

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

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

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22
23
24 **Conflict of interests**

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36 **Abstract**

37 Pain might be an important risk factor for common mental disorders. Insight into the longitudinal association between pain
38 and subsequent common mental disorders in the general adult population could help improve prevention and treatment
39 strategies. Data were used from two waves of the Netherlands Mental Health Survey and Incidence Study-2, which is based
40 on a multistage, stratified random sampling of households (N=5,303). Persons without a mental disorder 12 months prior to
41 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
42 any substance use disorder). Pain severity and interference due to pain in the past month were measured at baseline using
43 the 36-item Short Form Health Survey. DSM-IV mental disorders were assessed at both waves using the Composite
44 International Diagnostic Interview version 3.0. Moderate to very severe pain was associated with a higher risk for mood
45 (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
46 interference due to pain was also associated with a higher risk for mood (OR=2.14, 95%CI=1.30-3.54) and anxiety disorders
47 (OR=1.92, 95%CI=1.05-3.52) at follow-up. Pain was not significantly associated with substance use disorders. No interaction
48 effects were found between pain severity or interference due to pain and a previous history of mental disorders. Moderate
49 to severe pain and interference due to pain are strong risk factors for first-incident and recurrent mood and anxiety disorders,
50 independent of other mental disorders. Pain management programs could therefore possibly also serve as a preventative
51 program for mental disorders.

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54

55 **Introduction**

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

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

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

89 but as these are among the most common mental disorders in adults [28], they should be studied in
90 concert. This study aims to address these gaps.

91

92 **Methods**

93 Setting and participants

94 In short, the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) has a longitudinal
95 epidemiological cohort design. This study was conducted among the Dutch general population aged 18-
96 64 years. It is based on a multistage, stratified random sampling of households, with one respondent
97 randomly selected in each household. In the first wave (T0), performed from November 2007 to July
98 2009, a total of 6,646 persons were interviewed (response rate 65.1%; average interview duration 95
99 min). This sample was nationally representative, although younger subjects were somewhat under-
100 represented [5]. All T0 respondents were approached for follow-up (T1) three years after T0, from
101 November 2010 to June 2012. Of this group, 5,303 persons were re-interviewed (response rate 80.4%,
102 excluding those deceased; average interview duration 84 min). Attrition rate was not significantly
103 associated with all main categories of mental disorders (mood, anxiety, and substance use) and
104 individual 12-month mental disorders at baseline, after controlling for sociodemographic characteristics
105 (Graaf 2013). More severe pain was, however, significantly associated with less attrition (OR=.91; $p=.01$),
106 after adjustment for sociodemographic characteristics. The interviews were laptop computer assisted
107 and almost all were held at the respondent's home. The mean period between both interviews was three
108 years and seven days. The Medical Ethics Committee for Institutions on Mental Health Care (METIGG)
109 approved the study. After having been informed about the study objective, respondents provided written
110 informed consent. A more comprehensive description of the design is provided in De Graaf et al. (2010)
111 [15].

112 For this study, three at-risk groups were selected: 1) subjects without any mood disorder 12 months
113 prior to baseline (n=4,974); 2) subjects without any anxiety disorder 12 months prior to baseline
114 (n=4,979); and 3) subjects without any substance use disorder 12 months prior to baseline (n=5,073).
115 However, it was possible for subjects in each of these at-risk groups to have a mental disorder of the
116 other groups at baseline. For example, participants in the at-risk group for mood disorders, thus not
117 reporting a mood disorder 12 months prior to baseline, could have an anxiety or substance use disorder
118 12 months prior to baseline. Lifetime mental disorder was not an exclusion criterion. Therefore, subjects
119 who reported a mental disorder between T0 and T1 are either a first incident case or recurrent case
120 (hereafter called: incidence). Data were used from the first two waves of NEMESIS-2.

121

122 Variables

Commented [EdH1]: de Graaf, R., van Dorsselaer, S., Tuijthof, M., & ten Have, M. (2013). Sociodemographic and psychiatric predictors of attrition in a prospective psychiatric epidemiological study among the general population. Result of the Netherlands Mental Health Survey and Incidence Study-2. *Comprehensive Psychiatry*, 54(8), 1131-1139.

123 *Dependent variables: Mental disorders*

124 Mental disorders were assessed using the Composite International Diagnostic Interview (CIDI) version
125 3.0, a fully structured lay-administered diagnostic interview of mental disorders [21]. The CIDI was
126 developed and adapted for use in the World Mental Health Survey Initiative. In the Netherlands, the CIDI
127 3.0 was first used in ESEMeD, which is part of this initiative [4]. The CIDI 3.0 version used in NEMESIS-2
128 was an improvement of the one used in the Dutch ESEMeD study. The mental disorders considered in
129 this paper include: any mood disorder (major depression, dysthymia, bipolar disorder), any anxiety
130 disorder (panic disorder, agoraphobia, social anxiety disorder, generalised anxiety disorder) and any
131 substance use disorder (alcohol/drug abuse and dependence). Research has demonstrated acceptable
132 reliability and validity for assessing these common mental disorders [17]. The appearance of any
133 common mental disorder (i.e. any mood, anxiety or substance use disorder) between baseline and
134 follow-up was the outcome variable of this study.

