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Title: The risk of temporomandibular disorder in patients with depression: A population-based cohort study

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Running title: Depression and temporomandibular disorder

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ABSTRACT

Objective: This study used a population-based retrospective cohort design to examine whether depression is a risk factor of temporomandibular disorder (TMD). *Methods:* From a universal insurance database, we identified 7,587 patients newly diagnosed individuals with depression in 2000 and 2001. A total of 30,197 comparison subjects were randomly selected from a non-depression cohort. Both groups were followed until the end of 2008 to measure the incidence of TMD. *Results:* The incidence of TMD was 2.65 times higher in the depression cohort than in the non-depression cohort (6.16 vs. 2.32 per 1,000 person-years). The multivariate Cox proportional hazard regression analysis measured hazard ratio (HR) of TMD for the depression cohort was 2.21 (95% confidence interval (CI) 1.83 - 2.66), after controlling for sociodemographic factors and other psychiatric co-morbidities. Females had higher risk to develop TMD than males (HR 1.61, 95% CI 1.36 - 1.92 for females without depression; HR 3.54, 95% CI 2.81- 4.45 for females with depression). *Conclusion:* This study demonstrates that patients with depression are at an elevated risk of developing TMD.

Key word: depression; hazard ratio; population-based study; retrospective cohort design; temporomandibular disorder

Introduction

Temporomandibular disorders (TMD) are quite common among the general population, with a life-time prevalence of up to 93% in an epidemiological study (1). These disorders include complaints of the temporomandibular system, consisting of the temporomandibular joint (TMJ) and the associated neuromuscular system (2). A national survey among Dutch adults showed that 21.5% of the adult population had temporomandibular dysfunction but only 15% of those sought treatment (3). Most patients seek treatment because of TMD pain (4), in the temporomandibular region or involving the eyes, face, shoulder, neck, back and head (5, 6). Patients with TMD have a decreased quality of life due to orofacial pain, particularly for patients with severe TMD (7). The etiology of TMD has been regarded as multifactorial. Dworkin and Leresche (8) designed a two-axis diagnostic scheme to evaluate the patient's condition. The psychological variables were assessed with Axis II, emphasizing the relevant factors of TMD. Gracely (9) reported that individuals can have different levels of pain perception, which can be influenced by emotional factors. Hotopf et al. have noted the psychiatric disorder may promote 40% cases of multiple symptoms including arthritis, rheumatism and headache (10). Magni et al. found in a prospective study that the relationship between depressive systems and chronic musculoskeletal pain may operate in both directions (11).

Depressive symptoms are significantly related to the severity of pain in the TMD patients (12). Moreover, TMD pain and depression are often coexistent (13-15). Macfarlane et al. found in a case-control study that patients with pain dysfunction syndrome had high levels of psychological distress (15). Depression has now become a global burden disorder and the fourth leading cause of disability worldwide (16). Major depressive disorder presents in 5% to 10% of patients seeking primary care (17). The prevalence of depression may well be higher among the general population because some people may have depressive disorders which do not fully meet the diagnostic criteria for major depressive disorder of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

Among studies on the relationship between depressive systems and pain, there is a convergent association between depression and TMD pain, especially in the chronic pain group (2). Several studies on the relationship between depression and TMD have evaluated the mood condition among TMD patients (13-18). However, those studies were unable to answer whether depression is a source or consequence of TMD pain because of case-control and cross-sectional designs.

Slade et al. have recently conducted a prospective cohort study of 238 healthy female volunteers aged 18-34 years investigating the psychological influence on the risk of TMD. They found that depression, perceived stress, and mood are associated

with pain sensitivity with a 2- to 3-fold increase in the risk of TMD ($P < 0.05$) (19). But, this study was limited to a small sample size with only one gender and a short follow-up period. We therefore designed a population-based cohort study with higher statistical power to detect the development of TMD among the depressive patients. Not all patients with TMD complaints visit the dentists. We hypothesized that patients with depressive disorder would have a higher risk of TMD complaints, leading to a greater likelihood to seek dental services than the general population. To gain a better understanding of the relationship between depression and TMD, we conducted a population-based retrospective cohort study using claims data from the universal insurance program. The incidences of dentist-diagnosed TMD were compared between patients with depression and without depression.

