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Medical history and the onset of complex regional pain syndrome (CRPS)

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Abstract

Knowledge concerning the medical history prior to the onset of complex regional pain syndrome (CRPS) might provide insight into its risk factors and potential underlying disease mechanisms. To evaluate prior to CRPS medical conditions, a case–control study was conducted in the Integrated Primary Care Information (IPCI) project, a general practice (GP) database in the Netherlands. CRPS patients were identified from the records and validated through examination by the investigator (IASP criteria) or through specialist confirmation. Cases were matched to controls on age, gender and injury type. All diagnoses prior to the index date were assessed by manual review of the medical records. Some pre-specified medical conditions were studied for their association with CRPS, whereas all other diagnoses, grouped by pathogenesis, were tested in a hypothesis-generating approach. Of the identified 259 CRPS patients, 186 cases (697 controls) were included, based on validation by the investigator during a visit (102 of 134 visited patients) or on specialist confirmation (84 of 125 unvisited patients). A medical history of migraine (OR: 2.43, 95% CI: 1.18–5.02) and osteoporosis (OR: 2.44, 95% CI: 1.17–5.14) was associated with CRPS. In a recent history (1-year before CRPS), cases had more menstrual cycle-related problems (OR: 2.60, 95% CI: 1.16–5.83) and neuropathies (OR: 5.7; 95% CI: 1.8–18.7). In a sensitivity analysis, including only visited cases, asthma (OR: 3.0; 95% CI: 1.3–6.9) and CRPS were related. Psychological factors were not associated with CRPS onset. Because of the hypothesis-generating character of this study, the findings should be confirmed by other studies.

Keywords: Complex regional pain syndrome; Epidemiology; Medical history; Comorbidity; Risk factor; Pathogenesis

1. Introduction

The complex regional pain syndrome (CRPS) can be a painful disorder affecting one or more extremities. It usually occurs following a physical injury, for example, a fracture or surgery, but spontaneous onset may occur as well [47]. The diagnosis is based on its clinical presentation, whereby the diagnostic criteria as developed by the International Association for the Study of Pain (IASP) are the most widely accepted [40]. Apart from pain and sensory disturbances, these criteria demand the presence of edema, skin blood flow abnormalities or abnormal sudomotor activity. Functionality of the affected limb is often impaired [17,47], and ongoing pain and dysfunction can leave patients severely disabled [15]. The peak incidence of CRPS lies between 50 and 70 years of age, and women are affected more frequently than men [11,36].

In the past decade, insights into the mechanisms underlying CRPS have gradually increased. The role of inflammation is endorsed by the demonstration of

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inflammatory mediators in serum [38], blister fluid [19], and spinal fluid [2] from CRPS patients. Additionally, abnormal vasoconstriction patterns, either sympathetic nerve system driven [29] or due to local factors [37], can result in blood flow disturbances. These peripheral disease mechanisms may precede and sustain the sensitization [6] and altered sensory processing at spinal and supraspinal levels [24,32], which eventually lead to pain of neuropathic nature. Sympathetically maintained pain, probably caused by sympathetic-afferent coupling [21], occurs in a subset of patients [40].

To date, it is unknown whether other diseases that also involve inflammation, impaired (micro-) circulation, or neuropathic pain lead to an increased risk of CRPS. However, studies on the potential co-occurrence of these disorders with CRPS can be informative, since they might give clues to the potentially shared pathogenic or etiologic factors, as well as reveal risk factors for CRPS. The aim of this investigation was to identify whether and which medical conditions or categories of medical conditions are associated with the occurrence of CRPS.

2. Patients and methods

A retrospective case–control design was used to compare the disease history prior to the onset of CRPS between patients and controls from the general population. The study was nested in the Integrated Primary Care Information (IPCI) database, which is a general practice (GP) database of longitudinal electronic medical records of around 800,000 patients [45,48]. The project was initiated in 1992 and new practices have started to contribute data ever since. The IPCI population is considered representative of the general population in the Netherlands regarding age and gender distribution. The Dutch Health Care System requires all persons to be registered with one GP (even if they are healthy), who acts as a gatekeeper for further medical care and who receives and files all health care information. Therefore, the electronic records contain virtually complete medical information concerning each patient [39]. To optimize completeness of the data, GPs participating in the IPCI project do not keep additional paper records (except for specialist and discharge letters). This study has been approved by the Scientific and Ethical Advisory Group of the Project and by the Medical Ethical Board of the Erasmus Medical Center (protocol number 2006-099).

