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Comorbidity Among Multiple Pain Symptoms and Anxious Depression in a Dutch Population Sample

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Abstract: **Most studies on pain focus on specific disorders, which makes it difficult to compare characteristics across different types of pain symptoms. In this large population-based study, we examine the prevalence and comorbidity patterns among pain symptoms across a wide range of anatomic sites (back, neck, head, abdomen, joints, chest, face, teeth, and "other") in relation to anxious depression and a range of demographic, health, and lifestyle variables. Self-report data were collected in 11,787 adult participants of The Netherlands Twin Registry (mean age 44.5 years, 62% female), including twins and relatives of twins. Headache and abdominal pain were strongly associated with female sex, whereas chest pain and toothache were not. Joint pain strongly increased with age, whereas headache and abdominal pain decreased with age. Most other pain sites were only weakly associated with age. A highly consistent pattern of comorbidity was observed: All pain symptoms were correlated with all other pain symptoms, as well as with anxious depression. Frequent and widespread pain (ie, pain at multiple sites) was most strongly associated with anxious depression. These observations reflect important differences between specific pain symptoms, suggesting partly separate etiologies, but also highlight the importance of shared mechanisms underlying pain symptoms in general.**

Perspective: ***The association of pain with sex and age strongly depends on pain location. However, all pain sites are consistently associated with other pain sites as well as with anxious depression. This provides important clues with respect to both similarities and differences in the mechanisms underlying different types of pain.***

Key words: *Pain, prevalence, age, anxiety, depression, comorbidity.*

Some characteristics are shared by many pain disorders. For example, it is known that several pain disorders increase the risk of other pain disorders.[11] Patients with irritable bowel syndrome have increased rates of fibromyalgia, back pain, and migraine[29]; patients with chronic low back pain show higher rates of other musculoskeletal pain disorders as well as neuropathic pain disorders[14]; and patients with temporomandibular pain often suffer from neck pain as well.[36]

Pain disorders not only tend to cluster among each other but also co-occur with psychiatric disorders, in particular with anxiety and depression.[17,26] This seems to be relatively independent of the type of pain disorder. For example, we previously showed that more pain symptoms were reported in a clinical sample of patients with anxiety and/or depressive disorders than in controls, regardless of the location of the pain.[24] It is unknown whether this consistent comorbidity of anxiety,

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depression, and pain symptoms is also present at the general population level.

However, there are also some striking differences among pain disorders. Although pain tends to be more prevalent in females than in males, the strength of this relationship differs considerably depending on the disorder. Migraine has been found to be 2 to 3 times more prevalent in females,[33] but for low back pain the relationship with sex is much weaker.[2] And although migraine has a peak incidence in adolescence and decreases after menopause,[33] the prevalence of fibromyalgia is reported to increase steadily with age.[8]

Thus, although different pain disorders appear to share characteristics, suggesting a general susceptibility to pain disorders, the observed differences among pain conditions may provide important clues as to how the underlying mechanisms may differ. However, a good overview of the patterns in prevalence and comorbidity across different pain conditions is largely lacking, because most studies have focused on specific pain conditions. Studies assessing a wider range of pain symptoms simultaneously are rare and often restricted to a certain type of symptom, for example, musculoskeletal pain only.[4,18] This prevents a good comparison across different conditions because of inevitable methodologic differences among studies.

In this study, we first evaluate the extent to which pain symptoms differ as a function of sex, age, and other demographic, health, and lifestyle variables, as this may reflect differences in the mechanisms underlying these pain symptoms. Then we test the following 2 hypotheses: 1) pain symptoms consistently co-occur with other pain symptoms, irrespective of anatomic site, and 2) pain symptoms consistently co-occur with anxiety and depression. For this purpose, we conducted an extensive data collection on pain and anxious depression in 11,787 participants of the Netherlands Twin Registry (NTR).[40] This allowed us to obtain an overview of the patterns in prevalence and comorbidity among pain symptoms in a wide range of anatomic sites (back, neck, head, abdomen, joints, chest, teeth, face, and "other") in a general population sample.

Methods

The data described in this study were collected in participants of the NTR. The NTR conducts longitudinal questionnaire research, with a focus on health, personality, and lifestyle variables.[6,7,40] Adult NTR participants receive invitations to participate in questionnaire research approximately every 2 to 3 years. This study is based on data from the ninth wave of questionnaire research (survey 9). Data were collected in 2011 to 2012.

Participants

The participants in this study were twins (49.1%) and relatives of twins (parents, 33.6%; siblings, 10.6%; partners, 5.1%; children of twins, 1.3%; and children of siblings, .4%). Invited participants were aged 18 or older and came from families in which at least 1 person had completed the previous survey (survey 8).

