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Excess Risk of Temporomandibular Disorder Associated With Cigarette Smoking in Young Adults

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Abstract: Evidence suggests that the effect of cigarette smoking on chronic pain is stronger in younger than older adults. This case-control study investigated whether age modified an effect of smoking on temporomandibular disorder (TMD) in 299 females aged 18 to 60 years. It also investigated the extent to which this relationship was explained by psychological profile, inflammatory response, and allergy. Cases were defined using the Research Diagnostic Criteria for Temporomandibular Disorders based on clinical examination. Psychological profile was evaluated using standardized instruments. Inflammatory response was evaluated with 11 cytokines isolated in plasma. History of allergy conditions was self-reported. Odds ratios (ORs) for the effect of smoking were calculated using binary logistic regression. Stratified analyses and the likelihood ratio test examined effect modification by smoking. Compared with nonsmokers, ever smokers aged <30 years had higher odds of TMD (OR = 4.14, 95% CI: 1.57, 11.35) than older adults (OR = 1.23, 95% CI: .55, 2.78) (*P* (effect modification) = .038). Adjustment for psychological profile, cytokines, and history of allergy-like conditions attenuated the effect by 45% to statistical nonsignificance. The main finding was reproduced with secondary analyses of 2 nationally representative surveys of adults conducted in the US and Australia.

***Perspective:** This study showed that smoking was associated with TMD risk in females, but only in young adulthood. It replicated this finding in 2 nationally representative surveys of females in the US and Australia. Findings may alert clinicians to recognize that smoking is a concern for TMD in younger female patients.*

***Key words:** Epidemiology, case-control study, temporomandibular joint disorder, psychological stress, allergy and hypersensitivity, cytokines.*

Tobacco smoke plays a role in several chronic pain conditions.[29,41,47,51,70] A meta-analysis of the association between smoking and low back pain from 27 cross-sectional and 13 cohort studies showed that, compared to nonsmokers, smokers had greater risk of pain. There was a dose-response relation in which greater exposure to tobacco was associated with greater risk of pain.[54] The 13 prospective cohort studies in this meta-analysis helped clarify temporal ambiguity, showing that smoking preceded pain onset in current and former smokers. Of particular interest was that the effect of smoking on pain incidence was greater in younger than older adults.

Headache is another pain condition in which the effect of smoking is more pronounced at younger age. The Head-HUNT Study, a Norwegian population-based study of 51,383 adults, found an effect of smoking on headache was modified by age, peaking around 30 years and then declining (P effect modification < .0001).[1] In a New Zealand birth cohort, a 2-fold risk of headache due to smoking, present in adolescence, was no longer apparent when the cohort was aged 26 years.[62]

Three studies have examined smoking in temporomandibular disorder (TMD)[36,64,65] but none has examined whether its effect differs by age. Accounting for smoking is important in TMD research not only

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because of smoking's potential causal role, but also because smoking may account for effects of other TMD risk factors including perceived stress, anxiety, and depression.[10,12,35,48,49]

Psychological stress is well recognized for its relationship with TMD. Less well investigated are the roles of allergy and inflammation. This is surprising given that allergy is comorbid with several idiopathic pain conditions including fibromyalgia,[8] low back pain,[24] headache,[2] vulvodynia,[21] and irritable bowel syndrome.[60] In addition elevated levels of inflammatory cytokines are associated with headache,[27] fibromyalgia[6,8] and irritable bowel syndrome.[5] One possible mediator is monocyte chemoattractant protein-1 (MCP-1). This chemokine induces histamine release from basophils[7] and contributes to the pathogenesis of allergic disorders.[23,68] MCP-1 concentration was 2.3-fold higher in synovial fluids of TMD cases than noncases, although differences failed to reach statistical significance.[44]

Whether young smokers are more susceptible than nonsmokers and older adults to pain mediated by an inflammatory or allergy pathway is unknown. What is established is that smoking is associated with the production of pro-inflammatory cytokines and inhibition anti-inflammatory cytokines. Smoking increases sensitization to allergens[26] and facilitates permeability of the respiratory epithelium.[17] Serum immunoglobulin E (IgE) levels are higher in smokers than nonsmokers[59] and IgE levels decrease dramatically with age. The age-related reduction is especially noticeable in atopic females until 35 years, after which further age-related declines are not apparent.[4] Taken together, the findings imply that smoking may influence pain either through allergic or inflammatory pathways, or both.

To clarify these relationships, this study tested whether age modified a relation between smoking and TMD. We hypothesized that an effect of smoking on TMD was stronger in younger adults. If confirmed, the second aim was to quantify the extent to which psychological vulnerability, allergy-related conditions, and plasma cytokine levels attenuated the smoking-related effect.

Methods

This study was approved by the Biomedical Institutional Review Board of the University of North Carolina at Chapel Hill (UNC-CH). Written informed consent was obtained from all study participants.

Study Design and Recruitment

Data for this analysis were from a case-control study of risk factors for chronic TMD.