2.1. Source population

The dynamic source population comprised all persons of all ages with at least 1 year of valid history in the IPCI database during the study period (January 1996–June 2005). Observation time in the database started on the date that one year of valid history was available and ended upon transferring out of the practice, the date of last data supply by the GP, death, diagnosis of CRPS or at the end of the study period, whichever came first. Since additional data collection was required for the validation of the CRPS diagnosis, the source population was restricted to all practices that were still active in the IPCI database in 2006 and were able to provide additional information.

2.2. Cases

Details on the case identification procedure in the IPCI database have been described in our incidence study on CRPS in the Netherlands [11]. Briefly, potential incident CRPS cases were identified using a search algorithm including synonyms and abbreviations for CRPS in codes and narratives. Subsequently, GPs were asked to reconfirm or reject the CRPS diagnosis in a short questionnaire. Information regarding the precipitating injury for the CRPS was extracted from the GP journals and from specialist letters when provided by the GP. Injury categories included fracture, soft tissue injury, surgery, tendon injury and various other types of injuries (including nerve injury).

For this specific study, all the previously identified and GP reconfirmed cases were contacted to ask them to participate in a nationwide study on CRPS. Patients who provided written informed consent were visited by the primary investigator of this study (M.M.), a physician with clinical experience in diagnosing CRPS. A physical examination of the affected and contralateral extremity was performed and self-administered questionnaires were used to gain information on present and past symptoms of CRPS. Patients were included into the main analyses of this study if during the visit the CRPS diagnosis was verified by the investigator using the IASP criteria [40]. Additionally, cases were included who could not be visited, but of whom the CRPS diagnosis had been confirmed by a medical specialist (in a letter to the GP). The index date was chosen as the date of the precipitating injury, or the date of first symptoms in cases with spontaneous CRPS. Since some previous studies have revealed different results in 'warm' and 'cold' type CRPS patients [31,43,46], suggesting these to be distinct subtypes, cases were divided into subgroups based on their own reports of predominant temperature characteristics (visited patients only).

2.3. Controls

First, for each CRPS case all other persons in the IPCI database with similar age (year of birth) and gender were selected as potential controls. Subsequently, from these, up to four controls per case were chosen who had experienced an injury *identical* to the injury

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that precipitated the CRPS in the case (within a 2-year band of calendar time). This meant that cases with CRPS after a fracture were matched to up to four controls with a fracture, cases with a surgery to controls with a surgery, cases with a nerve injury to controls with a nerve injury, etc. Similar to cases, the index date in controls was defined as the date of the injury. When CRPS had occurred in a case without precipitating injury, controls were not required to have an injury either, and the index date was chosen as the date of first symptoms in the case.

2.4. Medical history

The medical history until the index date was extracted from the electronic medical records during the observation time in the database. While being blinded to the case or control status of the patient, the entire medical record was evaluated, and all GP contacts were classified into episodes of medical problems.

The association between CRPS and medical conditions prior to CRPS onset was studied in three different ways. First, in a hypothesis-generating approach, all medical conditions were categorized based on pathogenesis, and each category was examined for its association with CRPS. The chosen pathogenic categories were mutually exclusive and included the following (see also Supplemental appendix 1): anatomic, trauma-induced, degenerative, hormonal, metabolic, neoplasm, infections, inflammatory, psychological, no disease and miscellaneous. Sometimes, a patient had contacted the GP for complaints or symptoms for which no explanatory cause had been provided. These episodes were categorized as 'unexplained complaints' (including subjective complaints such as nausea) or 'unexplained symptoms' (including objective symptoms such as vomiting). The main pathogenic categories were divided further into mutually exclusive subcategories (see also Supplemental appendix 1). Initiating injuries for CRPS (fracture, sprain, nerve injury, etc.) were matching factors and were excluded from this categorization. The assignment of the medical conditions to a specific disease category was performed independently by two physicians (M.M. and J.S.H.A.K.), and kappa statistics were calculated to assess interrater agreement.

