Pain as risk factor for common mental disorders. Results from the Netherlands Mental Health Survey and Incidence Study-2: a longitudinal, population-based study

de Heer, Eric W.1,2; ten Have, Margreet; van Manwijk, Harm W.J.; Dekker, Jack; de Graaf, Ron; Beekman, Aartjan T.F.1,2 & van der Feltz-Cornelis, Christina M.1,2

1 Centre of excellence for Body, Mind and Health, GGz Breburg, Tilburg, the Netherlands
2 Tilburg School of Behavioural and Social Sciences, Tranzo Department, Tilburg University, Tilburg, the Netherlands
3 Netherlands Institute of Mental Health and Addiction, Department of Epidemiology, Utrecht, the Netherlands
4 Centre for primary care, Division of Population Health, Health Services Research and Primary Care of the School of Health Sciences, The University of Manchester, Manchester, United Kingdom
5 GGz inGeest, Mental Health Institute, Amsterdam, The Netherlands
6 Department of Psychiatry, EMGO Institute for Health and Care Research, VU University Medical Centre, Amsterdam, the Netherlands

* Correspondence to: Drs. E.W. de Heer, Centre of excellence for Body, Mind and Health, GGz Breburg, Lage Witsiebaan 4, 5042 DA, Tilburg, the Netherlands; e.deheer@ggzbreburg.nl

Key words: pain; pain severity; interference due to pain; common mental disorders; mood disorders; anxiety disorders; substance use disorders; general population

Conflict of interests

Prof. van der Feltz-Cornelis reports grants from Eli Lilly, non-financial support from GGz inGeest and Arkin outside the submitted work; Prof. Beekman reports personal fees from Lundbeck, outside the submitted work; all other authors have nothing to disclose.

Number of pages: 13
Number of tables: 2
Abstract

Pain might be an important risk factor for common mental disorders. Insight into the longitudinal association between pain and subsequent common mental disorders in the general adult population could help improve prevention and treatment strategies. Data were used from two waves of the Netherlands Mental Health Survey and Incidence Study-2, which is based on a multistage, stratified random sampling of households (N=5,303). Persons without a mental disorder 12 months prior to baseline were selected as the at-risk group (n=4,974 for any mood disorder; n=4,979 for any anxiety disorder; n=5,073 for any substance use disorder). Pain severity and interference due to pain in the past month were measured at baseline using the 36-item Short Form Health Survey. DSM-IV mental disorders were assessed at both waves using the Composite International Diagnostic Interview version 3.0. Moderate to very severe pain was associated with a higher risk for mood disorders (OR=2.10, 95%CI=1.33-3.29) and anxiety disorders (OR=2.12, 95%CI=1.27-3.55) at follow-up. Moderate to very severe interference due to pain was also associated with a higher risk for mood disorders (OR=2.14, 95%CI=1.30-3.54) and anxiety disorders (OR=1.92, 95%CI=1.05-3.52) at follow-up. Pain was not significantly associated with substance use disorders. No interaction effects were found between pain severity or interference due to pain and a previous history of mental disorders. Moderate to severe pain and interference due to pain are strong risk factors for first-incident and recurrent mood and anxiety disorders, independent of other mental disorders. Pain management programs could therefore possibly also serve as a preventative program for mental disorders.
Introduction

According to the International Association for the Study of Pain (IASP), pain is ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’ [6]. 19% of the adult European population suffers from moderate to severe pain [7]. Pain has substantial impact on quality of life and mental health. Thorough research exists examining the prevalence and cross-sectional association between pain and common mental disorders in population-based [e.g. 3,22] and clinical studies [e.g. 2,11,20,23,24]. The economic and societal burden of pain and common mental disorders is high [2,16,20,28], and therefore composes a relevant public health problem. A better understanding of the prospective contribution of pain in mental disorders might be instrumental in identifying better strategies for prevention and early interventions of mental disorders, particularly because pain is modifiable. However, results of longitudinal studies, assessing the effect of pain on first-incident and recurrent mental disorders, are scarce.

In studies from clinical settings [10,13,14] a longitudinal association between pain and mental disorders was found. Among at-risk stimulant (cocaine and methamphetamine) users, subjects with a higher number of days with pain (which interfered with work and social activities) were more likely to develop alcohol and opioid abuse/dependence compared to subjects without pain [10]. In two studies from the Netherlands Study of Depression and Anxiety (NESDA) – one among subjects with no previous history of and no current depressive or anxiety disorder [13], and one among subjects with a remitted depressive or anxiety disorder [14] – a higher number of pain locations and more severe pain were associated with the onset of a depressive and anxiety disorder, and with the recurrence of a depressive disorder. However, the extent to which results from these clinical studies can be generalized to the general population is unknown, and these results therefore need to be replicated and validated in population-based studies.

