Meta-Analysis

Association of Cigarette Smoking with Risk of Chronic Musculoskeletal Pain: A Meta-Analysis

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Background: Chronic musculoskeletal pain (CMP) management is a major global public health goal owing to increased social and economic burdens. However, the risk of CMP in smokers compared with nonsmokers remains uncertain.

Objectives: This study aims to determine the magnitude and importance of the relationship between cigarette smoking and risk of CMP.

Study Design: A meta-analysis of the CMP risk of cigarette smokers.

Methods: We systematically searched PubMed, Embase, and Cochrane library databases from inception to August 2020. Data extraction and quality assessment were performed by 2 independent reviewers using a standardized extraction checklist. Data were pooled using a random-effects model.

Results: In this meta-analysis of 32 studies involving 296,109 participants, current smoking was associated with increased CMP risk (OR: 1.23, 95% CI: 1.09-1.40), whereas ever and past smoking did not show such an association (OR: 1.14, 95% CI: 0.95-1.37; OR: 1.06, 95% CI: 0.83-1.35, respectively). Stratified analyses showed that there was a marked significance in almost all strata of current smokers compared with non-smokers, except for mean age (≥ 50 years), location of pain (neck pain, sacral pain, and knee pain), smoking frequency (occasionally), study design (cross-sectional), mean follow-up (< 10 years), and adjustment for confounding factors (≥ 6). Interestingly, there was statistically negative association between cigarette smoking and knee pain risk in current smokers, ever smokers, and past smokers.

Limitations: The major limitation of this meta-analysis relates to the heterogeneities across included studies.

Conclusions: Cigarette smoking was associated with increased risk of CMP. In view of the high prevalence of smoking in many countries and the increasing number of CMP patients worldwide, reducing tobacco use should be an important public health strategy to prevent and control the global epidemic of CMP. Future research should attempt to establish whether this association is causal and clarify its mechanisms.

Key words: Cigarette, smoking, tobacco, nicotine, risk, chronic musculoskeletal pain, meta-analysis, public health

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Chronic musculoskeletal pain (CMP) is generally defined as pain caused by joints, bones, muscles, and tendons lasting more than 3 months or beyond the expected period of healing of tissue pathology (1,2). CMP including chronic neck pain, chronic arm pain, chronic back pain, chronic low back pain, chronic sacral pain, chronic knee pain, and others, seriously affects quality of life and results in associated direct and indirect costs (e.g., disability payments, lost productivity). In the Eastern Mediterranean Region,

musculoskeletal pain conditions, especially lower back pain, neck pain, and osteoarthritis, have caused economic burdens to increase faster than in other regions of the world, reflected in disability-adjusted life years, prevalence, death, years of life lost, and years of disability (3). In the United States, about 9% of people who committed suicide in 18 states in 2003-2014 suffered from chronic pain, of which CMP accounted for 45.2% (4). Therefore, expanding the research on the pathological mechanism of CMP and discovering key targets for prevention and treatment of CMP has become an important and urgent research goal.

Cigarette smoke, as a carrier of nicotine, undergoes profound physiological changes after inhalation by the human body, of which nicotine has analgesic effects. As early as the 16th century, it was discovered that tobacco can relieve the pain caused by syphilis (5). But it was not until the 20th century that the main substance in tobacco, nicotine, was linked to the analgesic effect (6). The analgesic effect of nicotine, the main substance in tobacco, has been repeatedly verified in animals over the past 30 years, and may be exerted through the effect of central and peripheral nicotine acetylcholine receptors (7,8). However, cigarette smokers have been reported to be at an increased risk of developing back pain (9), and widespread pain (10). This apparent paradox has great scientific value in the search for pain drug targets and great clinical value in pain management and daily care of patients with CMP. Therefore, we conducted a systematic review and meta-analysis of observational studies describing the association between cigarette smoking and CMP risk.

Methods

Study Protocol

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analyses of Observational Studies in Epidemiology (MOOSE) (11) guidelines. The protocol was registered at the International Prospective Register of Ongoing Systematic Reviews (CRD42018095601).

Search Strategy

We systematically searched PubMed, Embase, and Cochrane library databases from inception to August 31, 2020, with the keywords and Medical Subject Headings (MeSH) terms, such as pain, ache, tobacco, cigarette, smoking, and smoker with no restrictions on the type of study design. The key word terms are listed in Supplementary Table 1. We also manually screened the reference lists of relevant records. One author conducted the search. Two authors independently screened the title/abstract and assessed full-text records for eligibility.

Inclusion and Exclusion Criteria

We selected studies fulfilling the following inclusion criteria: (i) were published as full-length articles in English; (ii) were cross-sectional, cohort, or case-control studies; (iii) ever, current, or past smoking was identified as exposure at baseline; (iv) had the general population without smoking as a control group; (v) the incidence of pain caused by joints, bones, muscles, and tendons lasting more than 3 months or beyond the expected period of healing of tissue pathology which diagnosed as CMP was the primary outcome; and (vi) the original articles contained sufficient information to calculate the odds ratios (OR) and corresponding 95% confidence interval (CI) for the incidence of CMP in smokers (ever, current, or past) compared with non-smokers. The diagnosis of CMP was consistent with the criteria applied in the original articles. Studies were excluded if they were reviews, letters to the editor, meeting abstracts, citations, or news releases. Studies that used other forms of nicotine intake as exposure and used non-chronic pain, or CMP undefined in original articles as an outcome were also excluded. If articles used a great deal of overlapping source material, recent studies that met the inclusion criteria were included in this meta-analysis.

Data Extraction and Quality Evaluation

After excluding ineligible records, data extraction and quality assessment were performed independently by 2 authors using a standardized extraction checklist. In case of discrepancies during data extraction and quality assessment, a consensus was reached through consultation with or the decision of a third author. Detailed characteristics of the studies including name of first author, year of publication, source of study population, study design, gender, sample size, number of CMP cases, smoking status (ever, current, past, or non-smoking), location of pain, years of follow-up, and adjustment of confounders were extracted. In addition, the Agency for Healthcare Research and Quality (AHRQ) cross-sectional study evaluation standard was used for the quality assessment of cross-sectional studies (12), which consisted of 11 items with the responses "Yes", "No", and "Unclear" regarding the source of information, inclusion and exclusion criteria for exposure

and outcome, time period identifying patients, consecutiveness of non-population-based subjects, subjective components of evaluators, assessments undertaken for quality assurance, explanation of any patient exclusions, how confounding was assessed and/or controlled, handling of missing data, summary of patient response rates and data collection integrity, and clarification of follow-up. A score ≥ 8 was categorized as high quality. The quality of cohort studies and case-control studies was evaluated using the Newcastle-Ottawa Scale (NOS) (13), each study was judged based on the selection of study groups, comparability of the groups, and ascertainment of exposure and outcome.

Statistical Analysis

RevMan, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata software, version 15.0 (StataCorp, College Station, Texas, USA) were used for statistical analyses. The ORs and the lower and upper limits of their 95% CIs were calculated to assess the relationship between smoking status (ever, current, past, and non-smoking) and CMP risk. The Cochran Q test and the I^2 statistic were utilized to evaluate statistical heterogeneity among the included studies. Values of $P < 0.10$ for the Q test and > 50% for I^2 statistic indicated study heterogeneity. Considering study heterogeneity, random-effects models were used to calculate pooled effect sizes for comparability (14). Subgroup analyses were performed on gender, age, location of pain, smoking frequency, study design, years of follow-up, and number of adjustments for confounding factors. Potential publication bias was assessed using a funnel plot and quantified using Begg and Egger tests (15,16).

Certainty of Evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to rate the certainty of evidence as high, moderate, low, and very low based on large effect, plausible confounding, and dose response gradient (17).