Materials and methods

Data resources

This study used the reimbursement claims data of The National Health Insurance program of Taiwan that reformed in March 1995 from 13 insurance systems. The insurance program has covered more than 96% of the 23 million population and contracted with more than 90% of hospitals and clinics in Taiwan since 1996 (20, 21). The Department of Health National Health Research Institute (NHIR) managed all medical claims data reported from the contracted health care facilities. With approval from NHRI, we were able to use a representative sub-datasets of one million insured persons randomly selected from all beneficiaries enrolled in the insurance program (21). This data set consisted of the registry of medical facilities, details of inpatient orders, ambulatory care, dental services and prescriptions linked with scrambled patient identification. Because all patient identifications were surrogated, this study was conducted with patients privacy secured and with a waiver from the institutional review board.

Study sample

We used the coding of the International Classification of Disease Diagnoses, Ninth Revision of Clinical Modification (ICD-9-CM) to identify 7,587 patients with depression (ICD-9-CM 296.2, 296.3, 300.4 and 311) newly diagnosed in 2000 and

2001 as the study cohort. In order to ensure the validity of the diagnosis, only new patients with at least three visits for depression care during the follow-up period after the index date were eligible for inclusion. For each case with depression identified, we used simple random sampling methods to select 4 persons without depression in the same period for the comparison cohort (N = 30,348). We excluded 102 subjects from the depressive cohort and 151 subjects from the comparison cohort. They were excluded because of a history of TMD diagnosis by the baseline index date (defined as the date the subject identified and selected) or missing information on age or sex. Our final sample includes 7,485 subjects in the depression cohort and 30,197 subjects in the non-depression cohort.

Socio-demographic variables and co-morbidities

The socio-demographic variables, including sex, age, occupation, employment category, residential area and monthly income, were available. The age of each study subject was measured by the difference between the index date and the date of birth. Using the National Statistics of Regional Standard Classification (22), we grouped all study subjects into four geographic areas (North, Central, South, and East and off Islands) and three urbanization levels (low, medium and high).

We considered anxiety state (ICD-9-CM 300.00), panic disorder (ICD-9-CM 300.01), generalized anxiety disorder (ICD-9-CM 300.02), obsessive-compulsive

disorders (ICD-9-CM 300.03) and psychiatric diseases (ICD-9-CM 290-319; except the main effect in this study – depression) as other psychiatric co-morbidities.

Study end-point

We linked study subjects to the inpatient and outpatient claims data of dental clinics to identify the newly diagnosed cases of TMD (ICD-9-CM 524.6) as the outcome of the study, using the scrambled patient identification number. We calculated person-years for each study subject until TMD was diagnosed, or until December 31, 2008 for those uncensored, or the censoring date because of death, emigration, termination of insurance, or loss to follow-up.

Statistical Analysis

We compared the distributions of categorical socio-demographic variables and co-morbidities between depression patients and non-depression patients using the Chi-square test. We also calculated the incidence density with person-years for these variables in the study cohort and comparison cohort. The rate ratio of TMD was calculated by each variable.

Cox's proportional hazard regression analysis was used to assess the risk of TMD associated with depression, adjusting for variables that were significantly related to depression from the prior Chi-square analyses. Hazard ratio (HR) and 95% confidence interval (CI) were calculated in the model. The sex and age stratification

analyses for the risk of TMD in association with depression were also examined using Cox's proportional hazard regression analysis.

All analyses were performed with SAS statistical software (version 9.1 for Windows; SAS Institute, Inc., Cary, NC, USA). Significance level was set to 0.05.

Results

Table 1 compares socio-demographic characteristics between the depression cohort and the non-depression comparison cohort. There were more females in the depression cohort than in the comparison cohort (60.6% vs. 48.1%). The depression cohort was also older, less white collar employment and had middle income.

Table 2 presents the incidence and crude hazard ratios of TMD by socio-demographic status. The overall incidence rate of TMD in the depression cohort was 2.65 times higher than that in the comparison cohort (6.16 vs. 2.32 per 1,000 person-years). The crude hazard ratios measured by categorized socio-demographic status ranged from 2.35 to 3.64, with the depression cohort of those more than 60 years of age having the highest hazard ratio. Older men in the non-depression cohort had the lowest risk of having TMD.

The multivariate Cox proportional regression analysis showed that the risk of TMD was significantly greater in the depression cohort than in the non- depression cohort (HR 2.21, 95% CI 1.83 - 2.66) after controlling for covariates (Table 3).

