Psychiatric disorders, personality traits and childhood traumatic events predicting incidence and persistence of chronic pain: results from the CoLaus|PsyCoLaus study

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INTRODUCTION

Chronic pain (CP) is a common and persistent problem in the community [4], responsible for substantial emotional distress and reduced quality of life [11], [41], [23]. Mental disorders (MD) are associated with excess mortality, injuries and several chronic diseases [7], [37] and may also play a role in the development, the persistence and the improvement of CP. Indeed, numerous previous cross-sectional studies suggested a link between CP and MD, particularly depression and anxiety [30], [20]. Aside from MD or psychiatric symptoms, few cross-sectional studies have also explored the links between the personality dimensions Neuroticism and Extraversion and pain. [20], [43], [15]. One earlier study found both Neuroticism and Extraversion to be associated with pain characteristics [43], whereas another study suggested that Neuroticism is associated with the way pain is experienced [20]. Moreover, a very recent study conducted during the Covid-19 pandemic revealed that higher Extraversion was associated with increase in pain interference after social distancing [15]. Several retrospective studies also found early-life traumatic events (ETE) to be associated with pain-related medical conditions in adulthood [38], [36], [44], [19].

However, the cross-sectional design of these studies impeded researchers to characterize the nature of these associations. Indeed, these associations could be attributable to unidirectional or reciprocal causal links or shared causality.

Up to this day, only few longitudinal studies have been conducted to prospectively establish the associations of depression, anxiety disorders, personality traits and ETE with the incidence or persistence of CP, providing inconsistent results. Depressive symptoms were shown to predict 2-year disabling low-back pain in older adults [29]. Negative mood and anxiety symptoms were shown to predict pain intensity in the 2 years following lower extremity trauma [6]. Another study found a relationship between anxiety and depressive symptoms and pain location and severity on a 4-year follow-up [18]. Psychological distress

[10] and depression [5] have been shown to predict 12-months subsequent neck [5] or low back pain [5] [10]. On the opposite, depressive symptoms did not predict subsequent pain over 3 years, except from head and chest pain [42]. Regarding specifically CP, depressive and anxiety symptoms mediated the link between insomnia and CP onset 6 years later [17]. However, except from one study showing psychiatric disorders assessed though diagnostic interviews to predict subsequent painful physical symptoms [22], the bulk of previous longitudinal studies assessed depressive symptoms using self-rated questionnaires. Finally, various psychological adversities in childhood were found to predict chronic widespread pain in adult life [24], and the onset of painful medical conditions [38]. However, no previous study has assessed the independent effects of depression, anxiety disorders, personality traits and ETE on the incidence or persistence of CP in the community.

Hence, using a cohort of middle-aged and older community dwellers, we aimed to establish the prospective associations of major depressive disorder (MDD) and anxiety disorders, personality traits and childhood traumatic events with 1) the incidence of CP during a nearly 5-year following-up period among participants initially exempt from CP and 2) the persistence of CP during this follow-up period among participants who already reported CP in the beginning of the follow-up period.

METHODS

Participants

The present data stem from CoLaus|PsyCoLaus, a prospective population-based cohort study designed to investigate cardiovascular risk factors and mental disorders in the community and to determine their associations. The study has been previously described in detail [14], [35]. CoLaus|PsyCoLaus initially included a sample of 6734 participants (age

range: 35-75 years) randomly selected from the residents of the city of Lausanne (Switzerland) according to the civil register. After a first physical and psychiatric assessment, which took place between 2003 and 2008, the cohort was followed-up three times. Since follow-up (FU) 1, participants were invited to complete pain questionnaires during the physical investigation. FU2 followed 5.2 (s.d. 0.5) years after FU1 and FU3 3.8 (0.4) years after FU2. Inclusion criteria for the present analyses were: 1) having jointly completed the psychiatric evaluation and the pain questionnaire either at FU1 or FU2 and 2) having again completed the pain questionnaire at the subsequent FU (FU2 or FU3) (**Figure 1**). A total of 2932 participants met these criteria. After excluding participants with missing information on personality, incomplete information on mental disorders or absence of information on ETE the final sample included 2578 participants with 4121 analysable intervals (56.4% women, mean age 60.5 (s.d. 9.9) years). For the 1746 participants who completed the psychiatric evaluations and the pain questionnaires at all three FU investigations, the intervals from FU1 to FU2 and from FU2 to FU3 were separately analysed.

Assessments

Participants underwent pain assessments at FU1, FU2 and FU3 using the STOPNEP questionnaire, an 11-question pain inventory designed and validated for epidemiological studies [4]. The first two questions aimed at identifying the presence of daily CP for at least three months. The subsequent questions only applied to participants who answered positively to these two questions. Participants had to locate their pain from a list of body parts and to report the location of the most troublesome pain if appropriate. The remaining 7 questions related to the pain duration, intensity and characteristics of the most troublesome pain. Pain duration was divided into four categories: <6 months, between 6 and 12 months, between 1 and 3 years, or ≥3 years. Participants then reported the highest, lowest, and average intensity of pain during the past 24 hours, on three numerical rating scales (0=no pain, 10=worst pain

imaginable) from the Brief Pain Inventory (BPI) [8]. The mean BPI score corresponded to the mean of the three above scores. Participants were also asked to specify the location of their most painful area. Pain locations were categorized into 1) head (scalp, face, tongue, neck), 2) arm (arm, elbow, forearm, wrist, hand, shoulders), 3) back (upper back, lower back, buttocks), 4) legs (hips, groin, leg, knee, thighs, ankle, foot) and 5) other (chest, other). In accordance to the International Association for Study of Pain (IASP) [40], CP was defined as persistent or recurrent daily pain lasting longer than three months [3] [4].

Diagnostic information on mental disorders including lifetime major depressive disorder (MDD) was elicited at each psychiatric evaluation using the semi-structured Diagnostic Interview for Genetic Studies (DIGS) [31]. The DIGS was developed by collaborators from the National Institute of Mental Health (NIMH) Genetics Initiative in order to more accurately assess phenotypes of schizophrenia and mood disorders through 1) a semi-structured design corresponding to a wide spectrum of DSM-III-R Axis I criteria and 2) collection of extensive information on the course and chronology of comorbid conditions. An updated version of the DIGS included DSM-IV criteria (NIMH Molecular Genetics Initiative (1995) Diagnostic Interview for Genetic Studies (DIGS) - Version 2.0). The DIGS has been translated into French by a group of bilingual collaborators of the INSERM in Paris and the Psychiatric University Hospital of Lausanne [27]. The inter-rater and test-retest reliability of both the original English [31] and the French versions [34], of this instrument were extensively tested for psychotic and mood disorders. The French version revealed kappa values of at least 0.85 for inter-rater and 0.62 for test–retest reliability for major mood disorders [34]. The DIGS was completed using the anxiety disorder sections of the French version [28] of the Schedule for Affective Disorders and Schizophrenia-lifetime and anxiety disorder version (SADS-LA) [12]. The French translation of the SADS-LA was found to have adequate test-retest reliability for panic disorder/agoraphobia (Yule's Y = 0.43), GAD (Yule's

Y = 0.61) and phobic disorders (Yule's Y = 0.66) [28]. At the follow-up evaluations, a shortened version of the DIGS was used focusing on the period since the last assessment. Lifetime diagnoses until the first pain assessment were assigned according to DSM-IV [1]. Participants were classified as currently depressed (i.e. meeting DSM-IV criteria for MDD) at the time of the first pain evaluation, remitted (i.e. not meeting criteria for MDD at the time of the first pain evaluation, but having previously met these criteria) and never depressed (i.e. having never met lifetime criteria for MDD up to the first pain investigation).

