ORIGINAL ARTICLE

Musculoskeletal pain as a predictor for depression in the general working population of Denmark

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Abstract

Aim: This study examines the association between musculoskeletal complaints and subsequent use of antidepressants and/or psychiatric hospital treatment for depressive mood disorders in the Danish labour force. *Methods:* The study is based on two cohorts. The first cohort is the total labour force in 21 Danish municipalities (*n*=693,860), where the risk of depression (psychiatric diagnosis or antidepressant treatment) during 2010–2015 was compared between individuals on long-term sickness absence due to musculoskeletal disorders (MSD) and non-sick-listed gainfully employed individuals. The second cohort is a random sample of the Danish labour force (*n*=9248) who were followed during 2011–2015 to estimate the association between self-rated musculoskeletal pain and depression. All analyses were controlled for age, sex, calendar period and socio-economic status. *Results:* Compared to non-sick-listed gainfully employed individuals, there was an increased risk of depression in individuals sick-listed with MSD, with rate ratios of 2.39 (99% confidence interval (CI) 2.22–2.58) for individuals with less severe MSD and 4.27 (99% CI 3.98–4.59) for individuals with more severe MSD. There was also an increased risk of depression associated with self-rated pain (yes vs. no), with a rate ratio of 2.17 (99% CI 1.69–2.78). The population attributable fraction of depression from musculoskeletal pain was 0.35 (99% CI 0.24–0.45). **Conclusions: The results of the present study indicate that musculoskeletal pain is an important predictor of indicators of depression in the general working population of Denmark.**

Keywords: *Blinded statistical analysis, musculoskeletal pain, depression, antidepressants, psychiatric hospital treatment, cohort study*

Introduction

Approximately 25% of the working population in the EU suffer from musculoskeletal disorders (MSD). MSD are, by themselves, major contributors to the global burden of disability [1]. Furthermore, it has been hypothesised that they also may play an important role in the development of major depression [2], which is the second leading cause of disability worldwide [1].

Musculoskeletal pain has been associated with reduced physical activity [3,4] and disturbed sleep [5], which in turn have been associated with increased rates of depression [6,7]. Since MSD may play an important role in the development of depression, it is

reasonable to believe that MSD may be an important predictor of depression among people in the general working population.

Several prospective studies have reported strong associations between MSD and the development of depressive symptoms [8–10]. The strong prospective association between MSD and depression has, however, never been confirmed in a study with a pre-published study protocol, in which all inclusion criteria, statistical models, hypotheses and test criteria are completely defined before the exposure data of the study are linked to the outcome data. The present study is based on a detailed protocol [11], which was written and published before we obtained access to the outcome data of the study.

SAGE

The study analyses data from two separate surveys: (a) the Danish National Work Environment Cohort Study, which collected data on health and occupational exposures in a random sample of the working population of Denmark in 2010 [12], and (b) a survey of individuals on long-term sickness benefit from 21 Danish municipalities, recruited in 2010–2012 for the Danish return-to-work project, which was designed to evaluate a program to enhance probabilities and rates of return to work among people on sickness benefits [13]. The exposure data obtained from these sources were linked to national registers on redeemed prescribed medications and psychiatric hospital treatments.

The first part of the present project aimed to estimate the prospective association between long-term sickness absence due to MSD and incident use of prescribed antidepressants and/or psychiatric hospital treatment due to a depressive mood disorder among people in the Danish labour force. The following end points were applied: (a) redeemed prescription for antidepressant drugs (ATC-code N06A); (b) psychiatric hospital treatment with a depressive mood disorder (ICD-10: F32–F33) as principal diagnosis; and (c) redeemed prescription for antidepressant drugs or psychiatric hospital treatment with a depressive mood disorder as principal diagnosis.

The second part of the project aimed to test the hypothesis of a positive dose–response relationship. The hypothesis was that a more severe episode of MSD-related sickness absence is associated with a higher risk than exposure to a less severe episode, which in turn is associated with a higher risk than that of the general working population.

The third part of the project aimed to estimate the prospective association between self-rated musculoskeletal pain in the neck, shoulders, elbow, forearm, hand or lower back and incident use of prescribed antidepressants and/or psychiatric hospital treatment due to a depressive mood disorder in a random sample of the Danish labour force.