Results

Literature Search Results

Figure 1 provides the PRISMA flowchart of the literature search and inclusion process. We examined

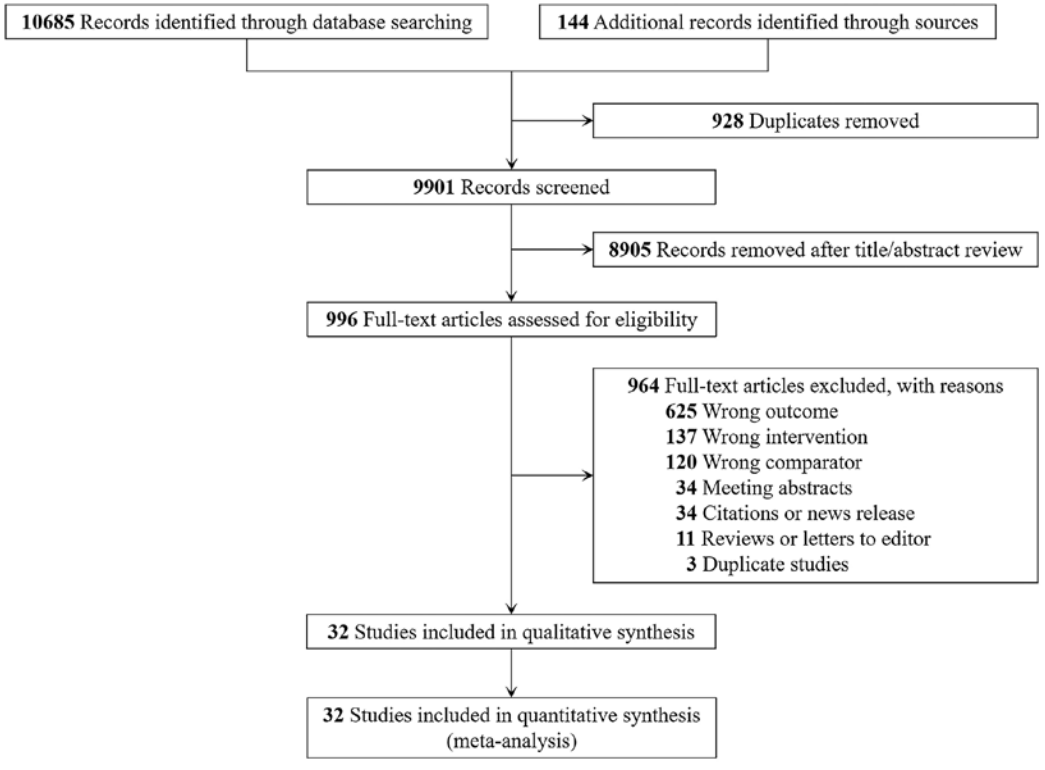

Fig. 1. *Flowchart of the literature search.*

10,829 records of titles and abstracts including 10,685 records identified from database searching and 144 from reference lists. After excluding unrelated and duplicate records, 996 records were retrieved for full-text screening. Of these, 964 records were excluded because 625 of them did not report the incidence of CMP, 137 did not report smoking as intervention, 120 did not have non-smokers as a comparator, 34 were meeting abstracts, 34 were citations or news releases, 11 were reviews or letters to the editor, and 3 were based on the same populations.

Study Characteristics and Quality Evaluation

Overall, 32 observational studies—19 cross-sectional studies (18-36), 11 prospective cohort studies (9,37-46), and 2 case-control studies (47,48), met the eligibility criteria. The baseline characteristics of the included studies are reported in Supplementary Table 2. Smoking status was self-reported in all studies, including ever, current, past, and never smokers. The sample size ranged from 78 to 73,507, with a total of 296,109 participants and 58,071 incident CMP cases. Of these, 17 were conducted in Europe (9,18-20,22,23,27,31,32,36,38-43,45), 10 in Asia (21,25,29,30,33-35,44,47,48), 4 in North America (24,26,28,37), and one in Oceania (46), with no research in South America and Africa. The studies were published between 1991 and 2019. A total of 4 studies included only females, one study included only males, and the remaining 27 studies included males and females. The follow-up period ranged from 1 to 28 years. In this study, the location of CMP included neck pain, arm pain, back pain, low back pain, sacral pain, and knee pain, etc. The quality of the included studies was generally moderate, with AHRQ values between 5 and 10 for cross-sectional studies and NOS values between 5 and 9 for cohort and case-control studies.

Smoking and Incidence of CMP

The meta-analysis results of the 32 observational studies showed that, compared with never smokers, current smokers had a significantly increased CMP risk (OR: 1.23, 95% CI: 1.09-1.40, 28 studies, 99,662 participants) (Fig. 2) according to the random-effects model, with significant heterogeneity ($P < 0.01$; $I^2 = 87\%$). However, our data did not show a similar positive association with CMP risk among ever (OR: 1.14, 95% CI: 0.95-1.37, 20 studies, 146,303 participants) (Fig. 3) and past smokers (OR: 1.06; 95% CI: 0.83-1.35, 16 studies, 50,144 patients) (Fig. 4), and substantial heterogeneity was detected ($P < 0.01$, $I^2 = 96\%$; $P < 0.01$, $I^2 = 92\%$, respectively).

Subgroup Analysis

To further explore the heterogeneity of studies, we conducted a subgroup analysis across some key characteristics and clinical factors (Table 1). The finding of increased CMP risk in ever smokers was found in the strata of gender (women and men), mean age (< 50 years), location of pain (chronic widespread pain, and low back pain), smoking frequency, study design (cohort study), mean follow-up (≥ 10 years), and adjustment for confounding factors (< 6) ($P < 0.05$). We found statistical significance in almost all strata of current smokers compared with never smokers except for mean age (≥ 50 years), location of pain (chronic neck pain, sacral pain, and knee pain), smoking frequency (occasionally), study design (cross-sectional), mean follow-up (< 10 years), and adjustment for confounding factors (≥ 6), however, the positive association of past smoking and CMP only appeared for gender, mean age (< 50 years), location of pain (chronic widespread pain, and low back pain), and mean follow-up (≥ 10 years), subgroups; the number of statistically significant groups decreased by more than 53%. Interestingly, cigarette smoking significantly decreased chronic knee pain risk in ever smokers (OR: 0.46, 95% CI: 0.41-0.52; $P < 0.01$), current (OR: 0.57, 95% CI: 0.49-0.67; $P < 0.01$), and past smokers (OR: 0.43, 95% CI: 0.31-0.60; $P < 0.01$).

Publication Bias and Sensitivity Analysis

The Begg and Egger test did not show significant publication bias in ever (Egger: $P = 0.28$; Begg: $P = 0.77$), current (Egger: $P = 0.30$; Begg: $P = 0.62$), or past (Egger: $P = 0.59$; Begg: $P = 0.82$) smokers (data were not shown). Since some studies only reported risk estimates for current but not former smokers, in order to allow an unbiased comparison between the 2 smoking classes, we also computed the OR for current smokers (1.10, 95% CI: 0.90-1.34; $P > 0.05$) from the 16 studies reporting both estimates. After removing the related studies of knee pain and neck pain, the OR value of current smokers was 1.32 (95% CI: 1.08 1.60; $P < 0.01$).

Certainty of Evidence

The certainty of evidence was judged to be low for both ever and current smoking, and very low for past smoking using GRADE approach. For ever and current smokers, given that daily smokers have a higher risk of CMP than occasionally smokers, we upgraded quality of evidence based on dose response gradient.

