29), 1.85 for rheumatoid arthritis (95% CI, 1.70 to 2.00), 1.76 for obesity (95% CI, 1.41 to 2.18), 1.52 for gout (95% CI, 1.40 to 1.64), and 1.19 for hypothyroidism (95% CI, 1.04 to 1.37). An age ≥ 55 years appeared to be a protective factor, with an adjusted OR of 0.45 (95% CI, 0.43 to 0.48). The Hosmer-Lemeshow test for the goodness of fit of the final multivariate model was significant ($p < 0.01$).

When we performed stratified analyses by age, we found that HRT was an independent risk factor for carpal tunnel syndrome in all age groups and that the risk increased with age. Specifically, the adjusted OR was 1.83 (95% CI, 1.66 to 2.02) in women 45 to 49 years old, 1.84 (95% CI, 1.60 to 2.10) in women 50 to 54 years old, 1.88 (95% CI, 1.62 to 2.19) in women 55 to 59 years old, 1.90 (95% CI, 1.58 to 2.29) in women 60 to 64 years old, and 1.93 (95% CI, 1.57 to 2.37) in women ≥ 65 years old. (Table 3) Rheumatoid arthritis and gout were independent risk factors in all age groups. While diabetes was associated with an increased risk of carpal tunnel syndrome in all age groups, the increase did not reach statistical significance in the age group 60 to 64 years old. Likewise, obesity was associated with an increased risk of carpal tunnel syndrome in all age groups, but the increase in the risk decreased with age and did not reach statistical significance in the two age groups above 59 years old. Hypothyroidism was not a significant independent risk factor for carpal tunnel syndrome in women between 50 and 64 years of age. The Cochran–Armitage trend test showed a significant trend ($p < 0.001$) in the increases of risks for carpal tunnel syndrome associated with HRT with increases in age.

Discussion

Prevalence of carpal tunnel syndrome

The prevalence of carpal tunnel syndrome in the general population varies substantially across studies, depending on factors including the diagnostic tool, survey method, population, etc. For example, in a study on 2,466 subjects in southern Sweden, the prevalence of clinically confirmed patients of carpal tunnel syndrome was 3.8%, electrophysiologically confirmed patients was 4.9%, and both clinically and electrophysiologically confirmed patients was 2.7%.[19] The 1988 National Health Interview Survey in the U.S. found that the prevalence of self-reported cases of

carpal tunnel syndrome was 1.55%.[20] A study using various methods on 715 subjects in the Netherlands found that the prevalence was 5.8% in women and 0.6% in men.[21]

In this study, we identified patients with a diagnosis of carpal tunnel syndrome for at least three ambulatory visits as confirmed cases. Of the 118,309 women ≥ 45 years old, 5,156 such patients were identified, yielding an estimated prevalence of 4.34%, which is close to the reported prevalence of clinically confirmed patients of carpal tunnel syndrome, 3.8%, of a study in southern Sweden.

Possible pathogenesis of carpal tunnel syndrome associated with HRT

While most cases of carpal tunnel syndrome are idiopathic, the pathogenesis of such cases is thought to be related to the decreased size of the carpal canal (the container) or the increased volume of the contents within the canal (contents).[22-24] For example, joint abnormalities caused by inflammatory arthritis and abnormalities of the shape or position of the bones caused by fractures are both abnormalities of the container that may lead to carpal tunnel syndrome. Metabolic tenosynovitis caused by diabetes, abnormalities of fluid distribution caused by pregnancy or hypothyroidism, and hematoma caused by trauma are examples of abnormalities of content that may lead to carpal tunnel syndrome.[23]

We found that HRT was an independent risk factor for carpal tunnel syndrome, which was observed in all women ≥ 45 years old. In carpal tunnel syndrome patients, the most common histological finding is non-inflammatory fibrosis of the subsynovial connective tissue. [25, 26] Hormonal fluctuations and fluid accumulation are generally believed to be the pathogenesis of the development of carpal tunnel syndrome symptoms in pregnant women.[27] In postmenopausal

women, some studies demonstrated that fluctuation of the estrogen level was associated with idiopathic carpal tunnel syndrome, although the pathogenesis remains unclear.[8]

Estrogens have some anti-inflammatory properties, and increased levels of some inflammatory cytokines such as IL-1, IL-6, and TNF-alpha are noted after menopause.[28] Therefore, decreases in the estrogen level, as in menopausal women who require HRT, may lead to high levels of cytokines, which may in turn cause cellular proliferation, angiogenesis, increased capillary permeability, edematous changes and then fibrosis.[29] When these changes occur in the carpal tunnel, they might contribute to the development of carpal tunnel syndrome.