Early-life traumatic events (ETE) were elicited using the questions on early-life and adolescence events as well as those on traumatic events in the PTSD chapter of the DIGS. The following stressful experiences occurring before the age of 17 years were considered as indicators of adversity: physical fight of parents, separation of parents, death of parents (mother or father), death of sibling as well as sexual abuse and physical abuse. According to the suggestion of Friedman et al. [16] exposure to early-life adversity was quantified by the sum of reported events. Interviewers were master-level psychologists trained over at least a one-month period. An experienced senior psychologist reviewed all interviews and diagnostic assignments.

Neuroticism and Extraversion traits were assessed by the Eysenck Personality Questionnaire-Revised (EPQ-R) [13], which was completed at baseline and FU2, and the NEO Five-Factor Inventory (NEO-FFI-R) [9], filled in at FU1. If participants had completed the two questionnaires prior to the analysed follow-up interval, data from the EPQ-R were used. In order to make data from the two questionnaires comparable, the scores were normalized and z-scores were computed for Neuroticism and Extraversion.

During the physical evaluations, information was collected on socio-demographic characteristics including age, sex, education as well as medication (analgesics (ATC code

N02), opioids (ATC code N02A + N02BG01), antidepressants (ATC code N06A), and anxiolytics (ATC code N05B)). Education was categorized into four levels: compulsory school, apprenticeship, high school/college and university degrees.

Ethics

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of the Canton of Vaud (www.cer-vd.ch) approved the baseline CoLaus|PsyColaus study (reference 16/03; 134-03,134-05bis, 134-05-2to5 addenda 1to4). The approval was renewed for the first (reference 33/09; 239/09), the second (reference 26/14; 239/09 addendum 2) and the third (PB_2018-00040; 239/09 addenda 3to4) follow-ups. The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants signed a written informed consent.

Statistical analysis

In order to assess the associations of lifetime mental disorders, personality traits and ETE prior to the FU period with pain status at the end of the FU period, four serially adjusted generalized linear mixed models were used. These models were all adjusted for sex, age, education, duration of FU, FU interval (FU1 to FU2 or FU2 to FU3), medication in the end of the interval and intra-personal correlations. In Model 1, only non-chronic pain (for analyses on the incident of CP) or location of CP (for analyses on the persistence of CP) reported in the beginning of the interval were entered. In Model 2, lifetime depression (current or remitted) and anxiety disorders (agoraphobia, panic disorder, generalized anxiety disorder, social phobia) were added. In Model 3 ETE and in Model 4 the personality scores Neuroticism and Extraversion were added. In order to assess the association between potential psychological

predictors and the persistence of CP, an additional fifth model was run, which also adjusted for analgesic medication at the beginning of the interval.

The results of all the tests were considered as significant at the level of $p < 0.05$. Statistical analyses were computed using the Statistical Analysis System, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Table 1 presents the characteristics of the analysable follow-up intervals. Within the 2280 intervals without CP in the beginning, in 750 (32.9%) CP was reported in the end of the interval. Within the 1841 intervals with CP in the beginning, in 1370 (74.4%) CP was still reported in the end of the interval.

Table 2 summarizes the locations of CP in the beginning of the interval for participants with CP. The most frequent locations concerned back, knees, shoulders, feet, hips, hands and joints. Additionally, the mean BPI score during the 24 last hours at the beginning of the interval was 3.4 (s.d. 1.8). Moreover, 43.2%, 27.6%, 15.4% and 13.8% of the participants reported pain duration of ≥3 years, 1-3 years, 6-12 months, and <6 months respectively.

The associations between potential predictors measured in the beginning and the reporting of CP in the end of the follow-up interval among participants exempt from CP in the beginning of the interval were provided in **Table 3**. After multiple adjustments for potential confounders, non-chronic pain was strongly associated with an increased likelihood of reporting CP in the end of the interval (Model 1). When mental disorders were added to the model, also current and remitted MDD but not anxiety disorders were associated with reporting of CP in the end of the interval (Model 2). After also adding ETE, non-chronic pain as well as current and remitted MDD remained associated with reporting of CP in the end of

the interval, whereas this was not the case for ETE (Model 3). Finally, after additional inclusion of personality traits (Model 4), non-chronic pain and higher scores of Neuroticism and Extraversion were associated with CP. In contrast, in this model MDD was no longer associated with CP. The variables assessed in Model 4 explained approximately 7% of the variance.

Table 4 presents the associations between potential predictors and persistence of CP during the follow-up interval. Model 1, which only included locations of CP in the beginning of the interval, showed only pre-existing back pain, pain in the arm and other pain to be associated with the persistence of CP across the follow-up. Model 2, which also included mental disorders, revealed associations of current and remitted MDD but not of anxiety disorders with persistence of CP, whereas the pain locations already tested in Model 1 remained significantly associated with the outcome variable. In Model 3 the additional variable ETE was not associated with persistence of CP, whereas in Model 4, which also included personality features, lower scores of Extraversion together with back pain, pain in the arm as well as current and remitted MDD were associated with the persistence of CP. The variables assessed in Model 4 explained nearly 10% of the variance. Similar results were obtained in an additional model that also adjusted for analgesic drugs in the beginning of the interval (data not shown).

DISCUSSION

This study is the first to simultaneously assess the prospective associations of MDD and specific anxiety disorders assessed through diagnostic interviews, as well as personality traits, and ETE with both the incidence and persistence of CP according to IASP criteria [40], [39] over time in a cohort of middle-aged and older community-dwellers. Our most salient findings were, that 1) both higher Neuroticism and Extraversion scores were associated with

higher incidence of CP, whereas the association between MDD and the incidence of CP disappeared after adjustment for the effects of personality traits; 2) current and remitted MDD as well as lower Extraversion scores were associated with persistence of CP and 3) ETE and specific anxiety disorders were not associated with incidence or persistence of CP.

