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ORIGINAL ARTICLE

Low-grade inflammation as a potential mediator between depressive symptoms and temporomandibular pain: an 11-year follow-up study on Finnish adults

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ABSTRACT

Background: Low-grade inflammation and depressiveness have been associated with chronic pain conditions.

Objective: To examine whether low-grade inflammation mediates the association between depressive symptoms and temporomandibular (TM) pain in Finnish adults based on the Health 2000/2011 Surveys (BRIF8901).

Methods: The sample comprised subjects who underwent clinical TM pain examination (pain on palpation of the masticatory muscles and temporomandibular joints) in 2000 and 2011 and responded to questions on TM pain symptoms in 2011. The serum level of hs-CRP was obtained in both years, and depressiveness was assessed using the Beck Depression Inventory-21 (BDI-21) in 2000 and BDI-13 in 2011. Four subgroups were formed based on the presence of TM pain: No pain, pain in 2000-only, pain in the 2011-only, and pain in both-years. Analyses included Rao Scott's chi-square test cross-sectionally, and multinomial logistic regression longitudinally with the level of hs-CRP and BDI-21 score in 2000 as predictors. Mediation was tested using Hayes A. Processv3.5.

Results: Higher BDI-21/-13 and hs-CRP levels corresponded to higher prevalences of TM pain in both years. Longitudinally, in men, higher hs-CRP level predicted TM pain in 2000-only and TM pain in both-years. Higher BDI-21 score predicted having TM pain in 2011-only. In women, higher BDI-21 score predicted TM pain in 2000-only and having TM pain in both-years. Both BDI-21 and hs-CRP had a direct effect on TM pain outcome with no mediation detected.

Conclusion: While depressiveness may increase the risk of chronic TM pain in women, the risk in men is increased by low-grade inflammation.

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Temporomandibular pain; inflammation; depressiveness; low-grade inflammation; depression; population; follow-up

Introduction

Pain and depression are often comorbid conditions, with an average of 65% of depression patients exhibiting one or more pain complaints [1]. This comorbidity can be due to overlapping pathways [2]. In healthy individuals, serotonin and norepinephrine are responsible for dampening the effect for nociceptive peripheral pain signals, and in case of depletion of those neurotransmitters during depression, pain signals become intensified thus increasing pain sensitivity [1,2]. Additionally, antidepressants that increase neurotransmitters like serotonin and norepinephrine have a pain-relieving effect [1]. Nevertheless, regions in the brain that are responsible for emotions send projections to pain modulation structures in the brainstem [1], which could explain why depression (a negative emotion) is often accompanied with intensified pain response. Similarly, temporomandibular pain (TM pain) could exist with comorbid depression or depression symptoms. According to clinical studies, the prevalence of major depression in patients reporting TM pain has been reported to vary between 53% [3] and 85% [1]. Further, it has been shown that 75% of patients with chronic TM pain show depressive symptoms [3]. Longitudinal population-based studies have also shown that depressiveness is a strong predictor for chronic facial pain [4,5], and increases the risk for developing TM pain [6,7].

Proinflammatory cytokines and their mediators have been shown to be associated with depression and increased pain sensitivity, which is believed to occur through dysregulation of the hypothalamus-pituitary-adrenal axis and nociceptive perception [2,8]; however, all the factors, i.e. cytokines, depression and pain sensitivity, seem to induce one another interchangeably. High levels of C-reactive protein (inflammatory marker) were often observed in both depression and

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Supplemental data for this article can be accessed here.

This article has been corrected with minor changes. These changes do not impact the academic content of the article.

chronic pain [2]. Accordingly, concerning also TM pain, high levels of CRP were associated with a poor prognosis of TM pain in men [9].

It appears that shared pathways exist between depression or depressiveness and TM pain. However, little is known about the potential role of inflammation as a mediator between them, and more population-based studies are needed to investigate this connection.

Aims

The aim of the present study was to evaluate the association of depression, current depressive symptoms, and low-grade inflammation with the course of TM pain in a population-based sample of Finnish adults. Another aim was to investigate the possible role of low-grade inflammation as a mediator between current depressive symptoms and TM pain, as well as the alternative possibility of current depressive symptoms as a mediator between low-grade inflammation and TM pain.

Material and methods

The data for the study were based on the comprehensive, nationally representative Finnish Health 2000 and Health 2011 Surveys, carried out by the Finnish Institute for Health and Welfare [10,11] (THL).

The main sampling frame in 2000 comprised 8028 adults aged 30 years or over, living in mainland Finland, of whom 6986 (87%) were interviewed in their home or at an institution, and 79% participated in general health examinations and oral health examination including temporomandibular disorder (TMD) assessment [12]. The two-stage stratified cluster sample was representative of the Finnish population aged 30 years or over, allowing for good generalizability of the results. Persons aged 80 years and over were oversampled by doubling the sampling fraction [10].

All participants included in the Health 2000 Survey were invited to participate in the Health 2011 Survey, which in addition included a new sample of young adults aged between 18 and 28 years old [11]. Of those invited, 6740 participated in at least one part of the survey [11]. Clinical oral examinations were carried out in the same manner as in the Health 2000 Survey; however, due to limited resources they only covered subjects who were living in Southern (Hospital Districts of Helsinki and Uusimaa) and Northern (Hospital Districts of Kainuu, Keski-Pohjanmaa, Pohjois-Pohjanmaa, Lappi, Länsi-Pohja, Pohjois-Savo, and Vaasa) Finland, with a 41% participation rate [13].