All study participants were female, aged between 18 and 60 years, and self-identified as Caucasian. Sampling was limited to females because prevalence of TMD is greater in females than males. The rationale for limiting inclusion to a single racial group was to simplify interpretation of genetic findings since 1 objective of the study is to investigate genetic risk factors for TMD. All study participants were recruited from the Central North Carolina community with the use of fliers, mass informational emails sent to the UNC-CH population, and advertisements in local newspapers, radio, and at the Orofacial Pain Clinic at the UNC-CH School of Dentistry between 2005 and 2009.

All potential participants were screened by a telephone interview to exclude those with diagnoses of any 1 of diabetes, kidney disease, heart failure, chronic respiratory disease, epilepsy or seizure disorder, or high blood pressure not controlled with medication. Also excluded were those who were pregnant, nursing, undergoing orthodontic treatment, renal dialysis, radiation or chemotherapy as well as persons with trauma or surgery on the head, face or neck within the last 6 months.

A medical history was recorded for all subjects prior to a clinical examination. Examinations were performed by 1 of 10 examiners trained in the examination protocol and calibrated for the reliability and validity of their diagnostic decisions every 6 months. Cases were persons who met Research Diagnostic Criteria for Temporomandibular Disorders[15] for myalgia, arthralgia, or both, based on a clinical examination performed by a trained calibrated examiner. In summary, cases were people who reported a 6-month history of pain in the temporomandibular structures, with at least 5 days of such pain in the month preceding the examination and where examiners found at least 3 muscle groups in the temporomandibular region that were tender to palpation or jaw maneuver. The threshold of 6 months was chosen to be consistent with the classification for chronic pain for research purposes described in the International Association for the Study of Pain Task Force on Taxonomy.[38] Controls reported no history of orofacial pain within the preceding 6 months and no prior diagnosis for TMD. Additionally, their examination confirmed that they did not have arthralgia or myalgia.

Smoking Status

Lifetime smoking status was evaluated with the question widely used in major US population surveys including the National Health Interview Survey (NHIS), the National Health and Nutrition Examination Survey, and the Behavioral Risk Factor Surveillance Survey: "Have you smoked at least 100 cigarettes in your entire life?" Those with a negative response were classified as lifetime nonsmokers. Those with an affirmative response were further classified as current or former smokers.

Allergy-Related Conditions

A medical history questionnaire presented a list of conditions against which participants checked Yes if they had ever had the condition; otherwise they checked No. Conditions included dermal mucocutaneous conditions (skin rashes), respiratory conditions (sinus trouble, allergies or hives), and any use of antihistamine medication.

Cytokines

Cytokines are small intracellular regulatory proteins that play a major role in immune response as well as

cell growth and tissue repair.[18,40,52] Peripheral blood samples were collected and plasma was isolated using multiplex technology (R&D Systems; Minneapolis, MN) to measure 11 cytokines. Cytokines included on the multiplex panel were: vascular endothelial growth factor; fibroblast growth factor; interleukin-1 receptor antagonist (IL-1Ra); monocyte chemoattractant protein-1 (MCP-1); interleukin-6; interleukin-8; epithelial neutrophil-activating protein 78; tumor necrosis factor-alpha; macrophage inflammatory protein 1 alpha; granulocyte-colony stimulating factor; and thrombopoietin. Concentrations of the 11 cytokines were standardized and each was tested for the strength of its association with TMD in logistic regression. Eight of these had significantly elevated concentrations in TMD cases compared with controls ($P < .05$). Those not significantly associated with TMD were fibroblast growth factor, granulocyte-colony stimulating factor, tumor necrosis factor-alpha, and interleukin-6. For the purpose of this analysis, we selected the 2 cytokines in which odds of TMD increased by ≥50% per standard deviation increase in cytokine concentration. One cytokine was IL-1Ra, a potent inhibitor of 2 pro-inflammatory cytokines; IL-1alpha and IL-1beta. The other, MCP-1, a chemokine, serves multiple functions including a role in the pathophysiology of allergy and activation of histamine release in basophils.[3,43]

Psychological Measures

We classified psychological vulnerability with 3 factors: psychological stress, trait anxiety, and history of depression. Psychological stress was evaluated with the 10-item Perceived Stress Scale[11] that measures the extent to which respondents consider their lives to have been unpredictable, uncontrollable, and overloaded during the preceding month. Responses were made on a 5-point scale of frequency ranging from "never" to "very often." Positive items were reverse scored before all responses were summed to yield an overall scale score where higher scores denote greater psychological distress. The 20-statement trait anxiety subscale of the Spielberger State and Trait Anxiety Inventory for adults[57] was administered to measure this stable, enduring component of anxiety. Responses were made on a 4-point scale of frequency ranging from "not at all" to "very much so." A single question in the medical history questionnaire asked whether or not participants had ever taken antidepressant medication (yes/no). This question serves as a proxy for lifetime history of depressive symptoms. Given that our interest was the study of chronic TMD, we were less interested in existing clinical depressive symptoms than in lifetime history of treatment for depression because risk of developing chronic TMD is likely to be influenced by exposures over a long period.