Second, and apart from our hypothesis-generating approach, we tested a priori hypotheses about associations between CRPS and a few medical conditions that had occasionally been suggested to be associated with CRPS (in one or more previously published studies). These conditions included headaches [42], osteoporosis [22], psychological factors [4,9] and fibromyalgia [27].

Third, we explored the association between CRPS and groups of medical conditions that might hypothetically be related to CRPS, based on similarities in the assumed underlying disease mechanisms. These groups of medical conditions involved hypersensitivity/exaggerated inflammation-related disorders (asthma, autoimmune disorders, allergies), disorders caused by impaired circulation (cardiovascular diseases, Raynaud's syndrome, chilblains, etc.), and preexisting disorders that were marked by sensory disturbances (neuropathies).

2.5. Data analysis

Standard comparative statistics were used to compare frequencies (Chi-square test) or means (Student's *t*-test and Mann–Whitney-*U* test). Associations between prior to CRPS medical history and CRPS were investigated by conditional logistic regression, adjusted for observation time in the database. Medical history was studied in two exposure windows: (1) the complete database history of patients and (2) the 1-year before the index date. Subgroup analyses were performed for 'warm' and 'cold' type CRPS. Sensitivity analyses were performed to inspect misclassification of outcome (CRPS) and determinants (diagnoses prior to CRPS). Misclassification of CRPS was limited in sensitivity analyses including only cases that could be visited and verified by the investigator (IASP criteria). Misclassification of diagnoses prior to CRPS was inspected by considering a diagnosis valid only when specific treatment was given (for example, inhalator medication for asthma and antimigraine drugs for migraine). Finally, in order to evaluate presence of Berkson's bias (patients who visit the physician more often may also be diagnosed with diseases earlier), we adjusted for the number of GP contacts. SPSS 12.0 was used for all statistical tests. Significance was established at $p < 0.05$.

3. Results

In the source population, comprising 204,281 persons, 259 CRPS patients were identified and reconfirmed by the GP. Some of these cases were untraceable for further contact due to retirement of the GP or software changes at the practice ($n = 25$ patients), patients having left the practice ($n = 16$) or death of patients ($n = 2$). In total, 216 (83.4%) cases could be contacted for study participation. Of these, 134 (62.0%) provided informed consent and completed study assessments. No significant differences in age, gender distribution and disease prevalences were observed between participants and non-participants.

During the study visit, eight (6.0%) cases turned out to be prevalent (the patient already had CRPS at the start of observation time in the database) and were therefore excluded from the final study population. Hundred-and-two (82.3%) of the remaining 126 incident CRPS cases had fulfilled the IASP criteria according to the investigator. Reasons for not fulfilling the IASP cri-

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teria were the presence of a possible alternative diagnosis ($n = 18$), the absence of pain ($n = 2$), and the absence of vasomotor or sudomotor disturbances ($n = 4$). Verification of the CRPS diagnosis using the additional information obtained during visits yielded a false positive rate of 19% for all patients who were initially reconfirmed by the GP and 13% for the patients with an additional medical specialist diagnosis.

A total of 186 CRPS cases were finally included in the main analyses (102 cases validated during a visit + 84 unvisited cases with a specialist confirmed diagnosis). A total of 697 controls matched to a case on age, gender and type of injury were selected from the source population in the database. The mean age at CRPS onset in the study population was 51 years and 77% was female. A fracture was the most common precipitating injury in 91 (49%) of the cases, while for 15 (8%) no precipitating event could be extracted from the records (similar percentages for the matched controls). Other initiating events included soft tissue injury (20%), surgeries (11%), tendon injuries (6%), and various others (6%). The summed observation time until the index date was 529 years for cases (mean: 2.8; range: 0.9–8) and 1994 years for controls (mean: 2.9; range: 1–10). The mean number of GP contacts and medical episodes per year did not differ significantly between cases (contacts: 4.3; episodes: 3.8) and controls (contacts: 3.8; episodes: 3.3; $p = 0.107$ and $p = 0.093$, respectively). However, cases had more medication prescriptions per year than controls (8.9 versus 6.4, respectively; $p = 0.009$).

The interrater agreement for the categorization of disease episodes into pathogenic groups (Supplemental Appendix 1) varied per group, but was very good (kappa > 0.80) for all groups, except for metabolic disorders and miscellaneous disorders, for which the interrater agreement was good (kappa > 0.60).

