The interplay between depression, anxiety and physical health

Gerrits, M.J.G.

2014

document version
Publisher's PDF, also known as Version of record

Chapter 3

Anxiety and depression are associated with migraine and pain in general: an investigation of the interrelationships

Lannie Ligthart, Marloes M.J.G. Gerrits,
Dorret I. Boomsma, Brenda W.J.H. Penninx

Published in: the Journal of Pain. 2013 Apr;14(4):363-70.

ABSTRACT

There is a well-established comorbidity between migraine and anxiety and depressive disorders (A/D). Here, we investigate whether this relationship is specific for migraine and A/D or whether other types of pain are also consistently associated with A/D. In addition, we test whether there is a consistent association between migraine and other types of pain when comorbidity with A/D is controlled for.

Data on anxiety and/or depressive disorders (A/D), migraine and six non-headache pain locations (back, neck, orofacial, abdominal, joints and chest) were analyzed in 2,981 participants from the Netherlands Study of Depression and Anxiety (NESDA). It was tested whether the prevalence of pain in each individual location, as well as the total number of pain locations depended on A/D and migraine status. A/D was consistently associated with pain in all measured locations. Migraine was also associated with pain in all anatomical sites, but these associations weakened substantially after correction for A/D severity, suggesting that a considerable part of the comorbidity of migraine and other types of pain may be explained by A/D. These findings emphasize the importance of accounting for A/D in studies of pain comorbidity. This will contribute towards a better understanding of the mechanisms underlying A/D and pain.

Perspective

Anxiety and depression are consistently associated with pain, regardless of anatomical site. These disorders may be important factors in the co-occurrence of different pain disorders. Awareness of this comorbidity and a better understanding of the underlying mechanisms may facilitate adequate treatment of both types of conditions.

INTRODUCTION

There is a well-established comorbidity between migraine and anxiety and depressive disorders. While both anxiety and depression individually are associated with an increased risk of migraine, the risk of migraine is even higher in patients with comorbid anxiety and depression[1]. A limited number of studies have investigated the order of onset of migraine, anxiety and depression. One study reported that anxiety tended to precede migraine, while depression most commonly followed migraine onset[1]. However, a study that focused on depression only, reported a bidirectional association between migraine and depression, with either migraine or depression occurring first, and each disorder predicting the onset of the other[2]. Migraine is probably the best-studied pain disorder in the context of comorbidity with anxiety and depression[2-6]. Other pain disorders have not received the same amount of attention, however, several of them have also been reported to be comorbid with anxiety and depressive disorders, including back pain, fibromyalgia and irritable bowel syndrome[4;7-9]. Migraine has also been reported to be comorbid with other pain disorders, consistent with the observation that pain disorders in general tend to cluster within patients[10;11]. For instance, studies in adults have reported comorbidity of migraine with musculoskeletal pain[12], fibromyalgia[13;14], and neck pain[15]. In children, headaches in general and migraine in particular were found to be comorbid with conditions including recurrent abdominal pain and neck-shoulder pain[16].

Although the complex pattern of comorbidity between pain disorders and anxiety is well-established, many studies still focus on specific disorders and do not take other comorbidities into account. This makes it difficult to integrate these findings into a comprehensive theory explaining the mechanisms underlying these comorbid relationships. The aim of the present paper is to perform a systematic study of these comorbidities, taking migraine (being among the best-studied pain disorders in the context of psychiatric comorbidity) as a starting point. With this study, we intend to answer two questions: first, is there a specific relationship between migraine and A/D, or is the comorbidity of A/D and pain disorders independent of anatomical site? And second, is there a consistent association between migraine and other pain disorders after correction for the well-known comorbidity of migraine and A/D?

METHODS

Participants

This study was conducted in 2,981 participants from the Netherlands Study of Depression and Anxiety (NESDA). This is a longitudinal cohort study that includes individuals with current (six-month recency) and remitted diagnoses of anxiety and depression, as well as healthy controls. Participants were recruited from a variety of settings: 1,610 entered the study through primary care, 807 were recruited from specialized mental health care and 564 came from two population-

based studies on mental health[17]. Of these participants, 1,002 (34%) were male and 1,979 (66%) were female. The participants were aged between 18 and 65, with a mean age of 41.9 (± 13.1) years. All participants underwent a 4-hour baseline assessment at one of seven clinic sites between September 2004 and February 2007. The assessment included an interview on somatic health, functioning and health care use, and the administration of several written questionnaires[18]. Pain and measurements of anxiety and depression were repeated in a two-year follow-up assessment that started in 2006. Migraine was only measured at the first assessment. A detailed description of data collection procedures in the NESDA study can be found elsewhere[17]. The research protocol was approved by the Ethics Committee of participating universities and all respondents provided written informed consent.

