Medically unexplained symptoms in later life

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CHAPTER 4

The temporal relation between pain and depression: Results from the Longitudinal Aging Study Amsterdam.

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Abstract

Objective: Pain and depression are both common in old age, but their (long-term) temporal relationship remains unknown. This study is designed to determine whether pain predicts the onset of depression and vice versa.

Methods: This is a prospective, population based cohort study with 12-year follow up and 3 years intervals in the Netherlands (Longitudinal Aging Study Amsterdam). At baseline participants were aged 55 to 85 years (n=2028). Main measurements outcomes were incident depression defined as crossing the cut-off of 16 and showing a relevant change (≥5 points) on the Center for Epidemiological Studies – Depression scale (CESD) among non-depressed participants and incident pain defined as a score of 2 or higher on the pain scale of the 5-item Nottingham Health Profile (NHP5) in pain free participants. Multiple imputation was adopted to estimate missing values.

Results: In non-depressed participants (n=1769), a higher level of pain was predictive of incident depression in multiple extended cox-regression analysis (Hazard rate [HR] = 1.13 [95% confidence interval [CI]= 1.05 – 1.22], p= .001) , which all remained significant after correction for socio-demographic characteristics , lifestyle characteristics, functional limitations and chronic diseases (HR=1.09 [95% CI=1.01 – 1.18], p=.035).

In the pain-free participants (n=1420), depressive symptoms at baseline predicted incident pain (HR = 1.02 [95% CI: 1.01 – 1.04], p= .006) , This depression measure did not independently predicted the onset of pain in the fully adjusted models.

Conclusion: As pain precedes the onset of depression, strategies to prevent depression in chronic pain patients are warranted. In contrast no effects of depression on subsequent pain were found when adjusting for covariates.

Introduction

Depression and pain are highly prevalent in older people. A comprehensive meta-analysis has reported prevalence rates of 1.8% for major depression, 9.8% for minor depression and 13.5% for clinically relevant depressive symptoms [1]. Reported prevalence rates for pain among older people vary between 25 and 88% [2]. The National UK statistics report that approximately 50% of older people are in some degree of pain or discomfort [3]. Cross-sectional studies report high comorbidity rates between pain and depression among older persons [4, 5] and the comorbidity rate increases with aging [6]. Moderate to severe pain symptoms that impair function and/or are refractory to treatment, are associated with more depressive symptoms and worsened depression outcomes. Similarly, depression in patients with pain is associated with more pain complaints and higher level of impairment [7, 8]. Although the direction of the association between pain and depression remains unclear [9, 10], a bidirectional, reciprocal association is most plausible. This means that the onset of either pain or depression is a factor that increases the likelihood of the reciprocal symptoms and/or that each syndrome is a factor that impedes recovery of the other. For clinical practice this is important, as it would entail that treatment should target both depression and pain and that systematic evaluation of pain/depressive symptoms is warranted in either disorder.

Longitudinal studies among older people consistently show that pain precedes depression and vice versa, despite the use of different and sometimes not validated measures for depression and/or pain [11-17]. Except one population based study including 4235 people aged 50 years and older [14], all studies adjusted their results for functional limitations and/or chronic diseases. Only in two studies the identified temporal pattern between pain and depression disappeared after the adjustment for covariates. In the first study, the predisposition of pain to depression disappeared after adjustment for physical functioning and chronic health conditions. Nonetheless, this study was limited as it was a population-based study with only 241 people due to a low and probably selective, attrition rate [12]. In the second study among 318 older patients referred to secondary health care, the predisposition of depression to pain already disappeared when adjusted for sociodemographic factors [16]. Probably more relevant than these two exceptions, are the following limitions:a), the lack of control in nearly all studies for pharmacological treatment of depression and pain; b), the lack of control in nearly all studies for life-style characteristics like smoking, use of alcohol and body mass index (BMI) because such characteristics may point to mediating mechanisms [10]; and c) limitations with respect to duration of follow-up or number of assessments. All studies among older adults were limited to a duration of follow-up of at most 3 years [17, 18] or a maximum of 1 or 2 follow-up measurements [11, 16]. One study among people aged 25 to 75 years, of which only 27% (629/2324) were aged 55 years or over, applied an 8-year follow-up and found that pain predicted depression and vice versa [19]. Nevertheless, this study was limited by only one follow-up measurement and neither adjusted for lifestyle characteristics nor for functional limitations or chronic diseases [19].

