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Carpal Tunnel Syndrome: A Nested Case-Control Study of Risk Factors in Women

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Risk factors for the development of carpal tunnel syndrome in women were studied by means of a nested case-control analysis of a prospective cohort study of the health effects of oral contraception in British women. A total of 1,264 women who had a diagnosis of carpal tunnel syndrome reported by their general practitioner between 1968 and 1993 were compared with 1,264 age-matched control women who did not have this diagnosis. The syndrome was associated in older women with some hormonal factors, notably past use of oral contraception (adjusted odds ratio in women aged 40 years and over = 1.38, 95 percent confidence interval: 1.08, 1.76) and more generally with obesity (adjusted odds ratio = 1.68, 95 percent confidence interval: 1.29, 2.18). However, the strongest link was with a previous history of another musculoskeletal complaint for which consultation had been sought (adjusted odds ratio = 1.98, 95 percent confidence interval: 1.61, 2.42). Previous findings of a higher risk in women with diabetes and myxoedema were confirmed, but these contribute only a small proportion of all cases in women. There was no link with psychologic problems or nonmusculoskeletal pain complaints. The previously described increased incidence of carpal tunnel syndrome in women may be partly due to hormonal factors, but is also related to an underlying propensity to musculoskeletal problems and their higher overall frequency in women. *Am J Epidemiol* 2000;151:566–74.

carpal tunnel syndrome; family practice; risk factors

Carpal tunnel syndrome (CTS), a condition resulting from compression of the median nerve at the wrist, is estimated to affect 8 percent of women and 0.6 percent of men (1). The cause of most CTS is not known, but a number of diseases that affect the local architecture of the wrist are associated with it, including rheumatoid arthritis (2) and Colles fracture (3, 4). Individuals with occupations that involve repetitive or forceful hand movements are also at risk of developing the condition (5–7). Those with certain hormonal and metabolic problems, notably thyroid disease (8, 9) and diabetes mellitus (10, 11), have a higher prevalence of CTS. An influence of specific risk factors for females on CTS is suggested by the higher incidence in women compared with men and the observation that incidence in women peaks around menopause (12). Furthermore, uses of combined oral contraceptives (13, 14), bilateral oophorectomy (15, 16), and pregnancy (17–19) have all been reported to be associated with CTS.

So far, the few studies that have assessed risk factors for CTS in women have examined individuals referred to hospitals (14, 20) or women in particular occupational settings (3, 6 ,7). Little is known about risk factors for CTS diagnosed in the community. We have conducted a nested case-control study of CTS diagnosed in general practice, using data collected in a prospective cohort study of the health effects of the oral contraceptive pill (the Royal College of General Practitioners' Oral Contraception Study) (21).

MATERIALS AND METHODS

The Royal College of General Practitioners' Oral Contraception Study began May 1968 as an investigation of the health effects of combined oral contraceptives (COCs) (21). During a 14-month period (1968–1969), 1,400 general practitioners throughout the United Kingdom recruited 23,000 women who were taking COCs and a similar number who had never used these preparations. At regular intervals since recruitment, the general practitioners have supplied, for all women still under observation, information about all illnesses reported to the doctors (either

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Abbreviations: CI, confidence interval; COC, combined oral contraceptive pill; CTS, carpal tunnel syndrome; ICD-8, *International Classification of Diseases*, Eighth Revision; OR, odds ratio.

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by the women themselves or in hospital correspondence) and about pregnancies, surgery, and use of hormonal preparations.

Specific diagnostic criteria were not supplied for any of the illnesses reported by the participating doctors. In the case of CTS, the diagnosis may have been made by the general practitioner without referral to hospital and without supporting evidence from neurophysiologic investigations. Coding and data entry of the practitioners' diagnoses were, however, subject to extensive checking procedures to ensure accuracy and consistency, with clarification sought from the reporting general practitioners when discrepancies arose. All morbidities were coded using the *International Classification of Diseases*, Eighth Revision (ICD-8) (22), and operations were coded using the Code of Surgical Operations and Procedures of the General Register Office (23). Two conditions (premenstrual tension and brachial neuralgia) that did not have specific ICD-8 codes were allocated special study codes.