Measures

Anxiety/Depression

During the baseline assessment, current and lifetime diagnoses of anxiety and depressive disorders according to DSM-IV criteria[9;19](APA) were made in all 2,981 participants, with the Composite International Diagnostic Interview (CIDI), version 2.1[20]. The anxiety diagnoses included social phobia, panic disorder, agoraphobia and generalized anxiety disorder; depressive disorder diagnoses included major depressive disorder and dysthymia. Based on these diagnoses, patients were classified into 5 categories: 1) *no anxiety or depression*, 2) *remitted anxiety and/or depression,* 3) *current anxiety only*, 4) *current depression only* , 5) *current anxiety and depression*. Individuals were only included in the remitted anxiety and/or depression category if no current diagnoses were present. The current diagnosis categories include both first onset cases and individuals with a previous history of anxiety and/or depression. For simplicity, anxiety and/or depressive disorders will be collectively referred to as "A/D" throughout the rest of the paper.

Two additional measures were used to assess the severity of anxiety and depressive symptoms. The severity of anxiety was measured using the 21-item Beck Anxiety Inventory (BAI)[21]. On this scale, a score of 0-9 is thought to indicate normal anxiety, 10-18 indicates mild-moderate, 19-29 indicates moderate-severe, and 30-63 indicates severe anxiety[22]. Depression severity was measured with the self-rated Inventory of Depressive Symptomatology (IDS-SR_{30})[23;24], which consists of 30 questionnaire items addressing all DSM-IV symptom domains for MDD, as well as some associated symptoms and melancholic and atypical features. Scores on this scale can vary between 0 and 84. A score of 0-13 is defined as no depression, 14-25 as mild depression, 26-38 as moderate depression, 39-48 as severe depression, and 49-84 as very severe depression (www.ids-qids.org). Several items in the BAI and IDS are potentially confounded with pain symptomatology: the BAI includes one item on numbness/tingling sensations (potentially confounded with migraine aura), and one on abdominal pain; the IDS includes four items on sleeping problems (which can exacerbate pain symptoms[25]), one item on the presence of aches and pains, and one item on other bodily symptoms (including chest pain). To test the potential confounding effects of these items, we also calculated scale scores that did not include these items. BAI scores were available for 2,946 participants (99%), and an IDS score was available for 2,942 participants (99%), from the first wave of data collection. Two-year follow-up data were available for 2596 subjects (87%)[26]. Of these participants, 2,503 and 2,504 provided complete BAI and IDS information, respectively.

Migraine

Migraine symptomatology was assessed in the context of the baseline assessment, using a written questionnaire that included items on the following symptoms relevant for an ICHD-II[27] migraine diagnosis: having had *at least 5 episodes* of migraine, headaches lasting *4-72 hours*, *pulsating quality*, *moderate/severe pain intensity*, *aggravation by physical activity*, *nausea/vomiting* accompanying the headache, *photo- or phonophobia* accompanying the headache, and *visual aura*. The questionnaire was completed by 2,601 of the 2,981 individuals (87%). Participants were classified as having strict migraine (ICHD-II 1.1, migraine without aura or 1.2, migraine with aura), probable migraine (ICHD-II 1.6.1, probable migraine without aura or 1.6.2, probable migraine with aura), mild non-migrainous headache (all headaches which did not meet the criteria above) or no headache, following the ICHD-II criteria as closely as possible based on the available symptom data. More detailed information on the migraine classification can be found elsewhere[28]. The clinical characteristics of the three groups of headache sufferers are shown in Table 1. Participants who provided insufficient symptom information to confirm or exclude a migraine diagnosis (because one or more of the ICHD-II criteria was missing, most commonly headache duration) were classified as having unknown headache status (n=113). Individuals with missing headache data or unknown headache status were excluded from analyses that involved the migraine data.

Table 1: Clinical features of migraine in the NESDA sample.

	non-migrainous headache		**probable migraine**		**strict migraine**	
>= several times a year	279	83%	382	90%	453	100%
Mean headache duration (hours)	2.92		8.14		14.78	
% Pulsating headache	113	34%	219	51%	252	56%
Moderate-severe headache	242	72%	401	94%	447	99%
Aggravation by physical activity	158	47%	346	81%	421	93%
Nausea and/or vomiting	29	9%	148	35%	270	60%
Photo and/or phonophobia	73	22%	304	71%	427	94%
Visual aura	90	27%	154	36%	195	43%
Total	335		426		453	

Pain

Pain symptoms in other locations of the body were assessed in all 2,981 participants, with a face-to-face structured interview that included the Graded Chronic Pain Scale (GCPS), developed by von Korff and colleagues[29]. This interview was part of the baseline assessment, and was repeated after two years. Participants were asked whether they had experienced pain in 7 different locations (back, neck, head, abdominal, joints, chest and orofacial) in the last 6 months. Based on these pain reports, the total number of pain locations was calculated, and investigated as a function of A/D and migraine status. Headache was excluded from this count to avoid overlap with the migraine assessment.