Data Collection

An invitation letter with a personal log-in code and a link to an online questionnaire was mailed to the participants. A hard copy version of the questionnaire was available on request. Invitations for participation in the study were mailed to a total of 27,892 participants in January, April, and September 2011 and February 2012. Participants who had not yet completed the questionnaire received a reminder by mail within a few months after the first invitation. Additional reminders were sent to targeted groups, such as twins whose co-twin had already completed the questionnaire, to maximize the number of complete twin pairs. These efforts resulted in 11,948 completed questionnaires, which equals a total response rate of 43%, comparable to previous studies in the adult NTR sample.[40] Of these individuals, 11,565 completed the questionnaire online and 383 on paper. For the present study, 6 individuals were excluded because they were younger than age 18 years and 155 because they did not complete the pain questionnaire, resulting in a sample of 11,787 individuals for analysis. Of these, 10,783 had already participated in previous surveys (mean number of surveys 2.9, standard deviation = 2.0); 1,004 participated for the first time. The study was approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam.

Measures

Pain

The pain inventory addressed pain in 9 different anatomic sites, experienced during the last year. The pain locations assessed were back, neck, head (headache or migraine, collectively referred to as headache throughout this paper), abdomen, joint, chest, tooth, face, and somewhere else (referred to as "other" throughout this paper). Participants who reported having pain somewhere else were asked to report the location of this pain (open-ended question). In some cases, this pain matched one of the other existing categories, in which case the participant was reclassified accordingly.

For each pain location, participants were asked how often they experienced pain (no pain, occasionally, a lot of the time). We refer to pain that was present occasionally in the last year as "occasional pain" and pain that was present a lot of the time in the last year as "frequent pain." Participants were asked whether there was a known cause for the pain (open-ended question). The pain that bothered the participant the most was further assessed with the Graded Chronic Pain Scale.[38] This is a validated scale that assesses pain intensity and pain-related disability. From the Graded Chronic Pain Scale, a "characteristic pain intensity" and a "disability score" can be derived, both of which range from 0 to 100. The characteristic pain intensity score reflects the intensity of the current, worst, and average pain, whereas the disability score reflects how much the pain interferes

with daily activities, social activities, and work. Disability points (ranging between 0 and 6) are calculated based on a combination of the number of disability days and the disability score. Based on the characteristic pain intensity and the number of disability points, an individual is assigned 1 of 5 different "pain grades." Grade 0 means the individual is pain free; grades I and II reflect low disability, with grade I representing low intensity and grade II reflecting high intensity; and grades III and IV reflect high disability, with grade III representing moderately limiting pain and grade IV representing severely limiting pain.

Demography, Health, and Lifestyle

The questionnaires included items on sex, age, and several other demographic, health, and lifestyle-related variables relevant to this study. Self-rated health was assessed with the question "How would you rate your health?" Participants were classified into 2 categories: *poor/fair/reasonable* and *good/excellent*. Body mass index was calculated from self-reported weight and height, with the formula weight (kg)/height^2 (m). Smoking was assessed with a single question about whether and how much a participant smoked. For this study, participants were classified into 3 categories: current smokers (cigarettes or other), ex-smokers, and never smokers. Finally, exercise was analyzed as a dichotomous variable. Individuals who reported participating in any type of sport were classified as exercisers, and individuals who did not report any sports were classified as nonexercisers. Information on educational attainment was obtained from previous questionnaires. This information was present for 8,532 individuals (72% of the total sample). Participants were classified into 2 categories: *high* (higher vocational college or university) and *low or intermediate* (all other). Country of birth information was also based on data from previous questionnaires and was available for 10,807 individuals (92%). For the purpose of this study, this variable was dichotomized into *The Netherlands* versus *other*.

Anxious Depression

Depression and anxiety are strongly related constructs, which are largely affected by the same genetic factors.[21] Although they are both individually associated with pain symptoms, the combination of both has been found to be strongly associated with pain.[24,39] Therefore, we used the anxious depression scale of the Adult Self-Report,[1,35] which combines aspects of both anxiety and depression and is therefore expected to optimally capture the association of pain with anxiety and depressive symptoms. This scale consists of 18 items, rated on a 3-point scale (0 = not true, 1 = somewhat or sometimes true, 2 = very true or often true), which can be summed up to a scale score, ranging from 0 to 36, reflecting a quantitative measure of anxious depression. Scores between 16 and 19 (depending on sex and age) and higher are considered to be in the clinical range (ie, of enough concern to potentially require mental health care).

Statistical Analyses

First, to describe the study population, demographic, health, and lifestyle-related variables were compared among 3 groups of individuals: a "no pain" group (participants who did not report any pain), an "occasional pain" group (participants who reported at least 1 occasional pain site), and a "frequent pain" group (participants who reported at least 1 frequent pain site). Differences between these groups were tested with linear or logistic regression analysis, depending on whether the variables were continuous or categorical. Furthermore, we assessed the prevalence of pain at each anatomic site and compared these prevalences in males and females, using logistic regression to assess sex differences. To assess age effects, the sample was subdivided into 6 age categories (18–25, 25–35, 35–45, 45–55, 55–65, and 65+), and the prevalence of pain at each anatomic site was calculated for all age categories.