Predictors of CP incidence

Although pain in the beginning of the interval as well as Neuroticism and Extraversion revealed highly significant associations with CP incidence according to the fully adjusted model, only a relatively small proportion of 7% of the variance was explained by the variables included in this model, indicating that unmeasured characteristics and measurement errors accounted for the major part of the variance. Prior to the adjustment for personality traits, both current and remitted MDD were also significantly associated with the incidence of CP during the follow-up interval. This finding is consistent with those of several longitudinal studies that showed either depressive disorder [22] or depressive symptoms [6], [18], [17] to predict the onset of pain. But the few studies including large samples and follow-up periods of at least two years, yielded mixed results. The study of Hotopf et al., which can be best compared with ours, given the use of a diagnostic interviews in 36 year-old community participants, provided evidence for a dose-response relationship between depression and anxiety and the number of subsequent painful physical symptoms [22]. Moreover, baseline depressive symptoms increased the odds of disabling low back pain in a large database of elderly community residents after two years [29]. Conversely, Arola et al. did not find an association between self-reported depressive symptoms and subsequent pain interference after a 3-year follow-up in a large cohort of community-dwellers aged 50-year and over, in multivariate analysis adjusted for anxiety [2]. Likewise, depressive symptoms were not associated with incident pain in adults initially free of pain and followed-up during 8.3 years [21]. In our study, the association between MDD and the incidence of CP disappeared after

adjustment for Neuroticism and Extraversion, which both remained associated with the incidence of CP in the fully adjusted model. The association between personality traits, in particular Neuroticism, and MDD is complex and still only poorly understood [32]. Five models were postulated to explain the association between neuroticism and depression, including the vulnerability model (postulates that neuroticism leads to depression either by directly causing its development or by enhancing the impact of causal risk factors such as stressful life events), the spectrum model (assumes that both are manifestations of the same process), common cause model (shared determinants for the two), state model (current depressive episode increases Neuroticism during the episode) and scar model (depressive episode increases Neuroticism permanently) [32]. According to the review of Ormel et al., none of these models by itself is able to fully explain the nature of the association, although regarding the link between Neuroticism and depression, the common cause model has the strongest support from existing research followed by the vulnerability model, the state and scar models and the spectrum model [32]. Assuming the vulnerability model, adjusting for the causally related personality traits should indeed remove the prospective association between MDD and the incidence of CP. However, assuming a scar model, adjusting for personality traits as a consequence of MDD would not be indicated and blur a true prospective association between MDD and the incidence of CP. As pointed out by Ormel et al. [32] despite some evidence for the vulnerability model in the literature, studies endorsing this model could have been easily confounded by unmeasured depressive symptoms at baseline or unrecalled episodes that occurred prior to the baseline of the studies causing increased Neuroticism measures. Hence, given the absence of personality measures prior to the first depressive episode in our study, we cannot determine the direction of the association between MDD and personality scores. For this reason, the question of whether adjusting for personality scores blurs a true prospective association between MDD and CP or alternatively

whether MDD is merely a weak mediator of the prospective association between personality traits and CP, remains elusive. Given that prospective studies repetitively measuring personality traits and mental disorders from early adolescence on up to the age when CP typically occurs are difficult to conduct, alternative designs such as familial aggregation studies and Mendelian randomization studies could more easily provide information on the direction of the observed associations.

The observed association between high Neuroticism and elevated CP incidence is in line with a previous cross-sectional study showing an association of Neuroticism with pain duration and pain severity [20]. With respect to Extraversion, the rather unexpected finding of an association between high Extraversion scores and the risk of developing CP, which contrasts with previous studies not revealing such an association [43], [20], could be due to a tendency of extraverted individuals to be especially attracted to social settings where alcohol, sex and risky driving behaviour are the norm. These people may subsequently develop a hazardous lifestyle [25]. Indeed, a higher risk of essentially non-professional accidents, which could lead to CP, has been documented in people with elevated Extraversion [26],[33]. Whereas in this study high Extraversion scores were associated with higher CP incidence, low Extraversion was associated with CP persistence. The association between low Extraversion scores and CP persistence was less surprising given that generally extraverted individuals tend to have stronger social networks, which are typically protective against negative health outcomes [25].

The observed absence of a prospective association between lifetime anxiety disorders and incident CP is consistent with a previous study that found panic disorder, generalized anxiety disorder, and social phobia not to be associated with pain-related medical conditions [41]. In contrast, a study measuring anxiety symptoms rather than specific disorders showed

an association of state but not trait anxiety with CP onset six to twelve months after surgery [3].

The observed absence of an association between ETE and CP incidence contrasts with the results of a previous study, showing that these events were risk factors for the incidence of chronic multisite musculoskeletal pain [20].

Predictors of CP persistence

With almost 10% of the variance explained according to the fully adjusted model, the prediction of CP persistence was better than that of CP incidence. Interestingly, although MDD was no longer associated with the incidence of CP after adjustment for personality traits, current and to a lesser extent remitted MDD remained associated with a higher risk of CP persistence during the follow-up interval in the fully adjusted model. One explanation for the strong association between current MDD and the persistence of CP could be that the presence of a depressive episode at baseline could have been a marker for severe CP. Conversely, Neuroticism was no longer a predictor of persistence of CP after adjustment for MDD. Again, we are confronted with the uncertainty regarding the nature of the association between personality traits and depression. Assuming a vulnerability model as discussed before, adjustment for MDD would not be warranted, whereas assuming a scar model, entering depression into the model would be straight forward.

Our results are consistent with a previous study which did not observe an association between the presence of ETE and the persistence of CP [19].

Limitations

Our results should be considered in the context of several limitations. First, given the advanced age of approximately 60 years of the cohort in the beginning of the follow-up

intervals, the absence of personality measures prior to the first mood episode and the risk of inaccurate recall particularly of remote depressive episodes did not allow us to disentangle the complex relationship between personality traits and MDD and subsequently their independent associations with the incidence and persistence of CP. Second, given that the study was conducted in an urban area, our results may not be generalized to other populations. However, although the specific sample characteristics are likely to affect the prevalence estimate of disorders and CP, it is less likely that they significantly biased the established associations among them.

Conclusions

Our study revealed evidence for significant associations of personality traits and MDD with the incidence and persistence of CP. From the clinical point of view personality traits particularly if treated earlier in life are accessible by psychotherapy. Hence, psychotherapeutic treatment of people with high Neuroticism and Extraversion scores that may involve hazardous behaviour might reduce the later risk of CP. Similarly, adequate treatment of major depressive episodes might also reduce this risk. The adequate treatment of these episodes as well as psychotherapeutic interventions in people with low Extraversion scores may also diminish the risk of the persistence of already manifest CP.

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Figure legend

Figure 1: Flow chart for the selection of analysable intervals.