Statistical analysis

The association of individual pain locations with A/D or migraine status was tested with logistic regression analyses, with pain in a particular location (dichotomous variable) as the dependent variable and sex, age and dummy variables representing A/D or migraine status as the independent variables. From these logistic regression analyses, odds ratios (OR) were obtained for each type of pain depending on A/D and migraine status.

Linear regression analysis was performed to test whether pain characteristics differed depending on A/D status or migraine status. In the first set of analyses, the number of pain locations was predicted from current and remitted A/D status, with sex and age included as covariates. In the second set of analyses, the number of pain locations was predicted from migraine status, with sex, age, BAI and IDS included as covariates. Since the association between A/D or migraine and number of pain sites did not depend on sex or age, no interaction effects were included in the final models.

To test whether changes in A/D severity were associated with changes in pain symptomatology over time, we calculated the difference between BAI and IDS scores at baseline and two-year follow-up, as well as the difference in the number of pain symptoms. A Spearman correlation was calculated between the difference scores for BAI and IDS and the pain difference scores. All statistical analyses were performed in SPSS 17 for Windows (SPSS Inc, Chicago, IL).

RESULTS

Table 2 shows the prevalence of each A/D and headache category, the prevalence of pain in each anatomical site, and the number of pain sites reported by the participants of this study. The severity of anxiety (BAI) and depression (IDS) is shown for each category of patients. A high level of psychiatric comorbidity was observed: 31% of participants had either an anxiety or a depressive disorder, and almost as many (26%) had a combination of both. Patients with combined anxiety and depression also had the highest mean BAI and IDS scores. Another 21% of participants had a remitted diagnosis of either anxiety or depression. Individuals with a remitted A/D diagnosis had considerably lower BAI and IDS scores than individuals with a current diagnosis, but a higher score than individuals who were never diagnosed with A/D. BAI and IDS scores were also associated with migraine status, confirming the association between migraine and A/D that is reported in the literature. Increasing BAI and IDS scores corresponded with increasing severity of the headache. Individuals who reported any of the six non-headache pain types also had a higher mean BAI and IDS score, compared to individuals who reported no pain at all in the last six months. Finally, a higher number of reported pain locations was associated with a higher mean BAI and IDS score. Reports of no pain (6%) or only one type of pain (13%) were relatively rare; the vast majority of participants (81%) reported pain in more than one region of the body.

Our first objective was to test whether there was a specific association between A/D and migraine or whether A/D was comorbid with pain, regardless of anatomical site. In Figure 1, sex and age-adjusted odds ratios are shown for pain reports in each body location by A/D status. Both anxiety and depression were strongly associated with pain in all reported locations. All types of pain were significantly associated with *current* anxiety or depression, and especially combined anxiety and depression. The associations were considerably weaker and commonly non-significant for *remitted* anxiety and/or depression. The strongest associations were observed between A/D and neck pain, chest pain and strict migraine. Probable migraine and mild non-migraine headache were less strongly associated with A/D than strict migraine, possibly reflecting stronger comorbidity with A/D in patients with more severe headaches. The associations with A/D were weakest for back and joint pain.

Linear regression analysis also showed a significant association between A/D and the total number of reported pain locations (Table 3). A current diagnosis of A/D was associated with a larger number of pain locations than a remitted diagnosis, and combined anxiety and depression were associated with a significantly larger average number of reported pain locations than anxiety only or depression only.

Table 2: Prevalence of depression, anxiety, headaches and pain in other locations, and severity of anxiety and depression by diagnosis.