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

139

140 *Predictor: Pain assessments*

141 At baseline, pain severity was assessed using a question from the SF-36-item Short Form Health Survey
142 [27]: "How much pain did you experience in the past four weeks?" Respondents could choose between
143 "no pain", "very little pain", "little pain", "moderate pain", "severe pain" and "very severe pain". These
144 answers were categorised into: 0 = no pain, 1 = very little pain, 2 = little pain, 3 = moderate to very
145 severe pain.

146 Interference due to pain was measured with the SF-36 question: "How much interference did you
147 experience with normal activities (including work outside household, and domestic work) in the past four
148 weeks as a consequence of pain?". Respondents could choose between "no interference", "little
149 interference", "moderate interference", "much interference" and "very much interference". These answers
150 were categorised into: 0 = no interference, 1 = little interference, 2 = moderate to very much
151 interference. Pain severity and interference due to pain were also modelled as continuous variables. The
152 pain scale of the SF-36, consisting of pain severity and interference due to pain, has a high reliability
153 [25]; in this study Cronbach's alpha was 0.84.

154

155 *Covariates*

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

163

164 Statistical methods

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

183

184 **Results**

185 *Descriptive data*

186 The baseline characteristics of all 5,303 respondents who participated at the first two waves, tabulated
187 according to the presence of the two pain characteristics (severity and interference) are shown in Table
188 1.

189 –insert Table 1 here–

190 Being female, less educated, not having a paid job, and presence of any mood, anxiety, and substance
191 use disorder 12 months prior to baseline were significantly associated with a higher score on pain
192 severity. Female gender, older age, lower education, not having a paid job, presence of any mood and
193 anxiety disorder 12 months prior to baseline were significantly associated with a higher score on
194 interference due to pain.

195 *Outcome data and main results*

196 Of the 4974 persons at risk for a mood disorder, 304 developed an incident mood disorder (185 a first-
197 incident disorder and 119 a recurrent disorder) over the next three years. Of the 4979 persons at risk
198 for an anxiety disorder, 179 developed an incident anxiety disorder (131 a first-incident disorder and
199 48 a recurrent disorder) over the next three years. Of the 5073 persons at risk for a substance use
200 disorder, 160 developed an incident substance use disorder (100 a first-incident disorder and 60 a
201 recurrent disorder) over the next three years. Thus, the majority of incident cases developed a first-
202 incident disorder.

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

206 –Insert Table 2 here–

207 Respondent with little pain at baseline (n=784, 14.0%) had a more than two times higher odds of
208 developing any anxiety disorder three years later (OR=2.33; 95%CI=1.41–3.85), compared to those
209 without pain. Respondents with moderate to very severe pain at baseline (n=797, 15.1%) had a two times
210 higher odds of developing any mood disorder (OR=2.10; 95%CI=1.33–3.29) and any anxiety disorder
211 (OR=2.12; 95%CI=1.27–3.55) at three year follow-up, compared to those without pain. Compared to
212 model 1, adjusting for the baseline presence of mental disorders other than the dependent variable
213 (model 2) slightly reduced the effect of baseline severity of pain. Respondents with little interference due
214 to pain at baseline (n=806, 14.4%) had approximately a two times higher odds of developing any mood
215 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
216 year follow-up, compared to those without pain. Respondents with moderate to very severe interference
217 due to pain at baseline (n=451, 8.3%) also had approximately a two times higher odds of developing any
218 mood disorder (OR=2.14; 95%CI=1.30–3.54) and any anxiety disorder (OR=1.92; 95%CI=1.05–3.52)
219 three years later, compared to those without interference due to pain. Compared to model 1, adjusting
220 for the baseline presence of mental disorders other than the dependent variable (model 2) slightly
221 reduced the effect of baseline interference due to pain. Both pain characteristics (severity and
222 interference) at baseline were not significantly associated with any incident or recurrent substance use
223 disorder at follow-up. The p for trend analyses showed that with higher pain severity and with more

224 interference due to pain, the risk of any incident or recurrent mood and anxiety disorder increased (all
225 models: $p < .01$). This did not apply for any incident substance use disorders.

226 No interaction effects were found for a previous history of a mood disorder with pain on the risk of
227 developing a mood disorder at 3-year follow-up, a previous history of an anxiety disorder with pain on
228 the risk of developing an anxiety disorder at 3-year follow-up, and a previous history of a substance use
229 disorder with pain on the risk of developing a substance use disorder at 3-year follow-up. These effects
230 applied for both pain severity and interference due to pain. This implies that the association between
231 pain and mental disorders did not significantly differ between subjects with a first onset and subjects
232 with a recurrent mental disorder.

233

234 **Discussion**

235 This is one of the first large scale studies assessing pain as a risk factor for the prospective development
236 of first or recurrent episodes of common mental disorders in the adult general population. Prevalence of
237 moderate to very severe pain was 15.1% and for moderate to very severe interference due to pain 8.3%.

