Chronic Widespread Pain and Its Comorbidities

A Population-Based Study

Kenji Kato, PhD; Patrick F. Sullivan, MD, FRANZCP; Birgitta Evengård, MD, PhD; Nancy L. Pedersen, PhD

Background: Chronic widespread pain (CWP), the cardinal symptom of fibromyalgia, is prevalent and co-occurs with numerous symptom-based conditions such as chronic fatigue syndrome, joint pain, headache, irritable bowel syndrome, and psychiatric disorders. Few studies have examined the comorbidities of CWP in the general population. Furthermore, little is known about the importance of familial (genetic and family environmental) factors in the etiology of co-occurrence.

Methods: Data were obtained from 44,897 individuals in the Swedish Twin Registry via computer-assisted telephone interview from 1998 through 2002 (age ≥42 years; 73.2% response rate). Screening for CWP was based on the American College of Rheumatology criteria without clinical evaluation. Measures for comorbidities were based on standard criteria when available. Odds ratios (ORs) were calculated in case-control and co-twin control designs to assess the effect of familial confounding in the associations.

Results: Considerable co-occurrences were found in CWP cases for chronic fatigue (OR, 23.53; 95% confidence interval [CI], 19.67-28.16), joint pain (OR, 7.41; 95% CI, 6.70-8.21), depressive symptoms (OR, 5.26; 95% CI, 4.75-5.82), and irritable bowel syndrome (OR, 5.17; 95% CI, 4.55-5.88). In co-twin control analyses, ORs were no longer significant for psychiatric disorders, whereas they decreased but remained significant for most other comorbidities. No changes in ORs were observed for headache.

Conclusions: Associations between CWP and most comorbidities are mediated by unmeasured genetic and family environmental factors in the general population. The extent of mediation via familial factors is likely to be disorder specific.

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FIBROMYALGIA IS A COMPLEX multifactorial disorder characterized by persistent widespread pain, tenderness, and abnormal pain sensitivity with unknown etiology.

Patients with fibromyalgia tend to have other unexplained clinical conditions such as chronic fatigue syndrome (CFS), irritable bowel syndrome, temporomandibular joint syndrome, and multiple chemical sensitivities. In addition, it has often been reported that psychiatric disorders such as major depression and generalized anxiety disorder are prevalent among patients with fibromyalgia in clinical settings. Despite the relative abundance of fibromyalgia and its comorbidity symptoms at clinics, a limited number of studies allow comparisons among a wide range of comorbidities of fibromyalgia or its cardinal symptom, chronic widespread pain (CWP), in general population samples. It is known that having 2 comorbid disorders can increase the likelihood of inclusion in a clinical sample, resulting in biases.

As yet, the etiology of overlapping symptoms in fibromyalgia or CWP and the comorbidities is largely unknown. Some argue that these medically unexplained syndromes should be viewed as a manifestation of psychogenic disorders, whereas others postulate that the associations reflect common etiologies that underlie the disorders. Although these studies suggest underlying mechanisms shared by those disorders, it remains unclear whether and to what extent the associations reflect confounding by genetic influences. Twin samples can be used for assessing those associations with control for genetic background and unmeasured family environment. To our knowledge, few studies have used twins to examine explicitly familial mediation of comorbidities. In 1 study, strong associations were found between fibromyalgia and chronic
fatigue. A small study based on the Swedish Twin Registry did not find an association between fibromyalgia and irritable bowel syndrome. However, because of limited sample sizes, conclusions are limited.

In the present study, we used a considerably larger population-based sample with systematic criteria for screening a variety of disorders and health conditions that have frequently been reported to co-occur with CWP. Our first objective was to assess a wide range of comorbidities of CWP in a large community sample of nearly 45,000 individuals. The second objective was to evaluate the influences of unmeasured genetic and family environmental factors that confound the associations of comorbidities with CWP. To perform this study, we used a 2-stage approach that included a classic case-control design and co-twin control design. A change in the association between these 2 stages suggests genetic and family environmental confounding.

**METHODS**

**SUBJECTS**

Subjects were participants in the Swedish Twin Registry, which consists of all twin births in Sweden from 1886 to 2000, with data on place of birth, current vital status, and the addresses of more than 160,000 individuals. All living, contactable, and consenting twins born in Sweden before 1959 were interviewed via telephone from 1998 to 2002. Interviews were conducted by trained personnel with adequate medical background using a computer-based data collection system. All participants provided verbal informed consent during this telephone interview, which was later confirmed by postcard.

Zygosity was based on responses to questions regarding physical similarity in childhood. This method has been validated repeatedly as having 98% or higher accuracy by using DNA markers.