The study population of the first and second part of the project was large enough to allow us to estimate the prospective association between long-term sickness absence due to MSD and psychiatric hospital diagnoses of depression. The results could thereby tell us if a hypothetical association with antidepressant drug use would also hold good when the outcome is based on psychiatric hospital diagnoses and vice versa. The results could not, however, tell us to what extent the association was due to musculoskeletal pain or other adverse effects of being on long-term sick leave. Hence, the third part of the project was needed to verify that a hypothetical prospective association between musculoskeletal pain and depression would also hold in a general working population of non-sick-listed individuals. All analyses were controlled for age, sex, socio-economic status (SES) and calendar period.

Methods

The methodological details of the study were given in our study protocol [11] and are repeated in the present method section.

Study populations

The study population of the first and second parts of the project consisted of people from the Danish labour force who fulfilled the following criteria on 1 January 2010: were employed, self-employed, assisting spouses or recipients of unemployment benefits; were between 25 and 64 years old; had their residence in any of 21 Danish municipalities that participated in the Danish return-to-work program [13]; and did not emigrate or immigrate, did not redeem any prescription for antidepressant drugs and did not receive hospital treatment for a mood disorder (ICD-10: F30-F39) between 1 January 2005 and 31 January 2010/26 April 2010 for the first and second parts of the study, respectively. Residents who received sickness benefits due to MSD sometime during the time period February 2010–September 2012 were the subjects of interest. The rest of the study population served as a comparison group (standard population). Our decision to consider only sickness absence in the time period February 2010–September 2012 was due to the lack of data about sickness absence episodes outside of this time interval.

The third part of the project was based on people who participated in a survey on working environment and health that was conducted on a random sample of the Danish population in 2010 [12]. This part of the project included all participants who, on 1 January 2011, had their residence in Denmark and fulfilled the previously mentioned criteria for SES and age. It was, moreover, required that they did not emigrate or immigrate, that they did not redeem any prescription for antidepressant drugs and that they did not receive hospital treatment for a mood disorder between 1 January 2006 and 31 December 2010.

Information about self-rated musculoskeletal pain was retrieved from the survey data. Information about MSD-related sickness absence was retrieved from data registered at municipal sickness benefit offices. Information about medicines, psychiatric hospital treatments, age, sex, deaths, migrations, employment and SES was retrieved from national registers.

Data registered at sickness benefit offices

The public sickness benefit scheme in Denmark covers long-term sickness absence (>21 days in 2010–2011; >30 days in 2012) among assisting spouses and self-employed, employed and unemployed residents. The system is administered by municipal sickness benefit offices, which according to the Sickness Benefits Act are committed to follow up and continuously evaluate each sick-listed person's prognosis of returning to the labour force [14]. In connection with the Danish return-to-work program, which ran from February 2010 to September 2012, data were collected from sickness benefit offices in 21 (out of 98) Danish municipalities. The obtained database contains inter alia the cause of the sickness absence, the date of the first consultation with the sickness benefit office and a personal identification number, which enable linkage to data in national registers. From 26 April 2010, it also contains a variable which denotes the estimated severity of the sickness absence episode. At the first consultation with the sickness benefit office, the sick-listed person was classified into one of the following severity categories: (a) likely to return to the labour force within three months, (b) unlikely to return to the labour force within three months but able to participate in activities aimed at facilitating a return, or (c) unlikely to return to the labour force within three months and unable to participate in activities [15].

Data from national registers

The project utilised data from the central person register, the employment classification module, the psychiatric central research register and the national prescription register. The central person register contains information on sex, addresses and dates of birth, death and migrations for every person who is or has been an inhabitant of Denmark sometime between 1968 and the present time. A person's SES, occupation and industry have been registered annually in the employment classification module since 1975. The psychiatric central research register has existed as a national register since 1970 and contains data from all psychiatric hospital departments in Denmark. From 1970 to 1994, the register only included inpatients, but since 1995, it has also covered outpatients and emergency ward visits. Since 1994, the diagnoses are coded according to the International Classification of Diseases, 10th revision (ICD-10) [16]. The national prescription register covers all redeemed prescriptions at pharmacies in Denmark since 1995, and the products are coded in accordance with the Anatomical Therapeutic Chemical (ATC) Classification System.