	N	%	mean BAI score (95% CI)	SD	mean IDS score (95% CI)	SD
Total sample	2,981	100%	12.1 (11.72 - 12.49)	10.7	21.5 (21.0 - 22.0)	14.1
No anxiety or depression	652	22%	4.0 (3.7 - 4.4)	4.9	8.6 (8.0 - 9.1)	7.5
Remitted anxiety or depression	628	21%	7.1 (6.6 - 7.7)	6.5	14.2 (13.5 - 14.9)	8.9
Current anxiety*	543	18%	14.8 (14.0 - 15.6)	9.4	22.0 (21.2 - 22.8)	9.6
Current depresssion*	396	13%	12.2 (11.4 - 13.1)	8.8	27.9 (26.8 - 29.0)	11.2
Current anxiety + depression*	762	26%	21.2 (20.4 - 22.0)	11.1	35.1 (34.2 - 35.9)	12.0
No headache	1274	43%	9.5 (9.0 - 10.0)	9.3	17.7 (17.0 - 18.4)	13.1
Mild non-mig. headache	335	11%	10.7 (9.6 - 11.7)	9.8	19.7 (18.3 - 21.0)	12.6
Probable migraine	426	14%	13.5 (12.5 - 14.5)	10.8	23.5 (22.1 - 24.9)	14.4
Migraine	453	15%	15.7 (14.6 - 16.7)	11.4	27.0 (25.6 - 28.3)	14.7
No pain	167	6%	5.1 (4.1 - 6.2)	6.9	11.6 (9.9 - 13.3)	11.3
Back pain**	1895	64%	13.8 (13.3 - 14.3)	11.0	23.8 (23.2 - 24.5)	14.1
Neck pain**	1532	51%	15.1 (14.5 - 15.6)	11.1	25.5 (24.8 - 26.2)	14.0
Facial pain**	401	13%	18.0 (16.8 - 19.3)	12.5	27.7 (26.3 - 29.1)	14.2
Abdominal pain**	1432	48%	15.3 (14.7 - 15.9)	11.1	25.5 (24.8 - 26.2)	13.8
Joint pain**	1435	48%	14.4 (13.8 - 15.0)	11.4	24.7 (24.0 - 25.5)	14.2
Chest pain**	764	26%	18.6 (17.7 - 19.5)	12.2	28.6 (27.6 - 29.6)	14.0
0-1 pain locations	557	19%	6.0 (5.4 - 6.6)	6.9	12.9 (11.9 - 13.8)	11.2
2-3 pain locations	1142	38%	10.1 (9.6 - 10.7)	9.4	19.0 (18.3 - 19.8)	13.0
4-5 pain locations	969	33%	14.5 (13.9 - 15.1)	9.9	25.6 (24.8 - 26.5)	13.2
6-7 pain locations	313	10%	23.1 (21.7 - 24.5)	12.3	33.2 (31.7 - 34.7)	13.4

Abbreviations: CI = confidence interval; SD = standard deviation.

NOTE. Total number of individuals in each category, and the mean BAI and IDS scores by category at baseline. The mean scores are based on a slightly lower number of individuals (2,942 and 2,946, respectively, total sample size 2,981) due to missing data for these measures.

*Individuals with current depression and/or anxiety may also have a remitted disorder, individuals classified as having remitted A/D do not have current diagnoses.

**Pain categories are non-mutually exclusive because many patients had pain in multiple locations in the six month period before the assessment.

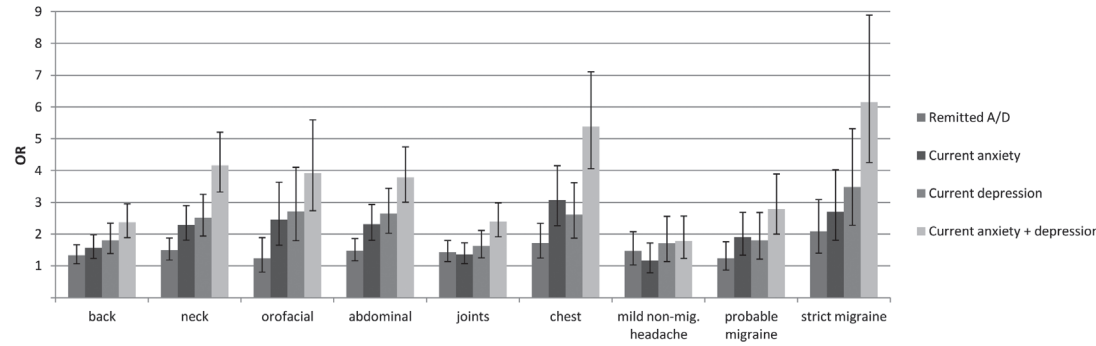

Figure 1 The sex and age-adjusted odds ratios (ORs) for pain reports at various body sites in patients with current and remitted anxiety and/or depression, compared to individuals without anxiety or depression. Results are reported for all non-headache pain sites and for several different classifications of (migrainous) headache: mild non-migraine headaches, probable migraine and strict migraine.

Table 3: Relationship between pain characteristics and A/D category.