**MEASURES FOR CWP**

The screening algorithm for CWP was based on the classification criteria for fibromyalgia proposed by the American College of Rheumatology, but differed in that our definition of CWP relied on self-reports without clinical examinations by physicians or inspections of medical records and that the count of tender points was not required. The stem question was, “Have you suffered from general pain during the last 3 months?” Interviewees who endorsed this item were then asked, “Did you have continuous pain during all 3 months?” Subjects who endorsed the second item were further asked, “Do you suffer from pain in both the upper and lower body?” and “Do you suffer from pain in both the right and left sides?” We also obtained information about axial skeletal pain by asking, “Have you had any back pain in the last 12 months?” Those who endorsed all 4 of these items were defined as CWP cases. Those who did not endorse the first or second question regarding general pain during the last 3 months were considered unaffected and were used as controls in the analyses. Further details concerning the sample and twin similarity for CWP are reported elsewhere.

**MEASURES FOR COMORBIDITIES**

Each comorbidity was evaluated using diagnostic items specific to each disease domain, and standardized instruments were used when available. None of these are exclusionary for CWP. Screening for chronic fatigue was based on criteria that emulated the 1994 criteria for CFS and were only asked of twins born in 1935 or later (ie, aged <65 years at the time of the interview). The 2 definitions of chronic fatigue used in the present study (chronic impairing fatigue and CFS-like illness) correspond to “CF-B” and “CF-C” in our previous report. Information about possible rheumatoid arthritis was obtained from a single question regarding the presence or absence of current or past rheumatoid arthritis. Prolonged joint pain was considered present if its duration was more than 4 weeks at a time. Osteoarthritis was considered present if the subject was diagnosed by a physician as having it in a knee or a hip. Subjects who endorsed any of these items about pain (ie, possible rheumatoid arthritis, prolonged joint pain, and osteoarthritis) were considered to have joint pain. Migraine and tension-type headache were assessed for subjects younger than 65 years with an algorithm in line with the International Headache Society criteria. Depressive symptoms were assessed using the Iowa Short Form of the Center for Epidemiology Studies Depression Scale with 11 items, and a score of 9 or above was considered as the presence of depressive symptoms. Major depression and generalized anxiety disorder were assessed by using the Composite International Diagnostic Interview—Short Form adapted from its original design for 12-month prevalence to assess lifetime prevalence. Eating disorders were assessed for subjects younger than 65 years via questions based on the Structured Clinical Interview for DSM-IV. Irritable bowel syndrome and gastroesophageal reflux disease were defined using previously reported criteria. Prolonged cough was assessed if the subject reported having recurrent cough more than 3 successive months per year. Possible asthma was considered present if the subject reported diagnosis by a physician. Allergy was assessed if the subject affirmed any type of allergy given in a list (eg, eczema). The presence of urological diseases (renal disease and urinary tract problems) was based on questions about lifetime occurrence. Furthermore, subjects were asked to rate their general health and categorized as having good to excellent health vs indifferent to bad health. Subjects were also categorized as reporting poorer vs the same or better health status than 5 years before the interview. When asked to report whether their health prevented activities, responses were categorized as “partially” or “to a great extent” vs “not at all.” The body mass index was calculated as the weight in kilograms divided by the square of height in meters. The cutoff points were 30 or higher for obesity and 23 or higher for overweight (http://www.cdc.gov/nccdphp/dnpa/obesity/defining.htm). Frequent infections were assessed if the subject usually had common colds or other infections more than twice per year. Subjects 55 years or older were asked how often during the past 6 months they were affected by waking up too early, feelings of not having had enough sleep on awakening, or feelings of having disturbed, uneasy sleep. Those who reported “usually” or “always” having any of the 3 problems were considered to have sleep problems.

**STATISTICAL ANALYSES**

We used generalized estimating equation (GEE) analyses to evaluate the association between CWP and comorbidities with commercially available software (PROC GENMOD in SAS, version 9). By using GEEs, we can account for the clustering or lack of independence of twins within a pair. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with adjustment for age and sex. In co-twin control analyses, we selected monozygotic (MZ) or same-sex dizygotic (DZ) twin pairs who were discordant for both CWP and comorbidity status. Odds ratios and 95% CIs were obtained using a procedure in the statistical software (PROC LOGISTIC in SAS, version 9).
If we find overlap in genetic effects for CWP and a comorbid disorder or symptom, the association could reflect confounding by genes. Using twins discordant for case status is more informative than using unrelated case-control samples because it allows matching for unmeasured familial factors that could be genetic or environmental. In particular, discordant MZ twins are ideal case-control pairs, with whom all genes and environmental effects in early life are shared. Thus, if the association found in GEE analyses decreases in co-twin analyses, this suggests familial confounding, and if the association further decreases when MZ twins are used, this suggests genetic confounding. In contrast, if a significant association remains when using MZ twins only, it means that the association reflects mechanisms other than genetic and family environmental effects.