It was also postulated that the stimulations of tenosynovial tissue may cause carpal tunnel syndrome. Receptors of estrogen (ER) and progesterone (PR) have been found in the transverse carpal ligament and flexor tenosynovium.[30] A study found an increase of the expressions of ER in tenosynovial tissue histologically and immunohistochemically in patients with carpal tunnel syndrome.[31] HRT might up-regulate ER in the transverse carpal ligament and flexor tenosynovium and thus increase fibroblasts and synovial lining cells in the tenosynovial tissue, which increases the risk of carpal tunnel syndrome. A study found prenatal and post-natal sex-hormones played some roles in carpal tunnel syndrome development in the context of ER activation and the pattern of fat distribution,[32] which supports the argument of an association between HRT and carpal tunnel syndrome. However, the pathogenesis of the association remains unclear and might be different from that of idiopathic carpal tunnel syndrome in postmenopausal women.

Other potential risk factors for carpal tunnel syndrome

Diabetes mellitus is one of the most common risk factors for carpal tunnel syndrome. A recent

study proposed that the ischemic damage and neoangiogenesis in diabetes patients contribute to the occurrence of carpal tunnel syndrome. The increased VEGF expression and neovascularisation within the subsynovial connective tissue are also believed to be contributing factors, as in diabetic nephropathy and retinopathy.[33] In multivariate analyses, we found that diabetes was associated with an increased risk of carpal tunnel syndrome. When we divided the participants into five age groups, the ORs were similar across all age groups (fluctuating between 1.18 and 1.36), although the OR did not reach statistical significance in the 60 to 64 year-old group, most likely because of the smaller case number (the smallest of all groups).

Rheumatoid arthritis has also been identified as a risk factor for carpal tunnel syndrome.[6] The pathogenesis of carpal tunnel syndrome in rheumatoid arthritis patients is believed to be a result of increasing intra-carpal-tunnel pressure caused by tenosynovitis around the transverse carpal ligament and flexor tendons.[34] In multivariate analyses, we found that rheumatoid arthritis was associated with an increased risk (OR = 1.85, $p < 0.001$). When we divided the participants into five age groups, the ORs were similar across all age groups (fluctuating between 1.67 and 2.25), and all reached statistical significance.

The mechanism of neuropathy in patients with hypothyroidism is unclear. Abnormalities of fluid distribution is a likely etiology carpal tunnel syndrome.[23] The deposition of mucopolysaccharides or mucinous material on the median nerve might also contribute to its occurrence.[35] In multivariate analyses, we found that hypothyroidism was associated with an overall OR of 1.19 ($p = 0.013$). When we divided the participants into five age groups, the OR showed a U shape dose-response relationship with age and reached statistical significance only in the youngest and the oldest groups. This implies that multiple factors are involved.

Gouty tophi can lead to the non-traumatic compression of the median nerve in the carpal tunnel, causing mechanical or neurological symptoms. Carpal tunnel syndrome secondary to gout is uncommon except in the cases with space-occupying lesions caused by tophi.[36] Except for the median nerve, tophi may also involve the flexor tendons inside the carpal tunnel.[37] In multivariate analyses, we found that gout was associated with an increased risk (OR = 1.52, $p < 0.001$). When we divided the participants into five age groups, the ORs were similar across all age groups (fluctuating between 1.33 and 1.91), all reaching statistical significance.

Our findings confirm that obesity is an independent risk factor for carpal tunnel syndrome.[6] It may be due to the increased fat tissue within the carpal tunnel and increased hydrostatic pressure throughout the carpal tunnel.[38] In multivariate analyses, we found that obesity was associated with an increased risk (OR = 1.76, $p < 0.001$). When we divided the participants into five age groups, the OR showed an inversed U shape dose-response relationship with age and did not reach statistical significance in the two oldest groups. This implies that multiple factors are involved, although the smaller case numbers in the two oldest age groups might also contribute to the results.

Strength and limitations

The large population in this study enabled us to obtain stable risk estimates and simultaneously adjust for many potential confounding factors. We were also able to conduct stratified analyses. In addition, the near 100% coverage of the NHIRD provides an unbiased study population, and therefore the results are representative of the whole country. Because we used the claim data from an insurance program with a 500-fold fine on treatment deemed to be unnecessary, both

over-diagnosis of carpal tunnel syndrome and over-use of HRT are unlikely. While the diagnosis coded in the claims may be tentative in some cases, we included cases with at least three claims. On the other hand, the NHI has a nearly 100% coverage and a very low co-pay, less than 20 U.S. Dollars. Therefore, patients are unlikely to be hindered from diagnosis or treatment because of financial consideration, and so misclassification of cases was minimum in our study.