Number of pain locations (non-headache)				
	B	**95% CI**	**β**	**P**
Constant	1.26	(1.04 - 1.48)		0.000
Remitted anxiety and/or depression	0.41	(0.25 - 0.57)	0.11	0.000
Current anxiety	0.81	(0.65 - 0.98)	0.20	0.000
Current depression	0.93	(0.74 - 1.11)	0.20	0.000
Current anxiety + depression	1.48	(1.33 - 1.64)	0.41	0.000
Age	0.01	(0.00 - 0.01)	0.05	0.007
Female sex	0.40	(0.29 - 0.52)	0.12	0.000

NOTE. Results of a regression analysis with number of pain locations as the dependent variable, and A/D status, sex and age as the independent variables.

The stronger association of pain with current than with remitted anxiety and depression suggests that changes in A/D are associated with changes in pain. However, it is also possible that individuals with a remitted diagnosis were less severely affected, on average, and that this is the reason they reported less pain symptoms. To further examine this, we tested whether changes in A/D severity corresponded with changes in pain symptomatology between the baseline measurement and the two-year follow-up. This was indeed the case; changes in the number of reported pain sites were modestly positively correlated with changes in IDS scores (Spearman's rho = .158, $p < .001$). The same was observed for the BAI difference scores, which showed a correlation of .147 ($p < .001$) with the number of pain locations. These effects were not explained by the pain-related items in the BAI and IDS: after exclusion of these items, the analyses produced very similar results (data not shown).

Our second objective was to investigate the association between migraine and pain in other anatomical sites. Again, a consistent association was found with pain in all body sites (Fig. 2A). Probable and strict migraine were significantly associated with all types of pain, as reflected by ORs significantly larger than one when compared to individuals without headache. Mild non-migraine headache was significantly associated with all pain locations except orofacial pain and joint pain.

Interestingly, however, the associations of pain with probable migraine, and particularly strict migraine weakened considerably after adjustment for comorbid A/D, as reflected by reduced ORs for all pain sites (Figure 2B). This effect was not explained by the pain-related items in the BAI and IDS: after exclusion of these items from the scale scores, the results were highly similar (data not shown). This indicates that the associations between migraine and pain in other locations were at least partly explained by the correlation between migraine and A/D. The remaining association between migraine and other pain disorders (i.e., the part of the association not explained by comorbid A/D) was strongest for neck, orofacial and abdominal pain. There was no longer a consistent pattern with respect to the severity of the headache and the strength of the association.

Similar results were obtained with a linear regression analysis in which the number of non-headache pain sites was predicted from migraine status, while correcting for sex and age only in the first model, and sex, age, BAI and IDS scores in the second model. Table 4 shows that, as expected, migraine status was a significant predictor of the total number of pain locations reported. The number of reported pain locations increased with the severity of the headache, with strict migraine sufferers reporting the largest number of other pain locations. However, consistent with our findings for the individual pain locations, a considerable proportion of the association between migraine status and number of pain sites was explained by A/D severity. After adjusting for BAI and IDS scores, the associations between the three headache categories and the number of pain locations were still significant, but the regression betas decreased considerably. The same was observed when pain-related items were excluded from the BAI and IDS scale scores, indicating that this effect was indeed explained by anxiety and depression, and not by confounding of BAI and IDS with pain symptomatology.

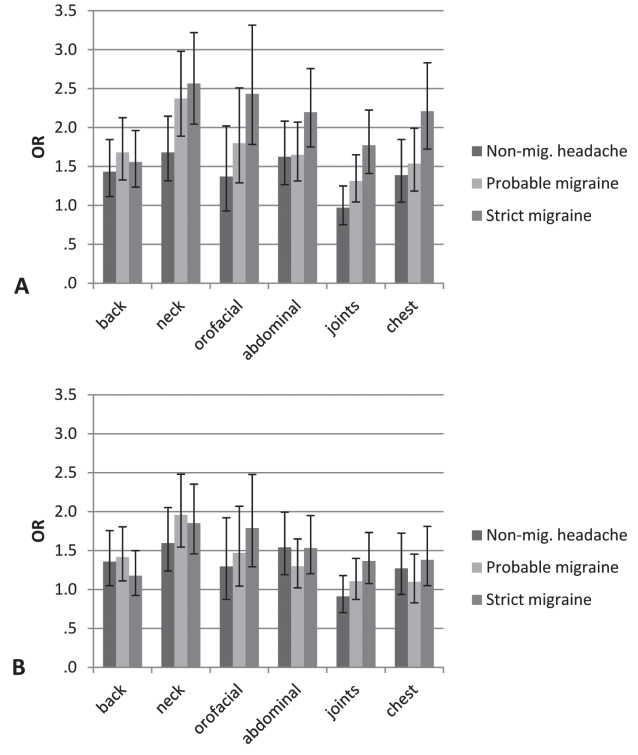

Figure 2 (A) Odds ratios (ORs) for pain in each location, in individuals with different categories of headache and migraine compared to individuals without headaches, adjusted for sex and age. (**B)** Odds ratios (ORs) for pain in each location, in individuals with different categories of headache and migraine compared to individuals without headaches, adjusted for sex, age and severity of anxiety and depression (BAI and IDS scores, respectively).

