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Does a history of depression *actually* mediate smoking-related pain? Findings from a cross-sectional general population-based study

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Conflicts of interest

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Abstract

Background: Smokers report more pain and worse functioning. The evidence from pain clinics suggests that depression affects this relationship: The association between smoking and chronic pain is weakened when controlling for depression. This study explored the relationship between smoking, pain and depression in a large general population-based cohort (Generation Scotland: Scottish Family Health Study).

Methods: Chronic pain measures (intensity, disability), self-reported smoking status and a history of major depressive disorder (MDD) were analysed. A multivariate analysis of covariance determined whether smoking status was associated with both pain measures and a history of depressive illness. Using a statistical mediation model any mediating effect of depression on the relationship between smoking and chronic pain was sought.

Results: Of all 24,024 participants, 30% ($n = 7162$) reported any chronic pain. Within this chronic pain group, 16% ($n = 1158$) had a history of MDD; 7108 had valid smoking data: 20% ($n = 1408$) were current smokers, 33% ($n = 2351$) former and 47% ($n = 3349$) never smokers. Current smokers demonstrated higher pain intensity and pain-related disability scores compared with former and non-smokers ($p < 0.001$ for all analyses). From the mediation model, the effect on pain intensity decreased ($p < 0.001$), indicating that the relationship between smoking and a history of depression contributes significantly to the effect of smoking on pain intensity. When applied to smoking-related pain disability, there was no mediation effect.

Conclusions: In contrast to smokers treated in pain clinics, a history of MDD mediated the relationship between smoking and pain intensity, but not pain-related disability in smokers in the community.

1. Introduction

The impact of both smoking and chronic pain on the population's health is well recognized; however, the relationship between smoking and chronic pain is less clear cut (Palmer et al., 2003; John et al., 2006;

Fishbain et al., 2007; Weingarten et al., 2008). Smoking is a major risk factor for cardiovascular disease (Doll et al., 1994), which has been associated with significant risk of mortality among people with chronic pain (Torrance et al., 2010; Goodson et al., 2013). Studies have shown that the smoking rate in chronic pain populations is consistently higher than in the general population (Vogt et al., 2002; Weingarten et al., 2008) and that smokers report greater pain intensity and worse functioning (John et al., 2006; Goesling et al., 2012). Although some research has postulated that the aversive physiological effects of smoking cause or aggravate painful conditions, this has not been proven (Shi et al., 2010). There is also recent evidence to suggest that depression may act as a mediating factor in helping to explain the relationship between smoking and chronic pain, where smokers reported more pain but this association weakened when controlling for depression (Hooten et al., 2011a; Goesling et al., 2012). However, this evidence is from relatively small studies conducted in pain clinics. The vast majority of people with chronic pain are never referred to a specialist pain clinic and are largely managed in primary care (Breivik et al., 2006; Smith and Torrance, 2011). Using methods similar to those employed by Goesling et al. (2012), we aimed to confirm this relationship between smoking, chronic pain and depression in a large general population-based cohort.

2. Methods

2.1 Study design and participants

Data were obtained from Generation Scotland: the Scottish Family Health Study (GS:SFHS) (Smith et al., 2013), a family-based epidemiology study with socio-demographic, clinical data and genetic samples from 24,042 participants recruited from general practice populations across Scotland between February 2006 and March 2011. Besides standard demographic data (age, gender, etc.), GS:SFHS included data of relative measure of deprivation, namely, the Scottish Index of Multiple Deprivation (SIMD). The 2006 index score ranks those areas from most deprived, ranked 1, to least deprived, ranked 5 (Office of the Chief Statistician, 2006). Further data included information from self-completed questionnaires and clinic-based examination on chronic pain, cardiovascular and mental health parameters, and participants provided consent for use of their data and samples for any research related to health and illness. As explained in the published article (Smith et al., 2006), Generation Scotland was not and could not be truly representative of the general population but was found to be broadly representative and to include all the main socio-demographic subgroups.

What's already known about this topic?

- Smoking is associated with more severe pain and worse pain-related disability.
- Evidence from specialized pain clinics suggests that depression may help explain the relationship between smoking and chronic pain intensity and pain-related disability, i.e., the effect of smoking on both chronic pain measures was not significant when controlling for depression.