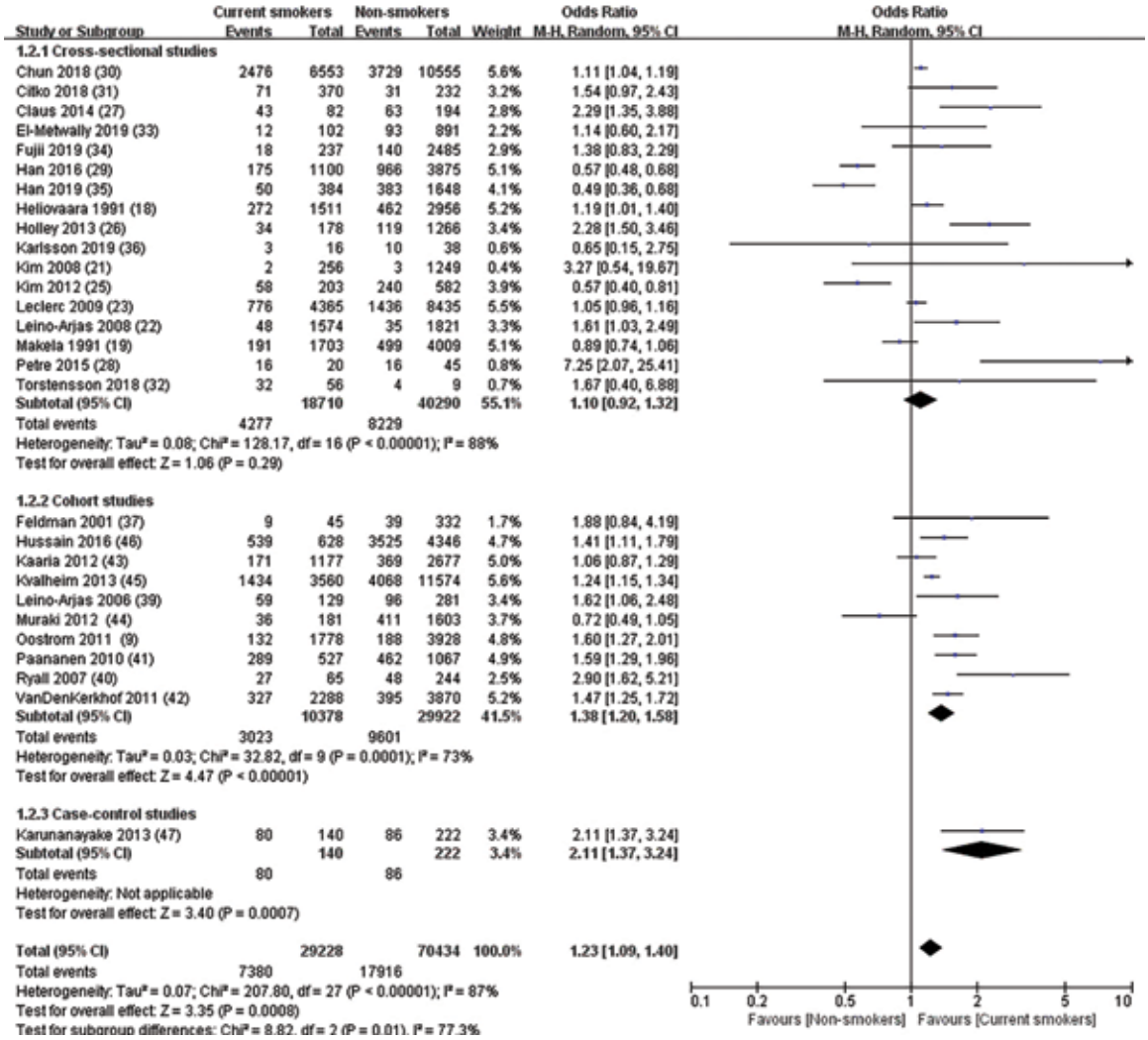

Fig. 2. *Risk estimates of chronic musculoskeletal pain for current versus nonsmokers.*

Discussion

Using data from 32 studies involving almost 300,000 participants, our meta-analysis demonstrated that for observational studies (including cross-sectional, cohort, and case-control studies), current smoking was statistically associated with an increased CMP risk. To our knowledge, this is the first meta-analysis of data from cross-sectional, cohort, and case-control trials to assess the effect of smoking on CMP risk. The findings suggest that cigarette smoking does not help alleviate most of CMP; on the contrary, smokers are at a higher risk of experiencing CMP compared with non-smokers.

For current, ever, and past smokers aged below the age of 50, the impact of smoking on CMP was significantly greater. Holley AL et al examined associations between CMP and smoking in young adult twins (n = 1,588, ages 18-30) participating in a statewide twin registry. Their results revealed a near 2-fold increased risk for CMP in twins who currently smoked compared to non-smokers (26). Hoftun GB found that both smoking and alcohol intoxication showed strong associations with pain; the associations were attenuated after adjustments for psychosocial factors (49). In young adults, psychosocial factors (such as depression) play a critical role in associations between CMP and smoking. Some researchers found that constant pain would cause

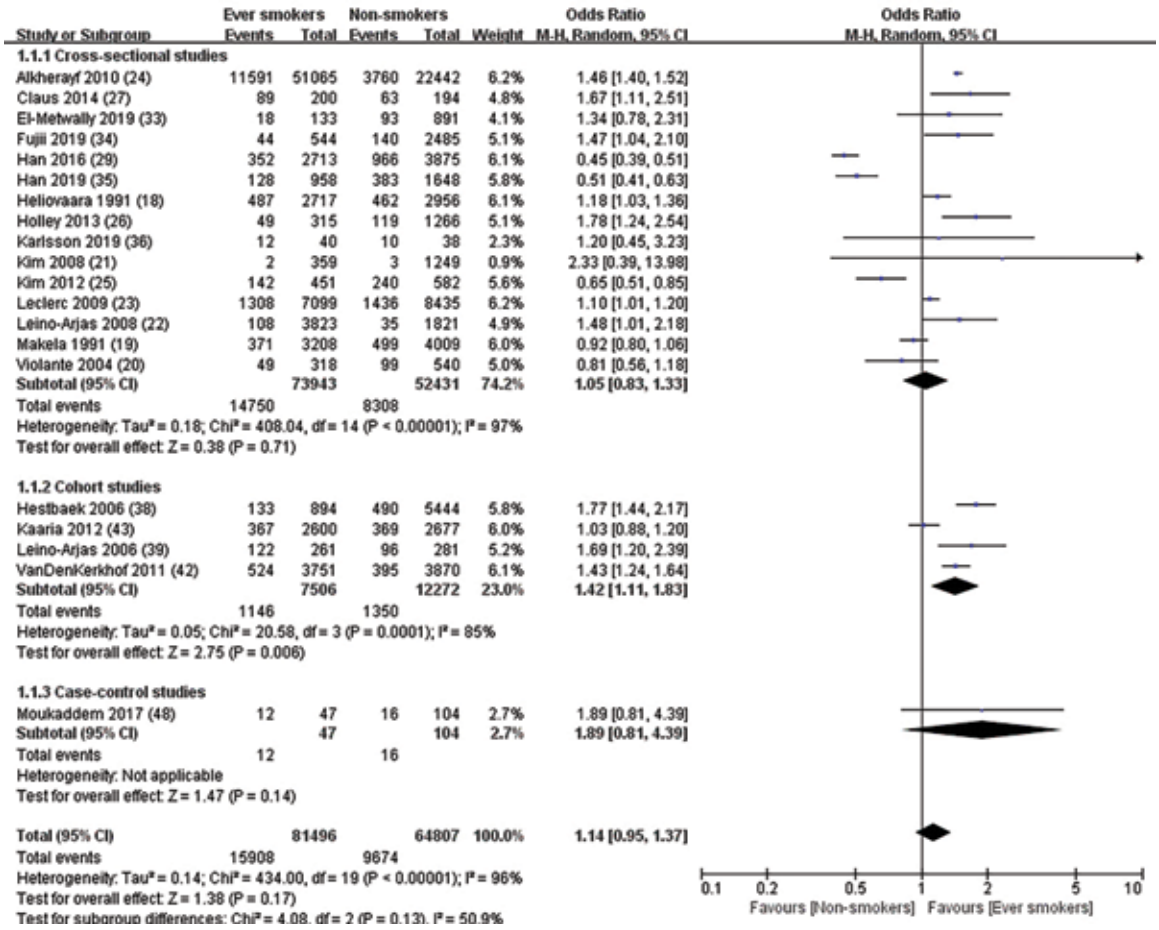

Fig. 3. *Risk estimates of chronic musculoskeletal pain for ever versus nonsmokers.*

signal enhancement mediated by the corticotropin-releasing factor (CRF) and the enhanced CRF signal would cause suppression of the reward system of the brain, reducing the motivation of happiness and leading to depression (50, 51). However, whether the CRF signal or other psychosocial related signals would be stronger in adolescents, still needs to be elucidated.

The meta-analysis showed that more current smokers had chronic lower back pain. The risk among past smokers was lower than that among current smokers, but higher than that among never smokers, consistent with findings of previous meta-analyses (52). The relationship between lower back pain and cigarette smoking was consistently found among ever, current, and past smokers. Interestingly, in the subgroup analysis, knee pain was the only chronic pain negatively related to smoking. A previous meta-analysis showed an inverse association between cigarette smoking and risk of knee osteoarthritis (53), but some meta-analyses have not supported this conclusion (54). This contradiction may be related to the pathological mechanisms of different diseases behind knee pain (55,56) or the nicotine-mediated cholinergic anti-inflammatory pathway (57).

In 2015 there were about a billion smokers around the world (58). With increases in the population, this number is likely to increase further. At present, globally, 25% of men and 5% of women are smokers. Tobacco abuse is currently one of the most serious worldwide public health problems (58). Smoking addiction is actually nicotine dependence, and it is commonly believed that nicotine has an analgesic effect. Although some studies found that smoking had an analgesic effect (59), other studies had contradictory opinions.