Table 4: Relationship between the number of (non-headache) pain sites and migraine status.

	Adjusted for sex and age				Adjusted for sex, age and A/D severity			
	B	95% CI	β	P	B	95% CI	β	P
Constant	1.539	(1.308 - 1.771)		.000	0.888	(0.670 - 1.106)		.000
Mild non-migr. headache	0.406	(0.225 - 0.587)	0.089	.000	0.311	(0.147 - 0.475)	0.068	.000
Probable migraine	0.649	(0.483 - 0.815)	0.158	.000	0.363	(0.211 - 0.514)	0.088	.000
Migraine	0.907	(0.743 - 1.071)	0.226	.000	0.461	(0.308 - 0.614)	0.115	.000
Female sex	0.230	(0.103 - 0.358)	0.070	.000	0.237	(0.122 - 0.352)	0.072	.000
Age	0.009	(0.005 - 0.014)	0.079	.000	0.007	(0.003 - 0.011)	0.060	.001
IDS score	-	-	-	-	0.020	(0.014 - 0.026)	0.180	.000
BAI score	-	-	-	-	0.041	(0.033 - 0.049)	0.275	.000

NOTE. Results of a regression model in which the number of reported pain locations is predicted from migraine status.

DISCUSSION

The first objective of this study was to test whether there is a specific comorbidity between A/D and migraine, or whether this comorbidity is present for all types of pain, regardless of anatomical site. The results of this study suggest the latter. The strongest associations were observed between A/D and neck pain, chest pain, and strict migraine. Probable migraine and mild non-migrainous headache were also associated with A/D, but more weakly. This suggests a stronger association with more severe headaches, but provides no evidence for a specific association between migraine and A/D, beyond the general association between A/D and pain. Consistent with previous findings[1;30], the association with pain was particularly strong in patients with combined anxiety and depression. Combined anxiety and depression was associated with a higher number of pain sites than anxiety alone or depression alone. This group also had the highest mean BAI and IDS scores, suggesting that anxiety comorbid with depression is associated with both greater pain complaints and more severe psychological symptoms than anxiety or depression alone. Furthermore, there was a much stronger association with current than with remitted A/D, suggesting that changes in A/D over time tend to coincide with changes in pain symptomatology. It is possible that patients with remitted A/D suffered from a less severe form of A/D, on average, than patients with current A/D, and that this might in part explain why participants with remitted A/D reported less pain symptoms. However, our results indeed suggest a correspondence over time: longitudinally we observed a modest but significant correlation between changes in severity of A/D and changes in the number of pain sites. The observation that remitted A/D was also (modestly) associated with pain symptomatology might be explained by residual A/D symptoms in these groups (reflected by slightly higher BAI and IDS scores compared to the individuals without a lifetime A/D diagnosis). Based on the present findings, we cannot determine whether the correspondence in A/D and pain over time might reflect a causal or "syndromic" relationship between them, although we have previously shown that this might indeed be the case for migraine and anxious depression[31]. Further studies are required to address this in more depth.

The second objective was to investigate whether migraine was consistently associated with pain in other body sites, and whether this was still the case after adjusting for comorbid A/D. Indeed, we observed a consistent association between migraine and pain in all other measured anatomical sites. However, the observed associations became considerably weaker after A/D was included in the model. The associations that remained after adjusting for the effects of comorbid A/D were most evident for neck, orofacial and abdominal pain. It is not unlikely that in many cases, these pain reports are directly related to the migraine itself. For example, neck and facial pain might reflect migraine-related allodynia; neck pain is indeed a highly prevalent symptom during migraine attacks[15]. Abdominal pain might be attributed to menstrual migraine, but also

to abdominal migraine, a form of recurrent abdominal pain often accompanied by headache and other migraine-related symptoms. This disorder is usually diagnosed in children (who often develop regular migraines later in life), but recent evidence shows it may also be relatively common in adults[32].

These findings raise the interesting question whether patients with multiple pain symptoms as well as A/D symptoms have a general liability to pain disorders, or whether the comorbidity of pain disorders is in fact largely explained by underlying anxiety or depression. The present findings suggest that this is at least partly true for the comorbidity of migraine with other types of pain. Further studies are needed to investigate this for other pain disorders.