For this study, those who participated in the clinical oral examination and TMD signs and symptoms assessment in the Health 2000 survey ($n = 6309$; men = 2860 and women = 3449) or in the Health 2011 survey ($n = 1524$; men = 681 and women = 843) were included for cross-sectional investigations. Additionally, those who participated in the clinical oral examination and TMD assessment in both the Health 2000 and the Health 2011 survey ($n = 1210$) were selected for longitudinal investigation [14], the final longitudinal sample comprised 1092 participants (men = 459, women = 633) after excluding cases with missing information (Figure 1).

Assessment of TMD signs and symptoms

In the Health 2000 survey, a standardized clinical oral examination was performed by five calibrated and experienced dentists, who assessed the signs of TMD [12]. The examiners were trained prior to the examinations by experienced specialists in order to increase the reproducibility of the clinical examination. The assessment of TMD signs included recording of maximum mouth opening, auscultation of the temporomandibular joint (TMJ) noises, and palpation of the TMJs and two masticatory muscles (MM), i.e. *temporalis anterior and masseter superficialis*. TMJ tenderness to palpation was assessed by applying a force of about 0.5 kg over the immovable condyle, and MM tenderness was assessed with a force of about 1 kg. Attempts were made to standardize the palpation force by exerting the forces on a measuring scale (using a letter weighing scale) between the examinations. TMJ and MM pain on palpation was recorded if the subjects reported pain when asked, or if they showed a protective reflex. Except for the maximum inter-incisal distance, all the findings were recorded separately for both sides. The percentage agreement between examiners and the referent examiner was: 92% (Kappa value, 0.26; 95% CI, 0.19–0.34) for pain on palpation in TMJs and 95% (Kappa value, 0.47; 95% CI, 0.41–0.53) for pain on palpation in masticatory muscles.

In the Health 2011 survey, the oral health examinations were performed by four calibrated and experienced dentists similar to the examinations in the Health 2000 Survey [11]. In addition to the assessment of TMD signs, TMD symptoms were inquired in the follow-up using the following questions, that have been shown to be valid for screening TMD pain [15]:

1. Do you have pain in your temples, face, temporomandibular joint, or jaws once a week or more?
2. Do you have pain when you open your mouth wide or chew once a week or more?

For the purpose of this study, only signs or symptoms of TM pain were included in the investigation. In the Health 2000 survey, and similarly in the Health 2011 survey, the subject was considered as having positive clinical TMJ-pain in the presence of pain on palpation on either side of TMJs, and negative in the absence of pain on both sides. The corresponding criteria were set for MM pain, i.e. those having pain in any of the four MM on either side were classified as positive clinical MM-pain. A positive answer to either of the TMD pain symptom questions was the basis for a subject being classified as having reported TM-pain.

In the longitudinal sample (those who participated in both years), the variable 'TM pain at baseline' included information only on clinical TM pain at baseline (clinical TMJ or MM pain) since no information on reported TM pain was obtained in the Health 2000 survey. Since the Health 2011

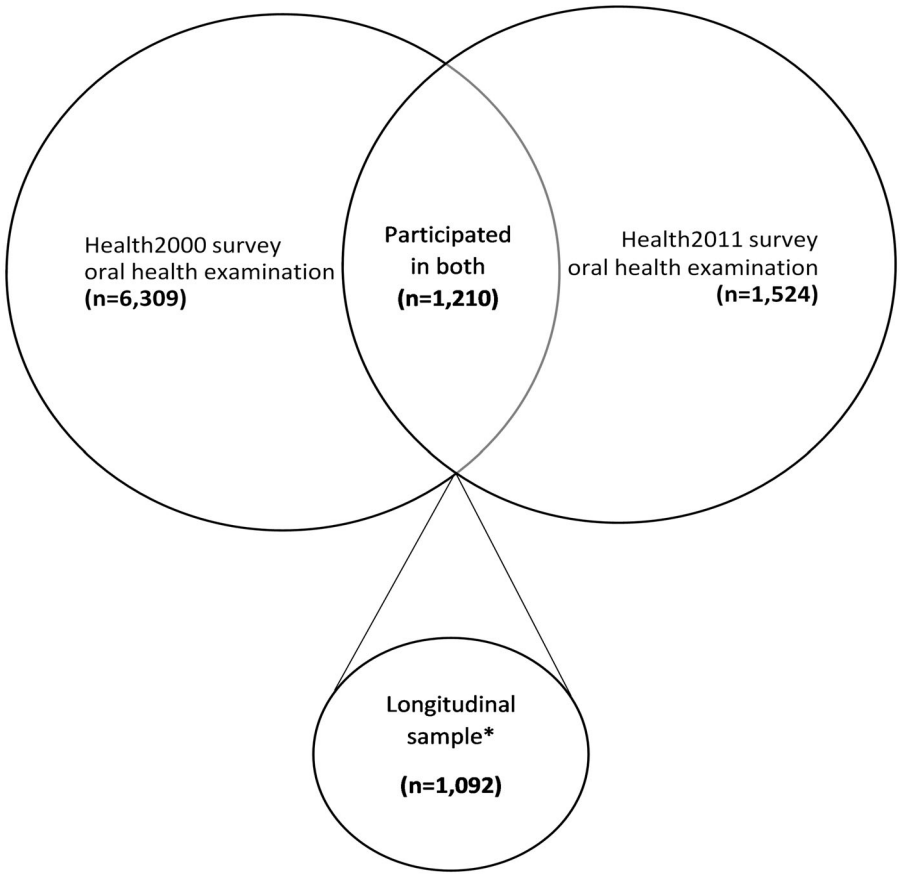

Figure 1. Description of the study sample. *From those who participated in both years.