Nested case-control study

All subjects for the matched nested case-control study were identified by using data that had accumulated in the main oral contraception study database by 1993. The study cases were defined as all "first ever episodes" of CTS in the cohort occurring between 1968 and 1993 (n = 1,264).

Each case was randomly matched with one control from the cohort who was born within 12 months of the case's date of birth, was still under observation in the main oral contraception study at the time of the case's first diagnosis of CTS, and had no history of CTS before this date.

Within each matched set, all characteristics were those that pertained on the date of the case's diagnosis of CTS, except social class and smoking habit, which were collected only at recruitment. All data concerning consultations prior to the onset of CTS relate to the period from 1968 to the date of the case's diagnosis of "first ever" CTS. The characteristics were examined in five groupings:

Risk factor groupings: personal characteristics at recruitment. Smoking (nonsmoker, smoker) and social class of spouse (in six categories using the United Kingdom Registrar General's Occupational Classification).

Risk factor groupings: main effect I, previous consultations related to hormonal function. These were classified as 1) menstrual problems, which embraced a history of primary amenorrhea (ICD-8 code 6260), scanty periods (ICD-8 code 6261), excessive periods (ICD-8 code 6262), painful periods (ICD-8 code 6263), frequent periods (ICD-8 code 6264), irregular periods (ICD-8 code 6265), intermenstrual bleeding (ICD-8 code 6266), and other menstrual problems (ICD-8 code 6269). They were analyzed as a total group (any menstrual disorder: ICD-8 codes 6260–6269), and, if numbers were sufficient, as separate diagnostic groups; 2) premenstrual tension; 3) menopausal problems (ICD-8 code 6270); 4) parity (0, 1, 2, and ≥3); and 5) exogenous hormones: COC use (never, current, former; or never, ever), duration of COC use, and use of hormone replacement therapy (never, ever).

Risk factor groupings: main effect II, previous consultations for musculoskeletal problems. Musculoskeletal problems were rheumatoid arthritis (ICD-8 codes 7120, 7122, and 7123), unspecified osteoarthritis (ICD-8 code 7130), osteoarthritis of the spine (ICD-8 code 7131), unspecified arthritis (ICD-8 code 715), fibrositis (ICD-8 code 7179), neck pain (ICD-8 code 7280), synovitis, bursitis and tenosynovitis (ICD-8 code 731), Dupuytren's contracture (ICD-8 code 7339), limb pain and swelling (ICD-8 codes 7871 and 7872), joint pain and swelling (ICD-8 codes 7873 and 7874), any arm fracture (ICD-8 codes N810–819), and brachial neuralgia. These were analyzed in total (any musculoskeletal disorder) and, when numbers permitted, as separate diagnostic categories.

Risk factor groupings: consultations for factors previously reported as being risks for CTS. These include myxoedema (ICD-8 code 244), diabetes mellitus (ICD-8 code 250), obesity (ICD-8 code 277), nonpsychotic psychiatric illness (ICD-8 codes 300–309), irritable bowel disease (ICD-8 code 5641), and symptoms referable to the gastrointestinal tract (ICD-8 code 785).

Risk factor groupings: confounding, markers of consultation frequency. Nonspecific factors that increase consultation frequency may cause apparent comorbidity because frequent consulters with one problem may be more likely to consult when they have another symptom. We therefore chose two proxy measures of consultation behavior to examine this potential confounding. The first was any recorded history of consultation for respiratory symptoms (ICD-8 codes 4600–5199) as proxy for general consultation behavior. The second, any recorded history of headache (ICD-8 codes 3068 and 7910), was used as a proxy for pain-related consultation behavior.

Statistical analysis

With 1,264 matched sets, the study had 96.0 percent power to detect a 50 percent increase in risk associated with a particular characteristic, given a 5 percent prevalence of the characteristic in the control group (alpha = 0.05).