Our finding of a consistent association between A/D and pain, regardless of anatomical site, supports the view that pain might be considered a symptom of depression[33-35]. Given the known overlap in brain regions and neurobiological processes involved in A/D and pain, and the effectiveness of antidepressants in treatment of both depression and pain[33;36], this is indeed quite plausible. For instance, it has been hypothesized that a depletion of serotonin and norepinephrine, as observed in depressed patients, might interfere with pain modulation, thus amplifying signals from the body that are normally suppressed. This might also explain why depression is often associated with pain in multiple regions. It is also thought that negative anticipation associated with A/D can activate brain regions involved in pain modulation, such as the anterior cingulate cortex[33;37].

Important strengths of this study include the large sample size, longitudinal design and extensive assessment of A/D and pain. Anxiety and depressive disorders were diagnosed with face-to-face standardized interviews based on DSM-IV criteria, and accompanied by an extensive assessment of pain and migraine symptomatology and several validated measures of A/D severity. A potential limitation is that, due to recruitment from general practice, the controls (i.e., individuals without A/D diagnoses), may not be entirely comparable with the general population in terms of pain pathology; they might have a slightly increased prevalence of pain and/or A/D symptomatology compared to the general population. However, given that this would decrease, rather than increase the differences between cases and controls in this study, it is unlikely to result in false positive findings. Nevertheless, it would be valuable to conduct a similar study in a population-based sample, such that the entire spectrum of healthy and affected individuals is covered. A second limitation is that no information regarding possible trauma or disease underlying the pain was available. Therefore, we could not determine whether a specific condition may have explained the associations we observed. In future studies, we recommend including information on the causes of pain, where possible. Furthermore, our analyses were restricted to the most common anxiety and depressive disorders; since less prevalent diagnoses such as post-traumatic stress disorder were not considered individually we do not know whether results can be generalized to less common anxiety and depressive disorders. Also, while anxiety,

depression and pain locations were assessed at two time points, migraine was only assessed in detail at baseline. Therefore, we could not evaluate the relationship between changes in A/D and changes in migraine symptomatology over time. Finally, we did not control for migraine chronicity or migraine due to medication overuse, due to a lack of specific information on these aspects. However, when we excluded all individuals with potentially chronic headaches (based on headache duration > 72 hours and headache frequency >= several times a week) our results were very similar (data not shown). Although some effect sizes related to migraine status were reduced slightly, all conclusions remained the same.

In conclusion, this study clearly demonstrates the important role of A/D in pain comorbidity. To date, many comorbidity studies have focused on the relationship between specific pain conditions and A/D. The present findings suggest that this focus is too limited, and that the role of general pain comorbidity in A/D patients should at least be taken into consideration. In the case of migraine, A/D appears to be an important factor that explains at least part of the comorbidity of this disorder with other types of pain. This may extend to other pain conditions as well. Fibromyalgia, for instance, is another pain disorder reported to be comorbid with migraine, for which high rates of depression have been reported, as well as considerable clinical heterogeneity with respect to psychiatric comorbidity[9;38]. It is of great importance to investigate the role of anxiety and depressive disorders in these patients. If the effects of A/D are not accounted for, the comorbidity between pain disorders may be misinterpreted and/or overestimated. Multiple pain symptoms associated with a severe anxiety or depressive disorder may require a different interpretation and treatment approach than pain symptoms that arise in the absence of psychiatric symptoms. Therefore we recommend that measures of A/D be included in any study aiming to address comorbidity of pain symptoms. This will help us obtain a more complete picture and a better understanding of the complex and fascinating relationship between A/D and pain.