survey included information about both clinical and reported TM pain, therefore the variable 'TM pain in the follow-up' included information on either clinical or reported TM pain in the follow-up. Based on the presence of TM pain at baseline or the follow-up the four following TM pain subgroups were constructed: 1. no TM pain in either years, 2. TM pain at baseline only, 3. TM pain in the follow-up only, and 4. TM pain both at baseline and in the follow-up.

Information about episodes of major depressive disorder (MDD) during the last 12 months were obtained using the Composite International Diagnostic Interview (CIDI) in both surveys. The Beck Depression Inventory (BDI)-21 questionnaire was used to assess the level of depressive symptoms in the Health 2000 survey. In the Health 2011 survey, BDI-13 was used [11] which has proved its validity and accuracy in determining the level of depressive symptoms [16]. Four categories were computed from BDI-21 total score: 0–9 no depressive symptoms, 10–16 mild depressive symptoms, 17–29 moderate depressive symptoms, and 30–63 severe depressive symptoms [17]. For BDI-13, the four categories were as follows: 0–4 no depressive symptoms, 5–7 mild symptoms, 8–15 moderate symptoms, and 16–39 severe depressive symptoms [18].

The serum level of highly sensitive C-reactive protein (hs-CRP) was obtained from participants' blood samples in the Health 2000 and the Health 2011 surveys, and was measured using an automated analyser and an ultrasensitive immunoturbidimetric test [10,11,19]. In this study, the level of hs-CRP was set as a possible mediator factor.

Based on previous empirical studies on TMD pain the following confounders were chosen: age, gender, education level, marital status, perceived health, occurrence of chronic illness or disability, psychosis medication, depression medication, neurosis medication, sleep medication, and a combination of psychoactive medication, all based on interviews [10,11].

Variables were categorized similarly for the Health 2000 and the Health 2011 surveys. Age was encoded into five age groups: 40 years or under, 41–50 years, 51–60 years, 61–70 years, and 71 or older. Marital status was classified as follows: married or in civil union, cohabitating, divorced or separated, widowed, and single. Educational level was trichotomized into basic, intermediate and higher education. The basic education category included those with no formal vocational training or senior secondary education. Intermediate education included those who had completed vocational training or passed the matriculation examination, and higher education included those with degrees or diplomas from higher vocational institutions, polytechnics and universities.

Perceived health comprised five levels: good, rather good, moderate, rather poor, and poor. Additionally, perceived health was trichotomized for the longitudinal sample as follows: good or rather good, moderate, and rather poor or poor. Furthermore, a variable for the use of psychoactive medication was created by combing the use of any of the following: psychosis medication, neurosis medication, sleeping medication, depression or combination

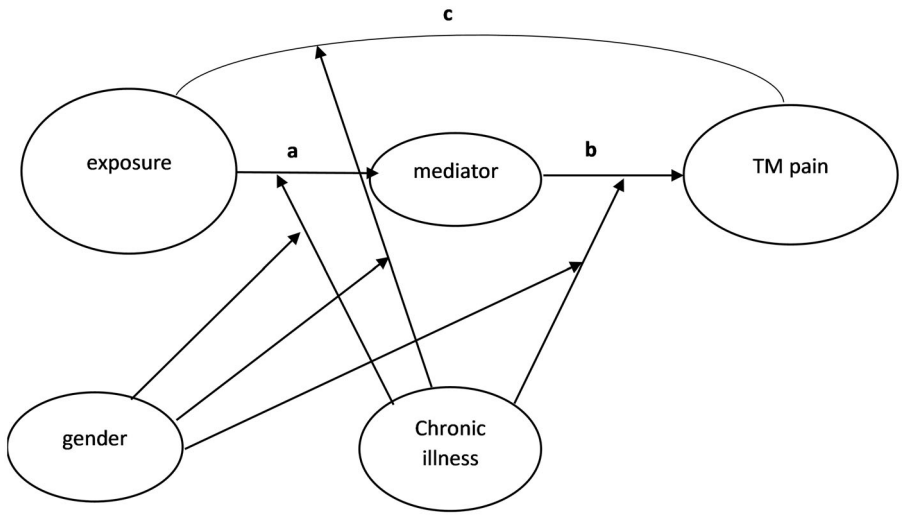

Figure 2. Conditional process illustration: the exposure (BDI-21 in first model and hs-CRP in second model) affects TM pain through the mediator (hs-CRP in first model and BDI-21 in second model); (a path) the effect of the exposure on the mediator; (b path) the effect of the mediator on TM pain; (c path) the direct effect of the exposure on TM pain. Chronic illness (moderator) interacting with the three paths, and gender (moderator) interacts with chronic illness interactions paths.

psychoactive medication. Highly sensitive C-reactive protein (hs-CRP) was dichotomized, using the cut-off point of hs-CRP for low risk of cardiovascular disease <1.00 mg/l as the first category and ≥ 1.00 mg/l as the second category [20].