Data from the national survey

In the autumn of 2010, a random sample of 20- to 69-year-old residents of Denmark (*n*=30,000) were invited to participate in a survey on working environment and health. Data were collected via a mailed questionnaire, which contained 62 questions. The response rate was 48%. Approximately 10,600 of the respondents were either employed or self-employed at the time of the interview [12].

Exposure categories in the first and second part of the project

In the first part of the project, we operated with two groups: (a) the standard population and (b) people who (according to the data that were collected at the sickness benefit offices) received sickness benefit due to a MSD sometime between February 2010 and September 2012.

The second part of the project operated with three groups: (a) the standard population; (b) people who, at their first consultation with the sickness benefit office, were evaluated as likely to return to the labour force within three months; and (c) people who were evaluated as unlikely to return to the labour force within three months.

At the start of the follow-up, everyone belonged to the standard population. The ones who received sickness benefit for MSD were shifted to groups 2/3 at the date of their first consultation with the sickness benefit office, wherein they remained throughout the rest of the follow-up period.

Exposure categories in the third part of the project

The participants in the national survey were asked to rate their average pain during the last three months in the neck/shoulders, elbow/forearm/hand and lower back, respectively, on an integer grading scale from 0 to 9, where 0=no pain and 9 represents the worst imaginable pain. The body regions were defined by illustrative drawings.

In keeping with Andersen et al. [17], participants who rated their pain as ≥4 in any of the three body regions were defined as exposed to musculoskeletal pain (in the neck, shoulders, elbow, forearm, hand or lower back), while the rest of the participants were defined as unexposed. On a continuous 0–10 visual analogue scale, it has been proposed that ≤3.4 should be interpreted as mild pain, 3.5–7.4 as moderate pain and ≥7.5 as severe pain [18]. In keeping with this interpretation, a rating of ≥4 on the scale in the present study may be interpreted as exposed to moderate or severe pain.

Follow-up

The follow-up started on 1 February 2010, 26 April 2010 and 1 January 2011 in the first, second and third parts of the project, respectively. The follow-up ended at the time the participant reached the clinical end point of the study, emigrated, died or the study period ended (31 December 2015), whichever came first. The reason for the different starting points of the follow-up in the first and second parts of the project (1 February and 26 April) was that the second part of the project required information on the severity of the sickness absence episode, and this information was not available in the period prior to 26 April 2010.

Clinical end points

The primary end point of a follow-up was reached if and when the participant either redeemed a prescription for antidepressant drugs (ATC-code N06A) or received psychiatric hospital treatment for a depressive mood disorder (ICD-10: F32–F33) as a principal diagnosis. We performed, however, a couple of sensitivity analyses in the first part of the project in which each of the components of the primary end point was treated separately, that is, one of the sensitivity analyses regarded a redeemed prescription for antidepressant drugs (ATC-code N06A) as the end point, while the other regarded psychiatric hospital treatment with a principal diagnosis of depressive mood disorder (ICD-10: F32–F33) as the end point.

Statistical analysis

We used Poisson regression to estimate the effect of long-term sickness absence due to MSD and self-rated musculoskeletal pain separately on the incidence of redeemed prescriptions for antidepressant drugs and/or hospital treatment due to a depressive mood disorder. The analyses were controlled for sex, age (five-year classes), calendar period (2010, 2011, 2012, 2013–2015) and SES (unemployed people; self-employed people and assisting spouses; legislators, senior officials and managers; professionals; technicians and associate professionals; workers in occupations that require skills at a basic level; workers in elementary occupations; gainfully occupied people with an unknown occupation). Calendar period were treated as a dynamic (time-varying) variable. The remaining control variables were fixed at baseline (1 January 2010 in the first and second parts of the project, and 1 January 2011 in the third part). The logarithm of person-years at risk was used as offset. Rate ratios for the comparisons, follow-up

periods and clinical end points given in Table I were estimated with 99% confidence intervals.