INTRODUCTION

Chronic pain (CP) is a common and persistent problem in the community [4], responsible for substantial emotional distress and reduced quality of life [11], [41], [23]. Mental disorders (MD) are associated with excess mortality, injuries and several chronic diseases [7], [37] and may also play a role in the development, the persistence and the improvement of CP. Indeed, numerous previous cross-sectional studies suggested a link between CP and MD, particularly depression and anxiety [30], [20]. Aside ~~of~~ from MD or psychiatric symptoms, few cross-sectional studies have also explored the links between the personality dimensions Neuroticism and Extraversion and pain. [20], [43], [15]. One earlier study found both Neuroticism and Extraversion to be associated with pain characteristics [43], whereas another study suggested that Neuroticism is associated with the way pain is experienced [20]. Moreover, a very recent study conducted during the Covid-19 pandemic revealed that higher Extraversion was associated with increase in pain interference after social distancing [15]. Several retrospective studies also found early-life traumatic events (ETE) to be associated with pain-related medical conditions in adulthood [38], [36], [44], [19].

However, the cross-sectional design of these studies impeded researchers to characterize the nature of these associations. Indeed, these associations could be attributable to unidirectional or reciprocal causal links or shared causality.

Up to this day, only few longitudinal studies have been conducted to prospectively establish the associations of depression, anxiety disorders, personality traits and ETE with the incidence or persistence of CP, providing inconsistent results. Depressive symptoms were shown to predict 2-year disabling low-back pain in older adults [29]. Negative mood and anxiety symptoms were shown to predict pain intensity in the 2 years following lower extremity trauma [6]. Another study found a relationship between anxiety and depressive symptoms and pain location and severity on a 4-year follow-up [18]. Psychological distress [10] and

depression [5] have been shown to predict 12-months subsequent neck [5] or low back pain [5] [10]. On the opposite, depressive symptoms did not predict subsequent pain over 3 years, except from head and chest pain [42]. Regarding specifically CP, depressive and anxiety symptoms mediated the link between insomnia and CP onset 6 years later [17]. However, except from one study showing psychiatric disorders assessed though diagnostic interviews to predict subsequent painful physical symptoms [22], ~~most~~ the bulk of previous longitudinal studies assessed depressive symptoms using self-rated questionnaires ~~except from one showing that diagnosed psychiatric disorders predicted subsequent painful physical symptoms [22]~~. Finally, various psychological adversities in childhood were found to predict~~ed~~ chronic widespread pain in adult life [24], and ~~were associated with~~ the onset of painful medical conditions [38]. However, no previous study has assessed the independent effects of depression, anxiety disorders, personality traits and ETE on the incidence or persistence of CP in the community.

Hence, using a cohort of middle-aged and older community dwellers, we aimed to establish the prospective associations of major depressive disorder (MDD) and anxiety disorders, personality traits and childhood traumatic events with 1) the incidence of CP during a nearly 5-year following-up period among participants initially exempt ~~of~~ from CP and 2) the persistence of CP ~~among participants with CP at the beginning~~ during this follow-up period among participants who already reported CP in the beginning of the follow-up period.

METHODS

Participants

The present data stem from CoLaus|PsyCoLaus, a prospective population-based cohort study designed to investigate cardiovascular risk factors and mental disorders in the community and to determine their associations. The study has been previously described in detail [14], [35].

CoLaus|PsyCoLaus initially included a sample of 6734 participants (age range: 35-75 years) randomly selected from the residents of the city of Lausanne (Switzerland) according to the civil register. After a first physical and psychiatric assessment, which took place between 2003 and 2008, the cohort was followed-up three times. Since follow-up (FU) 1, participants were invited to complete pain questionnaires during the physical investigation. FU2 followed 5.2 (s.d. 0.5) years after FU1 and FU3 3.8 (0.4) years after FU2. Inclusion criteria for the present analyses were: 1) having jointly completed the psychiatric evaluation and the pain questionnaire either at FU1 or FU2 and 2) having again completed the pain questionnaire at the subsequent FU (FU2 or FU3) (**Figure 1**). A total of 2932 participants met these criteria. After excluding participants with missing information on personality, incomplete information on mental disorders or absence of information on ETE the final sample included 2578 participants with 4121 analysable intervals (56.4% women, mean age 60.5 (s.d. 9.9) years). For the 1746 participants who completed the psychiatric evaluations and the pain questionnaires at all three FU investigations, the ~~two~~ intervals from FU1 to FU2 and from FU2 to FU3 were separately analysed.

Assessments

Participants underwent pain assessments at FU1, FU2 and FU3 using the STOPNEP questionnaire, an 11-question pain inventory designed and validated for epidemiological studies [4]. The first two questions aimed at identifying the presence of daily CP for at least three months. The subsequent questions only applied to participants who answered positively to these two questions. Participants had to locate their pain from a list of body parts and to report the location of the most troublesome pain if appropriate. The remaining 7 questions related to the pain duration, intensity and characteristics of the most troublesome pain. Pain duration was divided into four categories: <6 months, between 6 and 12 months, between 1 and 3 years, or ≥3 years. Participants then reported the highest, lowest, and average intensity of pain during the

past 24 hours, on three numerical rating scales (0=no pain, 10=worst pain imaginable) from the Brief Pain Inventory (BPI) [8]. The mean BPI score corresponded to the mean of the three above scores. Participants were also asked to specify the location of their most painful area. Pain locations were categorized into 1) head (scalp, face, tongue, neck), 2) arm (arm, elbow, forearm, wrist, hand, shoulders), 3) back (upper back, lower back, buttocks), 4) legs (hips, groin, leg, knee, thighs, ankle, foot) and 5) other (chest, other). In accordance to the International Association for Study of Pain (IASP) [40], CP was defined as persistent or recurrent daily pain lasting longer than three months [3] [4].

Diagnostic information on mental disorders including lifetime major depressive disorder (MDD) was elicited at each psychiatric evaluation using the semi-structured Diagnostic Interview for Genetic Studies (DIGS) [31]. The DIGS was developed by collaborators from the National Institute of Mental Health (NIMH) Genetics Initiative in order to more accurately assess phenotypes of schizophrenia and mood disorders through 1) a semi-structured design corresponding to a wide spectrum of DSM-III-R Axis I criteria and 2) collection of extensive information on the course and chronology of comorbid conditions. An updated version of the DIGS included DSM-IV criteria (NIMH Molecular Genetics Initiative (1995) Diagnostic Interview for Genetic Studies (DIGS) - Version 2.0). The DIGS has been translated into French by a group of bilingual collaborators of the INSERM in Paris and the Psychiatric University Hospital of Lausanne [27]. The inter-rater and test-retest reliability of both the original English [31] and the French versions [34], of this instrument were extensively tested for psychotic and mood disorders. The French version revealed kappa values of at least 0.85 for inter-rater and 0.62 for test–retest reliability for major mood disorders [34]. The DIGS was completed using the anxiety disorder sections of the French version [28] of the Schedule for Affective Disorders and Schizophrenia-lifetime and anxiety disorder version (SADS-LA) [12]. The French translation of the SADS-LA was found to have ~~satisfactory~~ adequate test-

retest reliability for panic disorder/agoraphobia (Yule's Y = 0.43), GAD (Yule's Y = 0.61) and phobic disorders (Yule's Y = 0.66) [28]. At the follow-up evaluations, a shortened version of the DIGS was used focusing on the period since the last assessment. Lifetime diagnoses until the first pain assessment were assigned according to DSM-IV [1]. Participants were classified as currently depressed (i.e. meeting DSM-IV criteria for MDD) at the time of the first pain evaluation, remitted (i.e. not meeting criteria for MDD at the time of the first pain evaluation, but having previously met these criteria) and never depressed (i.e. having never met lifetime criteria for MDD up to the first pain investigation).