Table 4 shows that females were at greater HRs to develop TMD than males. Compared with males without depression, females without depression had a HR of 1.61 (95% CI 1.36 - 1.92) and females with depression had the HR increased to 3.54 (95% CI 2.81 - 4.45). Compared with the non-depression cohort ≧ 60 years of age,

the HRs of TMD increased in patients with depression, and in particular, the highest risk was noted in depression patients ≧ 60 years of age (HR 3.22, 95% CI 2.20 – 4.73).

Discussion

Studies investigating whether the risk of TMD is higher in patients with depression using cohort designs are limited. Our study aimed to explore whether depression is a risk factor related to subsequent TMD problems. We measured the incidence of dentist-diagnosed TMD in depressive patients compared with that of a non-depression cohort, using a population-based retrospective cohort study design. This approach overcomes the major limitation of cross-sectional and case-control study designs by providing incidence information.

TMD disorders have a high degree of comorbidity with depression (13, 14, 23). Previous studies on TMD and depression have been unclear as to whether depression occurred prior to the onset of TMD or as a consequence of it. Slade et al. (19) found that depression was one of the predicted risk factors of the first-onset of TMD among healthy females with a small sample size. These studies collected information on depression based on self-reported questionnaires, which is different from clinically verified depressive disorder. Our population-based study on the association between depression and subsequent TMD found that there is a 2.21 to 2.64-fold higher risk of a diagnosis of TMD among patients with a physician diagnosed depressive disorder, compared with the control group within an 8-year follow-up period, after adjusting for demographic characteristics and comorbid anxiety disorders.

TMD are a heterogeneous group of disorders affecting temporomandibular joint, the masticatory muscles, or both, and might present with joint sounds or severe dysfunction. The most common symptom was pain and most patients sought help because of it. TMD has also been a chronic pain condition in many cases (24). Not only is depression prevalent among patients with chronic TMD-related pain conditions, but patients with TMD and comorbid psychological factors had a poor response to dental treatment alone (25). This could be explained by depression possibly increasing pain-perception thresholds (26, 27) and affecting the expression of TMD signs and symptoms (28). Therefore, depressive patients might have more TMD problems, which lead them to seek dental services.

In our study, the incidence of TMD among the depression group was 4.5% in the 8-year follow-up, which is higher than the incidence in a previous study (3.1%) for a Dutch adult population (3). This reflects a higher risk of TMD problems among the depressive population. Our definition of TMD was based the information from patients who had visited a dental clinics rather than from case-control study or general cross-sectional survey among the general population. Therefore, in our study, the difference in TMD incidences between the depressive patients and the general population without depression is more valid. However, our diagnosis of depression included both minor and major depressive disorders (ICD 296.2, ICD 296.3, ICD

300.4, and ICD 311), and may have identified subjects with a broader spectrum of depressive disorders. It still is likely that depression is underestimated in the general population, because not all patients seek help from physicians when depressed.

Our study was compatible with previous reports that found that females had a higher rate of TMD than males (29-31). Elderly depressive patients are also found to have a higher risk of TMD, which lead them to seek dental services. However, the non-depressive elderly had the least risk of TMD. Further research to evaluate TMD among geriatric patients is needed.

There are some limitations to interpret the results of our study. First of all, the diagnoses of depression, TMD and comobidity relied on claims data, so there may be missing information made under a standardized diagnostic process. Obtaining this kind of information for a large population-based cohort study would be extremely difficult. But our strength in this study was that working from a clinical diagnosis made it possible to avoid the limitations of self-reported questionnaires. To increase the diagnostic validity, all cases were diagnosed with depressive disorder at least three times, which provided a reliable cohort assessment. Second, some studies found that a myofascial type of TMD have a higher comorbidity of depression and required health care more frequently (32, 33). But, we did not have the type and severity of TMD, and the stress and mood status among our study cohort. We, therefore, could not further

evaluate the impact among them. Even though, we found a higher risk of developing TMD among the depressive patients than the general population, which supports the temporal relationship between depressive disorder and TMD. In addition, we could not definitively identify the real onset time of depression from the database. However, we still could hypothesis that life-time depression is one risk factor of TMD.