In the first and second parts of the project, long-term sickness absence due to MSD was treated as a time-varying variable. The study participants belonged to the standard population until the date of their first MSD-related consultation with the sickness benefit office, at which time they were shifted from the standard population to the MSD group, wherein they remained throughout the rest of the follow-up period. If the clinical end point of the study occurred between the start of the follow-up and the date of the first MSD-related consultation with the sickness benefit office, then the case was counted as having occurred in the standard population. Our decision to end the follow-up when the clinical end point of the study occurred ascertained that the MSD-related sick absence was present before the clinical end point among all cases that were counted as having occurred in the MSD group.

Statistical significance criteria

In the first and third parts of the project, we regarded an estimated rate ratio as statistically significant if its 99% confidence interval did not contain 1.

In the second part of the project, we regarded the dose–response hypothesis as confirmed if:

$$\mathrm{Min}\left(\frac{\log\left[\mathrm{RR}_{2-3,1}\right]}{SE_{2-3,1}}, \frac{\log\left[\mathrm{RR}_{1,0}\right]}{SE_{1,0}}\right) > \Phi^{-1}(0.9)$$

where $\mathrm{RR}_{2-3,1}$ is the estimated rate ratio for severity category 2–3 (unlikely to return to the labour force within three months) versus severity category 1 (likely to return to the labour force within three months), $RR_{1,0}$ is the estimated rate ratio for severity category 1 versus the standard population, the SEs are the standard errors of the logarithm of the estimated rate ratios and Φ is the standard normal distribution function.

Population attributable fraction

In the third part of the project, we estimated the population attributable fraction (PAF) of depression from musculoskeletal pain among economically active people in Denmark in accordance with the equation:

$$\mathrm{PAF} = p(RR-1)/\left[1+p(RR-1)\right]$$

where p is the prevalence of musculoskeletal pain in the neck, shoulders, elbow, forearm, hand or lower

Table I. Group comparisons, follow-up periods and clinical end points for which rate ratios were to be estimated according to the study protocol.

Comparison	Follow-up period	Clinical end point
People exposed to long-term sickness absence (LTSA) due to musculoskeletal disorders (MSD) vs. people in the standard population	1 February 2010–31 December 2015	Redeemed prescription for antidepressant drugs (ATC-code N06A) or psychiatric hospital treatment with a depressive mood disorder (ICD-10: F32–F33) as principal diagnosis
Same as above	Same as above	Redeemed prescription for antidepressant drugs (ATC-code N06A)
Same as above	Same as above	Psychiatric hospital treatment with a depressive mood disorder (ICD-10: F32–F33) as principal diagnosis
LTSA due to MSD in severity category 1[a] vs. the standard population	26 April 2010–31 December 2015	Redeemed prescription for antidepressant drugs (ATC-code N06A) or psychiatric hospital treatment with a depressive mood disorder (ICD-10: F32–F33) as principal diagnosis
LTSA due to MSD in severity category 2–3 vs. LTSA due to MSD in severity category 1	Same as above	Same as above
Exposed vs. not exposed to self-rated musculoskeletal pain in the neck, shoulders, elbow, forearm, hand or lower back	1 January 2011–31 December 2015	Same as above

[a]At the first consultation with the sickness benefit office, the sick-listed person is classified into one of the following severity categories: (a) likely to return to the labour force within three months, (b) unlikely to return to the labour force within three months but able to participate in activities aimed at facilitating a return or (c) unlikely to return to the labour force within three months and unable to participate in activities.

back, and RR is the rate ratio for subsequent prescribed antidepressants or psychiatric hospital treatment for depression among employees with versus without musculoskeletal pain in the concerned body regions.

A 99% confidence interval for the PAF estimate was obtained through Monte Carlo simulation.

Results

The first part of the project included 693,860 individuals (323,170 female). The mean (*SD*) age on 1 January 2010 was 43.1 (10.6) years among all included individuals and 45.0 (9.9) years among the individuals who were registered with MSD at a sickness benefit office sometime between February 2010 and September 2012 (*n*=14,903). In total, we observed 4111 incident cases of 'psychiatric hospital treatment for depression' in 4,085,619 person-years at risk; 52,835 incident cases of 'redeemed prescription for antidepressants' in 3,923,451 person-years at risk; and 53,262 incident cases of 'prescribed antidepressants or psychiatric hospital treatment for depression' in 3,922,179 person-years at risk.