238 These subjects had a more than twofold increased risk for developing a first-incident or recurrent mood
239 and anxiety disorder three years later. Adjusting for mental disorder at baseline, other than the one as
240 the dependent variable, only slightly attenuated the strength of the pain-mental disorder associations.
241 Moreover, the effect of pain on mental disorders did not differ between subjects who developed a first-
242 incident mental disorder and subjects who developed a recurrent mental disorder. Our findings,
243 therefore, show that pain is a common, strong and unique risk factor for mood and anxiety disorders.

244 Our findings are consistent with and extend previous longitudinal findings between pain and mood and
245 anxiety [1,13,14,18]. The strength of the association between pain severity and interference due to pain
246 with mood and anxiety disorders is higher in the current study compared to previous longitudinal
247 studies: In clinical studies more severe pain increased the risk for onset of a depressive and anxiety
248 disorder between a one- to twofold factor [13] and for recurrence of depression by a 1.2-fold factor
249 [14]; in population studies, among elderly, more severe pain increased the risk for depressive symptoms
250 by a 1.1-fold factor [18], and more interference due to pain increased the risk for depressive and anxiety
251 symptoms by almost a twofold factor [1]. In the present study, a more than 2-fold increased risk was
252 found for both pain severity and interference due to pain in developing a mood and anxiety disorder.

253 This may be attributed to methodological differences in study sample, study size and outcome measures.
254 For example, although the population studies [1,18] used non-depressed and non-anxious subjects,
255 depression and anxiety were measured with a self-report questionnaire regarding symptoms in the last
256 week. A major contribution of the present study is the use of a standardized diagnostic interview to
257 assess mental disorders in the last 12-months and lifetime history of mental disorders. This enabled us

258 to 1) assess clinical and chronic symptoms of common mental disorders, 2) assess the risk of pain in
259 subjects without a mental disorder in the last 12 months, and 3) evaluate whether the risk of pain differs
260 in subjects with a recurrent mental disorder and subjects with a first-onset mental disorder. Our findings
261 therefore extend previous literature by showing that when pain becomes more severe or interferes with
262 normal activities, the risk of full-blown first-incident or recurrent mood and anxiety disorders increases
263 substantially in the general adult population.

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

280

281 *Strengths and limitations*

282 This study had the advantage of a large population sample, which was followed-up for three years, the
283 use of a standardized instrument to assess common mental disorders and the possibility to adjust for a
284 wide variety of confounders in investigating the relationship between pain characteristics at baseline and
285 mental disorders at follow-up. However, some limitations have to be mentioned.

286 The outcome of the main analysis was aggregated as we have pooled both first-incident and recurrent
287 mental disorders. However, we did examine whether results would differ for subjects with a recurrent
288 mental disorder from those with a first-incident mental disorder, and found no significant difference.
289 This might be explained due to the relatively small number of subjects with a recurrent (lifetime) (n=119
290 for mood; n=48 for anxiety; n=60 for substance use) and first-incident (n=185 for mood; n=131 for
291 anxiety; n=100 for substance use) mental disorder at follow-up, and studies with larger sample sizes of

292 incident and recurrent mental disorders are needed to study this more accurately. Mental disorders were
293 also aggregated by pooling several specific mood, anxiety and substance use disorders due to the small
294 numbers reporting a specific mental disorder. As a consequence, no inferences can be made whether
295 pain is a risk factor in developing one of these specific disorders and in developing another mental
296 disorder not considered in our study. Additionally, the use of the SF36 to measure pain severity and
297 interference due to pain is limited. This questionnaire only asks for pain in the last four weeks, so no
298 inferences could be made on chronic pain. However, in two large clinical studies, chronic pain (pain with
299 a duration of at least 90 days) was not associated more strongly with the onset and recurrence of a
300 depressive and anxiety disorder when compared to less chronic pain [13,14], indicating that current
301 severe pain might be a more important risk factor when considering mental disorders. Despite a follow-
302 up period of three years in this study, we cannot make any inferences about a causal pathway of pain
303 towards a mental disorder. Besides, it is possible that factors not studied here might play a mediating
304 role in the link between pain and mental disorders. For example, sleep problems can play a mediating
305 role in the link between persistent pain and depression and anxiety [8,9]. Dysfunctional cognitive pain
306 responses, such as catastrophizing or hopelessness, also seem to mediate the association between pain
307 and depression [19]. In future research and interventions of pain, problems with sleep and dysfunctional
308 cognitive responses should therefore also be taken into account. Sleep problems and dysfunctional
309 cognitions are modifiable factors, and when these factors mediate the association between pain and
310 mental disorders, interventions targeted at sleep and cognitions might also be effective in reducing both
311 pain and the risk of mental disorders.

312

313 *Conclusion/clinical implications*

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

321

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330 Conflict of interests

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332 Arkin outside the submitted work; Prof. Beekman reports personal fees from Lundbeck, outside the
333 submitted work; all other authors have nothing to disclose.

334 Contributors

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

340

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