Results of the analysis that comprised all medical conditions prior to CRPS are demonstrated in Table 1. The odds ratios (OR) are displayed for all main pathogenic categories and for the subgroups only if significant. The association between menstrual cycle-related disorders and CRPS (OR: 2.60, 95% CI: 1.16–5.83) in the year before the index date was the only new observation that was not hypothesized a priori. In the 1-year window also the main groups of trauma-induced conditions (excluding known initiating events for CRPS), infections and the number of unexplained complaints were associated with CRPS, but none of its subgroups were significant.

From the medical conditions that have occasionally been associated with CRPS before, migraine (OR: 2.43, 95% CI: 1.18–5.02) and osteoporosis (OR: 2.44, 95% CI: 1.17–5.14) were significantly associated in our study (Table 2). No association was observed between

Table 1
Associations between CRPS and prior to CRPS medical conditions, categorized by pathogenesis

	Full journal prior to index date				Last year prior to index date			
	Main analysis[a] Cases: $N = 186$; controls: $N = 697$			Sens. analysis[b] Cases: $N = 102$; controls: $N = 381$	Main analysis[*] Cases: $N = 186$; controls: $N = 697$			Sens. analysis[b] Cases: $N = 102$; controls: $N = 381$
	Case	Contr.	OR[c] (95% CI)	OR[c] (95%CI)	Case	Contr.	OR[c] (95%CI)	OR[c] (95%CI)
Anatomic	38	131	1.22 (0.73–1.73)	1.3 (0.8–2.4)	20	3	1.14 (0.65–2.00)	1.6 (0.8–3.3)
Traumatic	35	119	1.19 (0.78–1.83)	1.4 (0.9–2.5)	19	56	1.43 (0.80–2.55)	**2.3 (1.1–4.8)**[*]
Degenerative	36	135	1.00 (0.63–1.62)	1.3 (0.7–2.4)	21	78	1.11 (0.63–1.94)	1.8 (0.9–3.5)
Metabolic	38	134	1.03 (0.66–1.62)	1.0 (0.5–1.9)	28	104	1.02 (0.61–1.72)	1.0 (0.5–1.9)
Hormonal	44	140	1.36 (0.89–2.18)	1.5 (0.9–2.6)	32	93	1.57 (0.99–2.51)	**2.0 (1.1–3.7)**[*]
Sex hormones	42	124	1.51 (0.98–2.32)	1.6 (0.9–2.7)	30	80	**1.77 (1.09–2.90)**[*]	**2.0 (1.1–3.8)**[*]
Menstrual cycle	14	33	1.81 (0.91–3.61)	2.3 (1.0–5.3)	10	17	**2.60 (1.16–5.83)**[*]	**3.0 (1.1–8.7)**[*]
Neoplasm	37	146	0.94 (0.61–1.44)	0.7 (0.4–1.3)	15	67	0.92 (0.51–1.69)	0.9 (0.4–1.9)
Infection	120	431	1.14 (0.78–1.67)	0.7 (0.4–1.3)	84	270	**1.46 (1.03–2.07)**[*]	1.4 (0.9–2.2)
Inflammation	67	258	0.96 (0.67–1.38)	1.4 (0.8–2.2)	46	163	1.19 (0.79–1.77)	1.4 (0.9–2.4)
Hypersensitivity	43	153	1.09 (0.73–1.64)	1.7 (1.0–2.8)	30	99	1.20 (0.70–1.88)	1.8 (1.0–3.1)
Asthma	14	32	1.68 (0.86–3.29)	**3.0 (1.3–6.9)**[*]	11	21	2.05 (0.94–4.50)	**3.0 (1.1–8.0)**[*]
Psychological	64	219	1.17 (0.83–1.67)	0.9 (0.5–1.5)	41	139	1.26 (0.84–1.88)	0.9 (0.5–1.6)
No disease	107	416	0.96 (0.65–1.42)	1.0 (0.6–1.8)	71	287	0.95 (0.66–1.38)	1.0 (0.6–1.5)
Miscellaneous	113	385	1.27 (0.89–1.82)	1.2 (0.8–2.0)	80	278	1.15 (0.82–1.62)	1.1 (0.6–1.7)
Mean number of unexplained complaints	4.45	3.10	1.03 (1.00–1.05)	1.0 (1.0–1.1)	1.47	1.05	**1.11 (1.04–1.21)**[**]	1.0 (1.0–1.2)
Mean number of unexplained symptoms	1.20	0.86	1.08 (1.00–1.16)	1.1 (1.0–1.2)	0.39	0.29	1.18 (0.97–1.43)	1.2 (0.9–1.5)

[*] $p < 0.05$ [**] $p < 0.01$.