Early-life traumatic events (ETE) were elicited using the questions on early-life and adolescence events as well as those on traumatic events in the PTSD chapter of the DIGS. The following stressful experiences occurring before the age of 17 years were considered as indicators of adversity: physical fight of parents, separation of parents, death of parents (mother or father), death of sibling as well as sexual abuse and physical abuse. According to the suggestion of Friedman et al. [16] exposure to early-life adversity was quantified by the sum of reported events. Interviewers were master-level psychologists trained over at least a one-month period. An experienced senior psychologist reviewed all interviews and diagnostic assignments.

Neuroticism and Extraversion traits were assessed by the Eysenck Personality Questionnaire-Revised (EPQ-R) [13], which was completed at baseline and FU2, and the NEO Five-Factor Inventory (NEO-FFI-R) [9], filled in at FU1. If participants had completed the two questionnaires prior to the analysed follow-up interval, data from the EPQ-R were used. In order to make data from the two questionnaires comparable, the scores were normalized and z-scores were computed for Neuroticism and Extraversion ~~were computed~~.

During the physical evaluations, information was collected on socio-demographic characteristics including age, sex, education as well as medication (analgesics (ATC code N02),

opioids (ATC code N02A + N02BG01), antidepressants (ATC code N06A), and anxiolytics (ATC code N05B)). Education was categorized into four levels: compulsory school, apprenticeship, high school/college and university degrees.

Ethics

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of the Canton of Vaud (www.cer-vd.ch) approved the baseline CoLaus|PsyColaus study (reference 16/03; 134-03,134-05bis, 134-05-2to5 addenda 1to4). The approval was renewed for the first (reference 33/09; 239/09), the second (reference 26/14; 239/09 addendum 2) and the third (PB_2018-00040; 239/09 addenda 3to4) follow-ups. The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants signed a written informed consent.

Statistical analysis

In order to assess the associations of lifetime mental disorders, personality traits and ETE prior to the FU period ~~and~~ with pain status at the end of the FU period, four serially adjusted generalized linear mixed models were used. ~~, which~~These models were all adjusted for sex, age, education, duration of FU, FU interval (FU1 to FU2 or FU2 to FU3), medication in the end of the interval and intra-personal correlations. In Model 1, only non-chronic pain (for analyses on the incident of CP) or location of CP (for analyses on the persistence of CP) reported in the beginning of the interval were entered. In Model 2, lifetime depression (current or remitted) and anxiety disorders (agoraphobia, panic disorder, generalized anxiety disorder, social phobia) were added. In Model 3~~,~~ ETE and in Model 4~~,~~ the personality scores Neuroticism and Extraversion were added. In order to assess the association between potential psychological

predictors and the persistence of CP, an additional fifth model was run, ~~that~~ which also adjusted for analgesic medication at the beginning of the interval.

The results of all the tests were considered as significant at the level of *p* ~~value~~<0.05. Statistical analyses were computed using the Statistical Analysis System, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

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RESULTS

Table 1 presents the characteristics of the analysable follow-up intervals. Within the 2280 intervals without CP in the beginning, in 750 (32.9%) CP was reported in the end of the interval. Within the 1841 intervals with CP in the beginning, in 1370 (74.4%) CP was still reported in the end of the interval.

Table 2 summarizes the locations of CP in the beginning of the interval for participants with CP. The most frequent locations concerned back, knees, shoulders, feet, hips, hands and joints. Additionally, the mean BPI score during the 24 last hours at the beginning of the interval was 3.4 (s.d. 1.8). Moreover, 43.2%, 27.6%, 15.4% and 13.8% of the participants reported pain duration of ≥3 years, 1-3 years, 6-12 months, and <6 months respectively.

The associations between potential predictors measured in the beginning and the reporting of CP in the end of the follow-up interval among participants ~~who had no~~exempt from CP in the beginning of the interval were provided in **Table 3**. After multiple adjustments for potential confounders, non-chronic pain was strongly associated with an increased likelihood of reporting CP in the end of the interval (Model 1). When mental disorders were added to the model, also current and remitted MDD but not anxiety disorders were associated with reporting of CP in the end of the interval (Model 2). After also adding ETE, non-chronic pain as well as current and remitted MDD remained associated with reporting of CP in the end of the interval,

whereas this was not the case for ETE (Model 3). Finally, after additional inclusion ~~also~~ of personality traits (Model 4), non-chronic pain and higher scores of Neuroticism and Extraversion were associated with CP. In contrast, in this model MDD was no longer associated with CP. The variables assessed in Model 4 explained approximately 7% of the variance.

Table 4 presents the associations between potential predictors and persistence of CP during the follow-up interval. Model 1, ~~that~~ which only included locations of CP in the beginning of the interval, showed only pre-existing back pain, pain in the arm and other pain to be associated with the persistence of CP across the follow-up. Model 2, ~~that~~ which also included mental disorders, revealed associations of current and remitted MDD but not of anxiety disorders with persistence of CP, whereas the pain locations already tested in Model 1 remained significantly associated with the outcome variable. In Model 3 the additional variable ETE was not associated with persistence of CP, whereas in Model 4, ~~that~~ which ~~added~~ also included personality features, lower scores of Extraversion together ~~still~~ with back pain, pain in the arm as well as current and remitted MDD were associated with the persistence of CP. The variables assessed in Model 4 explained nearly 10% of the variance. Similar results were obtained in an additional model ~~additionally~~ that also adjusted for analgesic drugs ~~at~~ in the beginning of the interval (data not shown).

DISCUSSION

This study is the first to simultaneously assess the prospective associations of MDD and specific anxiety disorders assessed through diagnostic interviews, as well as personality traits, and ETE with both the incidence and persistence of CP according to IASP criteria [40], [39] over time in a cohort of middle-aged and older community-dwellers. Our most salient findings were, that 1) both higher Neuroticism and Extraversion scores were associated with higher incidence of CP, whereas the association between MDD and the incidence of CP disappeared

after adjustment for the effects of personality traits; 2) current and remitted MDD as well as lower Extraversion scores were associated with persistence of CP and 3) ETE and specific anxiety disorders were not associated with incidence or persistence of CP.

Predictors of ~~the incidence of CP~~CP incidence

Although pain in the beginning of the interval as well as Neuroticism and Extraversion revealed highly significant associations with CP incidence ~~of CP~~ according to the fully adjusted model, only a relatively small proportion of 7% of the variance was explained by the variables included in this model, indicating that unmeasured characteristics and measurement errors accounted for the major part of the variance.