Objectives

To overcome these problems, we have examined the temporal relation between pain and depression over a 12-year follow-up within the Longitudinal Aging Study Amsterdam (LASA). Our objectives were to examine to what extent pain in the elderly predicts the onset of depression and to what extent depressive symptoms in the elderly population predicts the onset of chronic pain when adjusted for sociodemographic characteristics, lifestyle factors, functional limitations and the presence of chronic diseases.

Method

Study design and population

This study was conducted using data from the Longitudinal Aging Study Amsterdam (LASA), which is a prospective cohort study of Dutch people aged 55 to 85 years (n=3107). LASA started in 1992, and its methods have been described in detail elsewhere [20, 21]. The general aim of LASA was to study the autonomy and well-being of an aging population. A randomly selected age- and sexstratified sample (according to expected mortality figures) was drawn from the population registers of 11 municipalities in the Netherlands. The reason for this relative oversampling of men and older-old people (both men and women) was to compensate for an anticipated higher unavailability for follow-up among the older-old and men. The sample first took part in the cross-sectional NESTOR–living arrangements and social networks study [22] and was later interviewed and followed up every 3 years in LASA; 81.7% of the NESTOR–living arrangements and social networks study sample participated in LASA, with nonresponse being related to age but not to sex. All interviews were tape-recorded for quality control purposes. The study design was approved by the ethics committee and all participants provided informed consent.

For the present study, we used data up to 12 years of follow-up and excluded only those LASA participants in whom depressive symptoms (n=14), pain symptoms (n=1028) or both depressive and pain symptoms (n=37) were not evaluated at baseline, leaving a total study sample of 2028 participants (65.3%). Of these 2028 participants, 1769 (87.2%) had no depression at baseline and 1420 (70.0%) had no pain at baseline.

Because data on pain were gathered by self-administered questionnaires which participants were asked to fill in after the face-to-face main interview, the response on the pain questionnaire was relatively low. The 1028 persons with missing pain scores had significantly higher levels of depressive symptoms compared to persons without missing pain scores (mean (SD) CESD score of 9.0 (8.1) versus 7.5 (7.6), t=5.2, df=3054, p< .001), whereas the 14 persons with missing depression scores at baseline had significantly higher levels of pain scores compared to persons without missing depression scores (mean (SD) NHP5 score of 1.9 (2.1) versus 0.7 (1.3), t=3.4, df=2040, p= .001). As shown in table 1, excluded persons because of missing data were significantly older, were less often male, had more severe cognitive impairment, were less educated, used less often alcohol, and had more chronic diseases and functional impairments.

Table 1
Comparison of in- and excluded participants at baseline

		Included (n=2028)	Excluded (n=1079)	Statistics
Age (years)	mean (SD)	68.8 (8.5)	72.5 (8.8)	t=11.3, df=3105, p< .001
Male sex	n (%)	1030 (50.8)	476 (44.1)	χ^2=12.6, df=1, p< .001
Level of education	n (%)			χ^2=95.0, df=2, p< .001
• Lower education or less		771 (38.1)	605 (56.3)	
• Secondary education		993 (49.0)	377 (35.1)	
• Higher education		261 (12.9)	92 (8.6)	
Cognitive functioning (MMSE)	mean (SD)	27.4 (2.4)	25.7 (4.2)	t=-14.0, df=3089, p< .001
Smoking (yes)	n (%)	477 (24.6)	195 (26.7)	x^2=1.3, df=1, p= .26
Use of alcohol	n (%)			χ^2=26.1, df=2, p< .001
• No use		382 (19.8)	210 (29.0)	
• Moderate use		1385 (71.7)	457 (63.2)	
• Severe use		164 (8.5)	56 (7.7)	
Body Mass Index	mean (SD)	26.6 (3.9)	27.2 (4.4)	t=3.3, df=2574, p= .001
Chronic diseases	n (%)			χ^2=110.5, df=2, p< .001
• None		851 (42.0)	346 (32.6)	
• One		716 (35.3)	377 (35.6)	
• Two or more		460 (22.7)	337 (31.8)	
Functional limitations	n (%)			χ^2=153.7, df=2, p< .001
• None		1301 (64.5)	492 (47.0)	
• One		370 (18.4)	214 (20.5)	
• Two		345 (17.1)	340 (32.5)	
Use of antidepressants	n (%)	40 (2.1)	11 (1.5)	χ^2=0.8, df=1, p= .34
Use of analgetics	n (%)	290 (15.0)	117 (16.0)	χ^2=0.4, df=1, p= .52

Abbreviation: MMSE, Mini-Mental State Examination; SD, standard deviation.