[a] Including cases verified during a visit (IASP criteria, $N = 102$) + not visited cases diagnosed by a specialist ($N = 84$).

[b] Including only cases verified during a visit(IASP criteria, $N = 102$).

[c] OR calculated by conditional logistic regression matched for age, gender, type of injury and calendar time (2 year band), corrected for observation time.

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Table 2
Associations between CRPS and previously suggested associated disorders

	Full journal prior to index date				Last year prior to index date			
	Main analysis[a] Cases: $N = 186$; controls: $N = 697$			Sens. analysis[b] Cases: $N = 102$; controls: $N = 381$	Main analysis[a] Cases: $N = 186$; controls: $N = 697$			Sens. analysis[b] Cases: $N = 102$; controls: $N = 381$
	Case	Contr.	OR[c] (95% CI)	OR[c] (95%CI)	Case	Contr.	OR[c] (95%CI)	OR[c] (95%CI)
Headache	25	66	1.54 (0.94–2.53)	1.6 (0.8–3.0)	15	31	**2.02 (1.06–3.87)***	**2.3 (1.1–5.5)***
Migraine	13	22	**2.43 (1.18–5.02)***	**2.6 (1.1–6.5)***	8	12	**2.67 (1.08–6.62)***	2.6 (0.9–8.1)
Other headache	13	48	1.06 (0.56–2.0)	1.0 (0.5–2.4)	8	20	1.63 (0.69–3.81)	2.2 (0.8–5.9)
Osteoporosis	13	24	**2.44 (1.17–5.14)***	**3.9 (1.4–10.8)***	12	21	**2.84 (1.28–6.32)***	**5.6 (1.8–17.1)****
Fibromyalgia	0	3	n.a.	n.a.	0	3	n.a.	n.a.
Psychologic. factors	64	219	1.17 (0.83–1.67)	0.9 (0.5–1.5)	41	139	1.26 (0.84–1.88)	0.9 (0.5–1.6)
Anxiety	27	78	1.31 (0.80–2.13)	0.6 (0.2–1.7)	16	50	1.23 (0.68–2.24)	0.9 (0.4–2.4)
Depression	14	55	0.95 (0.51–1.77)	1.0 (0.5–2.0)	8	42	0.82 (0.37–1.82)	0.2 (0.0–1.5)
Psychosocial prob.	8	33	0.96 (0.43–2.15)	1.2 (0.4–3.4)	7	21	1.31 (0.52–3.30)	1.4 (0.4–4.9)
Stress	32	105	1.25 (0.80–1.97)	0.9 (0.5–1.7)	13	43	1.22 (0.63–2.34)	1.2 (0.5–2.8)

*$p < 0.05$ **$p < 0.01$.
[a] Including cases verified upon visitation (IASP criteria, $N = 102$) + not visited cases diagnosed by a specialist ($N = 84$).
[b] Including only cases verified upon visitation (IASP criteria, $N = 102$).
[c] OR calculated by conditional logistic regression matched for age, gender, type of injury and calendar time (2-year band), corrected for observation time.

psychological factors and CRPS (OR: 1.17, 95% CI: 0.83–1.67). The prevalence of fibromyalgia was too low to perform any meaningful analyses.

From the categories of diseases that were hypothesized to be related with CRPS based on the presumed pathogenic similarities, asthma (OR: 3.0; 95% CI: 1.3–6.9) was associated with CRPS, but only in the sensitivity analysis including visited cases that fulfilled the IASP criteria (Table 3). Preexisting neuropathies (OR: 5.7; 95% CI: 1.8–18.7) were also more frequent in CRPS patients in the 1-year window.