What does this study add?

- This large general population-based study supports evidence that smokers with chronic pain in the community experience worse pain compared with former and non-smokers.
- Unlike other findings from specialist pain clinics, a history of major depression in the community only influenced the relationship between smoking and pain intensity but not pain-related disability.

2.2 Measures

2.2.1 Chronic pain variables: characteristic pain intensity and characteristic disability scores

Chronic pain was defined as pain or discomfort persisting longer than 3 months. A validated self-report chronic pain questionnaire (the Chronic Pain Grade questionnaire) was used to assess pain severity based on its intensity and impact of pain on daily functioning (pain-related disability) (Von Korff et al., 1992) in the previous 3 months. Pain intensity was measured on a numeric rating scale with, 0 = 'no pain' and 10 = 'pain as bad as could be'. Characteristic or *typical* pain intensity was calculated as the average of current pain, worst pain and usual pain intensity (multiplied by 10) with range of 0–100 (Von Korff et al., 1992). We avoided the use of 'mean' pain intensity as this is potentially confusing from statistical point of view (mean implying a normal distribution). Similarly, characteristic pain-related disability was measured on a numeric scale, with 0 = 'no interference' and '10 = maximum pain interference' with daily, social and work activities. An overall disability score was calculated as the average of pain interference in their activities (multiplied by 10) with range of 0–100.

2.2.2 History of major depressive disorder (MDD)

All participants in GS:SFHS who attended the research clinic ($n = 21,462$) were screened for a history of emotional and psychiatric disorders using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition disorders (SCID) (First et al., 2002) – a well validated instrument for detecting a history of mental illness. Those who screened positively were invited to continue the SCID interview (which was conducted face to face by a trained health professional), focusing on a history of single or recurrent MDD. For the purposes of this study both those with a current and past history of depression were incorporated into the history of MDD.

2.2.3 Smoking variables

Participants were classified into three groups: current smokers, former smokers and never smokers based on responses to items in the questionnaire 'Have you ever smoked tobacco?' (Yes, currently smoke = 'current smoker'; Yes, but stopped = 'former smoker'; No, never smoked = 'never smoker'). Former smokers also provided information about how long it had been since they quit smoking. The maximum amount smoked was sought by the question, 'What is the maximum number you have smoked per week for as long as a year?' The number of cigars and packets of tobacco was converted to cigarette equivalent (Warwickshire PCT, 2007; National Cancer Institute, 2010).

2.3 Data analysis

Data were analysed using SPSS (version 18; SPSS, Inc., Chicago, IL, USA). Demographic characteristics included age, gender, education and SIMD. This index score ranks those areas from most deprived (ranked 1) to least deprived (ranked 5; Office of the Chief Statistician, 2006). Data were investigated for distribution, and if non-normal, nonparametric tests were used and median (range) reported (Kruskal–Wallis test) for continuous variables. Categorical variables (gender, education, SIMD) were summarized as proportions and investigated with chi-square methods.

A multivariate analysis of covariance (smoking status, age, gender, education, SIMD) was conducted to determine whether smoking status was associated with the two chronic pain measure scores (intensity and pain-related disability) and a history of past depressive illness. Due to differences in age, gender, education attainment and deprivation score between the three groups, all four demographic variables were used as covariates in the above analyses. *Post hoc* analyses between former smokers and never smokers were performed, when appropriate, with use of the Bonferroni correction of significance assessment to adjust for the effects of multiple testing.

We emulated the methods employed by Goesling et al. in which they used a four-step process using regression analysis. A reduction in the effect of smoking on the outcome variable (characteristic pain intensity or characteristic pain-related disability) after adjustment for a history of MDD (proposed mediator) would indicate

that a past history of major depression mediated the relationship between smoking and the two pain measures (suggesting that the link between smoking and pain is largely driven by depression). Due to differences in age, gender, education and level of deprivation across smoking groups, all demographic variables were used as covariates in analyses.