Statistical analysis

Stratified by gender, Rao Scott test was used to evaluate the association of clinical MM and TMJ pain in the Health 2000 and the Health 2011 surveys and reported TM pain in the Health 2011 survey with marital status, age group, education level, perceived health, chronic illness or disability presence, MDD during the last 12 months, depressive symptoms level and the use of psychoactive medication. Analysis weight was applied for each year, respectively. For the longitudinal sample (those who participated in both years), analyses for the baseline and the follow-up were carried out in the same manner as for the population samples using the variables 'TM pain at baseline and TM pain in the follow-up'. Additionally, a binary logistic regression was performed to predict TM pain at baseline against baseline parameters, to establish the basis for predictor's inclusion in the multinomial logistic regression model later on.

Multinomial logistic regression was used to predict TM pain subgroups outcome through 11 years in those who participated in both years: 1. TM pain at baseline only, 2.TM pain in the follow-up only, 3. TM pain both at baseline and in the follow-up, against no TM pain in either year (the reference group). Predictors in the multinomial regression were the following baseline measures: BDI-21 score as a continuous variable, hs-CRP level as a continuous variable, chronic illness, stratified by gender and controlling for age (continuous), education level and marital status. Analysis weight of the follow-up was applied to obtain representative results and correct the effect of missing data.

The potential mediation effect of hs-CRP at baseline between BDI-21 score at baseline and TM pain subgroups outcome and of BDI-21 between hs-CRP and TM pain subgroups outcome through the 11 years was tested using *Hayes Andrew F. Processv3.5 macro* [21]. With the use of Conditional process analysis, the two hypotheses were tested while accounting for the interaction of chronic illness at baseline and gender with the direct and indirect pathways, namely as moderators, while controlling for age and educational level (Figure 2). The notion for selecting BDI-21 over MDD was to avoid underrepresentation bias of undiagnosed depression, and that a diagnosed depression is possibly under control which could result in confounding effects and false inferences.

Results

Cross-sectional findings

In the Health 2000 survey, presence of MM pain in both genders associated significantly with higher age, low education level, being widowed, higher BDI-21 score, higher level of hs-CRP, poor perceived health, presence of chronic illness or disability and use of psychoactive medication, and also with occurrence of MDD in women (Table 1). The presence of TMJ pain in both genders associated significantly with occurrence of MDD, higher BDI-21 score and poor perceived health, and in women also with higher age, low education, being married, presence of chronic illness and use of psychoactive medication.

In the Health 2011 survey, the presence of MM pain in men associated with the occurrence of MDD, and in women with low education, being widowed, and in both genders, it associated significantly with higher age, higher level of hs-CRP, poor perceived health, the presence of chronic illness the use of psychoactive medication (Table 2). The presence of TMJ pain in men associated significantly with the presence of chronic illness, lower education and MDD, and in women with higher age, being divorced, high BDI-13 score, low level of hs-CRP, chronic illness and the use of psychoactive

Table 1. Numbers and weighted prevalence (%) of clinically determined pain on palpation of masticatory muscles (MM) and temporomandibular joint (TMJ) in subjects who participated in the oral health examination in the Health 2000 survey ($n = 6309$) by age group, education level, marital status, major depressive disorder episode (MDD) during the last 12 months, Beck Depression Inventory-21 score (BDI-21), highly sensitive C-reactive protein (hs-CRP), perceived health, chronic illness and the use of psychotropic medication.

	Men					Women				
		Clinical MM[a] pain		Clinical TMJ[b] pain			Clinical MM pain		Clinical TMJ pain	
All	Total 2860	% 7.5	*p* Value	% 2.4	*p* Value	Total 3449	% 19.4	*p* Value	% 5.0	*p* Value
Age group			<.001		.557			<.001		<.001
≤ 40	730	4.6		2.5		814	12.2		3.2	
41–50	725	5.3		2.5		819	15.1		4.7	
51–60	662	6.7		2.7		686	18.1		4.2	
61–70	417	12.6		1.8		514	23.4		6.5	
≥ 71	326	15.7		1.7		616	35.1		8.0	
Education			<.001		.523			<.001		<.001
Basic	1092	10.6		2.4		1338	25.7		6.5	
Intermediate	1072	6.1		2.6		941	17.6		5.5	
High	686	4.8		2.0		1098	13.1		2.8	
Marital status			<.001		.201			<.001		.001
Married or in a civil union	1821	6.9		2.1		1883	18.0		5.8	
Cohabitating	338	5.4		3.8		337	14.8		4.8	
Divorced or separated	227	10.2		2.0		385	16.7		3.4	
Widowed	108	15.5		1.0		492	32.4		5.7	
Single	355	8.8		3.1		344	18.2		2.4	
Mdd during the last 12 months			.740		.011			<.001		.001
No	2638	7.2		2.3		3032	18.2		4.7	
Yes	93	6.9		5.9		204	28.0		8.0	
BDI-21 score			<.001		.009			<.001		<.001
No depressive symptoms	2148	5.7		2.0		2265	14.1		4.0	
Mild	419	10.5		2.9		679	26.1		5.8	
Moderate	186	12.8		6.2		341	34.8		8.5	
Severe	33	25.7		0.0		52	50.0		16.7	
hs-CRP (mg/l)			.004		.135			<.001		.897
<1.00	1649	6.6		2.1		1905	17.2		5.1	
≥1.00	1181	8.8		2.8		1494	22.1		5.1	
Perceived health			<.001		<.001			<.001		<.001
Good	912	3.2		1.4		1096	9.8		2.6	
Rather good	844	7.7		2.4		1046	16.2		4.9	
Moderate	760	8.5		2.6		906	24.9		5.6	
Rather poor	231	16.4		4.2		286	41.4		12.0	
Poor	96	20.0		7.0		99	52.4		11.0	
Chronic illness			<.001		.283			<.001		<.001
No	1422	4.4		2.1		1574	12.1		3.0	
Yes	1427	10.8		2.7		1866	25.7		6.9	
Psychoactive medication			<.001		.453			<.001		<.001
No	2211	7.5		2.4		2715	16.7		4.8	
Yes	318	12.8		3.0		604	33.6		7.5	