REFERENCE LIST

1. Merikangas KR, Angst J, Isler H. Migraine and psychopathology. Results of the Zurich cohort study of young adults. *Arch Gen Psychiatry* 1990;47:849-853.
2. Breslau N, Lipton RB, Stewart WF, Schultz LR, Welch KM. Comorbidity of migraine and depression: investigating potential etiology and prognosis. *Neurology* 2003;60:1308-1312.
3. Lipton RB, Hamelsky SW, Kolodner KB, Steiner TJ, Stewart WF. Migraine, quality of life, and depression: a population-based case-control study. *Neurology* 2000;55:629-635.
4. McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: results from a nationally representative sample. *Pain* 2004;111:77-83.
5. Merikangas KR, Risch NJ, Merikangas JR, Weissman MM, Kidd KK. Migraine and depression: association and familial transmission. *J Psychiatr Res* 1988;22:119-129.
6. Zwart JA, Dyb G, Hagen K et al. Depression and anxiety disorders associated with headache frequency. The Nord-Trondelag Health Study. *Eur J Neurol* 2003;10:147-152.
7. Currie SR, Wang J. Chronic back pain and major depression in the general Canadian population. *Pain* 2004;107:54-60.
8. Gros DF, Antony MM, McCabe RE, Swinson RP. Frequency and severity of the symptoms of irritable bowel syndrome across the anxiety disorders and depression. *J Anxiety Disord* 2009;23:290-296.
9. Thieme K, Turk DC, Flor H. Comorbid depression and anxiety in fibromyalgia syndrome: relationship to somatic and psychosocial variables. *Psychosom Med* 2004;66:837-844.
10. Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders--pathways of vulnerability. *Pain* 2006;123:226-230.
11. Von Korff M, Crane P, Lane M et al. Chronic spinal pain and physical-mental comorbidity in the United States: results from the national comorbidity survey replication. *Pain* 2005;113:331-339.
12. Terwindt GM, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ. The impact of migraine on quality of life in the general population: the GEM study. *Neurology* 2000;55:624-629.
13. Ifergane G, Buskila D, Simiseshvely N, Zeev K, Cohen H. Prevalence of fibromyalgia syndrome in migraine patients. *Cephalalgia* 2006;26:451-456.
14. Le H, Tfelt-Hansen P, Russell MB, Skytthe A, Kyvik KO, Olesen J. Co-morbidity of migraine with somatic disease in a large population-based study. *Cephalalgia* 2011;31:43-64.
15. Calhoun AH, Ford S, Millen C, Finkel AG, Truong Y, Nie Y. The prevalence of neck pain in migraine. *Headache* 2010;50:1273-1277.
16. Anttila P, Metsahonkala L, Mikkelsson M, Helenius H, Sillanpaa M. Comorbidity of other pains in schoolchildren with migraine or nonmigrainous headache. *J Pediatr* 2001;138:176-180.
17. Penninx BW, Beekman AT, Smit JH et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res* 2008;17:121-140.

18. Licht CM, de Geus EJ, Zitman FG, Hoogendijk WJ, van Dyck R, Penninx BW. Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). *Arch Gen Psychiatry* 2008;65:1358-1367.
19. APA. APA. Diagnostic and Statistical Manual of Mental Disorders. Fourth edition. 2001. Washington D.C., American Psychiatric Publishing.
20. Wittchen HU. Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res* 1994;28:57-84.
21. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988;56:893-897.
22. Beck AT, Steer RA. BAI, Beck anxiety inventory: Manual. *Psychological Corporation* 1990.
23. Rush AJ, Giles DE, Schlesser MA, Fulton CL, Weissenburger J, Burns C. The Inventory for Depressive Symptomatology (IDS): preliminary findings. *Psychiatry Res* 1986;18:65-87.
24. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med* 1996;26:477-486.
25. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. *Sleep Med Rev* 2006;10:357-369.
26. Lamers F, Hoogendoorn AW, Smit JH et al. Sociodemographic and psychiatric determinants of attrition in the Netherlands Study of Depression and Anxiety (NESDA). *Compr Psychiatry* 2012;53:63-70.
27. Headache Classification Committee of the International Headache Society. The international classification of headache disorders. *Cephalalgia* 2004;24:9-160.
28. Ligthart L, Penninx BW, Nyholt DR et al. Migraine symptomatology and major depressive disorder. *Cephalalgia* 2010;30:1073-1081.
29. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *Pain* 1992;50:133-149.
30. Bair MJ, Wu J, Damush TM, Sutherland JM, Kroenke K. Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. *Psychosom Med* 2008;70:890-897.
31. Ligthart L, Nyholt DR, Penninx BW, Boomsma DI. The shared genetics of migraine and anxious depression. *Headache* 2010;50:1549-1560.
32. Roberts JE, deShazo RD. Abdominal migraine, another cause of abdominal pain in adults. *Am J Med* 2012;125:1135-1139.
33. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med* 2003;163:2433-2445.
34. Lepine JP, Briley M. The epidemiology of pain in depression. *Hum Psychopharmacol* 2004;19 Suppl 1:S3-S7.
35. Stahl SM. Does depression hurt? *J Clin Psychiatry* 2002;63:273-274.
36. Robinson MJ, Edwards SE, Iyengar S, Bymaster F, Clark M, Katon W. Depression and pain. *Front Biosci (Landmark Ed)* 2009;14:5031-5051.
37. Sawamoto N, Honda M, Okada T et al. Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study. *J Neurosci* 2000;20:7438-7445.
38. Hudson JI, Goldenberg DL, Pope HG, Jr., Keck PE, Jr., Schlesinger L. Comorbidity of fibromyalgia with medical and psychiatric disorders. *Am J Med* 1992;92:363-367.