Statistical Analyses

Analysis was guided by a directed acyclic graph (Fig 1). For young adults the graph depicts an indirect effect of cigarette smoking on TMD that is mediated by an inflammation or allergy pathway. The same pathways for older adults are depicted to bypass smoking. A binary logistic regression model was used to assess the association between smoking and TMD. Odds ratios (ORs) were calculated as estimates of the strength of association and 95% confidence intervals (CIs) for the ORs signified the precision of the OR estimates. Associations were deemed statistically significant when the 95% CI excluded the null value of 1.0. To test the study hypothesis that the association between smoking and TMD was modified by age, we dichotomized age (<30 versus ≥30 years) after fully exploring the age and TMD relationship. For descriptive purposes, odds of TMD were compared between tertiles of cytokine concentrations and scores for perceived stress and trait anxiety. In multivariable analysis these continuous variables were standardized so that the resulting ORs estimated the relative change in odds of TMD associated with 1 standard deviation of change in the continuous measure. Decisions regarding confounding were based on: 1) whether the covariate is associated with both smoking and TMD case status; and 2) whether inclusion of the covariate produces a change of ≥10% in the OR for the association between smoking and TMD.

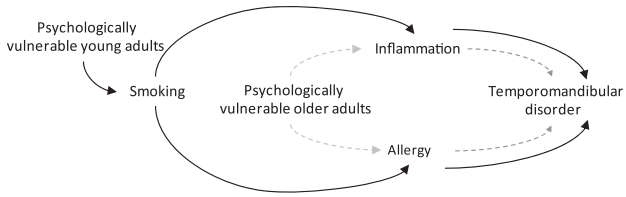

Figure 1. Directed acyclic graph depicting the pathway between smoking and temporomandibular disorder (TMD) in young (aged <30 years) and older adults defined as psychologically vulnerable (on the basis of psychological stress and trait anxiety scores and a history of antidepressant medication usage). The solid black line represents the proposed pathway for young adults. It passes through tobacco smoking to inflammation (cytokines IL-1Ra and MCP-1) and allergy (self-report of skin rashes, sinus trouble, allergies or hives, antihistamine use). The dashed gray line represents the causal pathway for older adults, which bypasses smoking. The graph assumes no unmeasured confounders given control for measured variables.

Because only a small number of participants were current smokers (19 cases and 9 controls), analyses of smoking combined former and current smokers into a single group labeled "ever smokers." To investigate allergic conditions, a composite variable was computed that summed the number of allergic conditions reported to yield a possible range from 0 (no allergic conditions) to 4 allergy conditions.

To test the second aim, odds of TMD was modeled through a sequence of 4 logistic regression models. Model 1 contained dichotomized smoking, dichotomized age, and their interaction term. Model 2 added the composite variable for allergy-related conditions. Model 3 added the cytokines; and Model 4 added the psychological variables. The purpose of this sequential model building was to quantify the extent to which each model attenuated the OR for smoking in each age stratum. This would determine whether the added variables act as mediators between smoking and TMD in early adulthood. To illustrate how adjustment for

covariates altered age-specific associations between smoking and TMD in this sample, the predicted proportion of TMD cases was calculated using parameter estimates from Model 1 (unadjusted) and Model 4 (fully adjusted), and the proportions were plotted. While the predicted probabilities are valid estimates for this study sample, they should not be interpreted as population estimates of prevalence because the overall proportion of cases was specified by the study design that purposefully selected approximately equal numbers of cases and controls.

To test the generalizability of an age effect on the smoking-TMD relationship, secondary analyses were undertaken using 2 population-based, nationally representative epidemiological surveys of adults in the US and Australia. These surveys were the 2007–2009 NHIS and the 2004–2006 National Survey of Adult Oral Health in the US and Australia.[56] Orofacial pain was self-reported in both surveys. Analyses were limited to females for the purpose of comparison with this study.

For the NHIS dataset, orofacial pain symptoms were evaluated with the question, "During the past three months, did you have facial ache or pain in the jaw muscles or the joint in front of the ear?" Response categories were Yes/No/Don't know. We estimated the prevalence of facial pain for various subpopulations that are defined by the cross-classification of age and smoking status. Since the collection of NHIS data is based on a multistage complex survey design and since our focus was confined to adults, we used the adult sampling weights to obtain unbiased estimates of facial pain prevalence and valid standard errors. Specifically, we combined data sets from 2007 to 2009 and divided the sampling weights by 3. Adults with missing facial pain response were omitted from analyses.

In the Australian national survey, prevalence of orofacial pain symptoms was determined from 7 screening questions that had been validated in a Canadian study.[34] Three questions asked about pain in the jaws, jaw joint, or pre-auricular region, and 4 questions addressed jaw function disturbance such as difficulty opening the mouth wide and freely. Responses of "yes" or "no" were recorded for each symptom in a self-completed questionnaire. The case definition required 1 or more affirmative response to the pain questions and at least 1 affirmative response to the jaw function disturbance questions. In data analysis, survey estimation commands corrected the standard errors of estimates by the Taylor series linearization method to take account of the complex survey design.

Data were analyzed in STATA I/C statistical software, v.11.1 IC (Stata Corporation, College Station, TX) and results reported for 133 cases and 166 controls with complete data.