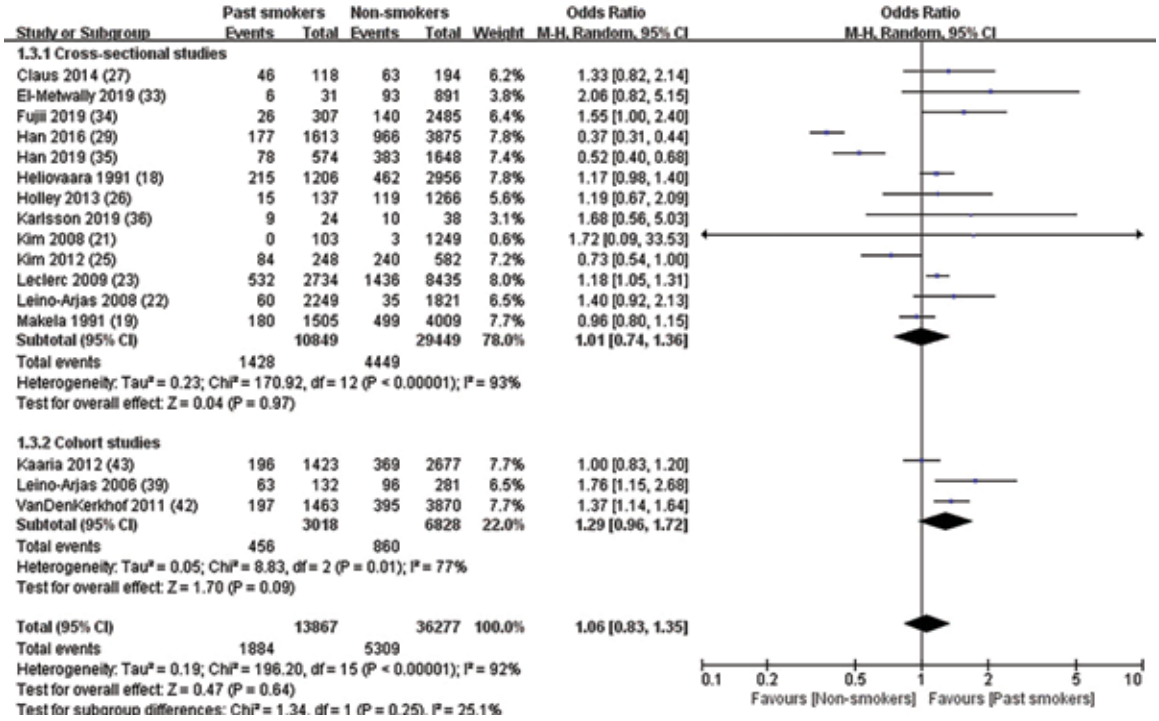

Fig. 4. *Risk estimates of chronic musculoskeletal pain for past versus nonsmokers.*

However, previously published meta-analyses did not comprehensively study CMP. In the results reported in this study, data were pooled for 296,109 participants to explore the relationship between cigarette smoking and CMP.

From the subgroup analysis, it can be seen that the relationship between past smoking and CMP is quite different from that between current smoking and CMP. Researchers have found that only the sympathetic nerve and hypothalamic-pituitary-adrenal (HPA) axis reaction of smokers was inversely proportional to pain sensibility, and the functions of the HPA axis of smokers decreased at rest and during stress. This indicates that the endogenous pain regulation mechanism of smokers might be abnormal (60). Compared with never smokers, smoking patients with chronic pain have worse pain and psychological and sleep disorders. Over time, smoking affects the recovery and improvement of patients. Smoking patients with chronic pain may have serious nicotine withdrawal symptoms in the early stages of smoking cessation and various sequelae related to pain (61). Combining these results with the findings of our study, when the follow-up period was less than 10 years, no significant correlation was found between smoking and CMP in the ever, current, and past smoker groups. However, when the follow-up period was increased to 10 years and greater, the relationship between CMP and smoking was found among ever, current, and past smokers. The mechanism of long-term smoking on CMP needs further study. We need to help smokers with chronic pain to develop the best cigarette quitting strategy and improve the success of smoking cessation.

Limitations

Limitations of this meta-analysis must be acknowledged. First, we found significant heterogeneities across studies for the association between cigarette smoking and CMP, which may result from the very large number of included studies, differences in study quality, analysis strategies, and participants' demography. Second, there was non-standard classification in the evaluation of exposure (self-reported smoking status only at the baseline in most studies) and outcome (self-reported or linkage-identified incident CMP in many studies). Such non-standard classification may be more substantial in the analysis of passive smoking, and the results might be biased towards null. Third, most stud-

Table 1. *Subgroup analysis of pooled odds ratio of chronic musculoskeletal pain for smokers and heterogeneity analysis.*

	Ever smokers						Current smokers						Past smokers					
Factors stratified	**No. of studies**	**No. of patients**	**OR (95% CI)**	**I^2 (%)**	***P* for Heterogeneity**	***P* Value**	**No. of studies**	**No. of patients**	**OR (95% CI)**	**I^2 (%)**	***P* for Heterogeneity**	***P* Value**	**No. of studies**	**No. of patients**	**OR (95% CI)**	**I^2 (%)**	***P* for Heterogeneity**	***P* Value**
All studies	20	146303	1.14 (0.95, 1.37)	96	< .01	.17	28	99662	1.23 (1.09, 1.40)	87	< .01	< .01	16	50144	1.06 (0.83, 1.35)	92	< .01	.64
Gender																		
Women	11	66674	1.20 (1.04, 1.37)	75	< .01	.01	11	26606	1.34 (1.11, 1.62)	70	< .01	< .01	8	21844	1.18 (1.04, 1.34)	22	.25	.01
Men	8	54314	1.45 (1.26, 1.68)	65	< .01	< .01	10	16945	1.36 (1.16, 1.59)	47	.05	< .01	7	12899	1.46 (1.19, 1.81)	51	.06	< .01
Mixed	9	25315	1.03 (0.68, 1.55)	96	< .01	.91	16	56111	1.17 (0.97, 1.41)	91	< .01	.11	8	15401	0.91 (0.58, 1.43)	94	< .01	.68
Mean age																		
< 50 years	9	27730	1.37 (1.14, 1.66)	73	< .01	< .01	16	40562	1.52 (1.36, 1.71)	52	< .01	< .01	7	16214	1.25 (1.06, 1.48)	30	.20	.01
≥ 50 years	5	15949	0.70 (0.48, 1.02)	90	< .01	.07	8	35402	0.79 (0.60, 1.03)	92	< .01	.09	5	12672	0.72 (0.44, 1.17)	91	< .01	.19
Location of pain																		
Widespread pain	4	9458	1.44 (1.26, 1.65)	0	.85	< .01	3	7717	1.46 (1.25, 1.71)	0	.37	< .01	3	6747	1.38 (1.15, 1.65)	0	.93	< .01
Neck pain	2	12494	0.97 (0.87, 1.08)	6	.30	.56	2	9566	0.97 (0.81, 1.15)	44	.18	.71	2	9614	0.98 (0.86, 1.11)	0	.74	.72
Arm pain	NA	NA	NA	NA	NA	NA	1	309	2.90 (1.62, 5.21)	NA	NA	< .01	NA	NA	NA	NA	NA	NA
Back pain	NA	NA	NA	NA	NA	NA	1	65	7.25 (2.07, 25.41)	NA	NA	< .01	NA	NA	NA	NA	NA	NA
Low back pain	9	111519	1.35 (1.17, 1.56)	86	< .01	< .01	12	36156	1.52 (1.28, 1.81)	73	< .01	< .01	6	22918	1.23 (1.12, 1.35)	3	.39	< .01
Sacral pain	NA	NA	NA	NA	NA	NA	1	65	1.67 (0.40, 6.88)	NA	NA	.48	NA	NA	NA	NA	NA	NA

Table 1 (con't). *Subgroup analysis of pooled odds ratio of chronic musculoskeletal pain for smokers and heterogeneity analysis.*