Several population-based studies have investigated such a longitudinal association between pain and symptoms of depression [1,12,18] and of anxiety [1,12]. In non-depressed subjects, those with moderate to severe interference due to pain [1], more severe pain [18], and chronic low back pain [12] were more likely to report depressive symptoms at follow-up, compared to those without pain. In non-anxious subjects, the same results were found for moderate to severe interference due to pain [1] and chronic low back pain [12]. After adjusting for affective disorder at baseline, the strength of the pain-affect associations was weakened [1], suggesting they modify each other’s association with pain. However, the results of these studies are limited as they focus on an elderly population [1,18], and relied on self-report questionnaires to measure symptoms of mental health problems in the last week [1,12,18] rather than on standardized diagnostic interviews to assess current and history of mental disorders. Furthermore, these studies focus either on depression and anxiety or on substance use disorders only,
but as these are among the most common mental disorders in adults [28], they should be studied in concert. This study aims to address these gaps.

Methods

Setting and participants

In short, the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) has a longitudinal epidemiological cohort design. This study was conducted among the Dutch general population aged 18-64 years. It is based on a multistage, stratified random sampling of households, with one respondent randomly selected in each household. In the first wave (T0), performed from November 2007 to July 2009, a total of 6,646 persons were interviewed (response rate 65.1%; average interview duration 95 min). This sample was nationally representative, although younger subjects were somewhat under-represented [5]. All T0 respondents were approached for follow-up (T1) three years after T0, from November 2010 to June 2012. Of this group, 5,303 persons were re-interviewed (response rate 80.4%, excluding those deceased; average interview duration 84 min). Attrition rate was not significantly associated with all main categories of mental disorders (mood, anxiety, and substance use) and individual 12-month mental disorders at baseline, after controlling for sociodemographic characteristics (Graaf 2013). More severe pain was, however, significantly associated with less attrition (OR=.91; p=.01), after adjustment for sociodemographic characteristics. The interviews were laptop computer assisted and almost all were held at the respondent’s home. The mean period between both interviews was three years and seven days. The Medical Ethics Committee for Institutions on Mental Health Care (METIGG) approved the study. After having been informed about the study objective, respondents provided written informed consent. A more comprehensive description of the design is provided in De Graaf et al. (2010) [15].

For this study, three at-risk groups were selected: 1) subjects without any mood disorder 12 months prior to baseline (n=4,974); 2) subjects without any anxiety disorder 12 months prior to baseline (n=4,979); and 3) subjects without any substance use disorder 12 months prior to baseline (n=5,073).

However, it was possible for subjects in each of these at-risk groups to have a mental disorder of the other groups at baseline. For example, participants in the at-risk group for mood disorders, thus not reporting a mood disorder 12 months prior to baseline, could have an anxiety or substance use disorder 12 months prior to baseline. Lifetime mental disorder was not an exclusion criterion. Therefore, subjects who reported a mental disorder between T0 and T1 are either a first incident case or recurrent case (hereafter called: incidence). Data were used from the first two waves of NEMESIS-2.
Dependent variables: Mental disorders

Mental disorders were assessed using the Composite International Diagnostic Interview (CIDI) version 3.0, a fully structured lay-administered diagnostic interview of mental disorders [21]. The CIDI was developed and adapted for use in the World Mental Health Survey Initiative. In the Netherlands, the CIDI 3.0 was first used in ESEMeD, which is part of this initiative [4]. The CIDI 3.0 version used in NEMESIS-2 was an improvement of the one used in the Dutch ESEMeD study. The mental disorders considered in this paper include: any mood disorder (major depression, dysthymia, bipolar disorder), any anxiety disorder (panic disorder, agoraphobia, social anxiety disorder, generalised anxiety disorder) and any substance use disorder (alcohol/drug abuse and dependence). Research has demonstrated acceptable reliability and validity for assessing these common mental disorders [17]. The appearance of any common mental disorder (i.e. any mood, anxiety or substance use disorder) between baseline and follow-up was the outcome variable of this study.

At baseline, respondents were asked whether a mental disorder lifetime occurred to them and, if so, if this happened in the past 12 months. At T1, respondents were asked the same questions about mental disorders, but then the time period referred to mental disorders they had experienced since the baseline interview.