To support the results of the first mediation calculation, we used a single, inclusive test of mediation (Sobel) MacKinnon et al., 2002) as performed by Goesling et al. in their study. The Sobel test provides a conservative estimate on whether the mediator (in this case, depression) significantly carries the influence of an independent variable (smoking status) to the dependent variable (chronic pain measure), i.e., whether the indirect effect of the independent variable on the dependent variable through the mediator variable is significant.

2.4 Ethics

Generation Scotland received ethical approval for the creation of the Generation Scotland Scottish Family Health Study (GS:SFHS) resources (05/S1401/89 NHS Tayside Committee on Medical Research Ethics A), and Research Tissue Bank status has also been granted providing generic ethical approval for a wide range of uses within medical research (10/S1402/20 NHS Tayside Committee on Medical Research Ethics B).

3. Results

3.1 Overview

Of the 24,042 participants included in GS:SFHS, 7162 (30%) reported any chronic pain. Just over one-fifth (21.7%) out of the total GS:SFHS cohort screened positive and were invited to complete the SCID interview; of these, 88% completed the face-to-face clinical interview.

Within the chronic pain group, 16% ($n = 1158$) had a history of MDD (Table 1).

Table 1 Demographic differences between smokers, former smokers and never smokers.

	Current smoker ($n = 1408$)	Former smokers ($n = 2351$)	Never smokers ($n = 3349$)	Overall p -value
Sex (male)	40.7%	40.7%	32%	<0.0001 (df 2)
Age [median (range)]	47 (18–86)	56 (18–97)	52 (18–94)	<0.0001 ^a
Education (higher/professional degree)	46.6%	60%	64.3%	<0.0001 (df 4)
Education (school leaving)	34.0%	26.8%	24.8%	<0.0001 (df 4)
Education (no qualification)	19.4%	13.2%	10.9%	<0.0001 (df 4)
SIMD 1 ^b (most deprived quintile)	25.5%	12.6%	10.4%	<0.0001 (df 8)
SIMD 5 (least deprived quintile)	16.5%	30.1%	33.5%	<0.0001 (df 8)

Data presented as percentages or median (range); chi-square unless indicated. df, degrees of freedom; SIMD, Scottish Index of Multiple Deprivation.

^aKruskal–Wallis test.

^bSIMD (range 1–5): 1 = most deprived; 5 = least deprived.

3.2 Smoking characteristics

Among those with chronic pain, 7108 had valid smoking data available: 20% ($n = 1408$) were current smokers, 33% ($n = 2351$) were former smokers and 47% ($n = 3349$) were never smokers. Thirty-six percent of smokers reported smoking at least 20 cigarettes (or equivalent) per day. The majority of former smokers (82%) reported having quit smoking over 5 years ago.

3.3 Demographic characteristics

Overall significantly ($p < 0.001$) more women than men reported chronic pain. *Post hoc* tests found no significant differences between current and former smokers with regard to gender ($p = 0.99$). Patients who had never smoked were more likely to be female compared with both current smokers and former smokers ($p < 0.001$). Former smokers were more likely to be older than current smokers (median age 56

vs. 47 years, $p < 0.001$), but current smokers were younger than non-smokers, 47 vs. 52 years ($p < 0.001$).

There were significant differences for deprivation (SIMD) (chi-square test, $p < 0.001$). *Post hoc* tests found that non-smokers were more likely to live in less deprived areas than former smokers ($p = 0.016$), and that current smokers tended to live in more deprived areas than former smokers ($p < 0.001$). The overall chi-square test was significant for education qualification ($p < 0.001$). Current smokers differed from both former and never smokers ($p < 0.001$) in that they were less likely to have graduated with a higher degree or professional/technical degree. However, former smokers were less likely to have a higher degree ($p < 0.003$) than those who had never smoked.

3.4 Effect of smoking on characteristic pain intensity and disability score

Multivariate analysis of covariance found that smoking status predicted both pain outcome variables, with current smokers reporting greater characteristic pain intensity ($p < 0.001$) and greater characteristic pain-related disability ($p < 0.001$). Pairwise comparisons (*Bonferroni* correction) revealed that these differences were significant for current smokers compared with former smokers and never smokers ($p < 0.001$), but not between former smokers and never smokers. There was an effect of the number of years since cessation on pain intensity ($p = 0.001$) with a shorter duration of smoking cessation associated with higher characteristic pain intensity (Table 2).