The 1,264 matched sets were analyzed by conditional logistic regression, using STATA (24). Unadjusted odds

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ratios and their 95 percent confidence intervals were first obtained for the association of each characteristic with CTS. These risk estimates were then included in a multivariate model (along with the two "propensity to consult" markers) if they were significantly elevated or reduced in the crude analysis at the 5 percent level of significance to adjust for potential confounding between variables.

Certain factors, such as menopausal symptoms or current or former use of the oral contraceptive, are strongly linked with age, and, therefore, we stratified the analysis of variables included in the multivariate model by three age groups. There were 505 cases and 511 controls under age 40 years, 488 cases and 475 controls aged 40–49 years, and 271 cases and 278 controls aged 50 and over; all ages were those at the time of the first ever consultation by the case for CTS. Some case-control pairs were in different age bands, and these pairs (n = 73) were excluded from the age-stratified analysis.

RESULTS

General characteristics

The mean age was 41.9 years for both cases and controls. Smoking was not associated with an altered risk of CTS (table 1). There was an overall trend of increasing CTS risk with lower social class (chi-square for trend = 8.66, p = 0.003), with an odds ratio (OR) for CTS of 1.23 (95 percent confidence interval (CI): 1.02, 1.50) associated with semiskilled and unskilled manual grouping that persisted in the multivariate analysis (table 2).

Hormonal influences: exogenous

CTS was associated with past use of oral contraceptives, but not with current use (table 1). The highest crude risk estimate was among women who had previously used this form of contraception for 4 years or less. Overall, this link with COC use disappeared on multivariate analysis (table 2).

Although the number of hormone replacement therapy users in this cohort was small, the therapy was more likely to have been prescribed for CTS cases than for controls (OR = 1.39, 95 percent CI: 0.90, 2.08). Adjustment of former oral contraceptive use for subsequent hormone replacement therapy alone did not alter the risk estimates, however.

Hormonal factors: endogenous

A history of consultation for any menstrual disorder was associated with subsequent consultation for CTS (OR = 1.36, 95 percent CI: 1.11, 1.66) (table 1). This was not explained by oral contraceptive use (adjusted OR = 1.33, 95 percent CI: 1.09, 1.63).

When the different menstrual problems were examined separately, three were associated with significantly elevated odds ratios for subsequent consultation with CTS: amenorrhea, heavy periods, and dysmenorrhea. The strongest association was with dysmenorrhea (OR = 1.52), while the most common menstrual complaint in the study sample was heavy periods, which had a crude association with CTS of 1.38. However, on multivariate analysis (table 2), none of these factors remained significantly associated with CTS.

There was a weak, but statistically significant, overall link between parity and CTS (chi-square for trend = 6.7; p = 0.01), which persisted after adjustment in the multivariate model (table 2). A history of menopausal symptoms was also associated with elevated risk estimates of CTS in the crude analysis (OR = 1.47), as was prior consultation for premenstrual tension (OR = 1.53), but these estimates were reduced in the multivariate model (table 2).

Previous musculoskeletal disorders

A prior history of a consultation for a musculoskeletal problem was generally associated with an increased risk of CTS, with an overall crude OR of 2.38 (95 percent CI: 1.98, 2.87) (table 3). The crude associations with prior consultation for arm fracture, osteoarthritis, osteoarthritis of the spine, fibrositis, neck pain, tennis elbow, and brachial neuralgia were statistically significant (table 4). There were also associations with consultation for less specific musculoskeletal problems (limb pain, joint pain, and arthritis). The numbers of women who had a record of a previous arm fracture or brachial neuralgia were relatively small, however.

In a preliminary multivariate model, the interrelation between these different prior musculoskeletal diagnoses was explored (table 4). Arm fracture, osteoarthritis of the spine, arthritis, fibrositis, tennis elbow, limb pain, and joint pain remained independently and significantly linked with CTS.

In the final multivariate model, arm fracture, osteoarthritis of the spine, tennis elbow, and joint pain were independently and significantly associated with subsequent CTS (table 2). The overall adjusted odds ratio for any musculoskeletal disorder was 1.98 (95 percent CI: 1.61, 2.42).