In the subgroup with self-reported 'warm' CRPS (cases = 48, matched controls = 182), all the previously mentioned associations decreased and became non significant. In the subgroup with self-reported 'cold' CRPS (cases = 42, matched controls = 156), associations increased for asthma (OR: 10.6, 95% CI: 2.1–53.5), migraine (OR: 4.6, 95% CI: 1.1–20.5), and for osteoporosis (OR: 5.8, 95% CI: 1.03–4.8), but not so much for menstrual cycle-related disorders (OR: 2.8, 95% CI: 1.0–8.0). However, power in these analyses was minimal due to low numbers.

Table 3
Associations between CRPS and disorders with potentially similar pathogenesis/etiology

	Full journal prior to index date				Last year prior to index date			
	Main analysis[e] Cases: $N = 186$; controls: $N = 697$			Sens. analysis[f] Cases: $N = 102$; controls: $N = 381$	Main analysis[e] Cases: $N = 186$; controls: $N = 697$			Sens. analysis[f] Cases:$N = 102$; controls: $N = 381$
	Case	Contr.	OR[g] (95% CI)	OR[g] (95%CI)	Case	Contr.	OR[g] (95%CI)	OR (95% CI)
Hypersensitivity	43	153	1.09 (0.73–1.64)	1.7 (1.0–2.8)	30	99	1.20 (0.70–1.88)	1.8 (1.0–3.1)
Autoimmunity[a]	7	27	1.04 (0.45–2.41)	1.2 (0.4–3.2)	4	21	0.82 (0.28–2.46)	0.6 (0.2–2.6)
Asthma	14	32	1.68 (0.86–3.29)	**3.0 (1.3–6.9)***	11	21	2.05 (0.94–4.50)	**3.0 (1.1–8.0)***
Allergy	33	126	1.02 (0.65–1.60)	1.6 (0.9–2.8)	23	73	1.31 (0.79–2.21)	1.8 (0.9–3.5)
Preexist. neuropathies[b]	14	37	1.55 (0.81–2.97)	1.9 (0.8–4.2)	7	13	2.01 (0.77–5.29)	**5.7 (1.8–18.7)****
Impaired microcirc.[c]	1	9	0.44 (0.06–3.50)	n.a.	0	3	n.a.	n.a.
Impaired macrocirc.[d]	43	160	0.94 (0.60–1.47)	1.0 (0.6–1.9)	35	137	0.93 (0.58–1.48)	0.7 (0.4–1.4)

*$p < 0.05$ **$p < 0.01$.
[a] Hypersensitivity: see Appendix 1.
[b] Preexisting neuropathies: including nerve entrapment, radicular syndromes, polyneuropathy, phantom pain, neuralgias, neuropathies, paresthesias and pain syndromes.
[c] Impaired microcirculation: including Raynauds syndrome, chilblains and syndrome of Klippel–Trenaunay.
[d] Impaired microcirculation: including cardiovascular disorders and venous insufficiencies.
[e] Including cases verified during a visit (IASP criteria, $N = 102$) + not visited cases diagnosed by a specialist ($N = 84$).
[f] Including only cases verified during a visit (IASP criteria, $N = 102$).
[g] OR calculated by conditional logistic regression matched for age, gender, type of injury and calendar time (2-year band), corrected for observation time.

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Table 4
Sensitivity analyses regarding diseases associated with CRPS

	Main analysis[a] Cases: $N = 186$; controls: $N = 697$			Sens. analysis[b] Cases: $N = 102$; controls: $N = 381$		
	OR[c] (95%CI)	OR[adj] (95%CI)	OR[sens] (95%CI)	OR[c] (95%CI)	OR[adj] (95%CI)	OR[sens] (95%CI)
Full journal						
Migraine	2.4 (1.2–5.0)	2.4 (1.2–5.0)	2.8 (1.2–6.1)	2.6 (1.1–6.5)	2.5 (1.0–6.2)	3.0 (1.2–8.0)
Osteoporosis	2.4 (1.2–5.1)	2.4 (1.1–5.1)	2.5 (1.2–4.1)	3.9 (1.4–10.8)	3.6 (1.3–10.1)	3.9 (1.4–10.8)
Asthma	1.7 (0.9–3.3)	1.8 (0.9–3.5)	1.6 (0.7–3.4)	3.0 (1.3–6.9)	3.1 (1.3–7.3)	2.4 (0.9–6.3)
One-year window						
Menstrual cycle related	2.6 (1.2–5.8)	2.3 (1.0–5.1)	3.5 (1.3–9.2)	3.0 (1.1–8.7)	2.6 (0.9–7.8)	4.0 (1.0–16.2)
Preexisting Neuropathies	1.6 (0.8–3.0)	2.0 (0.8–5.2)	2.9 (0.8–10.6)	5.7 (1.8–18.7)	5.2 (1.6–16.5)	6.4 (1.3–31.8)