Results

The mean age of cases was 36.4 years (95% CI = 34.3, 38.6) compared with 28.7 years for controls (95% = 27.1, 30.3). The older category of age was associated with greater odds of TMD (Table 1). One-third (37%) of cases reported having heard about the study through the UNC orofacial pain clinic; the remainder of cases and nearly all controls (98%) responded to advertisements and other methods of recruitment.

Compared to lifetime nonsmokers, current smokers had 3 times the odds of TMD (OR = 3.33, 95% CI 1.44, 7.70) while former smokers had twice the odds. Higher concentrations of IL-1Ra and MCP-1 were associated with higher odds of TMD in a dose-response relation. Likewise, perceived stress and trait anxiety were associated with TMD in a dose-response relation. All 4 allergy-related conditions were positively and strongly associated with TMD. When the allergy-related conditions were

Table 1. Selected Characteristics of Study Participants and Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Their Association With Temporomandibular Disorder (TMD) (n = 299 Females)

Characteristics	N (%)	OR for TMD	95% CI	P Value
Age in years				
18–29	178 (59.5)	Ref		
30–60	121 (40.5)	2.66	1.65, 4.27	<.001
Cigarette smoking status				
Current	28 (9.4)	3.33	1.44, 7.70	.005
Former	44 (14.7)	2.28	1.18, 4.40	.014
Never	227 (75.9)	Ref		
IL-1Ra (pg/mL)				
Low: 14.8–321.0	100 (33.4)	Ref		
Mod: 322.0–492.0	103 (34.5)	1.61	.90, 2.87	.110
High: 493.0–958.0	96 (32.1)	4.07	2.24, 7.38	<.001
MCP-1 (pg/mL)				
Low: 19.1–72.0	100 (33.4)	Ref		
Mod: 72.3–90.3	101 (33.8)	2.20	1.21, 3.98	.010
High: 90.8–142.0	98 (32.8)	5.12	2.79, 9.42	<.001
Psychological stress*				
Low	116 (38.8)	Ref		
Moderate	97 (32.4)	1.92	1.09, 3.38	.024
High	86 (28.8)	4.50	2.48, 8.18	<.001
Trait anxiety†				
Low	115 (38.5)	Ref		
Moderate	86 (28.8)	1.89	1.05, 3.38	.033
High	98 (32.8)	3.93	2.22, 6.96	<.001
Antidepressant medication				
No	203 (67.9)	Ref		
Yes	96 (32.1)	4.47	2.65, 7.52	<.001
Allergies or hives				
No	166 (55.5)	Ref		
Yes	133 (44.5)	3.03	1.89, 4.88	<.001
Skin rashes				
No	239 (79.9)	Ref		
Yes	60 (20.1)	3.79	2.06, 6.99	<.001
Sinus trouble				
No	194 (64.9)	Ref		
Yes	105 (35.1)	4.16	2.51, 6.89	<.001
Antihistamine medication				
No	104 (34.8)	Ref		
Yes	195 (65.2)	3.40	2.02, 5.72	<.001

Abbreviations: IL-1Ra, interleukin-1 receptor antagonist; MCP-1, monocyte chemoattractant protein-1.
*10-item Perceived Stress Scale.
†Spielberger Trait Anxiety Inventory.

Table 2. Relationship of Cigarette Smoking Exposure to TMD (Odds Ratio [OR], 95% Confidence Interval [CI]), Stratified by Age

	<30 Years		≥30 Years	
	OR	95% CI	OR	95% CI
Ever smoker	4.14	1.57, 11.35	1.23	.55, 2.78
Lifetime nonsmoker	Ref		Ref	

NOTE. Breslow-Day test of homogeneity, $P = .038$. 95% confidence interval is from the exact method for contingency tables.

summed, 16.7% of controls reported having all 4 conditions compared with 83.3% of TMD cases (Chi2, (4df) = 48.901, $P < 0.001$).

Examination of the stratum-specific ORs (Table 2) revealed that compared to lifetime nonsmokers, ever smokers had higher odds of TMD (OR = 4.14, 95% CI: 1.57, 11.35) in the age 18 to 29 stratum but the relationship was nonsignificant in the older stratum (OR = 1.23, 95% CI: .55, 2.78). The Breslow-Day test for homogeneity ($P = .038$) confirmed that the smoking effect differed significantly across age strata.

Greater concentrations of IL-1Ra and MCP-1, a lifetime history of skin rashes, or sinus trouble were associated with older age. Smoking was more frequent in older than younger people (Table 3). Among those who had ever smoked relative to never smoked, we observed higher concentrations of cytokines, greater perceived stress, and greater use of antidepressant medication, history of allergies, skin rashes, sinus trouble, and antihistamine use.

Mean IL-1Ra concentrations did not differ between subjects with and without history of allergy-related conditions (Table 4). However, mean MCP-1 levels were significantly higher in subjects with history of an allergy-related condition.