	Ever smokers						Current smokers						Past smokers					
Factors stratified	**No. of studies**	**No. of patients**	**OR (95% CI)**	**I^2 (%)**	***P* for Heterogeneity**	***P* Value**	**No. of studies**	**No. of patients**	**OR (95% CI)**	**I^2 (%)**	***P* for Heterogeneity**	***P* Value**	**No. of studies**	**No. of patients**	**OR (95% CI)**	**I^2 (%)**	***P* for Heterogeneity**	***P* Value**
Knee pain	2	9194	0.46 (0.41, 0.52)	0	.33	< .01	3	8791	0.57 (0.49, 0.67)	9	.33	< .01	2	7710	0.43 (0.31, 0.60)	77	.04	< .01
Smoking frequency																		
Daily	2	66685	1.60 (1.53, 1.67)	0	.33	< .01	5	22688	1.58 (1.24, 2.01)	80	< .01	< .01	NA	NA	NA	NA	NA	NA
Occasionally[a]	1	35602	1.10 (1.04, 1.17)	NA	NA	< .01	1	245	0.69 (0.27, 1.75)	NA	NA	.44	NA	NA	NA	NA	NA	NA
Study design																		
Cross-sectional	15	126374	1.05 (0.83, 1.33)	97	< .01	.71	17	59000	1.10 (0.92, 1.32)	88	< .01	.29	13	40298	1.01 (0.74, 1.36)	93	< .01	.97
Cohort	4	19778	1.42 (1.11, 1.83)	85	< .01	< .01	10	40300	1.38 (1.20, 1.58)	73	< .01	< .01	3	9846	1.29 (0.96, 1.72)	77	.01	.09
Case-control	1	151	1.89 (0.81, 4.39)	NA	NA	.14	1	362	2.11 (1.37, 3.24)	NA	NA	< .01	NA	NA	NA	NA	NA	NA
Mean follow-up, y																		
< 10	2	11615	1.34 (0.79, 2.28)	94	< .01	.28	5	7918	1.37 (0.94, 1.99)	84	< .01	.10	1	4100	1.00 (0.83, 1.20)	NA	NA	.99
≥ 10	2	8163	1.46 (1.29, 1.66)	0	.38	< .01	5	32382	1.40 (1.25, 1.57)	49	.10	< .01	2	5746	1.44 (1.18, 1.76)	13	.28	< .01
Adjustment for confounding factors																		
< 6	13	126803	1.29 (1.02, 1.65)	96	< .01	.04	15	42744	1.45 (1.14, 1.84)	89	< .01	< .01	10	35116	1.12 (0.78, 1.62)	94	< .01	.54
≥ 6	7	19500	0.92 (0.70, 1.22)	90	< .01	.57	13	56918	1.12 (0.97, 1.29)	85	< .01	.12	6	15028	0.98 (0.71, 1.34)	86	< .01	.87

[a] Means at least once a week but less than daily.

ies did not examine the amount of smoking; therefore, there was no more study on the impact of the amount of smoking on CMP in all smokers.

Conclusions

To our knowledge, this is the first meta-analysis to explicitly evaluate the relationship between cigarette smoking and CMP using accepted quality standards for meta-analysis reporting. In view of the high prevalence of smoking in many countries and the increasing number of CMP patients worldwide, reducing tobacco use should be an important public health strategy to prevent and control the global epidemic of CMP. We also found an inverse association between cigarette smoking and knee pain, irrespective of the study design. Future further investigations are still needed to determine the specific pathogenic mechanisms that underlies this relationship.

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Supplementary Table 1. ***Search strategy details***.

PubMed

#1 "Pain"[Mesh] OR "Abdominal Pain"[Mesh] OR "Abdomen, Acute"[Mesh] OR "Acute Pain"[Mesh] OR "Arthralgia"[Mesh] OR "Shoulder Pain"[Mesh] OR "Back Pain"[Mesh] OR "Failed Back Surgery Syndrome"[Mesh] OR "Low Back Pain"[Mesh] OR "Breakthrough Pain"[Mesh] OR "Cancer Pain"[Mesh] OR "Chest Pain"[Mesh] OR "Angina, Stable"[Mesh] OR "Angina, Unstable"[Mesh] OR "Angina Pectoris, Variant"[Mesh] OR "Chronic Pain"[Mesh] OR "Earache"[Mesh] OR "Eye Pain"[Mesh] OR "Facial Pain"[Mesh] OR "Toothache"[Mesh] OR "Flank Pain"[Mesh] OR "Glossalgia"[Mesh] OR "Headache"[Mesh] OR "Slit Ventricle Syndrome"[Mesh] OR "Labor Pain"[Mesh] OR "Mastodynia"[Mesh] OR "Metatarsalgia"[Mesh] OR "Morton Neuroma"[Mesh] OR "Musculoskeletal Pain"[Mesh] OR "Myalgia"[Mesh] OR "Pelvic Girdle Pain"[Mesh] OR "Neck Pain"[Mesh] OR "Neuralgia"[Mesh] OR "Morton Neuroma"[Mesh] OR "Neuralgia, Postherpetic"[Mesh] OR "Piriformis Muscle Syndrome"[Mesh] OR "Pudendal Neuralgia"[Mesh] OR "Sciatica"[Mesh] OR "Nociceptive Pain"[Mesh] OR "Visceral Pain"[Mesh] OR "Pain, Intractable"[Mesh] OR "Pain, Postoperative"[Mesh] OR "Phantom Limb"[Mesh] OR "Pain, Referred"[Mesh] OR "Renal Colic"[Mesh] OR "Pain Management"[Mesh]

#2 ache*[Title/Abstract] OR pain*[Title/Abstract]

#3 #1 OR #2

#4 "Tobacco Use"[Mesh] OR "Smoking"[Mesh] OR "Tobacco Smoking"[Mesh] OR "Cigar Smoking"[Mesh] OR "Cigarette Smoking"[Mesh] OR "Smoking"[Mesh] OR "Pipe Smoking"[Mesh] OR "Water Pipe Smoking"[Mesh] OR "Smoking Reduction"[Mesh] OR "Smoking, Non-Tobacco Products"[Mesh] OR "Cocaine Smoking"[Mesh] OR "Marijuana Smoking"[Mesh] OR "Tobacco Smoking"[Mesh] OR "Cigar Smoking"[Mesh] OR "Cigarette Smoking"[Mesh] OR "Vaping"[Mesh]

#5 tobacco[Title/Abstract] OR smok*[Title/Abstract] OR cigarette[Title/Abstract]

#6 "Nicotine"[Mesh]

#7 Nicotine[Title/Abstract] OR habitrol[Title/Abstract] OR nicabate[Title/Abstract] OR nicoderm[Title/Abstract] OR nicolan[Title/Abstract] OR nicopatch[Title/Abstract] OR nicorest[Title/Abstract] OR nicorette[Title/Abstract] OR nicostop[Title/Abstract] OR nicotin[Title/Abstract] OR nicotinell[Title/Abstract] OR nicotrans[Title/Abstract] OR nicotrol[Title/Abstract] OR nikofrenon[Title/Abstract] OR niquitin[Title/Abstract] OR niquitinclear[Title/Abstract] OR prostep[Title/Abstract] OR quit spray[Title/Abstract]

#8 #4 OR #5 OR #6 OR #7

#9 "Clinical Trials, Phase II as Topic"[Mesh] OR "Clinical Trials, Phase III as Topic"[Mesh] OR "Clinical Trials, Phase IV as Topic"[Mesh] OR "Controlled Clinical Trials as Topic"[Mesh] OR "Non-Randomized Controlled Trials as Topic"[Mesh] OR "Randomized Controlled Trials as Topic"[Mesh] OR "ntention to Treat Analysis"[Mesh] OR "Pragmatic Clinical Trials as Topic"[Mesh] OR " Clinical Trial, Phase II" [Publication Type] OR "Clinical Trial, Phase III" [Publication Type] OR "Clinical Trial, Phase IV" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Pragmatic Clinical Trial" [Publication Type] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh]

#10 trial*[Title/Abstract] OR random*[Title/Abstract] OR blind*[Title/Abstract] OR singleblind*[Title/Abstract] OR doubleblind*[Title/Abstract] OR trebleblind*[Title/Abstract] OR tripleblind*[Title/Abstract] OR group*[Title/Abstract]

#11"Case-Control Studies"[Mesh] OR "Retrospective Studies"[Mesh]

#12 case-control Stud*[Title/Abstract] OR case control Stud*[Title/Abstract] OR case-comparison Stud*[Title/Abstract] OR case comparison Stud*[Title/Abstract] OR case-compeer Stud*[Title/Abstract] OR case referent Stud*[Title/Abstract] OR case referent Stud*[Title/Abstract] OR case-referent Stud*[Title/Abstract] OR case referent Stud*[Title/Abstract] OR case-base Stud*[Title/Abstract] OR case base Stud*[Title/Abstract] OR case control Stud*[Title/Abstract] OR nested case control Stud*[Title/Abstract] OR nested case-control Stud*[Title/Abstract] OR matched case control Stud*[Title/Abstract] OR matched case-control Stud*[Title/Abstract]