Nonetheless, our study had some limitations. In particular, carpal tunnel syndrome is a common occupational disease, but no data on occupation risk factors such as repetitive hand use are available in the NHIRD. Although we were unable to adjust for occupational factors, we did observe the association in women more than 60 years old, and most women in Taiwan have retired by this age, not to mention that the association was also observed in the oldest age group (≥ 65 years). As in all non-experimental studies, the associations observed in our study are not necessarily causal relationships.

We defined patients who were diagnosed with carpal tunnel syndrome in at least three ambulatory care visits as cases of carpal tunnel syndrome, and this is a common approach applied by studies using data from the NHIRD.[39-41] In Taiwan, the diagnosis of carpal tunnel syndrome made in the first ambulatory visit may be tentative in some cases, and laboratory tests such as nerve conduction study and electromyography are arranged. In such cases, test results are usually available in the second visit. Therefore, when the diagnosis code has been put in the claims for three times, it is safe to say the diagnosis is confirmed. Otherwise, the diagnosis will be changed in the second or third visit. In fact, this is a relatively secure approach, because some of such studies defined CTS on the basis of just two, [42] or even one visit.[43, 44]

Conclusion

We observed an approximately two-fold increase in the prevalence of carpal tunnel syndrome in female HRT recipient ≥ 45 year old. In addition, we observed the increase in all age groups and found that it was independent of most risk factors that have been recognized, including diabetes, rheumatoid arthritis, hypothyroidism, gout, and obesity. While these factors were also found to be associated with carpal tunnel syndrome in our study, we found that hypothyroidism and obesity had different effects on different age groups, which should be a novel finding. Further studies are needed to identify the underlying mechanism, so that this side effect of HRT can be minimised.

Acknowledgments

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Contributors

All authors contributed to the study design (H-CT, Y-YC, and H-RG). H-RG led all aspects of the study. H-CT was responsible for the first draft of the manuscript. H-CT and Y-YC conducted the analysis. All authors (H-CT, Y-YC, and H-RG) participated in critical revisions of the manuscript, read and approved the final manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

This study has been reviewed and approved by the Institutional Review Boards of the Ditmanson Medical Foundation Chia-Yi Christian Hospital (approval No. 104068).

Data availability statement

All the data used in this study are available from the Taiwanese government after approval of the application.

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Figure legends

Figure 1. Flow chart of the study of the association between hormone replacement therapy (HRT) and carpal tunnel syndrome (CTS)

Table 1. The relationship of carpal tunnel syndrome and hormone replacement therapy (HRT) in women in different age groups.

	Carpal Tunnel Syndrome		
Age (year)	**No (N=113774)**	**Yes (N=4535)**	**Odds Ratio (95% CI*)**
45-49			
No HRT	15998 (58.7%)	740 (41.4%)	1.00
HRT	11266 (41.3%)	1046 (58.6%)	2.01 (1.82-2.21)
50-54			
No HRT	9490 (57.0%)	378 (39.3%)	1.00
HRT	7173 (43.1%)	583 (60.7%)	2.04 (1.79-2.33)
55-59			
No HRT	11377 (66.6%)	369 (49.2%)	1.00
HRT	5686 (33.3%)	381 (50.8%)	2.07 (1.78-2.39)
60-64			
No HRT	11462 (76.4%)	306 (60.4%)	1.00
HRT	3536 (23.6%)	201 (39.6%)	2.13 (1.78-2.56)
≥65			
No HRT	33489 (88.6%)	408 (76.8%)	1.00
HRT	4297 (11.4%)	123 (23.2%)	2.35 (1.92-2.88)

*confidence interval

Table 2. Logistic regression analyses of potential risk factors for carpal tunnel syndrome.