Previously reported associations

Nonpsychotic psychiatric illness was associated in the crude analysis with an increased likelihood of sub-

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TABLE 1. Crude associations between carpal tunnel syndrome and personal and hormonal factors, measured by odds ratios with 95% confidence intervals, in 1,264 matched case-control pairs of married women in general practice in the United Kingdom followed from 1968 to 1993

	Cases		Controls		OR*	95% CI*
	No.	%	No.	%		
Personal factors						
Smoking						
No†	693	54.8	707	55.9	1.00	
Yes	571	45.2	557	44.1	1.05	0.89, 1.23
Social class						
I & II†	293	23.3	319	25.6	1.00	
III	687	54.7	716	57.5	1.05	0.84, 1.31
IV & V	276	22.0	210	16.9	1.23	1.02, 1.50
Exogenous hormonal factors						
Oral contraceptive use						
Never†	455	37.3	520	42.0	1.00	
Ever	766	62.7	719	58.0	1.21	1.02, 1.44
Former	585	42.9	529	42.7	1.45	1.18, 1.78
Current	181	14.8	190	15.3	0.87	0.74, 1.03
Months of oral contraceptive use						
0†	455	38.5	520	42.9	1.00	
1–48	283	23.9	251	20.7	1.30	0.99, 1.70
49–108	275	23.3	256	21.1	1.14	0.99, 1.31
>108	170	14.4	186	15.3	0.98	0.87, 1.11
Hormone replacement therapy‡	61	4.8	47	3.7	1.39	0.90, 2.08
Endogenous hormonal factors						
Parity						
None†	66	5.2	87	6.9	1.00	
1	163	12.9	185	14.6	1.27	0.58, 2.80
2	492	38.9	495	39.2	1.18	0.93, 1.50
≥3	543	43.0	497	39.3	1.10	0.91, 1.33
Any menstrual disorder‡	332	26.3	271	21.4	1.36	1.11, 1.66
Amenorrhea	138	10.9	103	8.2	1.40	1.07, 1.85
Heavy periods	272	21.5	216	17.1	1.38	1.12, 1.71
Dysmenorrhea	84	6.7	57	4.5	1.52	1.07, 2.16
Polymenorrhea	50	4.0	44	3.5	1.14	0.76, 1.73
Irregular bleeding	107	8.5	83	6.6	1.32	0.98, 1.77
Intermenstrual bleeding	76	6.0	58	4.6	1.38	0.95, 1.99
Premenstrual tension‡	147	11.6	101	8.0	1.53	1.17, 2.00
Menopausal symptoms‡	103	8.2	74	5.9	1.47	1.06, 2.03

* OR, odds ratio; CI, confidence interval.
† Reference category. Numbers do not always add to 1,264 because of missing data.
‡ Reference categories for these patients are women without the disorder.

sequent consultation with CTS (table 3), but this risk disappeared when adjusted for other variables in the multivariate model (table 2).

Table 3 shows the other associations studied. Diabetes and myxoedema were both associated with elevated crude odds for CTS. However, the numbers of subjects were small, the estimates were nonsignificant, and they were not entered into the later model. In the crude analysis, CTS was associated with general gastrointestinal symptoms and with irritable bowel syndrome; this link was not evident after adjustment for confounders in the multivariate model. Numbers were small for renal failure and fluid retention, but crude estimates were consistent with an effect. By contrast, there was no link with hypertension. Finally, consultation about obesity had occurred in 19 percent of the cases and 11 percent of the controls; after adjustment for confounding, a link with future CTS persisted (adjusted OR = 1.68, 95 percent CI: 1.29, 2.18).