#13 "Cohort Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "National Longitudinal Study of Adolescent Health"[Mesh] OR "Prospective Studies"[Mesh] OR "Retrospective Studies"[Mesh]

#14 cohort fertility[Title/Abstract] OR cohort life cycle[Title/Abstract] OR cohort stud*[Title/Abstract] OR Follow-Up Stud*[Title/Abstract] OR Longitudinal Stud*[Title/Abstract] OR Prospective Stud*[Title/Abstract] OR Concurrent Stud*[Title/Abstract] OR Cohort Analysis[Title/Abstract] OR Cohort Analyses[Title/Abstract] OR Incidence Stud*[Title/Abstract] OR Closed Cohort Stud*[Title/Abstract] OR Historical Cohort Stud*[Title/Abstract]

#15 #9 OR N#10 OR #11 OR #12 OR #13 OR #14

#18 #3 AND #8 AND #15

EMBASE

#1 'pain'/exp OR 'abdominal pain'/exp OR 'abdominal angina'/exp OR 'lower abdominal pain'/exp OR 'upper abdominal pain'/exp OR 'allodynia'/exp OR 'application site pain'/exp OR 'bone pain'/exp OR 'metatarsalgia'/exp OR 'Schnitzler syndrome'/exp OR 'breakthrough pain'/exp OR 'breast tenderness'/exp OR 'burning sensation'/exp OR 'application site burning'/exp OR 'epigastric burning'/exp OR 'eye burning'/exp OR 'injection site burning'/exp OR 'skin burning sensation'/exp OR 'vaginal burning sensation'/exp OR 'cancer pain'/exp OR 'chronic pain'/exp OR 'cystalgia'/exp OR 'dysmenorrhea'/exp OR 'dyspareunia'/exp OR 'dysuria'/exp OR 'experimental pain'/exp OR 'experimental muscle pain'/exp OR 'experimental neuropathic pain'/exp OR 'formalin-induced pain'/exp OR 'eye pain'/exp OR 'eyelid pain'/exp OR 'female genital pain'/exp OR 'flank pain'/exp OR 'genital pain'/exp OR 'gingiva pain'/exp OR 'headache and facial pain'/exp OR 'chronic daily headache'/exp OR 'chronic tension headache'/exp OR 'hemicrania continua'/exp OR 'new daily persistent headache'/exp OR 'transformed migraine'/exp OR 'cough headache'/exp OR 'drug induced headache'/exp OR 'exertional headache'/exp OR 'face pain'/exp OR 'headache'/exp OR 'heavy-headedness'/exp OR 'hypnic headache'/exp OR 'migraine'/exp OR 'basilar type migraine'/exp OR 'complicated migraine'/exp OR 'episodic migraine'/exp OR 'hemiplegic migraine'/exp OR 'familial hemiplegic migraine'/exp OR 'sporadic hemiplegic migraine'/exp OR 'menstrual migraine'/exp OR 'migraine aura'/exp OR 'migraine with aura'/exp OR 'migraine without aura'/exp OR 'migrainous infarction'/exp OR 'ophthalmoplegic migraine'/exp OR 'retinal migraine'/exp OR 'transformed migraine'/exp OR 'vestibular migraine'/exp OR 'Persian Gulf syndrome'/exp OR 'postdural puncture headache'/exp OR 'posttraumatic headache'/exp OR 'postural headache'/exp OR 'primary headache'/exp OR 'secondary headache'/exp OR 'sinus headache'/exp OR 'slit ventricle syndrome'/exp OR 'stabbing headache'/exp OR 'temporal arteritis
tension headache'/exp OR 'chronic tension headache'/exp OR 'episodic tension headache'/exp OR 'thunderclap headache'/exp OR 'trigeminal autonomic cephalalgia'/exp OR 'cluster headache'/exp OR 'chronic cluster headache'/exp OR 'episodic cluster headache'/exp OR 'paroxysmal hemicrania'/exp OR 'chronic paroxysmal hemicrania'/exp OR 'episodic paroxysmal hemicrania'/exp OR 'SUNCT syndrome'/exp OR 'trigeminus neuralgia'/exp OR 'vascular