	Carpal Tunnel Syndrome		Odds Ratio (95% CI*)	
	No (N=113774)	Yes (N=4535)	Uni-variate	Multi-variate
Age (year)				
45-54	43827 (38.6%)	2747 (60.6%)	1.00	1.00
≥55	69847 (61.4%)	1788 (39.4%)	0.41 (0.39-0.44)	0.45 (0.43-0.48)
Hormone Replacement Therapy				
No	81816 (71.9%)	2201 (48.5%)	1.00	1.00
Yes	31958 (28.1%)	2334 (51.5%)	2.72 (2.56-2.88)	2.04 (1.91-2.17)
Diabetes Mellitus				
No	79117 (71.1%)	3044 (67.1%)	1.00	1.00
Yes	32159 (28.9%)	1491 (32.9%)	1.21 (1.13-1.28)	1.21 (1.13-1.29)
Rheumatoid Arthritis				
No	99946 (89.8%)	3730 (82.3%)	1.00	1.00
Yes	11330 (10.2%)	805 (17.8%)	1.90 (1.76-2.06)	1.85 (1.70-2.00)
Hypothyroidism				
No	107365 (96.5%)	4300 (94.8%)	1.00	1.00
Yes	3911 (3.5%)	235 (5.2%)	1.50 (1.31-1.72)	1.19 (1.04-1.37)
Gout				
No	96481 (86.7%)	3626 (80.0%)	1.00	1.00
Yes	14795 (13.3%)	909 (20.0%)	1.64 (1.52-1.76)	1.52 (1.40-1.64)
Obesity				
No	110342 (99.2%)	4439 (97.9%)	1.00	1.00
Yes	934 (0.8%)	96 (2.1%)	2.56 (2.07-3.16)	1.76 (1.41-2.18)

*CI: confidence interval

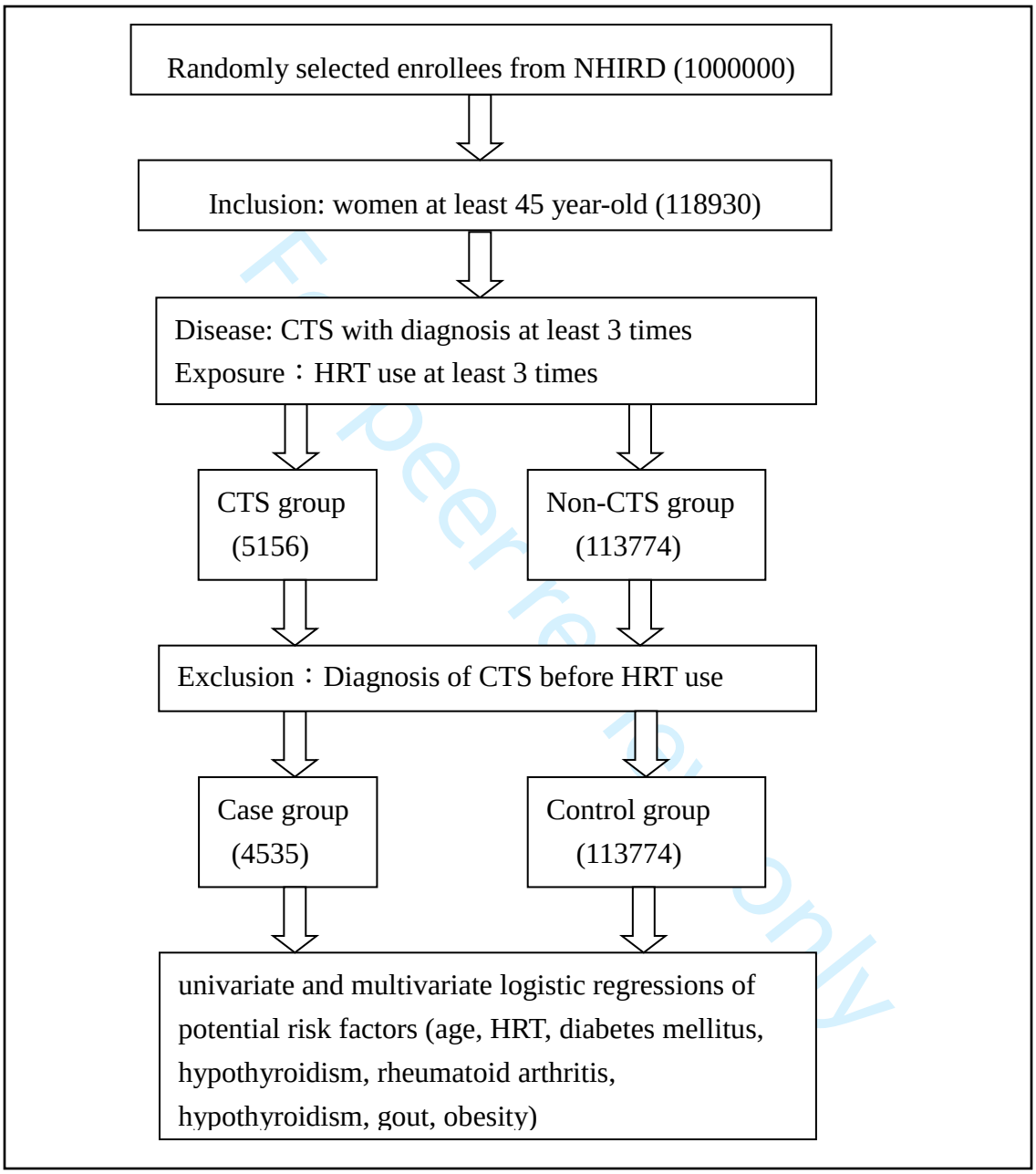
Table 3. Stratified multivariate logistic regression analyses of potential risk factors for carpal tunnel syndrome (CTS) by age.