**RESULTS**

Of all 61,355 eligible individuals, 44,897 (73.2%) responded to the interview (33,190 pair-wise respondents and 11,707 single respondents). Of the complete pairs, 4,310 pairs were MZ; 6137, same-sex DZ; 5980, opposite-sex DZ; and 168, of unknown zygosity. The mean ± SD age of the sample was 59.8 ± 11.1 years, and 53.5% were women. Of the 43,338 respondents who provided usable answers for the stem question, CWP was found in 1,776 individuals (4.1%), and 81.7% were women. The age of the sample was 59.8 ± 11.1 years, and 53.5% were women. The mean age at onset of CWP was 43.7 years, and the median duration of having CWP was 10 years.

**Table 1** shows the number of subjects with and without each comorbid illness or symptom in those who were affected (cases) and not affected (controls) with CWP. Nearly 60% of the cases reported that they had at least 1 of the manifestations of joint pain (i.e., possible rheumatoid arthritis, prolonged joint pain, and osteoarthritis), compared with only 16.2% in the controls. More than 80% of the cases answered that their general health was poor and that their health condition prevented their activities, whereas only 26.7% and 26.4%, respectively, of the controls did so.

**Table 2** shows ORs of having each comorbid illness or characteristic in cases relative to controls, by using (1) GEEs, (2) MZ and same-sex DZ co-twins, and (3) MZ co-twins. In GEEs, we found significant ORs for all of the comorbidities, of which chronic fatigue showed the highest. Odds ratios greater than 5 were also observed for poor self-rated health, “health prevents activities,” prolonged joint pain, possible rheumatoid arthritis, depressive symptoms, poorer health status compared with 5 years ago, and irritable bowel syndrome. The prevalences and ORs did not differ significantly when restricted to the pairs in which both members of the pair responded. When co-twin controls were used, ORs were reduced in almost all comorbidities and health conditions except migraine, tension-type headache, and frequent infections. Notable reductions from significant association in GEE to nonsignificance in co-twin control analyses were found for psychiatric disorders (major depression, generalized anxiety disorder, and eating disorders), prolonged cough, possible asthma, and overweight. The changes in the importance of these disorders and symptoms across the degree of adjustment suggest the presence of confounding from genetic and family environmental effects. Nevertheless, the ORs for most of the comorbidities were still significant in the analyses using MZ twins only, indicating that these comorbidities are not solely a function of genetic and family environmental mechanisms.

**COMMENT**

In the present study using a large population-based sample, we empirically confirmed clinical observations that considerable overlap exists between CWP and other symptom-based conditions such as chronic fatigue, irritable bowel syndrome, and psychiatric disorders. It has
In our analyses using affected twins and their unaf-


ection of CWP and its co-


Table 2. Associations Between CWP and Its Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>GEE</td>
</tr>
<tr>
<td>Chronic fatigue, age ≤64 y</td>
<td>10.15 (8.90-11.58)</td>
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<tr>
<td>Joint pain and headache</td>
<td></td>
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<tr>
<td>Joint pain††</td>
<td>5.74 (5.62-5.86)</td>
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<tr>
<td>Possible rheumatoid arthritis</td>
<td></td>
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<tr>
<td>Prolonged joint pain</td>
<td></td>
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<tr>
<td>Osteoarthritis, knee or hip</td>
<td></td>
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<tr>
<td>Migraine, age ≥64 y</td>
<td></td>
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<tr>
<td>Tension-type headache, age ≥64 y</td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
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<tr>
<td>Current depressive symptoms</td>
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<tr>
<td>Lifetime major depression</td>
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<td>Lifetime generalized anxiety disorder</td>
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<td>Lifetime eating disorders, age ≥64 y</td>
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<tr>
<td>Gastrointestinal tract disorders</td>
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<tr>
<td>Irritable bowel syndrome</td>
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<td>GERD</td>
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<tr>
<td>Urological diseases</td>
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<td>Renal disease</td>
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<td>Urinary tract problems</td>
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<tr>
<td>Allergy</td>
<td></td>
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<tr>
<td>Prolonged cough, &gt;3 mo</td>
<td></td>
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<tr>
<td>Possible asthma</td>
<td></td>
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<tr>
<td>Allergy, any</td>
<td></td>
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<tr>
<td>General health</td>
<td></td>
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<tr>
<td>Obesity, BMI ≥30</td>
<td></td>
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<tr>
<td>Overweight, BMI ≥25</td>
<td></td>
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<tr>
<td>Sleep problems, age ≥55 y</td>
<td></td>
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<tr>
<td>Poor general health</td>
<td></td>
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<tr>
<td>Health prevents activities</td>
<td></td>
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<tr>
<td>Poorer health status than 5 y ago</td>
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<tr>
<td>Frequent infections, &gt;2 per year</td>
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Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CFS, chronic fatigue syndrome; CI, confidence interval; CWP, chronic widespread pain; DZ, dizygotic; GEE, generalized estimating equation; GERD, gastroesophageal reflux disease; MZ, monozygotic; OR, odds ratio.