headache'/exp OR 'hyperalgesia'/exp OR 'mechanical hyperalgesia'/exp OR 'hypoalgesia'/exp OR 'inflammatory pain'/exp OR 'chronic inflammatory pain'/exp OR 'inguinal pain'/exp OR 'injection pain'/exp OR 'injection site pain'/exp OR 'intractable pain'/exp OR 'jaw pain'/exp OR 'labor pain'/exp OR 'larynx pain'/exp OR 'limb pain'/exp OR 'arm pain'/exp OR 'hand pain'/exp OR 'wrist pain'/exp OR 'leg pain'/exp OR 'ankle pain'/exp OR 'erythromelalgia'/exp OR 'foot pain'/exp OR 'heel pain'/exp OR 'hip pain'/exp OR 'knee pain'/exp OR 'patellofemoral pain syndrome'/exp OR 'lymph node pain'/exp OR 'mastalgia'/exp OR 'mouth pain'/exp OR 'musculoskeletal chest pain'/exp OR 'musculoskeletal pain'/exp OR 'backache'/exp OR 'discogenic pain'/exp OR 'failed back surgery syndrome'/exp OR 'low back pain'/exp OR 'neck pain'/exp OR 'shoulder pain'/exp OR 'myalgia'/exp OR 'compartment syndrome'/exp OR 'abdominal compartment syndrome'/exp OR 'eosinophilia myalgia syndrome'/exp OR 'experimental muscle pain'/exp OR 'fibromyalgia intermittent claudication'/exp OR 'myofascial pain'/exp OR 'Persian Gulf syndrome'/exp OR 'rheumatic polymyalgia'/exp OR 'neuralgia'/exp OR 'burning feet syndrome'/exp OR 'carpal tunnel syndrome'/exp OR 'cauda equina syndrome'/exp OR 'cervicobrachial neuralgia'/exp OR 'complex regional pain syndrome'/exp OR 'complex regional pain syndrome type I'/exp OR 'algodystrophy'/exp OR 'posttraumatic osteoporosis'/exp OR 'sympathetic dystrophy'/exp OR 'complex regional pain syndrome type II'/exp OR 'cubital tunnel syndrome'/exp OR 'deafferentation pain'/exp OR 'glossopharyngeal neuralgia'/exp OR 'herpes zoster oticus'/exp OR 'ischialgia'/exp OR 'meralgia paresthetica'/exp OR 'metatarsalgia'/exp OR 'neuropathic pain'/exp OR 'ophthalmoplegic migraine'/exp OR 'otalgia'/exp OR 'piriformis syndrome'/exp OR 'postherpetic neuralgia'/exp OR 'proctalgia'/exp OR 'pudendal neuralgia'/exp OR 'radicular pain'/exp OR 'sciatica'/exp OR 'SUNCT syndrome'/exp OR 'tarsal tunnel syndrome'/exp OR 'thorax outlet syndrome'/exp OR 'trigeminus neuralgia'/exp OR 'nociceptive pain'/exp OR 'noncardiac chest pain'/exp OR 'odynophagia'/exp OR 'oropharynx pain'/exp OR 'painful breathing'/exp OR 'painful defecation'/exp OR 'painful erection'/exp OR 'pelvic girdle pain'/exp OR 'pelvic pain'/exp OR 'pelvis pain syndrome'/exp OR 'piriformis syndrome'/exp OR 'perineal pain'/exp OR 'phantom pain'/exp OR 'postoperative pain'/exp OR 'postpartum pain'/exp OR 'posttraumatic pain'/exp OR 'precordial pain'/exp OR 'procedural pain'/exp OR 'psychogenic pain'/exp OR 'referred pain'/exp OR 'retrosternal pain'/exp OR 'salivary gland pain'/exp OR 'scrotal pain'/exp OR 'acute scrotum'/exp OR 'chronic scrotal pain'/exp OR 'sinus pain'/exp OR 'skin pain'/exp OR 'sore throat'/exp OR 'spinal pain'/exp OR 'substernal pain'/exp OR 'thorax pain'/exp OR 'tooth pain'/exp OR 'urethral pain'/exp OR 'vagina pain'/exp OR 'vein pain'/exp OR 'visceral pain'/exp OR 'biliary colic'/exp OR 'biliary tract pain'/exp OR 'colic'/exp OR 'epigastric pain'/exp OR 'epigastric burning'/exp OR 'epigastric discomfort'/exp OR 'epigastric fullness'/exp OR 'esophagus pain'/exp OR 'gastrointestinal pain'/exp OR 'kidney colic'/exp OR 'kidney pain'/exp OR 'liver pain'/exp OR 'pleural pain'/exp OR 'stomach pain'/exp OR 'urinary tract pain'/exp OR 'vulvodynia'/exp
#2 ache*:ab,ti or pain*:ab,ti
#3 #1 OR #2
#4 'tobacco use'/exp OR 'smoking'/exp OR 'adolescent smoking'/exp OR 'cigar smoking'/exp OR 'cigarette smoking'/exp OR 'parental smoking'/exp OR 'maternal smoking'/exp OR 'paternal smoking'/exp OR 'passive smoking'/exp OR 'smoking habit'/exp OR 'tobacco consumption'/exp
#5 tobacco:ab,ti or smok*:ab,ti or cigarette:ab,ti
#6 "Nicotine"[Mesh]
#7 Nicotine:ab,ti or habitrol:ab,ti or nicabate:ab,ti or nicoderm:ab,ti or nicolan:ab,ti or nicopatch:ab,ti or nicorest:ab,ti or nicorette:ab,ti or nicostop:ab,ti or nicotin:ab,ti or nicotinell:ab,ti or nicotrans:ab,ti or nicotrol:ab,ti or nikofrenon:ab,ti or niquitin:ab,ti or niquitinclear:ab,ti or prostep:ab,ti or 'quit spray':ab,ti
#8 #4 OR #5 OR #6 OR #7
#9 'multicenter study (topic)'/exp or 'phase 2 clinical trial (topic)'/exp or 'phase 3 clinical trial (topic)'/exp or 'phase 4 clinical trial (topic)'/exp or 'controlled clinical trial (topic)'/exp or 'randomized controlled trial (topic)'/exp or 'single blind procedure'/exp or 'double blind procedure'/exp
#10 random*:ab,ti or blind*:ab,ti or singleblind*:ab,ti or doubleblind*:ab,ti or trebleblind*:ab,ti or tripleblind*:ab,ti
#11 'cohort analysis'/exp
#12 cohort fertility':ab,ti or 'cohort life cycle':ab,ti or 'cohort study':ab,ti or 'Follow-Up Study':ab,ti or 'Longitudinal Study':ab,ti or 'Prospective Study':ab,ti or 'Concurrent Study':ab,ti or 'Cohort Analysisy':ab,ti or 'Cohort Analysesy':ab,ti or 'Incidence Study':ab,ti or 'Closed Cohort Study':ab,ti or 'Historical Cohort Study':ab,ti or 'cohort studies':ab,ti or 'Follow-Up Studies':ab,ti or 'Longitudinal Studies':ab,ti or 'Prospective Studies':ab,ti or 'Concurrent Studies':ab,ti or 'Incidence Studies':ab,ti or 'Closed Cohort Studies':ab,ti or 'Historical Cohort Studies':ab,ti
#13 'case control study'/exp
#14 'case-control Study':ab,ti or 'case control Study':ab,ti or 'case-comparison Study':ab,ti or 'case comparison Study':ab,ti or 'case-compeer Study':ab,ti or 'case referent Study':ab,ti or 'case referent Study':ab,ti or 'case-referent Study':ab,ti or 'case referent Study':ab,ti or 'case-base Study':ab,ti or 'case base Study':ab,ti or 'case control Study':ab,ti or 'nested case control Study':ab,ti or 'nested case-control Study':ab,ti or 'matched case control Study':ab,ti or 'matched case-control Study':ab,ti or 'case-control Studies':ab,ti or 'case control Studies':ab,ti or 'case-comparison Studies':ab,ti or 'case comparison Studies':ab,ti or 'case-compeer Studies':ab,ti or 'case referent Studies':ab,ti or 'case referent Studies':ab,ti or 'case-referent Studies':ab,ti or 'case referent Studies':ab,ti or 'case-base Studies':ab,ti or 'case base Studies':ab,ti or 'case control Studies':ab,ti or 'nested case control Studies':ab,ti or 'nested case-control Studies':ab,ti or 'matched case control Studies':ab,ti or 'matched case-control Studies':ab,ti
#15 #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16 #3 AND #8 AND #15

Cochrane Library

#1 MeSH descriptor: [Pain] explode all trees
#2 MeSH descriptor: [Abdominal Pain] explode all trees
#3 MeSH descriptor: [Abdomen, Acute] explode all trees
#4 MeSH descriptor: [Acute Pain] explode all trees
#5 MeSH descriptor: [Arthralgia] explode all trees
#6 MeSH descriptor: [Shoulder Pain] explode all trees
#7 MeSH descriptor: [Back Pain] explode all trees
#8 MeSH descriptor: [Failed Back Surgery Syndrome] explode all trees
#9 MeSH descriptor: [Low Back Pain] explode all trees
#10 MeSH descriptor: [Breakthrough Pain] explode all trees
#11 MeSH descriptor: [Cancer Pain] explode all trees
#12 MeSH descriptor: [Chest Pain] explode all trees

#13 MeSH descriptor: [Angina, Stable] explode all trees
#14 MeSH descriptor: [Angina, Unstable] explode all trees
#15 MeSH descriptor: [Angina Pectoris, Variant] explode all trees
#16 MeSH descriptor: [Chronic Pain] explode all trees
#17 MeSH descriptor: [Earache] explode all trees
#18 MeSH descriptor: [Eye Pain] explode all trees
#19 MeSH descriptor: [Facial Pain] explode all trees
#20 MeSH descriptor: [Toothache] explode all trees
#21 MeSH descriptor: [Flank Pain] explode all trees
#22 MeSH descriptor: [Glossalgia] explode all trees
#23MeSH descriptor: [Headache] explode all trees
#24 MeSH descriptor: [Slit Ventricle Syndrome] explode all trees
#25 MeSH descriptor: [Labor Pain] explode all trees
#26 MeSH descriptor: [Mastodynia] explode all trees
#27 MeSH descriptor: [Metatarsalgia] explode all trees
#28 MeSH descriptor: [Morton Neuroma] explode all trees
#29 MeSH descriptor: [Musculoskeletal Pain] explode all trees
#30 MeSH descriptor: [Myalgia] explode all trees
#31 MeSH descriptor: [Pelvic Girdle Pain] explode all trees
#32 MeSH descriptor: [Neck Pain] explode all trees
#33 MeSH descriptor: [Neuralgia] explode all trees
#34 MeSH descriptor: [Morton Neuroma] explode all trees
#35 MeSH descriptor: [Neuralgia, Postherpetic] explode all trees
#36 MeSH descriptor: [Piriformis Muscle Syndrome] explode all trees
#37 MeSH descriptor: [Pudendal Neuralgia] explode all trees
#38 MeSH descriptor: [Sciatica] explode all trees
#39 MeSH descriptor: [Nociceptive Pain] explode all trees
#40 MeSH descriptor: [Visceral Pain] explode all trees
#41 MeSH descriptor: [Pain, Intractable] explode all trees
#42 MeSH descriptor: [Pain, Postoperative] explode all trees
#43 MeSH descriptor: [Phantom Limb] explode all trees
#44 MeSH descriptor: [Pain, Referred] explode all trees
#45 MeSH descriptor: [Renal Colic] explode all trees
#46 MeSH descriptor: [Pain Management] explode all trees
#47ache*:ti,ab,kw or pain*:ti,ab,kw (Word variations have been searched)
#48 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47
#49 MeSH descriptor: [Tobacco Use] explode all trees
#50MeSH descriptor: [Smoking] explode all trees
#51MeSH descriptor: [Tobacco Smoking] explode all trees
#52MeSH descriptor: [Cigar Smoking] explode all trees
#53MeSH descriptor: [Cigarette Smoking] explode all trees
#54MeSH descriptor: [Pipe Smoking] explode all trees
#55MeSH descriptor: [Water Pipe Smoking] explode all trees
#56MeSH descriptor: [Smoking Reduction] explode all trees
#57MeSH descriptor: [Smoking, Non-Tobacco Products] explode all trees
#58MeSH descriptor: [Cocaine Smoking] explode all trees
#59MeSH descriptor: [Marijuana Smoking] explode all trees
#60MeSH descriptor: [Tobacco Smoking] explode all trees
#61MeSH descriptor: [Cigar Smoking] explode all trees
#62MeSH descriptor: [Cigarette Smoking] explode all trees
#63MeSH descriptor: [Vaping] explode all trees
#64 tobacco:ti,ab,kw or smok*:ti,ab,kw or cigarette:ti,ab,kw (Word variations have been searched)
#65MeSH descriptor: [Nicotine] explode all trees
#66 Nicotine:ti,ab,kw or habitrol:ti,ab,kw or nicabate:ti,ab,kw or nicoderm:ti,ab,kw or nicolan:ti,ab,kw or nicopatch:ti,ab,kw or nicorest:ti,ab,kw or nicorette:ti,ab,kw or nicostop:ti,ab,kw or nicotin:ti,ab,kw or nicotinell:ti,ab,kw or nicotrans:ti,ab,kw or nicotrol:ti,ab,kw or nikofrenon:ti,ab,kw or niquitin:ti,ab,kw or niquitinclear:ti,ab,kw or prostep:ti,ab,kw or quit spray:ti,ab,kw
#67 #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66
#68 #44 AND #67