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TABLE 2. Multivariate analysis of risk factors for carpal tunnel syndrome, measured by odds ratios with 95% confidence intervals, in 1,264 matched case-control pairs of married women in general practice in the United Kingdom followed from 1968 to 1993

	Total (n = 1,264 pairs)		Stratified by age					
			<40 years (n = 491 pairs)*		40–49 years (n = 445 pairs)*		50 years (n = 255 pairs)*	
	OR†	95% CI†	OR	95% CI	OR	95% CI	OR	95% CI
Personal factors								
Parity (0, 1, 2, and ≥3)	1.10	1.00, 1.23	1.15	0.96, 1.38	1.11	0.91, 1.34	1.13	0.90, 1.41
Social class (I & II, III, IV and V)	1.17	1.02, 1.34	1.23	0.97, 1.55	1.34	1.06, 1.70	0.88	0.65, 1.20
Hormonal factors								
Oral contraceptive use								
Former	1.15	0.94, 1.40	0.79	0.54, 1.17	1.37	0.99, 1.92	1.49	0.97, 2.29
Current	1.00	0.76, 1.32	0.91	0.63, 1.31	0.99	0.57, 1.71	0.49	0.07, 3.37
Menstrual disorders								
Amenorrhea	1.22	0.89, 1.65	1.24	0.72, 2.14	1.41	0.86, 2.33	0.73	0.35, 1.53
Heavy periods	1.14	0.90, 1.45	1.02	0.63, 1.66	1.04	0.70, 1.54	1.30	0.81, 2.09
Dysmenorrhea	1.31	0.88, 1.94	1.21	0.56, 2.61	1.72	0.96, 3.10	0.56	0.18, 1.79
Premenstrual tension	1.23	0.91, 1.66	0.97	0.53, 1.79	1.06	0.66, 1.70	1.48	0.77, 2.83
Menopausal symptoms	1.06	0.74, 1.52	1.88	0.16, 22.7	1.89	0.90, 3.96	0.84	0.51, 1.38
Musculoskeletal factors‡								
Arm fracture	2.52	1.14, 5.60	5.63	0.88, 36.1	3.59	0.84, 15.4	1.55	0.44, 5.46
Osteoarthritis of spine	1.92	1.33, 2.78	3.23	1.22, 8 58	1.14	0.64, 2.04	2.88	1.45, 5.74
Arthritis, unspecified	1.43	0.97, 2.10	1.21	0.47, 3.13	1.36	0.66, 2.78	1.90	1.00, 3.61
Fibrosis	1.07	0.84, 1.37	0.80	0.50, 1.29	1.39	0.91, 2.10	0.92	0.55, 1.54
Tennis elbow	1.73	1.34, 2.22	1.67	0.95, 2 96	2.03	1.34, 3.07	1.64	1.01, 2.66
Limb pain	1.28	0.95, 1.71	1.52	0.83, 2.79	1.07	0.64, 1.78	1.31	0.77, 2.25
Joint pain	1.54	1.14, 2.08	1.52	0.77, 2.99	1.56	0.92, 2.65	1.37	0.79, 2.39
Other factors								
Nonpsychotic psychiatric illness	1.06	0.88, 1.29	1.04	0.76, 1.43	1.04	0.74, 1.45	1.22	0.79, 1.88
Obesity	1.68	1.29, 2.18	1.42	0.90, 2.25	2.21	1.38, 3.56	1.72	1.00, 2.98
Gastrointestinal symptoms	0.97	0.75, 1.26	1.66	1.01, 2.72	0.82	0.53, 1.25	0.64	0.37, 1.09
Headache	0.95	0.75, 1.19	1.38	0.91, 2.10	0.89	0.61, 1.30	0.73	0.42, 1.25
Respiratory complaints	1.45	1.16, 1.80	1.79	1.27, 2.53	1.27	0.86, 1.89	1.65	0.94, 2.89

* The sum of the age-stratified pairs will be less than 1,264 because of 73 pairs with ages in different bands.

† OR, odds ratio; CI, confidence interval.

‡ Separately, "any musculoskeletal disorder" was entered into a second multivariate model, and the following odds ratios were recorded: 1.98 (95% CI 1.61, 2.42) for all age pairs; 1.97 (95% CI: 1.39, 2.77) for pairs aged <40 years; 2.03 (95% CI: 1.47, 2.81) for pairs aged 40–49 years; and 2.09 (95% CI: 1.23, 3.53) for pairs aged ≥50 years.