*Odds ratios were calculated by means of co-twin control analyses with MZ and same-sex DZ twins.
†Odds ratios were calculated by means of co-twin control analyses with MZ twins only.
‡Defined as having at least 1 of possible rheumatoid arthritis, prolonged joint pain, or osteoarthritis.

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association were observed for both definitions of chronic

fatigue. This supports the notion that CWP and chronic

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pathways through genetic and family environmental

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less reflect a common pathophysiology mediated via exogenous factors such as stress.

The associations between CWP and most psychiatric disorders essentially disappeared in the MZ case-control analyses, indicating the role of genetic factors. Arnold and colleagues21 found indirect evidence that genetic factors may be involved in the co-occurrence of mood disorders and fibromyalgia. Our results clearly indicate that not only major depression but also generalized anxiety disorder and eating disorders co-occur with CWP largely owing to genetic factors in common. Using the same sample as in this study, we recently found that the association between emotional instability and chronic fatigue was entirely mediated by familial factors.22 Genetic susceptibility to emotional instability may therefore play an etiological role in the links among psychiatric disorders, CWP, and chronic fatigue.

Genetic mediation was also evident for prolonged cough, possible asthma, and overweight (defined as having a body mass index of ≥25). Autonomic dysfunction and/or cytokine abnormalities may serve as the underlying pathogenesis in the association between asthma or prolonged cough and CWP.23 Although the co-occurrence of CWP and higher body mass index is usually understood as the consequence of physical inactivity,24 the present results implicate genetic mechanisms that influence both CWP and obesity.

Collectively, our findings indicate significant overlaps in underlying mechanisms between CWP and many of the comorbidities investigated. However, it is unlikely that the co-existence of CWP, chronic fatigue, headache, and psychiatric disorders merely reflects different manifestations of a single disorder, in that the extent to which genetic influences mediate these associations ranges from negligible (headache) to exhaustive (psychiatric disorders). Further investigations with genetically informative samples are therefore warranted to distinguish, for example, a group of disorders that share genetic susceptibility from a group of disorders that share environmental risk factors. Moreover, given that most of the cases with CWP and those with most of the comorbidities were women, a search for sex-specific mechanisms would also be warranted.

A notable strength of this study is that the participants can be considered a representative sample of the entire population of Sweden,18 and that the screening interviews were conducted in a blinded manner, ie, without prior knowledge about the health condition of each individual. Moreover, the number of participants was large enough to examine even relatively minor comorbidities of CWP (eg, frequent infections) with sufficient statistical power. Another major strength is that our study is based on a genetically informative sample, which permits controlling for influences of genes and family environment that are not measured directly.

Some limitations should be noted. First, the screening used in this study did not include clinical evaluation, which is required in the American College of Rheumatology criteria for fibromyalgia. Thus, inferences should be tempered when our findings are compared with those of studies based on clinical evaluation. However, questionnaire- or interview-based screening has suggested as useful in general population surveys, with relatively high positive predictive value and test-retest reliability.25 Second, the information about axial skeletal pain is based on back pain during the 12 months before the interview. We might have misclassified cases who did not have back pain for 3 consecutive months. However, we might have missed potential cases who actually had axial pain in another part of the body (eg, cervical spine) as well as generalized pain. Third, classification criteria used for screening the comorbidities depended on self-report, without validation by medical records. The information about some diseases was obtained from a single yes/no question, without asking whether they were diagnosed by a physician. However, most of the comorbidities were evaluated using standardized algorithms, such as the Composite International Diagnostic Interview—Short Form for major depression and generalized anxiety disorder. Finally, CWP had to be present at the time of the interview, whereas some of the comorbidities were diagnosed as lifetime occurrence. Thus, temporal order is unclear.

In conclusion, the present study demonstrated that, in the general population, CWP was significantly associated with comorbidities that are frequently observed in clinical settings. In addition, we found that those associations were partly or entirely mediated by unmeasured genetic and family environmental factors. Furthermore, the extent to which the associations were explained by these influences was specific to each disorder. We believe that our findings provide some evidence for better understanding of the mechanisms of CWP and its comorbidities.

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Author Contributions: Dr Pedersen had full access to the data and takes responsibility for the integrity of the data and the accuracy of analysis.

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