Depression

At all occasions, depressive symptoms were measured using the Center for Epidemiologic Studies Depression scale (CESD). This is a 20-item self-report scale developed to measure depressive symptoms in the community. Subjects were asked how often they had experienced each symptom during the previous week. Items were scored on a 4-point scale, ranging from 0 (rarely or none of the time) to 3 (most of or all the time). The values of these response categories were reversed for the positive affect items. The total CESD score ranges from 0 to 60. The psychometric properties of the scale were found to be good in older populations [23, 24]. The overlap with symptoms of physical illness has been shown to be very limited in a number of studies [25, 26]. A score of ≥16 has generally been used as indicative for clinically relevant

depressive symptoms [25]. In LASA, the cutoff of 16 or greater had a sensitivity of 100% and a specificity of 88% for major depressive disorder according to DSM-IV criteria [24].
The CESD was completed every 3 years during follow-up. Incident depression was defined as a score of 16 or higher at one of the follow-up assessments in patients who scored less than 16 points at baseline combined with an increase of 5 points or more compared to their baseline symptom score. This criterion of a minimum change of 5 points was chosen to avoid random fluctuations or clinically irrelevant changes of symptoms leading to a respondent being identified as incident depression [27].

Pain
The pain scale was derived from a subscale of the Nottingham Health Profile (NHP5) [28]. As described previously, the following 5 items were included: I am in pain when I am standing, I find it painful to change position, I am in pain when I am sitting, I am in pain when I walk, and I am in constant pain [17]. Response categories were 'no' and 'yes'. The total scale score ranges from 0 (low) to 5 (high). The reliability of the scale indexed by Cronbach's alpha was high ($\alpha = 0.82$) [17]. The pain scale was completed every 3 years during follow-up. Incident pain was evaluated in pain free persons (NHP5 sumscore = 0) and defined as a score of 2 or higher at one of the follow-up assessments. A score of 2 (clinically relevant change) was chosen to avoid random fluctuations or clinically irrelevant changes of symptoms leading to a respondent being identified as incident pain.

Covariates
Three categories of covariates were considered of interest and added block-wise to the regression analyses (see below). The first category included sociodemographic variables, medication use and cognitive functioning. The second category were life-style factors and the third category were chronic diseases and functional limitations.
The first category consisted of characteristics that were considered to be potential confounders and included sociodemographic variables (sex, age, and level of education), medication use (use of antidepressants and analgetics), and cognitive functioning. The originally 9 categories of educational level were categorized into 3 main categories, i.e. lower education or less (elementary education not completed, elementary education), secondary education (lower vocational education, general intermediate education, general secondary education), and higher education (higher vocational education, college education, university education). Use of antidepressants and analgetics was established by asking about the use of medication and by visually checking all of the participants' medications at each 3-yearly assessment. Cognitive functioning was measured with the Mini Mental State Examination (MMSE) [29]. The MMSE sumscore (range 0 – 30) was included in the analyses as a continuous variable. Persons scoring below the cut-off of 24 points (52/2028, 2.6%) were kept in the analyses. The second and third category consisted of variables, which may both confound and/or mediate the relationship between depression and pain.
The second category consisted of life-style factors, i.e. current smoking (yes/no), use of alcohol, defined as no use, severe usage (defined as 14 or more units per week for female