	Non-CTS	CTS	Odds Ratio (95% CI*)
45 to 49 years old			
HRT	11266 (41.3%)	1046 (58.6%)	1.83 (1.66-2.02)
Diabetes Mellitus	5069 (18.9%)	433 (24.2%)	1.21 (1.08-1.36)
Rheumatoid Arthritis	1621 (6.0%)	221 (12.4%)	1.86 (1.60-2.17)
Hypothyroidism	1005 (3.7%)	95 (5.3%)	1.24 (1.00-1.55)
Gout	2261 (8.4%)	259 (14.5%)	1.52 (1.32-1.76)
Obesity	318 (1.2%)	41 (2.3%)	1.55 (1.10-2.17)
50 to 54 years old			
HRT	7173 (43.1%)	583 (60.7%)	1.84 (1.60-2.10)
Diabetes Mellitus	4446 (27.0%)	313 (32.6%)	1.18 (1.02-1.36)
Rheumatoid Arthritis	1402 (8.5%)	188 (19.6%)	2.25 (1.89-2.67)
Hypothyroidism	740 (4.5%)	51 (5.3%)	0.97 (0.73-1.31)
Gout	2003 (12.2%)	186 (19.4%)	1.40 (1.18-1.67)
Obesity	201 (1.2%)	28 (2.9%)	2.08 (1.38-3.13)
55 to 59 years old			
HRT	5686 (33.3%)	381 (50.8%)	1.88 (1.62-2.19)
Diabetes Mellitus	5457 (32.3%)	296 (39.5%)	1.23 (1.05-1.43)
Rheumatoid Arthritis	1794 (10.6%)	158 (21.1%)	1.93 (1.60-2.32)
Hypothyroidism	2449 (14.5%)	162 (21.6%)	0.96 (0.67-1.36)
Gout	695 (4.1%)	34 (4.5%)	1.33 (1.10-1.60)
Obesity	171 (1.0%)	17 (2.3%)	1.81 (1.08-3.02)
60 to 64 years old			
HRT	3536 (23.6%)	201 (39.6%)	1.90 (1.58-2.29)
Diabetes Mellitus	5293 (35.8%)	218 (43.0%)	1.18 (0.98-1.42)
Rheumatoid Arthritis	1749 (11.8%)	107 (21.1%)	1.67 (1.33-2.08)
Hypothyroidism	522 (3.5%)	26 (5.1%)	1.27 (0.85-1.91)
Gout	2400 (16.2%)	151 (29.8%)	1.91 (1.57-2.34)
Obesity	126 (0.9%)	7 (1.4%)	1.22 (0.56-2.65)
≥ 65 years old			
HRT	4297 (11.4%)	123 (23.2%)	1.93 (1.57-2.37)

Diabetes Mellitus	11894 (32.8%)	231 (43.5%)	1.36 (1.14-1.63)
Rheumatoid Arthritis	4764 (13.1%)	131 (24.7%)	1.82 (1.48-2.23)
Hypothyroidism	949 (2.6%)	29 (5.5%)	1.82 (1.24-2.67)
Gout	5682 (15.7%)	151 (28.4%)	1.78 (1.46-2.16)
Obesity	118 (0.3%)	3 (0.6%)	1.19 (0.37-3.80)

*CI: confidence interval; HRT: [b]hormone replacement therapy

Figure 1. Flow chart of the study of the association between hormone replacement therapy (HRT) and carpal tunnel syndrome (CTS)



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6-7
		(*b*) For matched studies, give matching criteria and the number of controls per case	none
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how matching of cases and controls was addressed	none
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	8-9
		(c) Consider use of a flow diagram	25
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	none
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.