The second part of the project included 690,135 of the above-mentioned 693,860 individuals. A flow chart of the inclusion/exclusion procedure is given in Figure 1 of the Supplemental Appendix. Here, we observed 50,257 incident cases of 'prescribed antidepressants or psychiatric hospital treatment for depression' in 3,920,246 person-years at risk.

The third part of the project included 9248 individuals (4797 female) of whom 4217 had self-rated musculoskeletal pain according to the survey. The

mean (*SD*) age on 1 January 2011 was 46.6 (9.5) years among participants with pain and 45.7 (9.8) years among participants without pain. In total, we observed 487 incident cases of 'prescribed antidepressants or psychiatric hospital treatment for depression' in 44,629 person-years at risk. A flow diagram over the inclusion/exclusion procedure is given in Figure 2 of the Supplemental Appendix.

The SES distributions of the included individuals in the first and third parts of the project, respectively, are given in Table II.

We found that long-term sickness absence due to MSD statistically significantly predicted both psychiatric hospital treatment for depression with a rate ratio of 2.55 (95% CI 2.12–3.07; *p*<0.0001) and redeemed prescriptions for antidepressants with a rate ratio of 3.06 (95% CI 2.91–3.23; *p*<0.0001; Table III). There was a dose–response relationship with more severe episodes of MSD-related sickness absence associated with a higher risk than less severe episodes of MSD-related sickness absence (*p*<0.0001; Table IV).

We furthermore found that self-rated musculoskeletal pain was a statistically significant predictor of redeemed prescriptions for antidepressants or psychiatric hospital treatment due to depression among workers in the general population of Denmark (*p*<0.0001; Table V). The PAF was estimated at 0.35 (99% CI 0.24–0.45).

Discussion

The results of the present study indicate that musculoskeletal pain is an important predictor of indicators

Table II. Socio-economic status distribution of the participants in the first and third parts of the project, respectively.

Socio-economic status	First part		Third part	
	n	%	*n*	%
Self-employed or assisting spouses	45,520	6.6	499	5.4
Legislators, senior officials or managers	25,287	3.6	439	4.7
Professionals	128,128	18.5	1857	20.1
Technicians or associate professionals	157,789	22.7	2159	23.3
Workers in occupations that require skills at a basic level	215,155	31.0	2965	32.1
Workers in elementary occupations	45,472	6.6	583	6.3
Unemployed	16,565	2.4	174	1.9
Gainfully occupied people with an unknown occupation	59,944	8.6	572	6.2
Total	693,860	100.0	9248	100.0

Table III. Standardised rate ratios for prescribed antidepressants or psychiatric hospital treatment for depression among people on LTSA due to MSD.

End point data	LTSA due to MSD	Person-years at risk	Cases	Rate ratio	99% CI
PCRR[a]	Yes	71,654	207	2.55	2.12–3.07
	No	4,013,965	3904	1.00	–
NPR[b]	Yes	61,331	2585	3.06	2.91–3.23
	No	3,862,120	50,250	1.00	–
PCRR or NPR	Yes	61,285	2601	3.06	2.90–3.22
	No	3,860,894	50,661	1.00	–

[a]The psychiatric central research register.
[b]The national prescription register.

Table IV. Standardised rate ratios for prescribed antidepressants or psychiatric hospital treatment for depression among people on LTSA due to MSD stratified by severity category.

LTSA due to MSD	Person-years at risk	Cases	Rate ratio[a]	99% CI
Yes, severity category 2–3	22,257	1346	4.27	3.98–4.59
Yes, severity category 1	38,953	1248	2.39	2.22–2.58
Standard population	3,859,036	47,663	1.00	–

[a]Rate ratio for severity category 2–3 vs. severity category 1=1.79 (99% CI 1.61–1.98).

Table V. Standardised rate ratios for prescribed antidepressants or psychiatric hospital treatment for depression among employees with versus without musculoskeletal pain in the neck, shoulders, elbow, forearm, hand or lower back.

Musculoskeletal pain	Persons	Person-years at risk	Cases	Rate ratio	99% CI
Yes	4217	20,097	320	2.17	1.69–2.78
No	5031	24,532	167	1.00	–

of depression (redeemed prescriptions for antidepressants and psychiatric hospital treatment for depressive mood disorders). This finding was consistent in both samples, and applied to both objectively assessed and clinically diagnosed MSD among sick-listed individuals and self-rated symptoms of pain measured by a survey in the general working population of Denmark.