participants and 21 or more per week for male participants) and mild to moderate usage (those participants not scoring no alcohol or severe alcohol usage), and finally body mass index, calculated as weight in kilograms divided by height in meters squared.
The third category consisted of chronic comorbid diseases and functional limitations. The presence of 7 chronic physical diseases was measured by self-reports based on core questions and branching questions in case of positive answers. The selection of chronic diseases is based on prevalence (the most frequently occurring somatic chronic diseases in the Netherlands; roughly >5.0% in the age group 55 years and older) and functional consequences, and included 1) chronic non-specific lung disease, 2) cardiac disease, 3) peripheral arterial disease, 4) diabetes mellitus, 5) cerebrovascular accident or stroke, 6) arthritis, and 7) cancer. In a validation study, respondents' self-reports were compared to information obtained from their GPs, and proved to be sufficiently reliable [30]. For this study, the presence of chronic diseases was indicated at three levels: no disease, 1 disease or 2 or more diseases. The number of functional limitations was scored with a 3-item questionnaire and scored as none, 1, or 2 or more difficulties [31].

Analyses
Does pain predict the onset of depression? - To examine the impact of pain on the onset of depression, the analyses were restricted to participants without depression at baseline (CESD <16, n=1769). We performed Cox-regression to take the time to onset into account. All primary variables and covariates were checked for normality and collinearity, their associations with outcome variables were checked for proportionality of hazards. Collinearity refers to the possibility that two covariates are highly correlated in a way that both covariates virtually measure largely the same construct. This has been tested by bivariate correlations between covariates. Proportionality of hazards refers to the assumption that the hazards are proportional over time. Hazard functions have thus to be multiplicatively related, or in other words their ratio is assumed constant over the survival time, thereby not allowing a temporal bias to become influential on the end point. This has been tested by plotting the cumulative hazards functions for each covariate (at baseline) as well as by a complementary log-log plot.
Although Cox-regression partially corrects for dropout by censoring patients at the last available follow-up assessment, it requires at least one follow-up assessment in order to include participants in the analyses. In our case 314 participants (17.8%) dropped out before the first follow-up assessment. Participants who dropped out (n=314) were compared to included participants (n=1455) significantly older (t=9.6, df=1767, p< .001), more often male (χ^2=5.0, df=1, p= .026), had a lower level of cognitive functioning (t=-8.3, df=1763, p< .001), used less alcohol (χ^2=11.0, df=2, p= .004), and had more chronic diseases (χ^2=11.4, df=2, p= .003) and functional limitations (χ^2=29.9, df=2, p< .001). Dropouts, however, did not differ with respect to severity of depressive symptoms, pain, smoking status, BMI, use of antidepressants and use of analgetics. Furhtermore, the frequency of missing data for covariates was on average 2.0% per covariate (range 0 - 6.5%). To account for missing data, we performed multiple imputation using the Markov chain Monte Carlo method (fully conditional specification). Under the assumption of missing at random, this approach addresses biases inherent in deleting patients who do not

provide all data, and ulitimately allows for the inclusion of a larger and more representatieve sample in the analyses. We created 5 imputed data sets and all variables available (CESD score, NHP5 score and all covariates) were included in the imputation model as recommended [32]. No interaction terms were added to the imputation model and we used predictive mean matching for continuous variables. Analyses were run for each imputed dataset and the results were pooled using Rubin's [33] rules to derive one single pooled parameter etimate by taking into consideration the variance both within and between imputations. Only these pooled results were presented.

In order to examine the relationship between pain and incident depression in depth, pain was modelled in three different ways. First, we evaluated the effects of pain at baseline based on the continuous NPH5 score, ignoring pain scores during follow-up. Secondly, we calculated the mean severity of pain symptoms as the mean NHP5 score of all observations until the year of incident depression or censoring divided by the total number of observations in this interval as a proxy for a combined pain severity-chronicity score. Third, we included pain (continuous NPH5 score) as a time-dependent variable to evaluate whether pain occurs just before the onset of depression. All models were first corrected for subsyndromal depressive symptoms and covariates of the first category (potential confounders), then also for covariates of the second category (life-style factors) and finally also for covariates of the third category, that is functional limitations and chronic diseases as potential confounders and/or mediators. Covariates that may change over over time, were included as time-dependent covariates as Cox-regression allows the use of time independent (age, sex, education) and time dependent covariates (cognitive functioning, use of antidepressants, use of analgetics, smoking, use of alcohol, body mass index, functional limitations, chronic diseases).