Predictor: Pain assessments

At baseline, pain severity was assessed using a question from the SF-36-item Short Form Health Survey [27]: “How much pain did you experience in the past four weeks?” Respondents could choose between “no pain”, “very little pain”, “little pain”, “moderate pain”, “severe pain” and “very severe pain”. These answers were categorised into: 0 = no pain, 1 = very little pain, 2 = little pain, 3 = moderate to very severe pain. Interference due to pain was measured with the SF-36 question: “How much interference did you experience with normal activities (including work outside household, and domestic work) in the past four weeks as a consequence of pain?”. Respondents could choose between “no interference”, “little interference”, “moderate interference”, “much interference” and “very much interference”. These answers were categorised into: 0 = no interference, 1 = little interference, 2 = moderate to very much interference. Pain severity and interference due to pain were also modelled as continuous variables. The pain scale of the SF-36, consisting of pain severity and interference due to pain, has a high reliability [25]; in this study Cronbach’s alpha was 0.84.

Covariates
The demographics at baseline were as follows: age in categories (18–24, 25–34, 35–44, 45–54, 55+), gender, education (primary, lower secondary, higher secondary, higher professional/university), living situation (with partner or not) and working situation (having a paid job or not). Furthermore, mental disorders reported at baseline other than the dependent variable in the analysis were selected as covariates. For example, in the analyses for mood disorder, in which subjects with a mood disorder 12 months prior to baseline were excluded, 12-month anxiety disorder and 12-month substance use disorder at baseline were selected as covariates.

Statistical methods

First, cross-sectional analyses were performed to examine baseline differences regarding sociodemographic characteristics and mental disorders for pain severity and interference due to pain, for all the 5,303 subjects. Second, logistic regression analyses were performed, for each mental disorder separately, to examine the risks of both pain severity and pain interference on incidence of the mental disorder three years later. In all analyses, we first adjusted for demographics and the time between measurements (model 1) and additionally for other psychopathology at baseline (model 2). For example, in the fully adjusted model (model 2) to study risk indicators of any incident or recurrent mood, anxiety and substance use disorder 12 months prior to baseline were included as covariates. Persons with no pain and persons with no interference due to pain were selected as the reference category. To test for linear trends in both models, \( p \) for trend analyses were conducted. To study whether a previous history of a mental disorder increases the risk of a mental disorder at 3-year follow-up in persons with pain, separate interactions of recurrent mood, anxiety and substance use disorders (i.e. those with a lifetime mental disorder, but who did not report a mental disorder 12 months prior to baseline) and pain (severity and interference) were tested. Two-tailed testing procedures were used in all analyses with 0.05 alpha levels, except the interaction analyses, where an alpha of 0.001 was used. All statistical analyses were performed with Stata version 12.1, using weighted data to ensure they were representative of the national population. Robust standard errors were calculated to obtain correct 95% confidence intervals and \( p \) values.

Results

Descriptive data

The baseline characteristics of all 5,303 respondents who participated at the first two waves, tabulated according to the presence of the two pain characteristics (severity and interference) are shown in Table 1.
Being female, less educated, not having a paid job, and presence of any mood, anxiety, and substance use disorder 12 months prior to baseline were significantly associated with a higher score on pain severity. Female gender, older age, lower education, not having a paid job, presence of any mood and anxiety disorder 12 months prior to baseline were significantly associated with a higher score on interference due to pain.

Outcome data and main results

Of the 4974 persons at risk for a mood disorder, 304 developed an incident mood disorder (185 a first-incident disorder and 119 a recurrent disorder) over the next three years. Of the 4979 persons at risk for an anxiety disorder, 179 developed an incident anxiety disorder (131 a first-incident disorder and 48 a recurrent disorder) over the next three years. Of the 5073 persons at risk for a substance use disorder, 160 developed an incident substance use disorder (100 a first-incident disorder and 60 a recurrent disorder) over the next three years. Thus, the majority of incident cases developed a first-incident disorder.

Table 2 shows the odds ratios (OR) for incidence (first-incidence or recurrence) of any mood disorder, any anxiety disorder and any substance use disorder three years later by pain severity and interference due to pain at baseline. 