Next, 2 sets of analyses were performed in order to test our hypotheses with respect to comorbidity. First, the co-occurrence of pain symptoms across the measured anatomic sites was investigated by calculating tetrachoric correlations between each pair of sites. To test whether the degree of co-occurrence depended on pain frequency, each of the pain location variables was dichotomized in 2 ways: 1) no pain versus any pain and 2) no pain or occasional pain versus frequent pain. Second, we tested to what extent each pain site was associated with anxious depression. Mean anxious depression scores were calculated for individuals with no pain, occasional pain, and frequent pain at each anatomic site. Anxious depression scores were also calculated by pain grade. Differences in anxious depression score (between the no pain, occasional pain, and frequent pain groups, and between pain grade groups) were tested with linear regression. Finally, we investigated the relationship between anxious depression and the number of occasional and frequent pain sites by performing linear regression analysis with anxious depression as the dependent variable and the number of occasional and frequent pain sites as the predictor variables.

Descriptive statistics were produced using SPSS 20 (SPSS Inc, Chicago, IL). Regression analyses were performed in Stata 12 (StataCorp LP, College Station, TX), using a robust variance estimator and including family identifier as a cluster variable to account for nonindependence of family members. This procedure does not affect the point estimates but produces standard errors adjusted for the nonindependence of observations within a family. The statistical significance of linear and logistic regression analyses was evaluated based on the F statistic or Wald χ^2. Tetrachoric correlations were calculated in Mplus v5,[27] adjusting for nonindependence of family members by using the COMPLEX option and clustering by family identifier.

Results

Demography and Prevalence of Pain Symptoms

Table 1 shows the general and demographic characteristics of the sample. Results are presented for the total sample and for individuals with no pain, occasional

Table 1. Sample Descriptives and Demography

	All	*No Pain*	*Occasional Pain*	*Frequent Pain*
Male	4,510 (38.3)	757 (59.3)	3,079 (39.0)	674 (25.8)
Female	7,277 (61.7)	519 (40.7)	4,824 (61.0)	1,934 (74.2)
Age (y), M (SD)	44.5 (15.7)	43.4 (16.3)	44.3 (15.4)	45.7 (16.2)
Education level*				
Low or intermediate	4,479 (38.0)	415 (32.5)	2,930 (37.1)	1,134 (43.5)
High	4,053 (34.4)	475 (37.2)	2,853 (36.1)	725 (27.8)
Missing	3,255 (27.6)	386 (30.3)	2,120 (26.8)	749 (28.7)
Country of birth*				
The Netherlands	10,583 (89.8)	1,154 (90.4)	7,086 (89.7)	2,343 (89.8)
Other	224 (1.9)	16 (1.3)	148 (1.9)	60 (2.3)
Missing	980 (8.3)	106 (8.3)	669 (8.5)	205 (7.9)
Self-rated health				
Poor/fair/reasonable	2,007 (17.0)	65 (5.1)	983 (12.4)	959 (36.8)
Good/excellent	9,735 (82.6)	1,206 (94.5)	6,893 (87.2)	1,636 (62.7)
Missing	45 (.4)	5 (.4)	27 (.3)	13 (.5)
Body mass index, M (SD)	24.6 (3.9)	24.2 (3.4)	24.5 (3.8)	25.0 (4.5)
Smoking status				
Current smokers	1,614 (13.7)	173 (13.6)	1,033 (13.1)	408 (15.6)
Ex-smokers	3,944 (33.5)	374 (29.3)	2,627 (33.2)	943 (36.2)
Never smokers	6,195 (52.6)	728 (57.1)	4,222 (53.4)	1,245 (47.7)
Smoking data missing	34 (.3)	1 (.1)	21 (.3)	12 (.5)
Exercise				
Nonexercisers	3,744 (31.8)	349 (27.4)	2,397 (30.3)	998 (38.3)
Exercisers	8,043 (68.2)	927 (72.6)	5,506 (69.7)	1,610 (61.7)
Total	11,787	1,276	7,903	2,608

Abbreviations: M, mean; SD, standard deviation.
NOTE. Values are n (%) unless otherwise noted.
*These values are based on data from previous questionnaires; therefore, data are not available for the entire sample.

pain, and frequent pain. The general prevalence of pain symptoms was high: a total of 10,511 (89%) subjects reported having pain, including 2,608 (22% of the total sample) who reported at least 1 site with frequent pain. Only 1,276 individuals (11%) reported having no pain. Women were more likely than men to report pain: men were overrepresented (59.3%) in the no pain group, whereas women were overrepresented (74.2%) in the frequent pain group (Wald $\chi^2[2] = 378.09$, $P < .001$). There was a modest relationship with age; the frequent pain group had the highest mean age, followed by the occasional pain group ($F[2, 5224] = 9.86$, $P < .001$). Pain was also related to educational attainment, with the lowest number of highly educated individuals in the frequent pain group (Wald $\chi^2[2] = 67.59$, $P < .001$). No significant association was observed between pain and the participants' country of birth (Wald $\chi^2[2] = 4.38$, $P = .112$). There was a strong negative relationship between pain and the participants' self-rated health (Wald $\chi^2[2] = 822.34$, $P < .001$), and a modest but significant positive association between pain and body mass index ($F[2, 5202] = 18.47$, $P < .0001$). Pain was also significantly associated with smoking status, with current smokers and also ex-smokers reporting more pain symptoms (Wald $\chi^2[2] = 32.04$, $P < .001$). Finally, individuals in the occasional pain group and especially in the frequent pain group exercised less than individuals without pain (Wald $\chi^2[2] = 68.04$, $P < .001$).