Do depressive symptoms predict the onset of pain? – A similar set of analyses were conducted to examine the impact of depressive symptoms at baseline on the onset of pain. Cox-regression analsyes were conducted as described above, but in this case with incident pain as the dependent variable. First we restricted the analysis to participants without pain at baseline (NPH5 score = 0, n=1420). A total of 313 participants dropped out before the first follow-up (n=313). These dropouts were significantly older (t=11.4, df=1418, p<.001), less educated (x^2=15.6, df=2, p<.001) had a lower level of cognitive functioning (t=9.2, df=1416, p<.001), higher level of depressive symptoms (t=2.4,df== 2.4, df=1418, p=.017), more often smoked (x^2=3.9, df=1, p=.049), less often used alcohol (x^2=7.3, df=2, p=.026), and had more chronic diseases (x^2= 26.2,df=2, p<.001) and functional limitations (x^2=53.0, df=1, p<.001) compared to included participants (n=1107). Dropouts, however, did not differ with respect to sex, BMI, use of antidepressants and use of analgetics. Furhtermore, the frequency of missing data for covariates was on average 2.0% per covariate at baseline (range 0 - 6.2%) and up to 60.2% for body mass index at 12 years follow-up. To account for missing data, we performed a separate multiple imputation procedure for the subjects in this analysis using the same methods as described above. The imputations were done separately for both analyses as they address essentially different questions pertaining to different populations, i.e. those without baseline depression and those without baseline pain, respectively. All results presented are

based on the pooled results of the 5 imputed datasets.
To examine this relationship in depth, depressive symptoms were modelled in three different ways. First, we evaluated the effects of the severity of depressive symptoms at baseline based on the continuous CESD score, ignoring depressive symptom scores during follow-up. Secondly, we calculated the mean severity of depressive symptoms as the mean CESD score of all observations until the year of incident pain or censoring divided by the total number of observations in this interval as a proxy for a combined depression severity-chronicity score. Thirdly, we included the depressive symptom severity (continuous CESD score) as a time-dependent variable to evaluate whether an increase in depressive symptoms occurs just before the onset of pain. All models were first corrected for covariates of the first category (potential confounders), then also for covariates of the second category (life-style factors) and finally also for covariates of the third category, i.e. functional limitations and chronic diseases as potential confounders and/or mediators.

Results

Does pain increase the incidence of depression?
To predict the development of depression we first selected non-depressed participants at baseline (n=1769, 87.2%).
Of the 1769 non-depressed participants at baseline, a total of 402 (22.7%) developed depression during follow-up. The mean (SD) depression free duration of follow-up was 8.1 (3.6) years, which corresponds to an incidence rate of 28.2 per 1.000 person years.
In unadjusted Cox-regression models, incident depression was predicted by pain at baseline (Hazard Rate (HR) = 1.13 [95% CI: 1.05 – 1.22], p= .001), the combined severity-chronicity pain score (HR= 1.21 [95% CI: 1.12 – 1.32], p<.001), and by pain as a time-dependent covariate (HR = 1.15 [95% CI: 1.07 – 1.24], p< .001). The Hazard Rates count for each 1 point increase on the NPH5 scale. As shown in table 2, these associations remained significant when corrected for all three categories of covariates.

Table 2 Multivariate Cox Regression on Incident Depression

Variable	Imputed (N=1769)	
	HR (95% CI)	P Value
Pain symptoms at baseline		
• Adjusted for covariates category 1	1.05 (1.01 – 1.10)	.030
• Additionally adjusted for covariates category 2	1.08 (1.00 – 1.16)	.055
• Additionally adjusted for covariates category 3	1.09 (1.01 – 1.18)	.035
Combined severity – chronicity pain level		
• Adjusted for covariates category 1	1.13 (1.04 – 1.24)	.007
• Additionally adjusted for covariates category 2	1.14 (1.04 – 1.24)	.005
• Additionally adjusted for covariates category 3	1.17 (1.06 – 1.29)	.002
Pain symptoms (continuous at separate time-points)		
• Adjusted for covariates category 1	1.07 (0.99 – 1.16)	.088
• Additionally adjusted for covariates category 2	1.07 (0.99 – 1.16)	.092
• Additionally adjusted for covariates category 3	1.09 (1.00 – 1.19)	.047