Prior to the adjustment for personality traits, both current and remitted MDD were also significantly associated with ~~the~~ CP incidence ~~of CP~~ during the follow-up interval. This finding is consistent with those of several longitudinal studies that showed either depressive disorder [22] or depressive symptoms [6], [18], [17] to predict the onset of pain. But the few studies including large samples and follow-up periods of at least two years, yielded mixed results. The study of Hotopf et al., which can be best compared with ours, given the use of a diagnostic interviews in 36 year-old community participants, provided evidence for a dose-response relationship between depression and anxiety and the number of subsequent painful physical symptoms [22]. Moreover, baseline depressive symptoms increased the odds of disabling low back pain in a large database of elderly community residents after two years [29]. Conversely, Arola et al. did not find an association between self-reported depressive symptoms and subsequent pain interference after a 3-year follow-up in a large cohort of community-dwellers aged 50-year and over, in multivariate analysis adjusted for anxiety [2]. Likewise, depressive symptoms were not associated with incident pain in adults initially free of pain and followed-up during 8.3 years [21]. In our study, the association between MDD and the incidence of CP disappeared after adjustment for Neuroticism and Extraversion, which both remained

associated with the incidence of CP in the fully adjusted model. The association between personality traits, in particular Neuroticism, and MDD is complex and still only poorly understood [32]. Five models were postulated to explain the association between neuroticism and depression, including the vulnerability model (postulates that neuroticism leads to depression either by directly causing its development or by enhancing the impact of causal risk factors such as stressful life events), the spectrum model (assumes that both are manifestations of the same process), common cause model (shared determinants for the two), state model (current depressive episode increases Neuroticism during the episode) and scar model (depressive episode increases Neuroticism permanently) [32]. According to the review of Ormel et al., none of these models by itself is able to fully explain the nature of the association, although regarding the link between Neuroticism and depression, the common cause model has the strongest support from existing research followed by the vulnerability model, the state and scar models and the spectrum model [32]. Assuming the vulnerability model, adjusting for the causally related personality traits should indeed remove the prospective association between MDD and CP ~~the~~ incidence ~~of CP~~. However, assuming a scar model, adjusting for personality traits as a consequence of MDD would not be indicated and blur a true prospective association between MDD and the incidence of CP. As pointed out by Ormel et al. [32] despite some evidence for the vulnerability model in the literature, studies endorsing this model could have been easily confounded by unmeasured depressive symptoms at baseline or unrecalled episodes that occurred prior to the baseline of the studies causing increased Neuroticism measures. Hence, given the absence of personality measures prior to the first depressive episode in our study, we cannot determine the direction of the association between MDD and personality scores. For this reason, the question of whether adjusting for personality scores blurs a true prospective association between MDD and CP or alternatively whether MDD is merely a weak mediator of the prospective association between personality traits and CP, remains elusive.

Given that prospective studies repetitively measuring personality traits and mental disorders from early adolescence on up to the age when CP typically occurs are difficult to conduct, alternative designs such as familial aggregation studies and Mendelian randomization studies could more easily provide information on the direction of the observed associations.

The observed association between high Neuroticism and elevated CP incidence is in line with a previous cross-sectional study showing an association of Neuroticism with pain duration and pain severity [20]. With respect to Extraversion, the rather unexpected finding of an association between high Extraversion scores and the risk of developing CP, which contrasts with previous studies not revealing such an association [43], [20], could be due to a tendency of extraverted individuals to be especially attracted to social settings where alcohol, sex and risky driving behaviour are the norm. These people may subsequently develop a hazardous lifestyle [25]. Indeed, a higher risk of essentially non-professional accidents, which could lead to CP, has been documented in people with elevated Extraversion [26],[33]. Whereas in this study high Extraversion scores were associated with higher CP incidence, low Extraversion was associated with CP persistence. The association between low Extraversion scores and CP persistence was less surprising given that generally extraverted individuals tend to have stronger social networks, which are typically protective against negative health outcomes [25].

The observed absence of a prospective association between lifetime anxiety disorders and incident CP is consistent with a previous study that found panic disorder, generalized anxiety disorder, and social phobia not to be associated with pain-related medical conditions [41]. In contrast, a study measuring anxiety symptoms rather than specific disorders showed an association of state but not trait anxiety with CP onset six to twelve months after surgery [3].

The observed absence of an association between ETE and CP incidence contrasts with the results of a previous study, showing that these events were risk factors for the incidence of chronic multisite musculoskeletal pain [20].

Predictors of ~~the persistence of CP~~CP persistence

With almost 10% of the variance explained according to the fully adjusted model, the prediction of persistence of CP was better than that of the incidence of CP. Interestingly, although MDD was no longer associated with the incidence of CP after adjustment for personality traits, current and to a lesser extent remitted MDD ~~to a lesser extent~~ remained associated with a higher risk of persistence of CP during the follow-up interval in the fully adjusted model.

One explanation for the strong association between current MDD and the persistence of CP could be that the presence of a depressive episode at baseline could have been a marker for severe CP. Conversely, Neuroticism was no longer a predictor of persistence of CP after adjustment for MDD. Again, we are confronted with the uncertainty regarding the nature of the association between personality traits and depression. Assuming a vulnerability model as discussed before, adjustment for MDD would not be warranted, whereas assuming a scar model, entering depression into the model would be straight forward.

Our results are consistent with a previous study which did not observe an association between the presence of ETE and the persistence of CP [19].

Limitations

Our results should be considered in the context of several limitations. First, given the advanced age of approximately 60 years of the cohort in the beginning of the follow-up intervals, the absence of personality measures prior to the first mood episode and the risk of inaccurate recall particularly of remote depressive episodes did not allow us to disentangle the

complex relationship between personality traits and MDD and subsequently their independent associations with the incidence and persistence of CP. Second, given that the study was conducted in an urban area, our results may not be generalized to other populations. However, although the specific sample characteristics are likely to affect the prevalence estimate of disorders and CP, it is less likely that they significantly biased the established associations among them.

Conclusions

Our study revealed evidence for significant associations of personality traits and MDD with the incidence and persistence of CP. From the clinical point of view personality traits particularly if treated earlier in life are accessible by psychotherapy. Hence, psychotherapeutic treatment of people with high Neuroticism and Extraversion scores that may involve hazardous behaviour might reduce the later risk of CP. Similarly, adequate treatment of major depressive episodes might also reduce this risk. The adequate treatment of these episodes as well as psychotherapeutic interventions in people with low Extraversion scores may also diminish the risk of the persistence of already manifest CP.

~~Extraversion scores may also diminish the risk of the persistence of already manifest CP.~~

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Figure legend

Figure 1: Flow chart for the selection of analysable intervals.

Personality traits are associated with both the occurrence and persistence of CP, whereas the presence of major depressive episodes may be more associated with CP persistence.