Potential confounding by consultation behavior

The multivariate model in table 2 incorporated the two proxy measures of consultation frequency. The effect estimates shown for other variables in the model are thus assumed independent of "consultation proneness." Consultation for headache showed no link with future consultation for CTS, whereas there was an association between respiratory consultations and CTS.

Age-specific effects

In the multivariate model in table 2, we show the associations with CTS stratified by age at onset. There were no statistical interactions with age, but there were some age-specific associations, although these must be interpreted with some caution, given the number of cells in the table as a whole. The pooled effect of former COC use among all women aged 40 years and above in the study population was 1.38 (95 percent CI: 1.08, 1.76). Some menstrual disorder risks are age related (dysmenorrhea and amenorrhea as potential risks for CTS presenting before 50 years, and heavy periods for CTS onset at age 50 and above). Menopausal symptoms seem to influence onset only under age 50 years, suggesting early menopause as the risk, but these estimates are based on small numbers and have wide confidence intervals. There were no obvious contrasting patterns of age-related risk in relation to prior musculoskeletal diagnoses or other factors.

DISCUSSION

Using a large general practice-based cohort study, we have investigated a number of risk factors in women diagnosed with CTS. There was a significant trend of increasing risk of CTS with lower social class (measured by husband's occupation), but not with cigarette smoking. Oral contraceptive use overall did not confer an increased risk of subsequent CTS, nor was consultation for a range of gynecologic problems significantly related to CTS overall. Previous consulta-

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TABLE 3. Crude associations between musculoskeletal and other previous consulting conditions with carpal tunnel syndrome, measured by odds ratios with 95% confidence intervals, in 1,264 matched *case-control pairs of married women in general practice in the United Kingdom from 1968 to 1993

	Cases		Controls		OR†	95% CI†
	No.	%	No.	%		
Any musculoskeletal disorder	693	54.8	475	37.6	2.38	1.98, 2.87
Endocrine/metabolic disorders						
Diabetes	11	0.9	6	0.5	1.83	0.68, 4.98
Myxoedema	17	1.3	9	0.7	2.00	0.86, 4.67
Renal failure	12	1.0	8	0.6	1.50	0.61, 3.67
Fluid retention	57	4.5	45	3.6	1.28	0.86, 1.91
Hypertension	121	9.6	110	8.7	1.12	0.84, 1.49
Psychiatric illness						
Psychotic	65	5.1	48	3.8	1.36	0.93, 1.98
Nonpsychotic	696	55.1	620	49.1	1.31	1.11, 1.54
Weight						
Gain	91	7.2	68	5.4	1.37	0.99, 1.89
Obesity	237	18.8	134	10.6	2.01	1.58, 2.55
Gastrointestinal symptoms						
Any symptoms	220	17.4	179	14.2	1.29	1.04, 1.60
Irritable bowel syndrome	39	3.1	28	2.2	1.42	0.86, 2.35
Consultation behavior						
Headache	966	76.4	1,033	81.7	0.71	0.58, 0.87
Respiratory complaints	952	75.3	845	66.9	1.68	1.38, 2.04

* Reference category for all variables is women without the disorder.
† OR, odds ratio; CI, confidence interval.

TABLE 4. Associations between individual musculoskeletal group and carpal tunnel syndrome, crude odd ratios, and after adjustment for other musculoskeletal problems, in 1,264 matched case-control pairs of married women in general practice in the United Kingdom followed from 1968 to 1993*