The effect modification of age on the smoking and TMD relationship presented in Model 1 (Table 5) was attenuated following adjustment for allergy-related conditions in Model 2. After additional adjustment for the cytokine mediators in Model 3 and the psychological variables in Model 4, the association between smoking and TMD in people aged <30 years was rendered nonsignificant (OR = 2.28, 95% CI = .81, 6.43). Furthermore, the interaction between smoking and age was statistically nonsignificant. This attenuation of the smoking effect is depicted in Figs 2A (unadjusted) and 2B (adjusted). Here, the unadjusted findings from Model 1 show a lack of overlap in 95% CIs for proportion of cases between smokers and nonsmokers in the young stratum (Fig 2A). However, 95% CIs overlap (Fig 2B) in this younger age group when the estimates are adjusted using the variables listed from Model 4 in Table 5.

Secondary analyses of the National Health Interview Survey (2007–2009) in the US and the National Survey of Adult Oral Health (2004–2006) in Australia confirmed a relationship between smoking and orofacial pain in females (Figs 3A and 3B). Again, the effect was strongest in younger versus older females, although the threshold age at which smoking ceased to have an effect appeared to be older in these national surveys than in our case-control study. The effect modification was significant in the US ($P < .001$) but not in Australia ($P = .811$).

Table 3. Unadjusted Associations of Explanatory Variables With Age Group and Cigarette Smoking Status (n = 299)

	Age Group (Row %)			Smoking Status (Row %)		
Characteristics	<30	≥30	P Value	Lifetime Nonsmoker	Ever Smoker	P Value
Age in years						
18–29	—	—		86.0	14.0	<.001
30–60	—	—		61.2	38.8	
Smoking status						
Lifetime nonsmoker	67.4	32.6	<.001	—	—	
Ever smoker	34.7	65.3		—	—	
IL-1Ra (pg/mL)						
14.8–321.0	74.0	26.0	<.001	82.2	17.8	.054
322.0–492.0	62.1	37.9		77.5	22.6	
493.0–958.0	41.7	58.3		67.7	32.3	
MCP-1 (pg/mL)						
19.1–72.0	79.0	21.0	<.001	84.0	16.0	.001
72.3–90.3	65.4	34.7		80.8	19.2	
90.8–142.0	33.7	66.3		63.0	37.0	
Psychological stress*						
Low	64.7	35.3	.350	82.8	17.2	.025
Moderate	55.7	44.3		76.3	23.7	
High	57.0	43.0		66.3	33.7	
Trait anxiety†						
Low	56.5	43.5	.208	77.4	22.6	.616
Moderate	67.4	32.6		77.9	22.1	
High	56.1	43.9		72.5	27.6	
Antidepressant medication						
No	69.0	31.0	<.001	82.8	17.2	<.001
Yes	39.6	60.4		61.5	38.5	
Allergies or hives						
No	60.8	39.2	.606	83.7	16.3	<.001
Yes	57.9	42.1		66.2	33.8	
Skin rashes						
No	62.3	37.7	.048	79.5	20.5	.004
Yes	48.3	51.7		61.7	38.3	
Sinus trouble						
No	65.0	35.1	.009	81.4	18.6	.002
Yes	49.5	50.5		65.7	34.3	
Antihistamine medication						
No	65.4	34.6	.132	83.7	16.4	.022
Yes	56.4	43.6		71.8	28.2	

Abbreviations: IL-1Ra, interleukin-1 receptor antagonist; MCP-1, monocyte chemoattractant protein-1.
*10-item Perceived Stress Scale.
†Spielberger Trait Anxiety Inventory.

Discussion

To the best of our knowledge, this is the first study to have examined the relationship between smoking and TMD in age-specific strata. The key finding was that a history of cigarette smoking was strongly associated with TMD, but only among young adults. Specifically in this case-control study, smokers aged 18 to 29 years had 4

Table 4. Mean Concentration (95% Confidence Interval) of 2 Cytokines for Each Measured Allergy-Related Condition

		Interleukin-1 Receptor Antagonist				*Monocyte Chemotactic Protein-1*		
		Mean pg/mL	*95% CI*	*P Value*		*Mean pg/mL*	*95% CI*	*P Value*
Allergies or hives	No	464.3	426.0, 502.7	.950	No	80.2	76.7, 83.8	.003
	Yes	466.1	424.9, 507.4		Yes	88.5	84.2, 92.9	
Skin rashes	No	455.0	424.2, 485.8	.155	No	82.0	79.0, 84.9	.006
	Yes	505.5	439.1, 571.9		Yes	91.7	84.5, 99.0	
Sinus trouble	No	444.9	409.8, 479.9	.052	No	80.3	77.1, 83.5	.000
	Yes	502.6	456.5, 548.7		Yes	90.6	85.5, 95.7	
Antihistamine medication	No	438.6	391.8, 485.4	.173	No	76.6	72.7, 80.5	.000
	Yes	479.3	444.4, 514.2		Yes	87.8	84.2, 91.4	

times the odds of having TMD when compared with 18 to 29 year old nonsmokers. In adults aged 30 to 60 years, TMD case status had no association with smoking status.