Smokers were more likely to have a history of depression compared with former smokers [$p = 0.001$, degrees of freedom (df) 1] and non-smokers ($p < 0.001$, df 1), respectively. Non-smokers, however, were just as likely to have had a history of depression as former smokers ($p = 0.04$).

Sub-analysis of *recent* former smokers with chronic pain (stopped smoking within the last 12 months) showed no significant difference in pain intensity, compared with those who had stopped for longer than 12 months ($p = 0.35$) and compared with never smokers ($p = 0.26$). Similarly, recent former smokers showed no significant difference in disability scores compared with former smokers who had stopped for longer than 12 months ($p = 0.32$) and non-smokers ($p = 0.42$).

3.5 Mediation model

This replicated the four-step process set out by Goessling et al. using regression analysis.

Step 1: Characteristic pain intensity (first outcome variable) was regressed on smoking status and confirmed the association between the two ($\beta = 0.105$, $t = 8.110$; $p < 0.001$).

Step 2: Secondly, to determine the effect of smoking status on the proposed mediator, a history of MDD was regressed on smoking status ($\beta = 0.116$, $t = 8.465$; $p < 0.001$).

Table 2 Current smokers report greater characteristic pain intensity and disability score.

	Current smokers	Former smokers	Never smokers	<i>p</i> -value ^a
Characteristic pain intensity	52 (51.18–53.58)	47 (46.19–48.00)	47 (45.86–47.37)	<0.001
Characteristic pain-related disability	31 (29.75–32.94)	23 (21.79–24.20)	24 (22.57–24.57)	<0.001

^aMultivariate analysis of covariance, presented as mean (95% confidence interval), characteristic pain intensity and disability score (range 0–100).

Table 3 Mediating effect of a history of major depressive disorder on smoking-related pain intensity.^a

Step 1	Pain intensity versus smoking	^b $\beta = 0.105$ (5.57), $t = 8.110$; $p < 0.001$
Step 2	History of MDD versus smoking	$\beta = 0.116$ (0.11), $t = 8.465$; $p < 0.001$
Step 3	Pain intensity versus history of MDD	$\beta = 0.084$ (4.61), $t = 6.459$; $p < 0.001$
Step 4	Pain intensity versus history of MDD + smoking	$\beta = 0.101$ (5.39), $t = 7.538$; $p < 0.001$

MDD, major depressive disorder.

^aCovariates included in the analysis (age, gender, education, deprivation).

^b β = standardized regression coefficient (standardized coefficient).

Table 4 Absent mediating effect of depression on smoking-related pain disability.^a

Step 1	Pain disability versus smoking	^b $\beta = 0.115$ (8.01), $t = 8.758$; $p < 0.001$
Step 2	History of MDD versus smoking	$\beta = 0.116$ (0.11), $t = 8.465$; $p < 0.001$
Step 3	Pain disability versus history of MDD	$\beta = 0.123$ (8.84), $t = 9.338$; $p < 0.001$
Step 4	Pain disability versus history of MDD + smoking	$\beta = 0.102$ (7.11), $t = 7.502$; $p < 0.001$

MDD, major depressive disorder.

^aCovariates included in analysis (age, gender, education, deprivation).

^b β = standardized regression coefficient (standardized coefficient).

Step 3: The effect of the mediator (history of MDD) was regressed on characteristic pain intensity ($\beta = 0.084, t = 6.459; p < 0.001$).

Step 4: Finally, to test whether MDD mediated the relationship between smoking and pain, characteristic pain intensity was regressed on smoking status, controlling for a history of MDD ($\beta = 0.101, t = 7.538; p < 0.001$) (Table 3).

A reduction in the significance (β -coefficient) of smoking status (from 0.105 to 0.101) when controlling for a history of MDD showed that a history of depressive illness partially mediated the effect of smoking on pain intensity (Fig. 1). In order to further support this conclusion, we tested the indirect effect using a single (Sobel) test and this supported evidence of mediation, Sobel (Aroian) test = 5.16, $p < 0.001$.