[a]Right or left temporal or masseter muscle.
[b]Right or left temporomandibular joint.

medication. The presence of reported TM pain in both genders associated with lower education, higher BDI-13 score, poor health, the presence of chronic illness and the use of psychoactive medication. In men reported TM pain associated with younger age, being divorced, the occurrence of MDD and higher hs-CRP level, and in women with higher age.

Longitudinal findings

Results from the longitudinal sample at baseline and in the follow-up were consistent with the results from the cross-sectional samples, except for MDD which was not significantly associated with TM pain neither at baseline nor in the follow-up in both genders, and psychoactive medication at baseline in men, which could be due to the smaller sample size (Supplementary Tables 1 and 2).

TM pain subgroups

With no TM pain in either year set as the reference category, the results were as follows:

In men, high level of hs-CRP at baseline increased the odds of having TM pain at baseline only (OR = 1.1 95% CI 1.0–1.2), and in women high BDI-21 score at baseline increased the odds of having TM pain at baseline only (OR = 1.1 95% CI 1.0–1.1) (Table 3). In men, high BDI-21 score and chronic illness at baseline increased the odds of having TM pain in the follow-up only (OR = 1.1 95% CI 1.0–1.1, OR = 2.5 95% CI 1.0–6.3 respectively). In women, having chronic illness at baseline increased the odds of having TM pain in the follow-up only (OR = 2.3 95% CI 1.2–4.0). In men, a high level of hs-CRP at baseline increased the odds of having TM pain both at baseline and in the follow-up (OR = 1.1 95% CI 1.0–1.2). In women, a high BDI-21 score at baseline increased the odds of having TM pain both at baseline and in the follow-up (OR = 1.1 95% CI 1.0–1.13).

Table 2. Numbers and weighted prevalence (%) of clinically determined pain on palpation of the masticatory muscles (MM), temporomandibular joint (TMJ) and reported temporomandibular (TM) pain in subjects who participated in the oral health examination in the Health 2011 survey ($n = 1524$), by age group, education level, marital status, major depressive disorder episode (MDD) during the last 12 months, Beck Depression Inventory-13 score (BDI-13), highly sensitive C-reactive protein (hs-CRP), perceived health, chronic illness and the use of psychoactive medication.