Supplementary Table 2. *Characteristics of studies included in the meta-analysis.*

Trial	Source (Country or Region)	Mean age or age range, y	Gender	Case/Controls or Cohort Sizes	Smoking Rate (%)			Location of Pain	Maximum Follow-up, y	Adjustment	Study Quality
					Ever Smokers	Current Smokers	Past Smokers				
Cross-sectional study											
Alkherayf 2010 (24)	Canada	20-59	Both	15351/73507	65.6	NA	NA	Low back pain	NA	BMI, education, activity status	7
Chun 2018 (30)	Korea	≥50	Both	6205/17108	NA	38.3	NA	Musculoskeletal pain	NA	Age, sex, marital status, family income, education, occupation, alcohol use, physical activity, BMI, stress levels, osteoarthritis, rheumatoid arthritis, sleep duration	10
Citko 2018 (31)	Poland	41.0	Both	102/609	NA	50.4	NA	Low back pain	NA	NA	8
Claus 2014 (27)	Germany	44.9	Both	153/395	50.7	20.8	29.9	Back pain	NA	Age, mood, heavy loads, environment	7
El-Metwally 2019 (33)	Saudi Arabia	26.4	Both	111/1031	12.9	9.9	3.0	Musculoskeletal pain	NA	Age,weight, waist circumference, HDL, HbA1C, chronic disease, psychological disease	8
Fujii 2019 (34)	Japan	35.8	Female	188/3066	18.0	7.8	10.1	Low back pain	NA	Age, BMI, work experience, hospital department, work hours, night shift, managerial position, K6, FABQ-PA	10
Han 2016 (29)	Korea	≥50	Both	1318/6588	41.2	16.7	24.5	Knee pain	NA	Age, BMI, alcohol, exercise, condition status	6
Han 2019 (35)	Korea	≥50	Both	527/2658	36.0	21.6	14.5	Knee pain	NA	Age, sex, alcohol consumption,educational level, household income, physical activity, duration of sleep, comorbidities, PHQ-9	9
Heliovaara 1991 (18)	Finland	30-64	Both	949/5673	47.9	26.6	21.3	Low back pain	NA	Age, sex, body height, BMI, traumatic back injury, occupational physical stress, occupational mental stress, work-related driving motor vehicles, alcohol, number of births	7
Holley 2013 (26)	America	23.3	Both	168/1581	19.9	11.3	8.7	Musculoskeletal pain	NA	Age, sex, education	9
Karlsson 2019 (36)	Sweden	63	Both	22/78	51.3	20.5	30.8	Widespread pain	NA	NA	8
Kim 2012 (25)	Korea	51.4	Both	405/1077	41.9	18.9	23.0	Widespread pain	NA	Age, sex, marriage, education, occupation, alcohol, METs group	7
Kim 2008 (21)	Korea	18-20	Both	5/1608	22.3	15.9	6.4	Widespread pain	NA	NA	6

Supplementary Table 2 (con't). *Characteristics of studies included in the meta-analysis.*

Trial	Source (Country or Region)	Mean age or age range, y	Gender	Case/Controls or Cohort Sizes	Smoking Rate (%)			Location of Pain	Maximum Follow-up, y	Adjustment	Study Quality
					Ever Smokers	Current Smokers	Past Smokers				
Leino-Arjas 2008 (22)	Finland	53.1	Both	143/5644	67.7	27.9	39.9	Sciatica	NA	Age, BMI, exercise, physical work, education	7
Leclerc 2009 (23)	France	30-69	Both	2707/15534	45.7	28.1	17.6	Low back pain	NA	Age, sex, education, personal factors, physical constraints at work	9
Makela 1991 (19)	Finland	≥30	Both	870/7217	44.5	23.6	20.9	Neck pain	NA	Age, sex, mental and physical stress at work, obesity, parity	8
Petre 2015 (28)	Chicago	42.9	Both	160/225	NA	30.7	NA	Back pain	NA	Additional behavioral, mediation effect by brain NAc-mPFC functional connectivity	5
Torstensson 2018 (32)	Sweden	36.9	Female	36/65	NA	13.9	NA	Sacral pain	NA	NA	8
Violante 2004 (20)	Italy	35.7	Female	148/858	37.1	NA	NA	Low back pain	NA	Age, BMI, motherhood, trauma, spine pathologies, sport scores	7
Cohort study											
Feldman 2001 (37)	Canada	13.8	Both	32/389	NA	7.7	NA	Low back pain	1	Age, sex, high growth spurt, schober, hamstrings and quadriceps flexibility, sit and reach, abdominal strength, heigh, activity time, working time, mental health index	5
Hestbaek 2006 (38)	Denmark	17.4	Both	636/6554	19.0	NA	NA	Low back pain	8	Age, sex, alcohol, BMI	7
Hussain 2016 (46)	Australia	≥25	Both	539/4974	NA	12.6	NA	Low back pain	15	Age, education, dietary guideline index score, BMI	8
Kaaria 2012 (43)	Finland	49.2	Both	736/5277	49.3	22.3	27.0	Neck pain	7	Age, physical workload, emotional exhaustion, bullying, GHQ, sleep problems, acute neck pain, low back pain, BMI	8
Kvalheim 2013 (45)	Norway	44	Both	5502/15134	NA	23.5	NA	Musculoskeletal pain	11	Age, sex, education, work status, BMI, physical activity, systolic blood pressure, coffee drinking, alcohol drinking, depression, anxiety	8
Leino-Arjas 2006 (39)	Filand	NA	Both	218/542	48.2	23.8	24.4	Low back pain	28	Age, sex, occupational class	6
Muraki 2012 (44)	Japan	72.2	Both	447/2262	NA	8.0	NA	Knee pain	5	Age, BMI, grip strength,sex, K/L grade at baseline, previous knee injury, alcohol use	8
Oostrom 2011 (9)	Doetinchem	26-65	Both	320/5706	NA	31.2	NA	Low back pain	15	Age, sex, education, work status, BMI, physical activity	9

Supplementary Table 2 (con't). *Characteristics of studies included in the meta-analysis.*

Trial	Source (Country or Region)	Mean age or age range, y	Gender	Case/Controls or Cohort Sizes	Smoking Rate (%)			Location of Pain	Maximum Follow-up, y	Adjustment	Study Quality
					Ever Smokers	Current Smokers	Past Smokers				
Paananen 2010 (41)	Finland	18	Both	416/1670	NA	33.6	NA	Musculoskeletal pain	2	Internalisation, externalisation, physical activity, sitting time, sleeping time, obesity, education	6
Ryall 2007 (40)	Southampton area	15-64	Both	75/309	NA	21.0	NA	Arm pain	1	Resource	6
VanDenKerkhof 2011 (42)	Britain	45	Both	1056/8572	49.2	30.0	19.2	Widespread pain	12	Diet, lifestyle	6
Case-control study											
Karunanayake 2013 (47)	Sri Lanka	18-85	Male	166/196	NA	38.7	NA	Low back pain	NA	Posture, exercise, family history, education, animal protein and alcohol consumption, income, BMI	6
Moukaddem 2017 (48)	Lebanon	≥20	Female	34/136	27.7	NA	NA	Fibromyalgia	NA	Residence location, income, education, BMI, physical activity	7