The process was repeated to test for the mediation of the second outcome measure (characteristic pain-related disability) and is summarized in Table 4.

Although there was a reduction in the significance of the association between smoking and pain-related disability (from 0.115 to 0.102) when controlling for a history of MDD, indicating potential mediation, this mediation proved not significant using a Sobel (Aroian) test = 6.34, $p = 0$ (Fig. 2). This would suggest that a history of major depression does not carry the influence of smoking to pain-related disability.

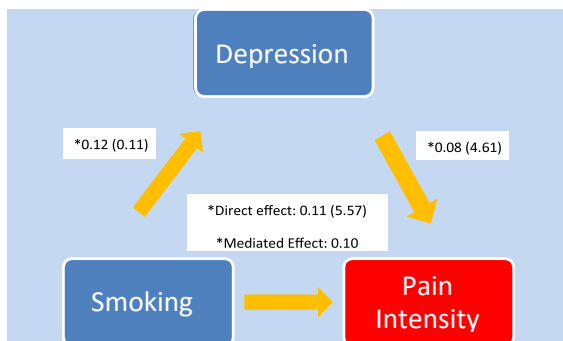


Figure 1 Confirmed mediating effect of depressive history on smoking-related pain intensity. $*p < 0.05$; reported statistics are standardized regression coefficients (unstandardized coefficients). ^aSobel (Aroian) test for indirect effect was significant ($p < 0.001$).

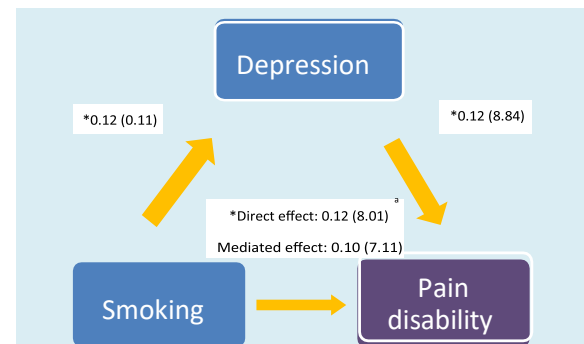


Figure 2 Absent mediating effect of depressive history on smoking-related pain disability. Reported statistics are standardized regression coefficients (unstandardized coefficients); $*p < 0.05$. ^aSobel (Aroian) test for indirect effect was not significant

4. Discussion

The relationships between smoking, depression and chronic pain intensity and pain-related disability are complex. Understanding their relationship is both scientifically and clinically important to inform management and prevention of both chronic pain and depression. This is the largest study to examine smoking and chronic pain to date, and confirms that smoking is associated with a worse chronic pain phenotype in a general population-based cohort. This finding is similar to other work that found smoking is associated with increased reporting of both chronic pain measures (Vogt et al., 2002; John et al., 2006; Weingarten et al., 2008).

A key finding from this study is that a history of major depressive illness partially mediated the relationship between smoking and one of the pain measures, namely, self-reported characteristic pain intensity. This indicates that it is the relationship between smoking and depression (and not smoking *per se*) that contributes to the self-report of greater pain intensity. This supports other evidence from smaller studies conducted in specialized pain clinics (Hooten et al., 2011a; Goesling et al., 2012) and suggests that depression in smokers triggers a mechanism leading to more intense perceived chronic pain.

However, the results of our mediation analysis differed from those of Goesling et al. (2012) and Hooten et al. (2011a) in that we found that although the association between smoking and pain-related disability scores was reduced when a history of depression was included in the statistical model, this proved not significant. This suggests that, in our general population-based cohort, pain-related disability is potentially independent of this association in that a history of MDD did not carry the influence of smoking onto pain-related disability. Possible reasons for this difference are that smokers with chronic pain in the general population are different in this regard from smokers being treated in pain clinics, i.e., relatively more active, less debilitated by pain and may still be able to carry on with their daily activities, take part in recreational and social activities and with minimal effect on their