	Cases		Controls		OR†	95% CI†	Adjusted OR‡	Adjusted 95% CI‡
	No.	%	No.	%				
Any musculoskeletal disorder	693	54.8	475	37.6	2.38	1.98, 2.87		
Arm fracture	27	2.1	10	0.8	2.70	1.31, 5.58	2.50	1.15, 5.45
Rheumatoid arthritis	21	1.7	14	1.1	1.50	0.76, 2.95	1.31	0.63, 2.70
Osteoarthritis, unspecified	78	6.2	51	4.0	1.60	1.10, 2.32	1.23	0.82, 1.85
Osteoarthritis of spine	139	11.0	69	5.5	2.49	1.76, 3.44	2.16	1.52, 3.06
Arthritis, unspecified	88	7.0	51	4.0	1.77	1.24, 2.52	1.49	1.02, 2.17
Fibrosis	245	19.4	184	14.6	1.44	1.16, 1.79	1.27	1.01, 1.59
Neck pain	55	4.4	34	2.7	1.68	1.08, 2.62	1.15	0.71, 1.86
Tennis elbow	258	20.4	147	11.6	2.00	1.59, 2.51	1.88	1.48, 2.39
Brachial neuralgia	36	2.9	19	1.5	1.89	1.09, 3.30	1.65	0.90, 3.02
Limb pain	190	15.0	127	10.1	1.68	1.30, 2.18	1.39	1.05, 1.83
Joint pain	178	14.1	99	7.8	2.03	1.54, 2.66	1.61	1.20, 2.16

* Reference category for all variables is women without the disorder.
† OR, odds ratio; CI, confidence interval.
‡ Adjusted OR with 95% CI gives the multivariate odds ratios when controlling each of the specific musculoskeletal variables for the others.

tion for obesity was linked to CTS, but the strongest risk in this group of women was prior consultation for another musculoskeletal disorder. This could not be explained by a generalized propensity to consult a doctor with symptoms, painful or otherwise. Nonpsychotic mental illness was not linked to CTS.

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A major advantage of the study was the availability of comprehensive consultation information on a large group of women. The prospective collection of the data avoided recall bias. There were several important limitations, however. All diagnoses made in the study, including that of CTS, were those reported by the general practitioners. Many women will have been diagnosed on the basis of symptoms alone, without neurophysiologic testing. Bias could occur if cases included non-CTS problems that were related to the various risk factors examined here. Distortion might also occur if the general practitioner were more likely to diagnose CTS because of prior knowledge of an earlier condition. However, given the poor understanding of the etiology of CTS, such diagnostic suspicion bias is unlikely to have contributed to our findings.

Frequent consulters in general practice have more opportunity to report hand and other symptoms, so associations may arise as a result of consultation behavior alone. However, adjustment for two proxy measures of consultation behavior (respiratory symptoms and headache) failed to explain many of the observed associations. Since consultation for respiratory symptoms was significantly more common in women who later presented with CTS, we conclude that there is an element of "consultation propensity" in the absolute incidence of CTS in this cohort. However, inclusion of respiratory consultation in the multivariate model means that risk estimates for other diagnoses were adjusted to account for this propensity.

Other evidence that diagnosed CTS consulters in this cohort do reflect the true incidence of CTS in women is found from comparison with other studies. The incidence density in our cohort was 2.3 per 1,000 woman-years of observation. This compares with 1.5 per 1,000 woman-years for cases referred to hospitals from a defined population in a Mayo Clinic report (12), 1.0 per 1,000 woman-years for hospital referrals from a defined population cohort in Britain (14), and 2.0 per 1,000 person-years in a register-based incidence study of worker cohorts in United States (3). Since primary care case ascertainment would be expected to exceed hospital referrals and numbers based on occupation-based registers, these figures are compatible with each other.

Current use of oral contraceptives was not associated with CTS at any age. This contrasts with other studies that have found a positive association between use of COC and CTS (13, 14). Sabour and Fadel (13) found that current use of COCs increased the risk, but that within 1 month of stopping the Pill, the symptoms of CTS had disappeared. Vessey et al. (14) found that the longer a woman used COCs, the greater her chances were of developing CTS severe enough for hospital referral (14). The hypothesis is that COCs exert their effects through fluid retention, causing pressure on the median nerve. It is difficult to reconcile such a mechanism with our observation that former users of COCs are those with the elevated risk of CTS and that the risk declines with duration of use. One possible explanation is that women who develop pain or neurologic symptoms in the upper limb while using oral contraceptives may have been advised by the family doctor to stop using them and that the actual CTS diagnosis was made at a later date, by which time the woman was a "former" user. If this happened soon after a woman started the oral contraceptive pill, it would lead to an apparent link of CTS with short duration former use, while continuing users would be "healthy survivors." However, our age-stratified analysis directly contradicts this explanation. Cases would be expected to cluster among younger women who have recently been on the oral contraceptive; in fact, there was no elevated risk in former users below age 40 years. The risk was concentrated among former users who subsequently developed CTS for the first time over age 40 years, including those whose onset was beyond age 50 years. Diagnostic bias is unlikely to account for this relation in former users, many of whom would have stopped using COCs years earlier. It is, however, difficult to explain why there should be such a delayed effect of pill use. The overall conclusion must be that the oral contraceptive pill does not contribute substantially to CTS risk in women.