Table 2 shows the prevalence of the individual symptoms for the total sample and for males and females separately. The 1-year prevalence for occasional pain was highest for pain in the back, neck, head, abdomen, and joints (all above 30%). The most common types of frequent pain were back and joint pain (reported by 9.1% and 9.6% of the population, respectively). The overall prevalence of frequent pain was 22.1% (2,608 of 11,787 individuals; see Table 1). With the exception of chest pain and toothache, all pain types were more prevalent in females than in males, for both frequent and occasional pain. Females not only reported a higher overall pain prevalence but also had a comparatively higher risk of frequent pain, as indicated by the fact that the odds ratios for women compared to men were larger for frequent pain than for occasional pain (with the exception of chest pain). However, the strength of the sex effect varied considerably depending on the pain site. Headache showed the strongest relationship with sex, followed by abdominal pain, and facial and neck pain. Moderate sex effects were also observed for musculoskeletal pain symptoms (back, neck, and joints). Chest pain and toothache, on the other hand, were not significantly related to sex.

As shown in Table 1, there was a modest positive overall relationship between pain and age. However, as can be seen in Fig 1, this relationship strongly depended on the pain site. Age effects were modest for most pain locations, with a few exceptions. The prevalence of occasional headache increased with age in young adults but decreased after age 50 years. For frequent headache, the prevalence decreased with age, particularly in women, without the initial increase in young adulthood

Table 2. Pain Prevalence by Location and Sex

	Prevalence in Total Sample (N = 11,787)			Prevalence in Males (n = 4,510)		
	No Pain	Occasional Pain	Frequent Pain	No Pain	Occasional Pain	Frequent Pain
Males						
Back	4,774 (40.5)	5,874 (49.8)	1,068 (9.1)	2,046 (45.4)	2,143 (47.5)	299 (6.6)
Neck	6,819 (57.9)	4,096 (34.8)	754 (6.4)	3,086 (68.4)	1,232 (27.3)	154 (3.4)
Head	5,329 (45.2)	5,822 (49.4)	518 (4.4)	2,756 (61.1)	1,635 (36.3)	70 (1.6)
Abdomen	7,546 (64.0)	3,703 (31.4)	374 (3.2)	3,458 (76.7)	923 (20.5)	64 (1.4)
Joints	6,408 (54.4)	4,181 (35.5)	1,132 (9.6)	2,639 (58.5)	1,545 (34.3)	301 (6.7)
Chest	10,237 (86.8)	1,356 (11.5)	58 (.5)	3,907 (86.6)	533 (11.8)	23 (.5)
Teeth	10,132 (86.0)	1,447 (12.3)	42 (.4)	3,919 (86.9)	519 (11.5)	12 (.3)
Face	10,659 (90.4)	869 (7.4)	120 (1.0)	4,241 (94.0)	206 (4.6)	18 (.4)
Other	9,803 (83.2)	1,194 (10.1)	281 (2.4)	3,872 (85.9)	428 (9.5)	72 (1.6)

	Prevalence in Females (N = 7,277)			Females Compared to Males, OR (95% CI)	
	No Pain	Occasional Pain	Frequent Pain	Occasional Pain	Frequent Pain
All					
Back	2,728 (37.5)	3,731 (51.3)	769 (10.6)	1.31 (1.21–1.41)	1.93 (1.67–2.23)
Neck	3,733 (51.3)	2,864 (39.4)	600 (8.2)	1.92 (1.77–2.09)	3.22 (2.67–3.88)
Head	2,573 (35.4)	4,187 (57.5)	448 (6.2)	2.74 (2.53–2.97)	6.86 (5.26–8.93)
Abdomen	4,088 (56.2)	2,780 (38.2)	310 (4.3)	2.55 (2.33–2.78)	4.10 (3.10–5.41)
Joints	3,769 (51.8)	2,636 (36.2)	831 (11.4)	1.19 (1.10–1.30)	1.93 (1.68–2.23)
Chest	6,330 (87.0)	823 (11.3)	35 (.5)	.95 (.85–1.07)	.94 (.55–1.60)
Teeth	6,213 (85.4)	928 (12.8)	30 (.4)	1.13 (1.01–1.27)	1.58 (.82–3.03)
Face	6,418 (88.2)	663 (9.1)	102 (1.4)	2.13 (1.80–2.51)	3.74 (2.27–6.18)
Other	5,931 (81.5)	766 (10.5)	209 (2.9)	1.17 (1.03–1.32)	1.90 (1.44–2.49)

Abbreviation: OR, odds ratio.
NOTE. Values are n (%) unless otherwise noted. The ORs indicate the prevalence in females compared to males.

observed for occasional headache. Abdominal pain (both occasional and frequent) showed a gradual decrease with age, particularly in women. Pain in the joints, on the other hand, showed a sharp increase in prevalence in both males and females, particularly after age 45 years. Inspection of the reported causes of pain showed that many reports of pain in the joints were due to osteoarthritis. A keyword search of all 3,020 reported causes of joint pain indicated that 579 individuals mentioned osteoarthritis, 294 mentioned degradation of the joints, and 139 reported that their pain was due to old age. Taking into account individuals reporting more than 1 of these, this sums up to 967 individuals reporting an age-related joint problem (18% of all reports of joint pain and 32% of all reported causes for joint pain), possibly explaining the strong observed relationship with age compared to the other pain types.