Three previous studies have examined the prospective relationship between musculoskeletal pain and subsequent depression or depressive symptoms among people in company-based or general working age populations that are free from depressive symptoms at baseline [8,9,19]. The prospective relationship has, moreover, been properly examined by Gerrits et al. [10] in a study population predominately recruited from primary care and secondary mental health care, as well as by Veronese et al. [20] in a patient population consisting of predominately older people who either suffered from or were at increased risk of incurring osteoarthritis (OA) of the knee. Gerrits et al. reported hazard ratios for depressive symptoms of 2.64 (95% CI 1.42–4.91), 2.63 (95% CI 1.47–4.68) and 2.68 (95% CI 1.45–4.95)

among participants with pain versus no pain in the neck, back and joints, respectively. Veronese et al. reported an odds ratio for depressive symptoms of 1.48 (95% CI 1.07–2.05) among people with multi-site OA versus no OA

Leino and Magni [19] investigated clinically assessed MSD and self-rated musculoskeletal symptoms (ache, stiffness, sensitivity to movement, numbness or pain) in the neck/shoulders, lower back, upper limbs and lower limbs as predictors for a subsequent change in depressive symptom scores among 607 metal industry employees in Finland. The association between self-rated musculoskeletal symptoms and change in depressive symptoms was tested for each of the four body regions as well as for all body regions combined. The same was done for the association between clinical musculoskeletal findings and change in depressive symptoms. Hence, a total of 20 tests of the prospective association between musculoskeletal morbidity and depressive symptoms were performed, of which none was statistically significant. This null finding by Leino and Magni [19] is not in line with the findings of the present study – a discrepancy which could be related to a lack of statistical power in the study by Leino and Magni.

Magni et al. [8] estimated the odds of having depressive symptoms at an eight-year follow-up as a function of chronic musculoskeletal pain at baseline as 2.85 (95% CI 2.52–3.18) in a sample of 1790 people aged 25–74 years from 'the non-institutionalized US population'. Depressive symptoms were defined as a score of ⩾16 on the Center for Epidemiologic Studies Depression (CES-D) scale [21]. The same definition of depressive symptoms was used by Carrol et al. [9] who estimated the hazard ratio for development of depressive symptoms as a function of pain in the neck or lower back in a sample of 845 residents of Saskatchewan aged 20–69 years. The hazard ratios were estimated as 2.10 (95% CI 1.09–4.04) for 'mild pain', 1.98 (95% CI 0.91–4.32) for 'intense, non-disabling neck or low back pain' and 2.45 (95% CI 1.06–5.69) for 'disabling pain in the past six months'. The findings by Magni et al. [8], Carrol et al. [9], Gerrits et al. [10] and Veronese et al. [20] are in line with the findings of the present study, suggesting that MSD is an important predictor of depression. The outcome data in these previous studies were, however, collected by volunteer participation in follow-up interviews, which is open to bias from missing follow-up data. Moreover, none of the previous studies were based on a representative sample of a general working population. The present study does not share these drawbacks and thereby adds certainty about the strength of the prospective association between musculoskeletal pain and depression in a general working population.

Concerning the associations between working conditions and depression, much attention has been given over recent years to the potential link between psychosocial working conditions and depression. A multitude of studies show longitudinal associations between psychosocial working conditions such as high demands and low control, and the development of depression [22,23], although methodological concerns remain which preclude firm conclusions regarding the causality of the association [23]. Little attention has been paid, however, to the role of physical working conditions and pain in these associations [22]. The strong and consistent associations between pain and depression in the present study suggest that pain and physical working conditions are important factors to consider as potential confounders or mediators in future studies of associations between working conditions and depression. Our finding of a 35% population attributable fraction of depression from musculoskeletal pain among economically active people furthermore suggests a potential to prevent depression by strategies which targets work environmental causes and consequences of MSD. Further research is needed to explore this potential.