The second major contribution of this study is the first reported finding of an association between any history of allergy-related conditions and TMD. We showed that the effect of smoking on TMD in young adults was attenuated 20% after adjustment for 4 allergy-related conditions. The effect was further attenuated 45% to statistical nonsignificance after additional adjustment for cytokines and psychological profile.

Our finding that age modified the effect of smoking on TMD is in accordance with previous studies of low back pain. Pooled estimates from a meta-analysis showed that the association between current smoking and incident low back pain was stronger in adolescence (OR = 1.82, 95% CI = 1.12, 2.33) than in adults (OR = 1.16; 95% CI = 1.02, 1.32).[54]

Our results also build on evidence of an association between allergy and chronic pain. In the third US National Health and Nutrition Examination Survey, adults aged 20 to 39 with any history of asthma, hay fever, and other allergies were 50% more likely to report low back pain than 20 to 39 year olds without allergies.[24] Elsewhere, a case-control study of vulvodynia showed that odds of the condition were elevated between 2.0-fold to 2.5-fold in women with a history of any of seasonal allergies, reactions to insect bites, or hives. In that study, the self-reported allergy conditions preceded the first report of vulvar pain.[21] The authors suggested that an altered immune-inflammatory response to environmentally induced allergic reactions was a possible explanatory mechanism. And in the 51,383 Head-Hunt Study participants, headache was 1.5 times more likely among those with asthma, asthma related symptoms, hay fever, and chronic bronchitis.[2] Based on their findings from a population-based study, Hurwitz and Morgenstern[24] hypothesized that hypersensitivity reactions evoke dysfunctional reactivity of the hypothalamic–pituitary–adrenal axis to psychological stress with consequences for chronic pain.

We found that an inflammatory response and allergic conditions had independent effects on odds of TMD in young adult smokers (Model 3, Table 4). In young adults, adjustment for inflammation as indexed by 2 cytokines,

Table 5. Odds Ratios (ORs) and 95% Confidence Interval (CI) From a Logistic Regression Model Testing for the Effect of Ever Smoking Compared With Lifetime Nonsmoking on TMD

	*Model 1**		*Model 2†*		*Model 3‡*		*Model 4§*	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Effect of smoking in adults aged <30 years	4.14	1.70, 10.04	3.14	1.20, 8.22	2.69	1.00, 7.27	2.28	.81, 6.43
Effect of smoking in adults aged ≥30 years	1.23	.58, 2.59	.86	.38, 1.93	.74	.32, 1.76	.66	.26, 1.68
Sum of allergy-related conditions			1.90	1.54, 2.35	1.88	1.50, 2.35	1.88	1.47, 2.39
Interleukin-1 receptor antagonist					1.57	1.16, 2.12	1.50	1.08, 2.08
Monocyte chemotactic protein-1					1.38	.99, 1.92	1.28	.90, 1.83
Perceived stress score							1.33	.93, 1.89
Trait anxiety score							1.67	1.18, 2.37
History of antidepressant medication use							1.84	.97, 3.47
¶*P* value for smoking × age interaction		.040		.043		.054		.081

NOTE. The 95% CI is from Wald's estimate from the logistic regression model.

*Model 1 reports the effect of smoking on odds of TMD among adults aged <30 years and adults aged ≥30 years, along with the *P*-value for the interaction term.

†Model 2 additionally adjusts for the sum of allergy conditions.

‡Model 3 additionally adjusts for the 2 cytokines.

§Model 4 additionally adjusts for psychological profile.

¶The *P* value for the interaction term (smoking × age group) in each of Models 1–4 appears below the table and is taken from the likelihood ratio test.

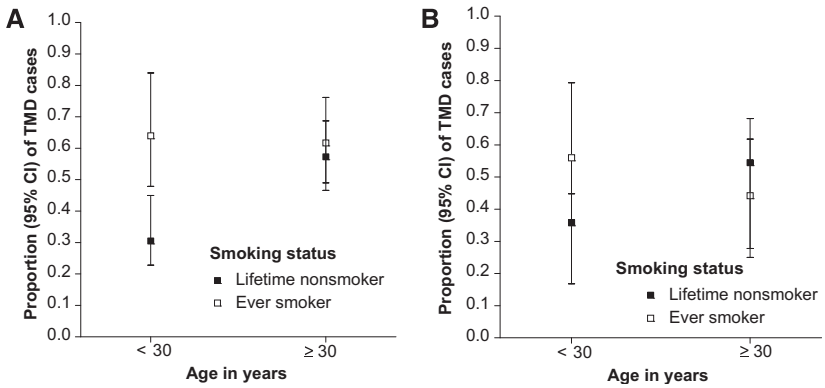

Figure 2. **(A)** Illustration of interaction between age and smoking with no adjustment for covariates. Parameter estimates from Model 1 of Table 5 were used to calculate predicted proportions of TMD cases within this sample of 299 people in Chapel Hill, NC, USA. (*P* value for interaction = .039.) **(B)** Illustration of interaction between age and smoking with adjustment for covariates shown in Model 4 of Table 5: sum of allergies, Interleukin-1 receptor antagonist and monocyte chemotactic protein-1 concentrations, perceived psychological stress, trait anxiety, and lifetime history of antidepressant medication usage. Parameter estimates from Model 5 of Table 5 were used to calculate predicted proportions of TMD cases within this case-control sample of 299 people in Chapel Hill, NC, USA. (*P* value for interaction = .118.)

a history of allergy-related conditions, and psychological profile fully accounted for the effect of smoking on TMD.