Respondent with little pain at baseline (n=784, 14.0%) had a more that two times higher odds of developing any anxiety disorder three years later (OR=2.33; 95%CI=1.41-3.85), compared to those without pain. Respondents with moderate to very severe pain at baseline (n=797, 15.1%) had a two times higher odds of developing any mood disorder (OR=2.10; 95%CI=1.33-3.29) and any anxiety disorder (OR=2.12; 95%CI=1.27-3.55) at three year follow-up, compared to those without pain. Compared to model 1, adjusting for the baseline presence of mental disorders other than the dependent variable (model 2) slightly reduced the effect of baseline severity of pain. Respondents with little interference due to pain at baseline (n=806, 14.4%) had approximately a two times higher odds of developing any mood disorder (OR=1.73; 95%CI=1.19-2.53) and any anxiety disorder (OR=1.90; 95%CI=1.21-2.99) at three year follow-up, compared to those without pain. Respondents with moderate to very severe interference due to pain at baseline (n=451, 8.3%) also had approximately a two times higher odds of developing any mood disorder (OR=2.14; 95%CI=1.30-3.54) and any anxiety disorder (OR=1.92; 95%CI=1.05-3.52) three years later, compared to those without interference due to pain. Compared to model 1, adjusting for the baseline presence of mental disorders other than the dependent variable (model 2) slightly reduced the effect of baseline interference due to pain. Both pain characteristics (severity and interference) at baseline were not significantly associated with any incident or recurrent substance use disorder at follow-up. The p for trend analyses showed that with higher pain severity and with more
interference due to pain, the risk of any incident or recurrent mood and anxiety disorder increased (all models: p<.01). This did not apply for any incident substance use disorders. No interaction effects were found for a previous history of a mood disorder with pain on the risk of developing a mood disorder at 3-year follow-up, a previous history of an anxiety disorder with pain on the risk of developing an anxiety disorder at 3-year follow-up, and a previous history of a substance use disorder with pain on the risk of developing a substance use disorder at 3-year follow-up. These effects applied for both pain severity and interference due to pain. This implies that the association between pain and mental disorders did not significantly differ between subjects with a first onset and subjects with a recurrent mental disorder.

Discussion

This is one of the first large scale studies assessing pain as a risk factor for the prospective development of first or recurrent episodes of common mental disorders in the adult general population. Prevalence of moderate to very severe pain was 15.1% and for moderate to very severe interference due to pain 8.3%. These subjects had a more that twofold increased risk for developing a first-incident or recurrent mood and anxiety disorder three years later. Adjusting for mental disorder at baseline, other than the one as the dependent variable, only slightly attenuated the strength of the pain–mental disorder associations. Moreover, the effect of pain on mental disorders did not differ between subjects who developed a first-incident mental disorder and subjects who developed a recurrent mental disorder. Our findings, therefore, show that pain is a common, strong and unique risk factor for mood and anxiety disorders. Our findings are consistent with and extend previous longitudinal findings between pain and mood and anxiety [1,13,14,18]. The strength of the association between pain severity and interference due to pain with mood and anxiety disorders is higher in the current study compared to previous longitudinal studies: In clinical studies more severe pain increased the risk for onset of a depressive and anxiety disorder between a one- to twofold factor [13] and for recurrence of depression by a 1.2-fold factor [14]; in population studies, among elderly, more severe pain increased the risk for depressive symptoms by a 1.1-fold factor [18], and more interference due to pain increased the risk for depressive and anxiety symptoms by almost a twofold factor [1]. In the present study, a more than 2-fold increased risk was found for both pain severity and interference due to pain in developing a mood and anxiety disorder. This may be attributed to methodological differences in study sample, study size and outcome measures. For example, although the population studies [1,18] used non-depressed and non-anxious subjects, depression and anxiety were measured with a self-report questionnaire regarding symptoms in the last week. A major contribution of the present study is the use of a standardized diagnostic interview to assess mental disorders in the last 12-months and lifetime history of mental disorders. This enabled us
to 1) assess clinical and chronic symptoms of common mental disorders, 2) assess the risk of pain in subjects without a mental disorder in the last 12 months, and 3) evaluate whether the risk of pain differs in subjects with a recurrent mental disorder and subjects with a first-onset mental disorder. Our findings therefore extend previous literature by showing that when pain becomes more severe or interferes with normal activities, the risk of full-blown first-incident or recurrent mood and anxiety disorders increases substantially in the general adult population.