	Men							Women						
		Clinical MM[a] pain		Clinical TMJ[b] pain		Reported TM[c] pain			Clinical MM pain		Clinical TMJ pain		Reported TM pain	
All	Total 681	% 2.2	*p* Value	% 2.2	*p* Value	% 8.2	*p* Value	Total 843	% 7.2	*p* Value	% 4.7	*p* Value	% 12.7	*p* Value
Age group			<.001		.088		<.001			<.001		<.001		<.001
≤ 40	120	2.2		2.9		14.4		149	7.4		5.1		11.8	
41–50	153	0.7		1.4		7.1		206	7.6		7.0		14.0	
51–60	160	2.1		2.1		5.7		192	5.2		3.9		11.0	
61–70	157	0.7		1.5		7.4		178	6.5		2.2		6.6	
≥ 71	91	7.7		2.6		5.1		118	11.0		3.7		21.3	
Education			.256		.001		<.001			<.001		.054		<.001
Basic	128	4.0		1.6		9.7		170	14.8		4.5		16.8	
Intermediate	257	1.6		1.6		9.2		197	8.5		6.0		13.9	
High	287	2.0		2.8		6.4		471	3.7		4.2		10.2	
marital status			.525		.686		<.001			.043		.043		.750
Married or in a civil union	444	2.5		2.3		6.8		472	7.2		4.3		11.8	
Cohabitating	94	3.2		2.2		10.6		105	7.6		6.5		13.0	
Divorced or separated	49	4.2		0.0		14.9		93	4.1		6.8		12.0	
Widowed	15	0.0		0.0		6.7		76	11.6		2.9		15.9	
Single	70	0.0		4.2		8.5		92	6.4		5.1		13.0	
MDD during the last 12 months			<.001		<.001		<.001			.685		.733		.085
No	631	2.0		2.2		7.8		740	6.8		4.7		12.8	
Yes	23	10.0		5.0		25.0		63	7.5		5.7		9.4	
BDI-13 scores			.485		.571		.002			.071		<.001		<.001
No depressive symptoms	532	2.0		2.4		7.1		622	6.6		4.1		10.1	
Mild	72	4.8		4.8		7.9		90	7.6		2.5		15.2	
Moderate	38	0.0		0.0		14.3		82	8.7		11.6		20.3	
Severe	16	0.0		0.0		11.1		28	12.5		4.2		33.3	
hs-CRP (mg/l)			.042		.556		<.001			.011		.021		.094
<1.00	348	1.3		2.3		7.2		390	6.2		5.5		11.8	
≥1.00	332	3.0		2.0		11.0		449	8.9		3.4		14.5	
Perceived health			<.001		.391		<.001			<.001		.088		<.001
Good	331	1.0		1.9		5.8		394	4.0		3.7		7.6	
Rather good	212	2.1		2.1		5.7		261	7.0		4.2		11.3	
Moderate	94	5.7		2.3		18.4		139	12.1		7.3		21.0	
Rather poor	29	3.7		7.4		18.5		33	10.3		6.9		24.1	
Poor	6	16.7		0.0		16.7		11	60.0		10.0		60.0	
Chronic illness			.001		<.001		<.001			<.001		.005		<.001
No	449	0.9		1.2		6.4		534	5.2		4.0		10.4	
Yes	223	4.4		4.4		11.8		304	10.9		5.4		16.7	
Psychoactive medication			<.001		.614		.003			<.001		.007		<.001
No	623	1.7		2.4		7.6		726	6.4		4.1		10.7	
Yes	50	6.5		0.0		15.2		112	12.4		8.2		23.7	

[a]Right or left temporal or masseter muscle.
[b]Right or left temporomandibular joint.
[c]Pain in the jaw, face or during mouth opening.

Table 3. Weighted and adjusted[a] odds ratio (OR) with 95% confidence interval (CI) of temporomandibular (TM) pain (i.e. clinical pain at baseline, clinical or reported pain in the follow-up) outcome in a multinomial model in those who attended both in the Health 2000 and 2011 surveys ($N = 1092$) as predicted by baseline parameters of Beck Depression Inventory-21 score (BDI-21), highly sensitive C-reactive protein (hs-CRP), perceived health, chronic illness and the use of psychoactive medication stratified by gender.

	Baseline only	The follow-up only	Baseline and in the follow-up
Men ($N = 459$)	**2.7**%	**7.5**%	**3.2**%
BDI-21 score (continuous)	1.03 (0.9–1.1) $p = 0.517$	**1.1 (1.0–1.1) $p = 0.023$**	1.1 (1.0–1.1) $p = 0.071$
hs-CRP level at (mg/l) (continuous)	**1.1 (1.0– 1.2) $p = 0.040$**	1.04 (1.0–1.1) $p = 0.241$	**1.1 (1.0–1.2) $p = 0.006$**
Chronic illness			
No (ref.)	1.0	1.0	1.0
Yes	0.95 (0.2–3.9) $p = 0.538$	**2.5 (1.0–6.3) $p = 0.044$**	0.5 (0.1–2.3) $p = 0.333$
Women ($N = 633$)	**9.6**%	**11.1**%	**6.1**%
BDI-21 (continuous)	**1.1 (1.0– 1.1) $p < 0.001$**	1.04 (1.0–1.1) $p = 0.053$	**1.1 (1.0–1.13) $p = 0.001$**
hs-CRP level (mg/l) (continuous)	1.03 (1.0–1.1) $p = 0.198$	1.01 (1.0–1.08) $p = 0.600$	1.04 (1.0–1.1) $p = 0.228$
Chronic illness			
No (ref.)	1.0	1.0	1.0
Yes	**2.1 (1.1–4.2) $p = 0.030$**	**2.3 (1.2–4.0) $p = 0.007$**	1.2 (0.5–2.8) $p = 0.632$

[a]Weighted and adjusted for age, education level, and marital status.
Note: significant values in bold.

Table 4. Conditional process analysis for temporomandibular (TM) pain outcome when the exposure is the Beck Depression Inventory-21 score (BDI-21) and the mediator is the level of highly sensitive C-reactive protein (hs-CRP), under the interaction with two moderators gender (men, women) and chronic illness (no = 0, yes = 1), controlling for age and educational level, and values for the direct exposure-to-outcome effect represented with 95% confidence intervals (CI), and the indirect exposure-to-outcome effect through the mediator by bootstrap confidence interval (CI).