Comorbidity

A strong and consistent co-occurrence of pain symptoms was observed. The tetrachoric correlations in Table 3 indicate that having pain at any anatomic site was significantly associated with having pain at any other site. Particularly strong correlations were observed between sites located relatively close together, such as back and neck, and face, neck, and head. Somewhat weaker, but still significant, associations were observed between toothache and other pain sites. Correlations were stronger for frequent pain versus no pain/occasional pain than for all pain versus no pain, indicating that frequent pain symptoms tend to co-occur more than occasional pain symptoms.

Furthermore, all types of pain were associated with higher mean anxious depression scores. In the overall sample, the mean anxious depression score was 3.34 (standard deviation = 4.58, range = 0–35) for men and 5.04 (standard deviation = 5.49, range = 0–36) for women. Table 4 shows that for each pain site, individuals with occasional pain had significantly higher anxious depression scores than individuals with no pain, and individuals with frequent pain in turn had significantly higher anxious depression scores than individuals with occasional pain (with the exception of facial pain, which showed the same trend but did not reach significance). This effect was observed in both males and females, indicating that there is a strong relationship between pain and anxious depression that is not explained by sex differences in pain and anxious depression. A similar relationship was observed between anxious depression and pain grade (Table 5): with increasing pain grade, higher anxious depression scores were reported ($F[4, 5123] = 169.77$, $P < .001$). Again, this effect was seen in both males and females ($F[4, 2975] = 43.18$, $P < .001$, and $F[4, 4260] = 96.05$, $P < .001$, respectively).

Finally, we investigated the relationship between the co-occurrence of pain symptoms and anxious depression. The results showed that the number of both frequent