Figure 1

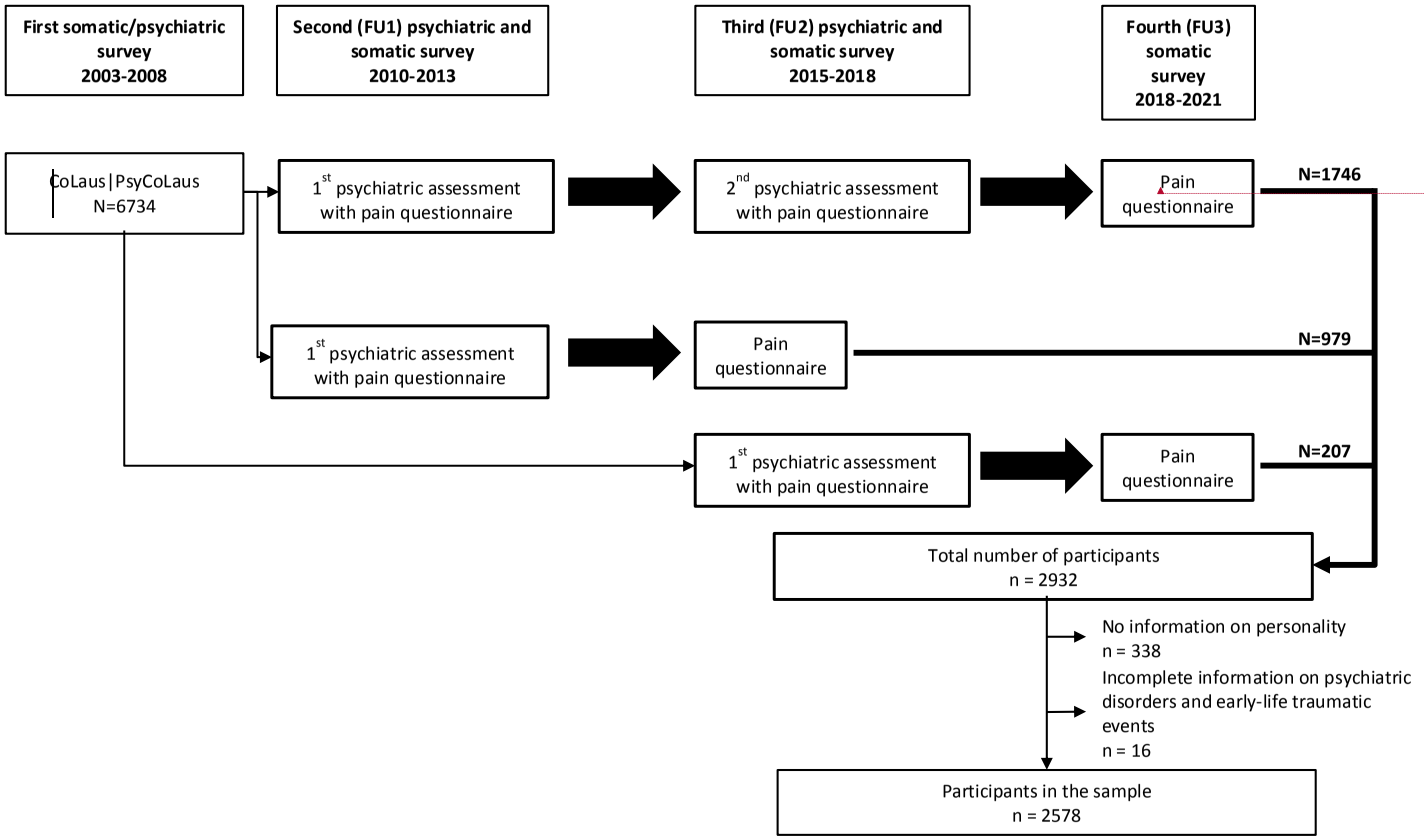

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Table 1: Description of the two analysable intervals according to chronic pain status at the beginning of the interval

	Presence of chronic pain n=1841	**Absence of chronic pain** n=2280
Socio-demographic factors		
Age in the beginning (years), mean (sd)	60.5 (9.9)	57.4 (9.7)
Men, %	37.1	49.1
Education level, %		
University	18.4	27.7
High education except for university	30.1	28.9
Apprenticeship	40.0	34.1
Compulsory school	11.6	9.3
Length of follow-up (years), mean (sd)	4.6 (0.8)	4.6 (0.9)
Medication in the beginning, %		
Analgesics	9.9	1.9
Opioids	2.7	0.3
Antidepressants	16.8	6.0
Anxiolytics	5.4	2.3
Depression and anxiety in the beginning, %		
Major depressive disorder	51.8	42.9
Current	8.8	5.5
Remitted	43.0	37.5
Never depressed	48.2	57.1
Lifetime anxiety disorders (any)	23.0	17.8
Agoraphobia	4.6	3.1
Panic disorder	3.6	2.1
Generalised anxiety disorder	4.6	2.9
Social phobia	14.6	12.2
Early-life traumatic events (before age 17 years)		
Early-life events or abuse, %	32.3	25.8
Number of early-life event or abuse, mean (sd)	0.40 (0.64)	0.33 (0.63)
Personality (z score), mean (sd)		
Neuroticism	0.17 (0.97)	-0.19 (0.95)
Extraversion	-0.07 (1.01)	0.03 (0.99)
Medication in the end, %		
Analgesics	14.0	4.5
Opioids	4.0	0.6
Antidepressants	12.9	6.2
Anxiolytics	5.6	2.4

sd: standard deviation

Table 2: Pain location at the beginning of the interval in participants with chronic pain (n=1841)

	Presence of chronic pain
	% (n)
Head	11.2 (207)
Scalp	1.7 (31)
Face	1.4 (26)
Tongue	0.8 (14)
Neck	9.0 (166)
Back	**54.3 (1000)**
Upper part of back	22.4 (413)
Lower part of back	**43.8 (806)**
Buttocks	7.7 (141)
Arm	**50.2 (925)**
Arm	12.9 (238)
Elbow	10.5 (194)
Forearm	6.1 (112)
Wrist	11.9 (219)
Hand	20.5 (378)
Shoulder	**29.4 (541)**
Leg	**65.7 (1209)**
Hips	22.6 (416)
Groin	5.6 (104)
Thighs	7.8 (143)
Knee	**32.5 (599)**
Leg	16.8 (310)
Ankle	11.8 (218)
Foot	22.9 (422)
Other location	17.1 (314)
Chest	4.8 (89)
Other	13.0 (240)

In bold: most frequent pain locations, concerning more than one subject in 4.