Strengths and limitations

The strengths of this study include the pre-published study protocol [11] which specified all hypotheses, inclusion criteria, data material and statistical methods of the study before exposure and outcome data were linked. The protocol was followed, which means that the study is free from hindsight bias and selective outcome reporting. The use of national registers eliminated bias from missing follow-up data, and the problem of reversed causation was mitigated through the exclusion of prevalent cases.

The study was further strengthened by the complementary nature of our two data sets. The first data set was used in sub-projects 1–2 to estimate the association between long-term sickness absence due to MSD and subsequent depression. The data set was large enough to verify that the association was present not only when depression was operationalised by antidepressant treatment, but also when it was operationalised on the basis of psychiatric hospital diagnoses. Consequently, the association found is not likely to be attributable to antidepressants being prescribed to alleviate pain [24]. It was, moreover, large enough and had the necessary information to test for a dose–response relationship between severity of long-term sickness absence due to MSD and subsequent depression, allowing us to conclude that the strength of the association increases with the severity of MSD. The drawback of the first data set was that it

did not allow differentiation between effects from MSD and other effects of being on long-term sick leave. Long-term sickness absence may, for example, be associated with job insecurity, and employees on long-term sickness absence risk unemployment [25], which are both predictors of depressive symptoms [26]. A positive association between long-term sickness absence due to MSD and depression in Denmark would therefore not necessarily mean that there is a positive association between musculoskeletal pain and depression in the general workforce of Denmark. Our second data set rectified this shortcoming by allowing us to estimate the association between musculoskeletal pain and subsequent use of antidepressants or hospital treatment due to depression in a random sample of the Danish labour force.

However, some limitations of the study should be noted. First, antidepressants are not only used to treat depression. They are also prescribed for many other conditions, such as pain, anxiety and insomnia [24]. It is, moreover, known that depression can be treated with medication other than antidepressants, for example lithium [27]. A rate ratio of redeemed prescriptions for antidepressants is therefore quite a rough estimate of the association between pain and medically treated depression, and this should be taken into account in the interpretation of the results.

Second, we cannot rule out the possibility of detection bias. All else equal, depressed people with musculoskeletal pain would have more reasons to visit a medical doctor than depressed people without musculoskeletal pain. MSD may thereby be associated with an increased probability that depression will be detected and treated, which would bias rate ratios upwards.

Third, the pain scores and the diagnostic criteria for depression [28] are based on self-reported symptoms of physical and mental discomfort, respectively. People who are prone to tone down/exaggerate their physical discomforts may also be prone to tone down/exaggerate their mental discomforts, which would bias rate ratios upwards.

Fourth, in our third sub-project, we used the prevalence of pain among the responders of our national survey to estimate the PAF of depression due to musculoskeletal pain among all economically active people in Denmark. The survey sample was selected at random from the target population, but the response rate was low (48%). We therefore cannot rule out the possibility that the PAF estimation was biased by non-participation. If the prevalence was greater among the non-responders than it was among the responders, then the PAF estimate would be biased downwards. If the opposite was true, then it would be biased upwards.

Fifth, some individuals in the comparison group may have experienced pain prior to baseline, and some of them would have experienced pain during the follow-up, which would dilute the exposure contrast and thereby bias the estimation of rate ratios for exposed versus non-exposed people towards unity.

Moreover, in a study on the relationship between retirement and antidepressant use, Oksanen et al. defined antidepressant use as the purchase of antidepressants of at least 30 defined daily dosages (DDD) [29]. In the present project, we did not have access to information about the DDD of the prescriptions. One redeemed prescription was enough for the case definition to be fulfilled. The average severity of the cases of the present study is therefore expected to be less than it would have been if we had required the purchase of a pre-specified amount of daily dosages before the case definition was fulfilled. We cannot rule out the possibility that the estimated rate ratios for antidepressant use would have been lower if our case definition had been based on a certain amount of daily dosages instead of a redeemed prescription without further specifications.

Conclusions

To conclude, we found strong and consistent longitudinal associations between MSD and indicators of depression (redeemed prescriptions for antidepressants and psychiatric hospital treatment for depressive mood disorders) in two separate cohorts from the Danish workforce. These findings suggest that musculoskeletal pain is an important predictor of depression, which should be considered in future studies on the aetiology of depression.

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Supplemental material

Supplemental material for this article is available online.

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