Adj: analysis additionally adjusted for the contact frequency at the GP (to correct for potential Berkson's bias).
Sens: analysis in which the determinant (prior to CRPS diagnosis) is considered only when specific treatment is given (to correct for potential misclassification of the determinants).
[a] Including cases verified during a visit (IASP criteria, $N = 102$) + not visited cases diagnosed by a specialist ($N = 84$).
[b] Including only cases verified during a visit (IASP criteria, $N = 102$).
[c] OR calculated by conditional logistic regression matched for age, gender, type of injury and calendar time (2-year band), corrected for observation time.

If specific disorders in the medical history were considered only when treatment was given (for example, treated asthma or migraine), an increasing OR was observed for migraine, menstrual cycle-related disorders, and neuropathies; an unchanged OR for osteoporosis; and a lower OR for asthma (Table 4). Adjustment for the contact frequency at the GP did not affect the OR substantially (Table 4).

4. Discussion

In this study, we systematically investigated the associations between medical history and CRPS occurrence with the purpose to find potential risk factors and leads towards disease mechanisms underlying CRPS. While the study confirmed the previously reported associations between CRPS and osteoporosis and headaches [22,42], the increased prior to CRPS prevalences of asthma and menstrual cycle-related disorders were new findings. In addition, we did not find evidence that psychological factors were related to CRPS. Although a few have reported otherwise [4,9], this is in line with the conclusions of several other studies on psychological factors and CRPS [10,28,44]. Subgroup analyses in 'warm' and 'cold type' CRPS patients revealed that the observed high OR for migraine, osteoporosis, and asthma were mainly attributable to 'cold' type CRPS.

CRPS shares pathogenic mediators with both migraine and asthma. First, neurogenic inflammation, marked by neuropeptides such as calcitonin gene-related peptide (CGRP) and Substance P (SP), is likely to play a role in all three disorders [5,14,16,49]. Asthma patients show hyper-responsiveness to SP [30], while migraine and other headache patients have increased serum levels of both SP and CGRP [1,13]. In CRPS patients, CGRP was systemically elevated and SP release was facilitated [7,23]. Second, in both asthma [8] and migraine [41] mast cells are involved, while tryptase (a product released by mast cells) is elevated in blister fluids [20] of CRPS patients. Finally, another common mediator in asthma and migraine is the nuclear factor kappa B [3,34], a transcription factor involved in inflammation and apoptosis, that was recently hypothesized to be of importance in CRPS based on the results of automated information retrieval from Medline [18].

The strong association between CRPS and osteoporosis and menstrual cycle-related disorders needs further exploration. Interestingly, osteoporosis has been considered as a consequence of CRPS rather than as a risk factor. Although one could argue that osteoporosis predisposes to fractures and thereby to CRPS, this cannot explain the observations of this study, since controls were matched to cases on injury type (for example fracture). Inflammatory mediators in CRPS, such as IL-1 and TNFα, have also been suggested to be increased in post-menopausal osteoporosis, but a definite role was never established [26,50]. Remarkably, bisphosphonates, frequently used in the treatment of osteoporosis, have been proven effective in CRPS treatment [25]. Sex hormones, such as estrogens, are of interest with regard to CRPS, due to its high incidence in women and at postmenopausal age. The observations in this study warrant further investigation regarding hormonal factors in CRPS.

The increased presence of preexisting neuropathies (that included mainly radicular syndromes and polyneuropathies) in the year before CRPS onset suggests that existing sensitization predisposes to new sensitization. It is unlikely that the reported neuropathies were early unrecognized symptoms of CRPS, since they were reported prior to the CRPS precipitating injury. However, since the actual numbers are very small, the results should be interpreted with caution.