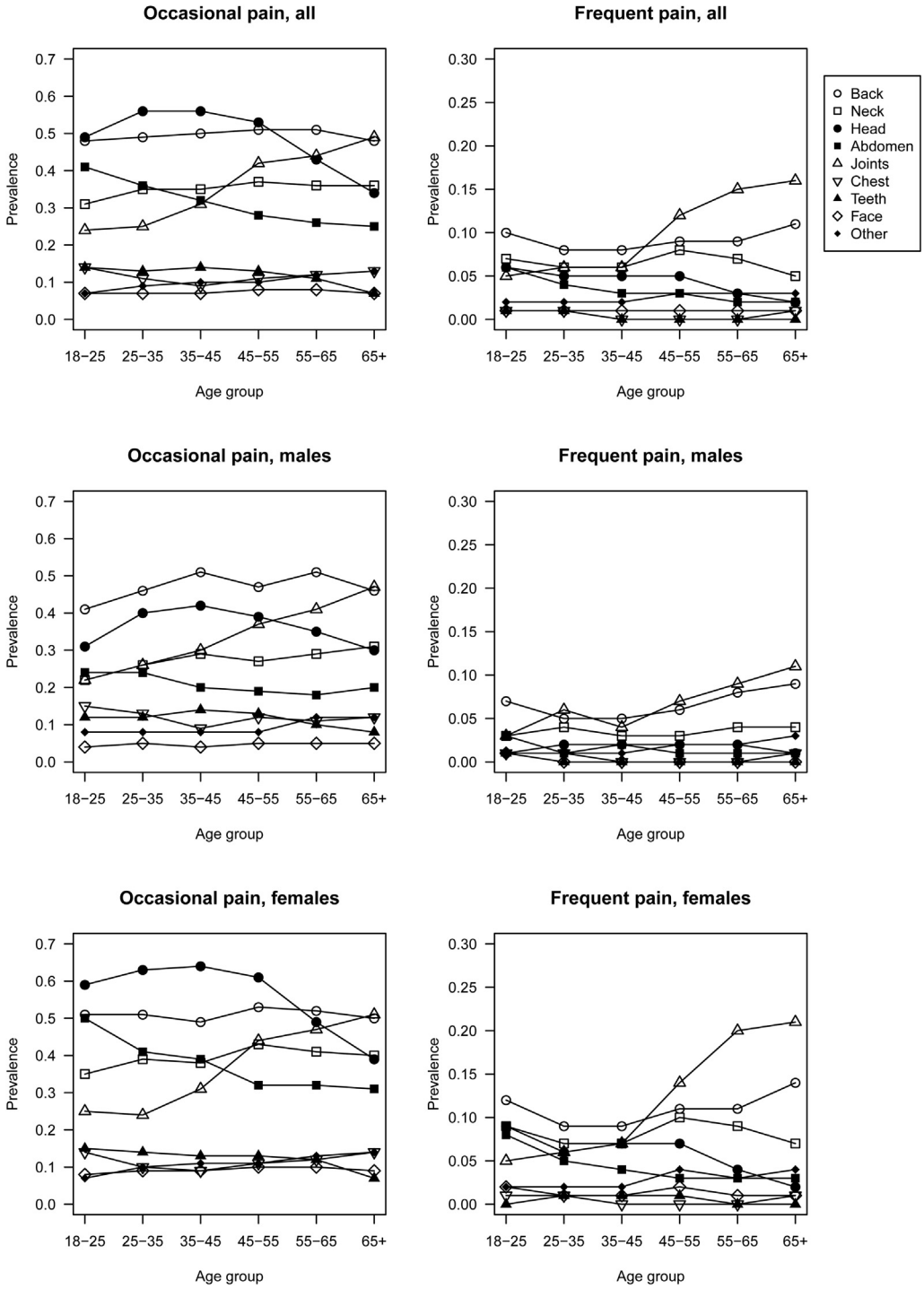

Figure 1. Prevalence of each pain type by age, sex, and pain frequency.

and occasional pain locations was positively and significantly associated with anxious depression scores (F[2, 5204] = 603.54, $P < .001$). The unstandardized regression coefficient (reflecting the difference in anxious depression score associated with one additional reported pain site) was substantially larger for frequent pain (b = 1.74, t = 22.59, $P < .001$) than for occasional pain (b = .81, t = 26.57, $P < .001$), indicating that the number of frequent pain sites is more strongly associated with anxious depression than the number of occasional pain sites. In other words, high anxious depression scores are associated most strongly with frequent pain in multiple anatomic sites. As in the previous analyses, the effect was not explained by sex; after including sex in the analyses as a covariate, the regression coefficients remained similar (b = 1.68, t = 21.46, $P < .001$, and b = .77, t = 24.77, $P < .001$, for frequent and occasional pain, respectively). The relationships between multisite pain and the other variables assessed in this study are illustrated in Table 6, which shows the mean age, sex distribution, and mean anxious depression scores for individuals with 0 or 1, 2 or 3, 4 to 6, and 6 to 9 reported pain sites, separated by

Table 3. Tetrachoric Correlations Between Pain in Different Locations

	Back	Neck	Head	Abdomen	Joints	Chest	Teeth	Face	Other
2 categories, any pain versus no pain									
Back	1.00								
Neck	.47	1.00							
Head	.31	.43	1.00						
Abdomen	.27	.31	.40	1.00					
Joints	.33	.36	.19	.19	1.00				
Chest	.21	.29	.23	.34	.27	1.00			
Teeth	.12	.13	.15	.19	.12	.17	1.00		
Face	.24	.40	.38	.33	.29	.33	.24	1.00	
Other	.18	.22	.16	.20	.39	.27	.14	.34	1.00
2 categories, chronic pain versus all other									
Back	1.00								
Neck	.68	1.00							
Head	.39	.63	1.00						
Abdomen	.45	.47	.45	1.00					
Joints	.55	.53	.32	.38	1.00				
Chest	.42	.47	.43	.60	.38	1.00			
Teeth	.24	.29	.35	.34	.25	.52	1.00		
Face	.38	.55	.51	.46	.43	.55	.61	1.00	
Other	.49	.43	.24	.40	.65	.52	.21*	.38	1.00

NOTE. P values $\leq$.001, except *P = .057.

number of occasional and frequent pain sites. Consistent with the analyses for the separate pain sites, the mean age is similar in all groups. However, the percentage of females and mean anxious depression scores increase considerably with the number of reported pain sites.

Discussion

This study is one of the largest to date to investigate the prevalence of pain across a wide range of pain sites. In addition, we investigated the comorbidity among these different pain sites, as well as between pain sites and anxious depression, which allowed us to obtain a unique overview of patterns in prevalence and comorbidity in a general population sample. The prevalence of frequent pain in this sample (22.1%) was similar to the estimate of 18% for chronic pain in The Netherlands, reported in a large European study.[9] The results of this study confirm our hypotheses of a consistent pattern of comorbidity among pain symptoms, as well as between pain and anxious depression. In general, an unfavorable pattern was observed with respect to health and lifestyle variables; low educational attainment, poor self-rated health, high BMI, and smoking and lack of exercise were all associated with a higher prevalence of pain symptoms. Overall, women reported more pain symptoms, and a modest relationship was observed between pain and older age. However, closer inspection showed that these effects cannot be generalized across different types of pain: Remarkable differences between pain sites were observed.

The observation that, overall, women report more pain symptoms than men is consistent with previous literature.[13,16,30] However, we found that the strength of this relationship strongly depends on the location of the pain. Headache and abdominal pain showed the strongest association with sex, followed by facial, neck, back, and joint pain, categories that include mostly musculoskeletal pain symptoms. Chest pain and toothache, on the other hand, were not (significantly) associated with sex. This indicates that the female preponderance in pain may depend on mechanisms underlying specific pain types.[28] These findings are largely in accordance with other studies, which typically also report a strong female preponderance especially for headache and abdominal pain.[16,32-34,37]