ability to work, unlike the minority of those with reported chronic pain who attend a specialized pain clinic. There are also patient-level differences (e.g., level of education, deprivation) in depression among different pain populations that may explain these conflicting findings between smokers with pain in the general population and those treated at pain clinics (Barnett et al., 2012). For example, the previous studies (Hooten et al., 2011a; Goesling et al., 2012) were unable to test associations with deprivation and education, which are known to be associated with smoking, depression and most chronic illnesses. As a general population-based cohort (GS:SFHS), our sample was broadly representative of the Scottish population, although somewhat healthier and wealthier (Smith et al., 2013). We did include participants from all socio-economic subgroups, with information on these that allowed statistical testing of the effect of relative deprivation and educational attainment on the relationships between smoking, depression and pain. There are also other possible reasons that might explain this difference but that are not included in this study, e.g., employment status, level of anxiety and/or evidence of catastrophizing.

It follows that when exploring the association between smoking and pain, researchers should consider the role of depressive illness in their participants. In a recent study within the Scottish population, the presence of a mental health disorder was strongly associated with the number of other co-morbid physical conditions. For example, people with five or more chronic disorders had an odds ratio of 6.74 (95% confidence interval 6.59–6.90) of having a mental disorder compared with those with none (Barnett et al., 2012). As the number of physical conditions increases, it is likely that the level of disability (including that associated with painful conditions) will increase. Not only does this add to the overall disease burden among these individuals, but the co-morbidity, co-prescribing and co-occurrence of disability all lead to greater challenges in managing each condition and reducing impact.

Depression in chronic pain is probably less amenable to medical treatment in isolation, and outcomes are more favourable when depressive symptoms are addressed together with appropriate pain management (Kroenke et al., 2009).

One question that remains unanswered is whether smoking cessation actually improves pain. The evidence informing this is limited, predominately cross sectional and conflicting (John et al., 2006; Weingarten et al., 2008). This is compounded by relatively low rates of successful smoking cessation among patients attending pain clinics (Hooten et al., 2009) as patients are thought to use smoking as a way to manage pain-related emotional distress and as a distractor from pain (Hooten et al., 2011b). However, there is recent evidence from secondary care that patients who stopped smoking during the course of care (>5000 patients with painful spinal disorders) resulted in greater improvement in pain in visual analogue scale pain ratings for worst, current and average weekly pain (Behrend et al., 2012). In support of this, sub-analysis of our findings supports other evidence that former smokers (who had quit within the last 12 months) showed similar pain score measures to those who had stopped for longer than 1 year and non-smokers. These results are from cross-sectional data, so it is not possible to make any statements of causality or temporality. There is also recent evidence of an age-dependent effect of smoking on the occurrence of chronic musculoskeletal complaints, whereby daily smoking decreased this risk with increasing age up to 50 years. Beyond this age, there was no significant association (Kvalheim et al., 2013).

Nonetheless, smoking remains a major risk factor for cardiovascular disease that has also been shown to be a major co-morbidity with significantly increased risk of mortality among people with chronic pain (Torrance et al., 2010). All patients with chronic pain, who smoke, should be advised of the benefits of quitting as part of a chronic pain management programme. However, current evidence to date suggests that the standard approach to smoking cessation may not be effective in this subgroup and may require more intensive smoking interventions (Hooten et al., 2009).

Future studies should aim to include longitudinal assessments of treatment outcomes in both smokers and non-smokers with chronic pain in order to test any causal and/or temporal relationship between smoking and chronic pain, any differential outcomes conferred by a history of depression and consider adjusting for heritability of chronic pain (Hocking et al., 2012). Longitudinal research would also clarify whether, if smokers are indeed reporting higher pain measure scores compared with non-smokers, this means that they are a more challenging group to treat from a clinical perspective.

5. Conclusion

Our study based on a large general population cohort and broadly representative of chronic pain patients in the community supports evidence that smoking and pain are related, and that a history of MDD mediated the association between smoking and characteristic pain intensity. Depression did not mediate the association between smoking and characteristic pain-related disability score. Our study provides support for pragmatic trials within the community and other clinical settings to address questions on whether smoking cessation (with or without simultaneous treatment of depression) improves pain outcomes.

Author contributions

All authors were given the opportunity to discuss the results and comment on the manuscript.

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