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In the past, it has been suggested that CRPS is a (partially) psychosomatic disorder, and associations with several psychological factors have occasionally been described [33,35]. However, the methodology of these studies was considered as poor [4,9] and the results were not confirmed in several other studies [10,28,44]. In this study, where psychological factors were registered in the records prospectively by the GP before the onset of CRPS, no association was observed between any type of psychological factors and CRPS. Also, in contrast to the previous suggestions [12], there was no strong indication for a general tendency of somatisation in CRPS patients. We found no significant increase in the prior to CRPS GP contact frequency in cases compared to controls, although our study may have lacked enough power to demonstrate potential minor differences. If so, such an eventual small increase could be explained as the consequence of a higher prevalence of pre-existing somatic illnesses. A marginal, however significant, increase in unexplained complaints was observed in CRPS patients in the last year before the index date alone, but this was not strengthened in a sensitivity analysis.

Being observational, this study should be interpreted in the light of its limitations. Major threats to the validity of this study are selection bias and misclassification of the outcome (CRPS) or determinants (prior to CRPS medical conditions).

Selection of the study population was limited by still including part of cases that could not be visited (refusers and untraceable patients), namely the specialist diagnosed cases. Additionally, no significant differences in age and gender distribution or prevalences of medical conditions were observed between participants and non-participants.

Misclassification of the outcome (CRPS) was reduced due to an extensive case validation procedure and by performing sensitivity analyses including only cases that could be verified by the investigator during a visit. Despite this, some misclassification may have remained since the ascertainment of CRPS had to be done retrospectively, combining patient-reported symptoms and disease course with GP reconfirmation and specialist letters if available. However, at the time of acute CRPS, the diagnosis was always assessed clinically by a physician based on the clinical features symptoms and signs at that moment, and only cases that had been reconfirmed afterwards by the GP were included. The additional validation step that implied visiting the cases that were identified during the previously described CRPS incidence study [11] yielded a false positive CRPS diagnosis for 19% of the cases and a 6% misclassification of the date of onset. This suggests an overestimation of the incidence rate calculated using the reported methods in that study (validation by GP reconfirmation only). A revised incidence calculation after the additional validation step (in which we were rather strict in excluding cases in order to prevent misclassification) would roughly provide an estimate of 20 incident cases per 100,000 person years (instead of the previously reported [26]. This incidence rate is still much higher than that mentioned previously [36].

Misclassification of the determinants (medical conditions prior to CRPS) may be of relevance. The dynamic character of the IPCI database has led to variation in the length of observation time within the study population, this being shorter in patients who entered the database early during the study period or who got CRPS soon after the start of their observation period in the database. To deal with this, a minimum observation time of one year before CRPS onset was required for each patient, while also in the analyses we adjusted for observation time, thereby preventing against confounding by the length of the observation period. Diagnoses could have been missed if they occurred before the start of observation in the database, although we suspect that serious ongoing medical conditions will have been noted again during the actual observation period. Moreover, diagnoses mentioned in the journal may be false positive since for efficiency reasons in general practice they are not always validated with complementary research. However, any misclassification resulting from this was likely indifferent between cases and controls and would, therefore, only have led to an underestimation of associations. The actual observed associations increased in sensitivity analyses, wherein the diagnoses (determinants) were strengthened by a specific treatment.

The fact that all medical conditions have been assessed and registered in patients before the onset of CRPS, meaning that both doctor and patient did not know that the patient was susceptible to CRPS, is a strong feature of the study. Recall bias and differential information bias are therefore not an issue. The second advantage is the availability of a relatively large population-based control group that was matched to the cases on the same type of injury preceding CRPS (in addition to age and gender). As CRPS generally occurs after an injury, matching on this risk factor is important if additional risk factors are sought. For 8% of the CRPS patients, no precipitating injury could be extracted from the journal, which is in line with the previously reported percentages of spontaneous CRPS [47]. Finally, due to the gatekeeper role of the GP in the Netherlands, it was possible to study the medical history of the patient from the electronic medical records, which is likely to be more accurate than a self report by the patient.

In conclusion, a medical history of asthma, migraine, and osteoporosis, and a recent history of menstrual cycle-related problems and preexisting neuropathies were associated with CRPS. Since the etiologies of some

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of these diseases are better understood they may give leads to potential disease mechanisms underlying CRPS. The association with asthma and migraine favors the existing ideas of neurogenic inflammation involvement in CRPS.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2008.07.002.

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