Table 3 without marks

Table 3: Associations between pain and psychiatric disorder status, early-life traumatic events and personality traits in the beginning and the presence of chronic pain in the end of the follow-up interval among participants without chronic pain in the beginning of the interval (n=2280)

		Presence of chronic pain in the end of the interval			
		Model 1	Model 2	Model 3	Model 4
	%	OR[a] (95CI)	OR[b] (95CI)	OR[b] (95CI)	OR[b] (95CI)
Pain in the beginning					
Pain	47.6	**2.41*** (1.82;3.18)**	**2.39*** (1.80;3.17)**	**2.39*** (1.80;3.18)**	**2.38*** (1.78;3.18)**
No pain	25.6	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Depression and anxiety disorders in the beginning					
Major depressive disorder					
Current	36.8		**1.76** (1.15;2.71)**	**1.73* (1.13;2.67)**	1.52 (0.98;2.38)
Remitted	31.9		**1.33** (1.08;1.63)**	**1.31* (1.07;1.62)**	1.22 (0.99;1.52)
Never depressed	24.4	-	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Lifetime anxiety disorders					
Agoraphobia	38.0	-	1.29 (0.72;2.31)	1.29 (0.72;2.30)	1.33 (0.73;2.41)
No agoraphobia	27.5	-	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Panic disorder	34.0	-	1.05 (0.47;2.35)	1.04 (0.46;2.37)	1.02 (0.45;2.31)
No panic disorder	27.7	-	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Generalized anxiety disorder	34.9	-	1.38 (0.78;2.47)	1.39 (0.78;2.48)	1.25 (0.69;2.27)
No generalized anxiety disorder	27.6	-	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Social phobia	28.1	-	0.88 (0.65;1.18)	0.87 (0.64;1.17)	0.89 (0.65;1.21)
No social phobia	27.8	-	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Early-life traumatic events (before age 17 years)					
Number of early-life event or abuse (cont.)	-	-	-	1.08 (0.98;1.19)	1.07 (0.97;1.18)
Personality traits					
Neuroticism (cont.)	-	-	-	-	**1.21*** (1.08;1.36)**
Extraversion (cont.)	-	-	-	-	**1.18** (1.06;1.32)**
QIC		2600.9445	2599.9972	2599.4494	2585.0655
QICu		2600.8523	2597.8552	2597.2197	2582.4583

PCC (%)	73.3	73.0	72.8	72.6
Marginal R^2	0.0562	0.0621	0.0637	0.0707

*p<0.05; **p<0.01; ***p<0.001.
OR: odds ratio; 95CI: 95% confidence interval; cont.: continuous; ref.: reference; QIC: quasilikelihood under the independence model criterion; PCC: percent correctly classified, Marginal R^2: pseudo R^2 as an estimation for the percentage of variation explained by the fixed part of the model.
[a] Logistic regression model adjusted for sex, age, education, length of follow-up interval, follow-up interval (FU1-FU2 or FU2-FU3), medication in the end of the interval, within-participant correlations.
[b] All variables simultaneously entered to the logistic regression model with same adjustments as Model 1.

Table 4: Associations between pain location, psychiatric status, early–life traumatic events and personality traits in the beginning and the persistence of chronic pain in the end of the follow-up interval among participants with chronic pain in the beginning (n=1841)

		Persistence of chronic pain			
		Model 1	**Model 2**	**Model 3**	**Model 4**
	%	**OR[a] (95CI)**	**OR[b] (95CI)**	**OR[b] (95CI)**	**OR[b] (95CI)**
Pain location in the beginning					
Head[c]	76.8	1.10 (0.77;1.56)	1.08 (0.76;1.54)	1.08 (0.76;1.54)	1.07 (0.75;1.53)
Not in head	69.3	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Back[d]	76.6	**1.82*** (1.47;2.24)**	**1.78*** (1.44;2.20)**	**1.78*** (1.44;2.20)**	**1.76*** (1.42;2.18)**
Not in back	62.4	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Arm[e]	74.4	**1.35** (1.10;1.67)**	**1.35** (1.09;1.66)**	**1.35** (1.09;1.66)**	**1.35** (1.09;1.67)**
Not in arm	65.8	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Leg[f]	74.3	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Not in leg	62.2				
Other location[g]	75.8	**1.37* (1.03;1.83)**	**1.35* (1.01;1.79)**	**1.35* (1.01;1.80)**	1.32 (0.99;1.76)
Not in other location	69.0	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Depression and anxiety disorders in the beginning					
Major depressive disorder					

Current	83.4	-	**2.28*** (1.45;3.58)**	**2.30*** (1.46;3.61)**	**2.14** (1.34;3.44)**
Remitted	71.7	-	**1.32* (1.04;1.68)**	**1.33* (1.04;1.69)**	**1.29* (1.00;1.66)**
Never depressed	66.3	-	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Lifetime anxiety disorders					
Agoraphobia	72.6	-	1.12 (0.64;1.97)	1.12 (0.64;1.96)	1.12 (0.64;1.99)
No agoraphobia	70.0	-	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Panic disorder	71.2	-	1.06 (0.58;1.94)	1.06 (0.58;1.95)	0.99 (0.54;1.85)
No panic disorder	70.1	-	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Generalised anxiety disorder	69.1	-	0.78 (0.45;1.34)	0.78 (0.45;1.34)	0.72 (0.42;1.26)
No generalized anxiety disorder	70.2	-	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Social phobia	69.8	-	0.97 (0.71;1.31)	0.97 (0.71;1.31)	0.82 (0.60;1.12)
No social phobia	70.2	-	*1 (ref.)*	*1 (ref.)*	*1 (ref.)*
Early-life traumatic events (before age 17 years)					
Number of early-life event or abuse (cont.)	-	-	-	0.99 (0.88;1.10)	1.00 (0.89;1.12)
Personality					
Neuroticism (cont.)	-	-	-	-	1.10 (0.96;1.26)
Extraversion (cont.)	-	-	-	-	**0.83** (0.74;0.93)**

QIC	2105.6886	2102.3420	2104.3924	2091.9814
QICu	2105.3324	2101.3992	2103.3252	2090.5395
PCC (%)	70.3	70.7	70.7	71.4
Marginal R^2	0.0809	0.0887	0.0887	0.0997

*p<0.05; **p<0.01; ***p<0.001.
OR: odds ratio; 95CI: 95% confidence interval; cont.: continuous; ref.: reference; QIC: quasilikelihood under the independence model criterion; PCC: percent correctly classified, Marginal R^2: pseudo R^2 as an estimation for the percentage of variation explained by the fixed part of the model.
[a] One logistic regression model adjusted for sex, age, education, length of follow-up period, follow-up interval (FU1-FU2 or FU2-FU3), medication in the end of the interval, within-participant correlations.
[b] All variables simultaneously entered to the logistic regression model with same adjustments as Model 1.
[c] Head = scalp, face, tongue, neck.
[d] Back = upper part of back, lower part of back, buttocks.
[e] Arm = arm, elbow, forearm, wrist, hand, shoulder.
[f] Leg = hips, groin, thighs, knee, leg, ankle, foot.
[g] Other location = chest, other.