Abbreviations: HR, hazard ratio; CI, confidence interval
Covariates category 1 include age, sex, and education (baseline), as well as Mini-Mental State Examination score, use of analgetics, use of antidepressants, subsyndromal depressive symptoms (time-dependent).
Covariates category 2 include smoking, use of alcohol, and Body Mass Index (time-dependent)
Covariates category 3 include functional limitations and chronic diseases (time-dependent)

Do depressive symptoms increase the incidence of pain?
To predict the development of pain, we first selected participants with no pain at baseline (n=1420, 70.0%).
Of the 1420 participants with no pain at baseline, a total of 346 (24.4%) developed pain during follow-up. The mean (SD) pain free duration of follow-up was 8.3 (3.6) years, which corresponds to an incidence rate of 29.3 per 1.000 person years.
In unadjusted Cox-regression analyses, incident pain was predicted by baseline depressive symptoms (HR = 1.02 [95% CI: 1.01 – 1.04], p= .006) as well as the combined severity-chronicity score of depression (HR = 1.03 [95% CI: 1.01 – 1.05], p= .011), but not by including depressive symptoms as a time-dependent covariate (HR = 1.01 [95% CI: 0.99 – 1.03], p= .160). The Hazard Rates count for each 1 point increase on the CESD scale. As shown in table 3, the effect of depression on incident pain fully disappeared after correction for confounders.

Table 3 Multivariate Cox Regression on Incident Pain

Variable	Imputed (N=1420)	
	HR (95% CI)	P Value
Depressive symptoms at baseline		
• Adjusted for covariates category 1	1.01 (1.00 – 1.03)	.121
• Additionally adjusted for covariates category 2	1.01 (1.00 – 1.03)	.134
• Additionally adjusted for covariates category 3	1.01 (1.00 – 1.03)	.137
Combined severity – chronicity depression level		
• Adjusted for covariates category 1	1.01 (0.99 – 1.04)	.265
• Additionally adjusted for covariates category 2	1.01 (0.99 – 1.04)	.274
• Additionally adjusted for covariates category 3	1.01 (0.99 – 1.04)	.290
Depressive symptoms (continuous at separate time-points)		
• Adjusted for covariates category 1	1.00 (0.98 – 1.03)	.823
• Additionally adjusted for covariates category 2	1.00 (0.98 – 1.03)	.801
• Additionally adjusted for covariates category 3	1.00 (0.98 – 1.03)	.797

Abbreviations: HR, hazard ratio; CI, confidence interval
Covariates category 1 include age, sex, and education (baseline), as well as Mini-Mental State Examination score, use of analgetics, use of antidepressants (time-dependent).
Covariates category 2 include smoking, use of alcohol, and Body Mass Index (time-dependent)
Covariates category 3 include functional limitations and chronic diseases (time-dependent)

Sensitivity analysis

We checked whether the results differed from analyses based on cases with complete data only, i.e. n=1139 and n=987 for analyses on incident depression and incident pain, respectively. Similar results were obtained when predicting incident depression, whereas with respect to incident pain, the baseline CESD score significantly predicted incident pain when corrected for socio-demographic and medication use only (HR=1.01 (95% CI: 1.00 – 1.05, p= .047).

Discussion

Main findings

Among community-dwelling older people, pain precedes the onset of clinically relevant depressive symptoms. The predictive value of pain with respect to depression is a robust finding, as not only pain at baseline was predictive of incident depression, but also the combined severity-chronicity pain score as well as by taking fluctuations in pain during follow up into account by including pain as a time-dependent variable. In contrast to our hypotheses, depressive symptoms only predicted pain in the unadjusted models.

Comparison with previous findings

The finding that pain precedes the development of depression is consistent with earlier longitudinal studies with shorter durations of follow-up in humans [11, 15-17, 19] as well as with experimental short-term animal research in which psychological and sociodemographic confounders are less important [34]. Our data add that this predictive value of pain for developping depression remains over a 12-year follow-up period when assessed at 3-yearly intervals in a large group of community dwelling older people. Moreover, this relation is not mediated by disability, and remains significant when corrected functional limitations and number of chronic diseases, which is consistent with earlier findings [17].