	Conditional direct effect (based on chronic illness and gender)				Conditional indirect effect (based on chronic illness and gender)			
	0		1		0		1	
	Effect 95% CI	*p* Value	Effect 95% CI	*p* Value	Effect	Bootstrap CI	Effect	Bootstrap CI
Men								
Tm pain at baseline only	0.1092 (−0.0092, 0.2276)	.0706	−0.0276 (−0.1667, 0.1115)	.6969	−0.0012	(−0.0088, 0.0229)	0.0006	(−0.0579, 0.0143)
Tm pain in the follow-up	0.0861 (0.0114, 0.1608)	.0239	0.0518 (0.0014, 0.1021)	.0439	0.0008	(−0.0049, 0.0300)	0.0007	(−0.0058, 0.0050)
Tm pain in both years	0.0729 (−0.0418, 0.1876)	.2128	0.0781 (0.0037, 0.1525)	.0396	0.0109	(−0.0138, 0.0845)	0.0047	(−0.0342, 0.0497)
Women								
Tm pain at baseline only	0.0783 (0.0280, 0.1286)	.0023	0.0747 (0.0226, 0.1269)	.0050	0	(−0.0021, 0.0071)	0.0047	(−0.0104, 0.0045)
Tm pain in the follow-up	−0.0011 (−0.0687, 0.0664)	.9738	0.0514 (0.0068, 0.0961)	.0240	−0.0003	(−0.0023, 0.0031)	−0.0005	(−0.0032, 0.0214)
Tm pain in both years	0.0961 (0.0324, 0.1597)	.0031	0.0702 (0.0014, 0.1391)	.0456	0.0012	(−0.0029, 0.0218)	−0.0035	(−0.0100, 0.0193)

Table 5. Conditional process analysis for temporomandibular (TM) pain outcome when the exposure is the level of highly sensitive C-reactive protein (hs-CRP) and the mediator is the Beck Depression Inventory-21 score (BDI-21), under the interaction with two moderators gender (men, women) and chronic illness (no = 0, yes = 1), controlling for age and educational level, and values for the direct exposure-to-outcome effect represented with 95% confidence intervals (CI), and the indirect exposure-to-outcome effect through the mediator by bootstrap confidence interval (CI).

	Conditional direct effect (based on chronic illness and gender)				Conditional indirect effect (based on chronic illness and gender)			
	0		1		0		1	
	Effect 95% CI	*p* Value	Effect 95% CI	*p* Value	Effect	Bootstrap CI	Effect	Bootstrap CI
Men								
Tm pain at baseline only	0.0745 (−0.1304, 0.2793)	.4762	0.0855 (0.0102, 0.1607)	.0260	−0.0048	(−0.0332, 0.0157)	−0.0003	(−0.0211, 0.0258)
Tm pain in the follow-up	−0.0315 (−0.2945, 0.2315)	.8142	0.0271 (−0.0471, 0.1013)	.4738	−0.0078	(−0.0370, 0.0056)	0.0032	(−0.0176, 0.0163)
Tm pain in both years	−0.4246 (−1.4793, 0.6302)	.4301	0.0740 (0.0070, 0.1411)	.0304	−0.0051	(−0.0334, 0.0103)	0.0074	(−0.0553, 0.0459)
Women								
Tm pain at baseline only	0.0036 (−0.0900, 0.0973)	.9391	0.0679 (−0.0072, 0.1430)	.0763	−0.0012	(−0.0083, 0.0235)	−0.0086	(−0.0320, 0.0028)
Tm pain in the follow-up	0.0098 (−0.0600, 0.0796)	.7830	0.0167 (−0.0589, 0.0922)	.6657	0.0001	(−0.0035, 0.0048)	−0.0040	(−0.0286, 0.0062)
Tm pain in both years	−0.0368 (−0.2056, 0.1319)	.6688	0.0605 (−0.0319, 0.1528)	.1994	−0.0050	(−0.0144, 0.0109)	−0.0089	(−0.0381, 0.0036)

Conditional process analysis

Test values are shown in Tables 4 and 5. In the first model (Table 4), BDI-21 score at baseline had a significant direct effect on having TM pain at baseline-only in women with and without chronic illness at baseline, with no mediation by the baseline level of hs-CRP. Having TM pain in the follow-up only, BDI-21score at baseline had a significant direct effect in men with or without chronic illness at baseline, and women with chronic illness at baseline, no significant indirect effect through hs-CRP was found. The baseline score of BDI-21 had a significant direct effect on having TM pain in both years in men with chronic illness and in women with or without chronic illness, with no mediation by hs-CRP.

In the second model (Table 5), the level of hs-CRP at baseline had a significant direct effect on having TM pain at baseline only and TM pain in both years in men with chronic illness at baseline with no significant indirect effect through BDI-21 score at baseline.

Discussion

This study explored the association of 12-month diagnosis of MDD, current depressive symptoms and low-grade inflammation with TM pain, and the possible mediation of low-grade inflammation for the associations of depressiveness with TM pain and the alternative possibility of depressiveness being the mediator between low-grade inflammation and TM pain over an 11-year follow-up in Finnish adults. In both the Health 2000 Survey and the Health 2011 survey, 12-month diagnosis of MDD, current depressive symptoms, and low-grade inflammation were significantly associated with clinical and reported TM pain, with variations between men and women. In a longitudinal setting, depressive symptoms at baseline increased the risk of TM pain in both genders with or without suffering from chronic illness, and low-grade inflammation appeared to increase the risk of TM pain in men with chronic illness.