Similar observations were made with respect to age. A unique aspect of this study was the possibility to evaluate the role of age in a wide range of pain sites, treating pain in the joints as a separate category. In many studies, the latter is not possible because widespread pain is typically assessed by physical location (eg, legs/feet, arms/hands, lower/upper back, etc), not treating pain in joints throughout the body as a separate "site." Interestingly, we observed that joint pain was the only pain type that showed a sharp increase with age. Headache and abdominal pain were also associated with age but showed a different pattern. For occasional headache, we observed the pattern typically reported for migraine and tension-type headache in the literature, with an initial increase in prevalence from childhood to adolescence, and a decrease after the age of 50.[32,33] Chronic headache and abdominal pain decreased with age. Most other pain sites showed at most a moderate relationship with age. These results are fairly consistent with those of Rustøen et al and Hardt et al, who also observed a distinctive age-related prevalence pattern for headache.[16,31] Although joint pain was not assessed as a separate category in these studies, Rustøen et al report a sharp increase in the prevalence of osteoarthritis with age, consistent with our observation that osteoarthritis was a commonly reported cause of joint pain that is likely to explain the distinctive age pattern. With respect to headaches, it is commonly

Table 4. Mean Anxious Depression Score by Pain Location, Frequency, and Sex

	Mean Anxious Depression Score			P Value	
	No Pain	Occasional Pain	Frequent Pain	Occasional Pain Versus No Pain	Frequent Pain Versus Occasional Pain
All					
Back	3.6	4.6	6.7	<.001	<.001
Neck	3.5	5.2	8.0	<.001	<.001
Head	3.3	5.1	8.6	<.001	<.001
Abdomen	3.4	5.8	10.2	<.001	<.001
Joints	3.9	4.7	6.2	<.001	<.001
Chest	4.0	7.1	12.7	<.001	<.001
Teeth	4.2	5.7	10.1	<.001	.001
Face	4.1	7.4	8.8	<.001	.062
Other	4.0	5.9	8.0	<.001	<.001
Males					
Back	2.8	3.6	5.5	<.001	<.001
Neck	2.8	4.3	6.4	<.001	<.001
Head	2.8	4.0	8.6	<.001	<.001
Abdomen	2.8	5.0	8.2	<.001	.001
Joints	2.9	3.8	5.0	<.001	<.001
Chest	3.0	5.6	8.7	<.001	.04
Teeth	3.2	4.4	11.4	<.001	.012
Face	3.2	6.3	9.1	<.001	.164
Other	3.1	4.7	6.2	<.001	.063
Females					
Back	4.2	5.2	7.2	<.001	<.001
Neck	4.0	5.6	8.4	<.001	<.001
Head	3.7	5.5	8.6	<.001	<.001
Abdomen	3.9	6.1	10.5	<.001	<.001
Joints	4.6	5.2	6.6	<.001	<.001
Chest	4.6	8.1	15.3	<.001	<.001
Teeth	4.8	6.5	9.6	<.001	.022
Face	4.7	7.8	8.8	<.001	.213
Other	4.7	6.6	8.7	<.001	<.001

NOTE. *P* values are shown for the comparison between occasional pain and no pain and for frequent pain versus occasional pain.

hypothesized that hormonal factors explain at least part of the age- and sex-related differences in prevalence.[10,19] A similar mechanism might apply to abdominal pain (eg, menstrual pain). An additional explanation might be that headache and abdominal pain are strongly related to daily life stress experienced by young adults, such as work and care for children,[34] which may affect men and women differently. Given the more modest sex effects and the different age-related patterns observed for facial, neck, back, and joint pain, we might speculate that in musculoskeletal pain, these factors are relatively less important. This would be worth investigating further in future studies.

Our findings are consistent with observations in experimental pain research on the effects of sex and age. A review summarizing 10 years of literature on experimental pain research reported that females had lower pressure and thermal pain thresholds compared to males, but that this was not the case for other pain modalities.[28] Studies on age-related changes in experimental pain

Table 5. Mean Anxious Depression Score by Pain Grade and Sex

	All		Male		Female	
Pain Grade	n	Anxious Depression Score, M (SD)	n	Anxious Depression Score, M (SD)	n	Anxious Depression Score, M (SD)
0	1,223	2.14 (3.57)	728	2.00 (3.54)	495	2.34 (3.60)
I	5,347	3.87 (4.56)	2,301	3.13 (4.13)	3,046	4.43 (4.79)
II	3,409	5.36 (5.79)	950	4.50 (5.50)	2,459	5.69 (5.87)
III	801	6.14 (6.27)	209	4.76 (5.59)	592	6.63 (6.42)
IV	471	6.98 (6.75)	110	5.55 (6.52)	361	7.41 (6.76)
Missing	412	3.34 (4.24)	170	2.21 (3.02)	242	4.13 (4.77)
Overall	11,663	4.39 (5.23)	4,468	3.34 (4.58)	7,195	5.04 (5.49)

Abbreviations: M, mean; SD, standard deviation.