The negative results we found with respect to the effect of depression on the development of pain strengthens the finding of previous studies among older people showing no effect of depression on the development of pain. Our findings are in line with a review that found that 9 out of 13 studies (among younger adults) also did not find support for the predisposition of depression to pain [10], as well as with three studies among older persons. First, among 318 Chinese elderly people referred to secondary care, the predictive value of depression also became non-significant after correction for age, sex and educational level [16]. Second, a recent European population-based study among 4234 people aged 50 years and over, showed that the effect of depression on incident pain did not disappear after adjustment for sociodemographic factors, but did so after additional correction for baseline co-morbid psychopathology [11]. Unfortunately, this last study did not correct for functional limitations and/or chronic diseases. Finally, within a highly selective community sample of 529 older persons suffering from osteoarthritis, depressed mood did not led to a worsening of pain [35]. The studies among older persons that did find an effect were indeed limited to a follow-up duration up to 3 years [11, 13, 15] or were conducted in specific populations as middle-aged patients who were already suffering from musculoskeletal pain [36] or low-back pain [37] or limited to the development of low-back pain in the older population [13]. Our 12-year follow-up period is probably the major difference with previous studies and unique in this field of research. Nevertheless, as we measured depression and pain only once every three year, we can not rule out that depression impacts on the development of pain at much shorter intervals. Such short-term effects may led to analgetic drug use, change in lifestyle behaviour or inforce the development of functional impairment [18], al of which could explain our negative results in our adjusted models. Other positive findings of depression are not focussed on the incidence of pain, but on worsening of existing pain [36, 37]. Depression might have differential effects in patients with no pain compared to patients already suffering from a painfull somatic condition. Depression may amplify physical pain sensations due to changes in motivational-affective processess and cognitive-evaluative processes that can affect the processing and perception of noxious input. This might also lead to different results between chronic diseases that are rarely accompanied by pain like cerebrovascular accidents and chronic diseases that are typically accompanied by physical pain sensations like osteoarthritis [38]. Nonetheless, motivational-affective and cognitive-evaluative processes of pain experience also interfere with very low or even absence of noxious stimuli [39].

Methodological considerations

Our study is unique in having a 12-year follow-up and being able to adjust for the use of antidepressants and analgetics as well as for lifestyle variables. Nevertheless, for proper interpretation some limitations have to be acknowledged. First, selective loss to follow-up is an inevitable consequence of a longitudinal study in the elderly [40]. The selective dropout of patients with more pain symptoms and more severe depression in our study may have biased our effects. Nonetheless, completed case analyses and analyses after multiple imputation yielded comparable results. Nevertheless, the high number of excluded participants due to missing baselinedata, may limit the external generalization of our results to the more frail elderly. On the other hand, multiple imputation of the whole dataset, did not yield different results (data available on request). Second, the interval period of 3 years hampers the observation of more direct temporal correlations between pain and depression. Nevertheless, earlier studies with shorter interval periods have shown that in the elderly the presence of pain and depression were remarkably stable over time [18]. A third potential source of bias is the fact that all data relied on self-report measures of depression and pain. This might have caused an overestimation of the associations under study. However, if data indeed were contaminated due to self-report assessments, it would have lessened the chance to find differential results as we did. Furthermore, depressive symptoms were measured with the CESD, a frequently used and well-validated instrument that is sensitive to change, whereas the NHP5 pain scale is a much lesser used and less validated instrument in pain research. Especially the 5 dichotomous items may have led to a less sensitive pain measure. A fourth potential bias factor is the disregard of treatment other than antidepressants and analgetics received by the participants for depression or pain. The influence of this factor, however, is supposed to be mild because there is evidence that a large proportion of the elderly with pain or depression receive no adequate treatment [41].

Conclusion / implications

The comorbidity of depression and pain places a high burden on both the society, patients and families who it concerns and results in less favourable outcomes for both conditions. The reciprocal relationship of depresion and pain over time is thus of particular of importance for preventive medicine. We found that chronic pain in older adults places them at risk for depression. This underscores the importance of early detection of depressive symptoms in older persons experiencing pain, because older persons in general are less inclined to seek emotional help [42] and rates of underrecognition of and inadequate treatment for depression are high [43, 44]. Further research should thus examine whether specific strategies to prevent depression in chronic pain patients are effective in this at risk population. A reverse pathway of depression to pain could not be demonstrated.

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