Occurrence of diagnosed major depression (MDD) during the past 12 months showed significant association with clinical TM pain in the Health 2000 Survey but associated only with clinical and reported TM pain in men in the Health 2011 Survey. Men with diagnosed MDD during the past 12 months had a higher prevalence of clinical and reported TM pain than women in the same group. Interestingly, the prevalence of reported TM pain in women was higher in those with no MDD than those with MDD, however, the difference was not significant. More severe current depressive symptoms were observed among those with TM pain in both years, which was consistent with previous studies [22–24].

Longitudinally, the present study showed that women with more severe current depressive symptoms at baseline, had a higher risk of exhibiting TM pain at baseline only, independently from presence of chronic illness at baseline and increased the risk of exhibiting TM pain in both years as well. Nevertheless, in men higher current depressive symptoms at baseline increased the risk of exhibiting TM pain in the follow-up in those men who did not have TM pain at baseline and was independent from the presence of

chronic illness at baseline. These results indicate that current depressive symptoms increase the risk for TM pain and especially chronic TM pain, which is supported by previous studies showing that depressive symptoms can impair healing and is associated with a higher rate of TM pain chronicity [4,5,25].

A high level of hs-CRP at baseline was predictive for men having TM pain at baseline; furthermore, it increased the risk of them having TM pain in both years. This may suggest a possible involvement of low-grade chronic inflammation in both current TM pain and also in chronic condition. Autoimmunity could be one reason for inflammation; a clinical study on TMD pain patients found that men with TMD who tested positive for antinuclear antibody and rheumatoid factor had a higher CRP level and a poor TMD prognosis compared to those who tested negative [9]. Studies have reported that local proinflammatory cytokines found in the synovial fluid of the TMJ articular capsule were associated with the presence of pain symptoms in degenerative TMJ [26]. On the other hand, systemic low-grade inflammation is believed to be induced by chronic stress and depression [2,27].

While the present study found no mediation effect of hs-CRP or depressive symptoms, it revealed that gender and chronic illness could moderate their potential risk on TM pain. However, these results should be interpreted with caution. After running the conditional process analysis, it gave a deeper insight on the results from the logistic regression. Low-grade inflammation seemed to be a prominent risk factor in men with chronic illness. Even though the significant direct effect for depressive symptoms in men who developed TM pain in the follow-up was equally significant without or with chronic illness, this effect seemed to be attenuated in those with TM pain in both years, when the presence of chronic illness was conditional, highlighting the influence of low-grade inflammation that might have been perpetuated by chronic illness. In women depressive symptoms rather than chronic illness and low-grade inflammation appeared to put them at risk of chronic TM pain.

However, the possibilities of mediation cannot be ruled out. In a previous study based on the Health 2000 survey, higher current depressive symptoms as well as 12-month diagnosis of MDD were associated with higher levels of hs-CRP in men but not in women [19]. An association between depression and hs-CRP was explained in women by other risk factors, most notably by body mass index, whereas in men this association persisted after adjusting for potential confounding factors [19]. Giving that, it could be plausible that in the current study a mediation effect was not detected by low-grade inflammation and depressive symptoms due to the low number of TM pain cases which could have affected the analysis power.

Different studies [2,19,28] investigating the association between depressive symptoms and low-grade inflammation have found that this association is more remarkable in men. Furthermore, depression was shown to induce upregulated nociceptive perception through inflammatory mediators [2,8]. It could be deduced that TM pain associates with depressive symptoms differently between genders. Among women, this association could be related to depletion in pain dampening neurotransmitters during depression [1,2]. This could be plausible knowing that women show a lower pain threshold and a greater vulnerability to central sensitization compared to men, which was also shown in TMD pain cases [29–32].

Although in the present study women had a higher prevalence of TM pain than men, men's TM pain could be under-reported. Women were found to have only marginally higher incidence of TM pain than men [33].

Strengths and limitations

This study presented novel results on the role of low-grade inflammation in TM pain. Among the study's strengths is the use of specific quantitative measures to test for mediation within a relatively large population-based sample, which reduces sample bias. Furthermore, the results from the Health 2000 Survey were representative of Finnish adults, and despite the lower participation rate in the Health 2011 Survey, the results were representative of adults in two areas in Finland, southern and northern Finland which represent the whole Finland pretty well. One of the limitations of this study is the low participation rate in the follow-up compared to the baseline. Additionally, the lack of information about TM pain status between 2000 and 2011, which would have helped to assess fluctuation of TM pain and possibly confirm chronicity. Another limitation was that only single signs of TMD pain were assessed without more definite diagnoses, such as recently published, validated DC/TMD Criteria [34] that were not published at the time of the study. This was also due to practical reasons linked with the large sample size. Lack of TMD symptom questions in the Health 2000 was another limitation of this study.

Conclusion

Based on the results, the risk of TM pain seems to differ between genders; while the effect of current depressive symptoms on TM pain seemed presumably direct in women, it appeared that low-grade inflammation is a more prominent risk factor in men. Low-grade chronic inflammation could be potentially relate to chronic TM pain in men. The severity of depressive symptoms could increase the risk of recurrence or chronicity of TM pain in women. Depressive symptoms and TM pain seem to share pathophysiological pathways, which should be considered in the comprehensive treatment of TM pain. Good general health could provide some protection against developing TM pain.

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Disclosure statement

The authors declare no conflict of interests.

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