Regarding first-incident and recurrence of substance use disorder, we found no association with pain severity or with interference due to pain at baseline. In a study among at-risk stimulant users, more days of pain (which interfered with work and social activities) was associated with a two- to threefold increase of developing a substance use disorder [10]. It could therefore be expected that, in the present study, interference due to pain would also be associated with substance use disorder. A possible explanation for this discrepancy might be attributed to several methodological differences. Edlund et al. (2013) [10] used a sample of at-risk stimulant users, which might not be comparable to the general adult population. Furthermore, they used a non-validated measure for pain and adjusted their results only for severity of depression, based on a short self-report questionnaire. However, it could also indicate that pain is a risk factor for developing a substance use disorder in an at-risk sample, but not in the general adult population. Nevertheless, Volkow et al. (2016) [26] warn for the possible abuse hazards of opioid use by chronic pain patients, as opioid analgesics are the most commonly prescribed class of medications for pain, with a high risk of abuse and addiction. In our study, we were unable to distinguish between specific substance use disorders, such as opioid use, due to a small number of subjects in this category. Therefore, in future studies, the specific association between pain, mental disorders and opioid use should be taken into account.

Strengths and limitations
This study had the advantage of a large population sample, which was followed-up for three years, the use of a standardized instrument to assess common mental disorders and the possibility to adjust for a wide variety of confounders in investigating the relationship between pain characteristics at baseline and mental disorders at follow-up. However, some limitations have to be mentioned. The outcome of the main analysis was aggregated as we have pooled both first-incident and recurrent mental disorders. However, we did examine whether results would differ for subjects with a recurrent mental disorder from those with a first-incident mental disorder, and found no significant difference. This might be explained due to the relatively small number of subjects with a recurrent (lifetime) (n=119 for mood; n=48 for anxiety; n=60 for substance use) and first-incident (n=185 for mood; n=131 for anxiety; n=100 for substance use) mental disorder at follow-up, and studies with larger sample sizes of
incident and recurrent mental disorders are needed to study this more accurately. Mental disorders were also aggregated by pooling several specific mood, anxiety and substance use disorders due to the small numbers reporting a specific mental disorder. As a consequence, no inferences can be made whether pain is a risk factor in developing one of these specific disorders and in developing another mental disorder not considered in our study. Additionally, the use of the SF36 to measure pain severity and interference due to pain is limited. This questionnaire only asks for pain in the last four weeks, so no inferences could be made on chronic pain. However, in two large clinical studies, chronic pain (pain with a duration of at least 90 days) was not associated more strongly with the onset and recurrence of a depressive and anxiety disorder when compared to less chronic pain [13,14], indicating that current severe pain might be a more important risk factor when considering mental disorders. Despite a follow-up period of three years in this study, we cannot make any inferences about a causal pathway of pain towards a mental disorder. Besides, it is possible that factors not studied here might play a mediating role in the link between pain and mental disorders. For example, sleep problems can play a mediating role in the link between persistent pain and depression and anxiety [8,9]. Dysfunctional cognitive pain responses, such as catastrophizing or hopelessness, also seem to mediate the association between pain and depression [19]. In future research and interventions of pain, problems with sleep and dysfunctional cognitive responses should therefore also be taken into account. Sleep problems and dysfunctional cognitions are modifiable factors, and when these factors mediate the association between pain and mental disorders, interventions targeted at sleep and cognitions might also be effective in reducing both pain and the risk of mental disorders.

Conclusion/clinical implications

Our finding that pain has a large impact in the development of a mental disorder in the adult general population is important for health professionals, who would do well by monitoring and detecting possible symptoms of a mental disorder when pain symptoms are present. Pain management programs could then possibly also serve as a preventative program for mental disorders in subjects with pain; reducing pain symptoms might lead to a reduced risk for developing a mental disorder. However, more longitudinally research is needed exploring causality and other mediating factors in the association between pain and mental disorders.

Acknowledgments

NEMESIS-2 is conducted by the Netherlands Institute of Mental Health and Addiction (Trimbos Institute) in Utrecht. Financial support has been received from the Ministry of Health, Welfare and Sport, with supplementary support from the Netherlands Organization for Health Research and Development
(ZonMw) and the Genetic Risk and Outcome of Psychosis (GROUP) investigators. The funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. The views expressed are those of the author and not necessarily those of the Ministry of Health, Welfare and Sport.

Conflict of interests
Prof. van der Feltz-Cornelis reports grants from Eli Lilly, non-financial support from GGz inGeest and Arkin outside the submitted work; Prof. Beekman reports personal fees from Lundbeck, outside the submitted work; all other authors have nothing to disclose.

Contributors
MtH and RdG are part of the NEMESIS-2 research team and obtained funding for the NEMESIS-2 study. EdH, MtH, RdG and CvdFC conceived the initial idea for the present study and all authors contributed to its planning, including defining the aims, variables of interest, and analysis strategy. Analyses were done by MtH, but all authors had access to the statistical outputs. EdH drafted the article and all authors contributed to revisions. All authors approved the final manuscript.
References