CTS is common in pregnancy (17–19), but normally resolves toward the end of pregnancy or postpartum (17, 25). In our study, most women had completed their families, so we were unable to examine the effect of pregnancy directly. However, the association between parity and CTS would be consistent with long-term hormonal effects of pregnancy or with mechanisms associated with child rearing. We examined the association between CTS and gynecologic problems, especially menstrual abnormalities, as these may further reflect the influence of endogenous hormones. After adjustment for potential confounders, there was no clear elevation in risk in association with these. The exception was premenstrual tension, for which there was some suggestion of a link with later onset in older women in the cohort. An earlier study found a relation between CTS and menstrual irregularity (14), as did ours prior to adjustment for confounding. Fluid retention is the suggested mechanism, but our data suggest that the relation may be weaker than previously thought and may be partly explained by confounding by other factors.

Data on anthropomorphic features that have been found to be important in other studies (26–28) were

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not available. However, more than 10 percent of the cohort had consulted about obesity, and such consultation was a predictor of subsequent CTS, which persisted after adjustment and across age groups. Mechanical or metabolic effects of obesity may be responsible.

The clearest finding, unaffected by age and persisting after adjustment for confounding, was that other musculoskeletal problems were associated with the subsequent onset of CTS. Several other studies have found that osteoarthritis is more common in individuals with CTS (14, 29, 30). There is a growing body of literature on the comorbidity of musculoskeletal problems, and the clustering of such syndromes is one of their most consistent features. One explanation has been a common link with psychologic factors, a link that may be stronger in women (31), but our study has found no evidence for an association between mental illness and CTS. Another possible explanation is the presence of a mechanical problem in the neck that contributes to the etiology of multiple disorders in the upper limbs (32). The strength of the associations observed for tennis elbow and spinal osteoarthritis support this idea. However, the evidence is inconclusive because neck pain was a relatively infrequent reason for consultation in this cohort and "cervical spondylosis" was recorded under "spinal osteoarthritis." Alternatively, the musculoskeletal problem may modify the woman's use of her hand and arm, resulting in the onset of CTS. Local mechanical factors would also explain the link with arm fracture.

There is contradictory evidence that systemic inflammatory conditions are related to the development of CTS (32–34). There were too few women in our study with rheumatoid arthritis, for example, to examine this possibility. CTS has often been reported to occur secondarily to diabetes (11, 20, 33) as one of its neuropathic complications, and myxoedema is also said to be commonly associated with CTS (8, 10), possibly because of swelling of the contents of the carpal canal causing median nerve compression (17). Although based on small numbers, our community-based findings confirm these reports, but indicate that population-attributable risk is low.

Two studies have described CTS in patients receiving lithium for manic depressive illness (35, 36). In our study, there was no evidence of a relation with psychotic illness. Studies on the effects of smoking have been contradictory. Our findings support one earlier study that reported no risk (10), but contradict two that suggested an elevated risk (14, 37). We were also unable to confirm earlier reports of positive associations between gastrointestinal symptoms and irritable bowel syndrome and CTS (14).

In conclusion, hormonal factors, both endogenous and exogenous, may account for some of the differences in the frequency of CTS between men and women, including past use of the Pill in older women and obesity. However, major issues that require further research are the nature of the link between CTS and other musculoskeletal syndromes, the unique aspects of this link in women, and how this link relates to the generally higher frequencies of most nonsystemic rheumatologic syndromes in women.

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