In line with results from previous clinical studies,[16,45,46] we found that levels of the cytokines MCP-1 and IL-1Ra were associated with increased odds of TMD. MCP-1 is a chemotactic cytokine expressed in a variety of cell types, including leukocytes in the periphery[69] and neurons in the central nervous system.[66] IL-1Ra is member of the interleukin-1 cytokine family that is largely expressed in macrophages and epithelial cells[22] as well as in brain.[32] IL-1Ra binds the proinflammatory cytokines interleukin-1α and interleukin-1β, thus inhibiting their activity.[14] Studies in animal models demonstrate that expression of both MCP-1 and IL-1Ra is strongly upregulated following injury or inflammation.[25,37,63,66] A mechanistic role for MCP-1 in chronic pain is supported by recent studies showing that MCP-1 is able to excite sensory neurons.[66] While a mechanistic role for the anti-inflammatory cytokine IL-1Ra in chronic pain is less clear, its synthesis and release is stimulated by the proinflammatory cytokine IL-1. Kinetic studies have demonstrated that the balance between IL-1Ra and IL-1 production is dependent upon the phase of the inflammatory response.[58] Thus, IL-1Ra may be viewed as a marker of IL-1, which is deemed a prototypical proinflammatory cytokine well known for its ability to activate and sensitize nociceptors[28] as well as drive hypothalamus-pituitary-adrenal-related stress responses.[19] Collectively, these results suggest that MCP-1 and IL-1Ra/IL-1 inflammatory pathways contribute to TMD.

One explanation for why the smoking and TMD relationship was found only in young adults is that 1 or more of the explanatory factors operate differently between young and older individuals. Support of this supposition comes from a study of the Swiss adult population, where odds of being atopic decreased by 21.0% on average with every 10-year increase in age.[67]

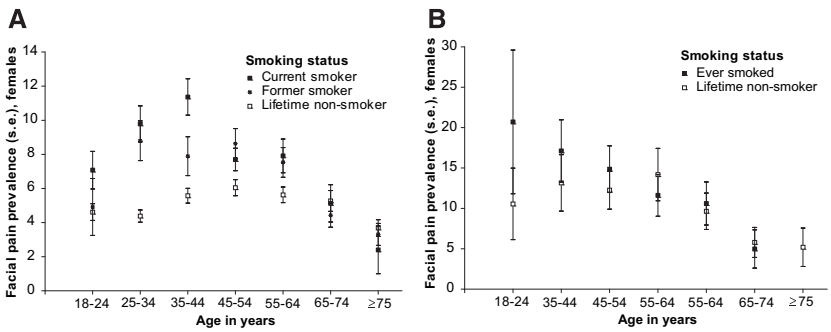

Figure 3. **(A)** Relationship between smoking status and facial pain across age strata among females living in the US. Prevalence is the percentage of subjects who answered affirmatively to the question, "During the past three months, did you have facial ache or pain in the jaw muscles or the joint in front of the ear?" Data are nationally representative estimates for female participants aged 18 years and older in the National Health Interview Survey 2007–2009 (n = 40,337). *P* value for the age*smoking interaction <.001. **(B)** Relationship between smoking status and orofacial pain symptoms across age strata among females living in Australia. Prevalence of orofacial pain symptoms was assessed in a self-administered questionnaire with 7 screening questions. Three questions asked about pain in the jaws, jaw joint or preauricular region and 4 questions addressed jaw function disturbance such as difficulty opening the mouth wide and freely. The case definition used in this study required 1 or more affirmative response to the 3 pain questions and at least 1 affirmative response to the 4 jaw function disturbance questions. Data are nationally representative estimates for females in the National Survey of Adult Oral Health 2004–2006 (n = 2,461). *P* value for the age*smoking interaction = .8109.

Little is known about exposure to tobacco smoke and IL-1Ra and MCP-1 concentrations in humans. One report of a positive association between smoking and plasma concentration of IL-1Ra in healthy subjects[13] conflicted with the finding of higher IL-1ra concentrations in nonsmokers than smokers.[39] In the periodontal literature, a comparison of gingival crevice fluid IL-1ra concentrations in smokers and nonsmokers found smokers had significantly higher IL-1ra concentrations in healthy periodontal sites than nonsmokers. However, in subjects with deep bleeding periodontal sites, smokers had significantly lower IL-1ra concentrations than nonsmokers.[50] A recent experimental study showed that cigarette smoking and nicotine significantly induced MCP-1 expression in pancreatic ductal adenocarcinoma cells.[30] In humans, MCP-1 concentration was significantly elevated in healthy smokers compared with healthy former smokers.[9]