Table 6. Age and Sex Distribution and Anxious Depression Scores by Reported Number of Occasional and Frequent Pain Sites

No. of Sites	No. of Subjects, n (%)	Age, M (SD)	% Female	Anxious Depression Score, M (SD)
Occasional pain sites				
0 or 1	3,845 (33)	44.3 (16.2)	50.6	3.0 (4.4)
2 or 3	4,981 (42)	44.6 (15.6)	63.6	4.4 (5.1)
4–6	2,773 (24)	44.6 (15.3)	73.2	6.0 (5.7)
7–9	188 (2)	45.2 (15.3)	72.3	8.8 (7.5)
Total	11,787 (100)	44.5 (15.7)	61.7	4.4 (5.2)
Frequent pain sites				
0 or 1	10,737 (91)	44.4 (15.7)	60.1	4.0 (4.8)
2 or 3	895 (8)	45.4 (16.5)	77.3	7.6 (6.9)
4–6	147 (1)	45.3 (14.7)	86.4	11.6 (8.1)
7–9	8 (0)	44.9 (17.0)	87.5	17.6 (10.0)
Total	11,787 (100)	44.5 (15.7)	61.7	4.4 (5.2)

Abbreviations: M, mean; SD, standard deviation.

typically report that although pain tolerance tends to decrease or remain stable, pain thresholds increase with increasing age. Endogenous pain inhibition, on the other hand, appears to decrease with age.[22] Thus, findings in experimental pain research support sex differences for some, but not all, pain modalities, and both increased and decreased pain symptomatology in the elderly, depending on the underlying mechanisms. Therefore, it seems plausible that pain conditions differ in how they relate to sex and age, if the underlying biological mechanisms are (partly) different. Taken together, the lack of obvious patterns in sex and age effects on both clinical and experimental pain emphasizes that generalized statements regarding these effects should be avoided. It also indicates that further investigation is warranted, as these seemingly inconsistent patterns may reflect relevant differences in the mechanisms underlying different types of pain. Importantly, the effects of age and sex should be studied separately for different pain sites, as distinctive patterns were observed depending on pain location.

In our analyses of comorbidity, we observed a consistent co-occurrence of pain symptoms, which was stronger for frequent pain than for "any pain" (ie, frequent and occasional pain taken together), indicating that frequent pain in particular tends to occur in multiple sites. Relatively strong correlations were observed for body sites located close together (eg, back and neck, and face, neck, and head), possibly reflecting that overlapping symptomatology caused some inflation of the correlations. Relatively low (but significant) correlations were observed between toothache and other pain types, suggesting that toothache may be relatively distinct from the other pain types. Possibly, dental pain is specifically associated with dental health–related behavior, caries susceptibility, dental decay, or other oral problems.

In addition, we observed that pain was consistently associated with anxious depression, regardless of its location. Frequent pain was associated with higher anxious depression scores than occasional pain. These effects were observed in both males and females, indicating that they are not explained by the fact that both pain and anxious depression are more prevalent in females. This adds to our previous findings in a cohort of patients with anxiety and/or depressive disorders,[24] indicating that these findings are not limited to clinical populations but also apply to the general population. Finally, we found that the number of reported pain sites was strongly related to anxious depression, particularly for locations with frequent pain. In other words, participants with high anxious depression scores have more widespread and more frequent pain symptoms. Because our analyses do not address direction of effect, this could be interpreted in several ways. First, it could indicate that long-lasting pain eventually results in anxious depressive symptoms. However, in a prospective study of depressive symptoms in patients with back pain, pain duration was not associated with depression severity, as would be expected if depression were a psychological reaction to the long-lasting disability and suffering associated with chronic pain.[39] Moreover, if depression and anxiety were a consequence of pain, it would be expected that these conditions follow, rather than precede, pain in the majority of cases. However, longitudinal studies have shown that this is not the case. For example, Gureje et al investigated whether anxiety and depression predicted persistent pain and vice versa and observed a symmetrical relationship where each predicted the other with equal strength, suggesting no particular direction of causality.[15] Several other studies report similar findings.[3,23] A second possibility is that pain should be viewed as a symptom of anxious depression, and that pain related to anxious depression tends to be widespread and chronic.[5,23] It has been hypothesized that pain and depression co-occur because they are both affected by the same modulatory neural system. A disturbance in this system (eg, due to serotonin depletion) might cause the amplification of incoming signals that are normally suppressed.[5,12] The same might be hypothesized for anxiety disorders. This could explain our finding that anxious depression tends to be associated with multiple pain symptoms, as well as reports that patients with comorbid anxiety or depression often have "medically unexplained" pain.[5,20] Indeed, it has been found that pain with a defined cause is associated with psychiatric disorders less often than is "medically unexplained" pain.[25] Further research is needed to elucidate which mechanisms underlie the consistent co-occurrence of pain disorders and (anxious) depression we observed.

In summary, this study shows that although there are remarkable similarities among pain disorders in terms of comorbidity, there are also remarkable differences among them. All pain symptoms investigated in this study, regardless of anatomic site, were found to be associated with anxious depression, as well as with other pain symptoms. On the other hand, sex and age effects are prominent for some pain sites, and modest or absent in others. This indicates that although investigating different types of chronic pain jointly is essential given the extensive comorbidity between them, the specific

mechanisms underlying certain types of pain are at least partly distinct. Therefore, any generalized statement regarding the effects of age and sex on "chronic pain" should be interpreted with caution. These findings highlight important differences as well as similarities in the etiology of pain symptoms, which may help us better understand the nature of specific pain conditions as well as pain in general.

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