The active ingredients in tobacco smoke that alter pain perception are not fully understood, but it is generally assumed that nicotine is the primary substance that modifies pain perception. The effects of nicotine on pain perception are complex. (For a review, see Shi et al.[53]) Experimental studies that use brief noxious stimuli following the ingestion of nicotine provide evidence that nicotine has analgesic properties. Chronic exposure to tobacco smoke leads to changes in pain perception such that smokers deprived of nicotine show greater sensitivity to pain-evoking stimuli.[42,55] In the postoperative pain setting, the administration of nicotine produces analgesia in nicotine naïve participants and produces little or no analgesic effect in smokers.[20,61] The chronic exposure to nicotine can induce biological states that produce hyperalgesia and dependency similar to that seen with the chronic exposure to opioids when nicotine levels are acutely reduced. We speculate that the diminished effect of smoking at ages older than 30 results from a diminished effect of smoking on the production of proinflammatory substances, which diminishes the likelihood of developing postnicotine exposure hyperalgesic states.

The risk of chronic TMD in young former or current smokers was more than 4 times as high compared with older adults who had never smoked. Simultaneous adjustment for psychological profile, cytokines, and allergy conditions approximately halved this effect and rendered the effect of smoking in young adults statistically nonsignificant, showing these to be explanatory factors for excess risk. Nonetheless, in the fully adjusted model, allergy conditions, interleukin-1 receptor antagonist, and trait anxiety score remained significantly associated with TMD in young adults showing these to be independent risk indicators beyond the effects of tobacco. These findings highlight noteworthy age-related differences. For instance, ever smokers were twice as likely as lifetime nonsmokers to perceive high psychological distress but this effect was evident only in young adults. In addition, ever smokers were twice as likely as nonsmokers to have a history of allergy conditions and to use antihistamines, and again these effects were more pronounced in young versus older adults. Furthermore, ever smokers had 4 times the odds of chronic TMD than lifetime nonsmokers, but only among young adults. This consistency of evidence suggests that the relationships between smoking, psychological stress, allergy, and TMD risk differ on the basis of age; indeed, these case-control results formally confirmed that age significantly modified the smoking and TMD relationship. Of these risk indicators in young adults, smoking may be the most easily modified and smoking cessation may have long-term benefits for inflammatory function, psychological health, and conditions such as allergic rhinitis[33] and urticaria.[31] However, it is not known whether smoking cessation might negate any analgesic effects of nicotine on TMD pain.

Strengths of this study were use of the well-validated Research Diagnostic Criteria for determining TMD case status and the diverse dataset that included psychological instruments and cytokines. Another major strength was that we were able to reproduce our findings in 2 large national surveys with representative samples of female adults. The self-reported nature of TMD symptoms in these national surveys inevitably results in over- or under-estimation of TMD prevalence. Despite this misclassification, the relationship was sufficiently strong to replicate our case-control findings, which strengthened this study's external validity.

Nonetheless, several possible limitations should be considered when interpreting our study findings. This case-control study design and the cross-sectional design of the national survey did not establish a temporal sequence between smoking and onset of TMD. It is plausible that some people might have begun to smoke as a consequence of developing TMD symptoms. Moreover, anxiety and psychological stress may make smoking cessation efforts more difficult, as smokers with TMD may rely on tobacco to elevate mood and relieve comorbid depressive symptoms. This "reverse causation" might account for some of the observed association between smoking and TMD. However, the evidence from prospective cohort studies of other chronic pain conditions suggests that the predominant effect is in the expected causal direction.[54]

The degree to which TMD cases and controls were misclassified during examination is unrelated to the exposures of interest in this study (tobacco use, psychological profile, cytokines, allergy conditions). Therefore, any misclassification of case status would produce nondifferential bias, which does not pose a concern to the strength or direction of associations reported in this study. The only adverse impact of misclassification is increased variance (ie, widened 95% CIs) around our estimates. A related concern with case-control studies is whether controls are selected from the same source population that gives rise to the cases.[46] Yet, most controls heard about the study through the same methods reported by nearly all cases, suggesting that the majority of cases and controls came from the community at large.

Due to the relatively small number of current smokers, we limited the analysis of effect modification to a binary exposure measure. Hence, the risk of TMD associated with smoking cannot be attributed solely to elevated concentrations of nicotine or other substances inhaled

in cigarette smoke because there is no such elevation in former smokers. Yet, the bivariate findings in Table 1 show that the OR for TMD is greater in current smokers than in former smokers. This suggests that exposure to tobacco itself confers an additional risk for TMD, in addition to behavioral characteristics or other antecedents of smoking behavior. The small number of current smokers in this study reduces precision of estimates, making interpretation of the strength of the smoking and TMD relationship more difficult.

Finally, our measures of allergy-related conditions were taken by convenience from the medical history questionnaire and were not planned in advance. However, in future analyses, we will examine IgE levels in stored blood. We used history of antidepressant medication as a marker of psychological profile. This may introduce misclassification as chronic pain sufferers are sometimes prescribed antidepressants for pain control as well as fatigue or sleep disturbances.

This study has shed light on a complex interplay of allergy, cytokines, and smoking in a case-control study of chronic TMD. Understanding the mechanisms underlying these relationships can best be addressed in large prospective studies of chronic TMD pain.

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