In conclusion, a temporal relationship between depression and TMD seems to exist. These results imply that that dentists involved in the management of TMD need to be aware of the co-morbidity of depression in these patients. Further research on the clinical efficacy of decreasing dental services for TMD after the treatment of depression is needed.

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References

1. Carlsson CR. Epidemiology and treatment need for temporomandibular disorders. J Orofac Pain 1999;13:232-237.
2. Kafas P, Leeson R. Assessment of pain in temporomandibular disorders: the bio-psychosocial complexity. Int J Oral Maxillofac Surg 2006;35:145-149.
3. De Kanter RJ, Käyser AF, Battistuzzi PG, Truin GJ, Van t'Hof MA. Demand and need for treatment of craniomandibular dysfunction in the Dutch adult population. J Dent Res 1992;71:1607-1612.
4. Dworkin SF, Huggins KH, LeResche L, Von Korff M, Howard J, Truelove E, et al. Epidemiology of signs and symptoms in temporomandibular disorders: clinical signs in cases and controls. J Am Dent Assoc 1990;120:273-281.
5. Pollmann L. Sounds produced by the mandibular joint in a sample of healthy workers. J Orofac Pain 1993;7:359-361.
6. Kafas P, Chiotaki N, Stavrianos Ch, Stavrianou I. Temporomandibular joint pain: diagnostic characteristics of chronicity. J Med Sci 2007;7:1088-1092.
7. Barros Vde M, Seraidarian PI, Côrtes MI, de Paula LV. The impact of orofacial pain on the quality of life of patients with temporomandibular disorder. J Orofac Pain 2009;23:28-37.
8. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular

disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:302-355.

9. Gracely RH. Studies of pain in human subjects. In: Wall PD, Melzack R, editors. Textbook of pain. 4th ed. London, UK: Churchill Livingstone, 1999; 385-408.

10. Hotopf M, Mayou R, Wadsworth M, Wessely S. Temporal relationships between physical symptoms and psychiatric disorder. Results from a national birth cohort. Br-J-Psychiatry. 1998; 173: 255-61

11. Magni G, Moreschi C, Rigatti-Luchini S, Merskey H. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. Pain 1994; 56: 289-297

12. Auerbach SM, Laskin DM, Frantsve LM, Orr T. Depression, pain, exposure to stressful life events, and long-term outcomes in temporomandibular disorder patients. J Oral Maxillofac Surg 2001;59:628–633.

13. Korszun A, Hinderstein B, Wong M. Comorbidity of depression with chronic facial pain and temporomandibular disorders. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;82:496–500.

14. Vimpari SS, Knuuttila ML, Sakki TK, Kivela SL. Depressive symptoms associated with symptoms of the temporomandibular joint pain and dysfunction syndrome. Psychosom Med 1995;57:439–444.

15. Macfarlane TV, Gray R, Kincey J, Worthington HV. Factors associated with the temporomandibular disorder, pain dysfunction syndrome (PDS): Manchester case-control study. Oral Diseases 2001;7: 321-330.

16. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997;349:1498-1504.

17. Katon W, Schulberg H. Epidemiology of depression in primary care. Gen Hosp Psychiatry 1992;14:237-247.

18. Macfarlane TV, Kincey J, Worthington HV. The association between psychological factors and oro-facial pain: a community-based study. European Journal of Pain 6: 427-434 (2002).

19. Slade GD, Diatchenko L, Bhalang K, Sigurdsson A, Fillingim RB, Belfer I, et al. Influence of psychological factors on risk of temporomandibular disorders. J Dent Res 2007;86:1120-1125.

20. Lu JF, Hsiao WC. Does universal health insurance make health care unaffordable? Lessons from Taiwan. Health Aff (Millwood) 2003;22:77-88.

21. National Health Insurance Research Database, Taiwan. http://www.nhri.org.tw/nhird/en/index.htm

22. Liu CY, Hung YT, Chuang YL, Chen YJ, Weng WS, Liu JS, Liang KY. Incorporating development stratification of Taiwan townships into sampling

design of large scale health interview survey. J Health Manag.2006;14:1 –22.

23. Mongini F, Ciccone G, Ceccarelli M, Baldi I, Ferrero L. Muscle tenderness in different types of facial pain and its relation to anxiety and depression: A cross-sectional study on 649 patients. Pain 2007;131:106-111.

24. Dworkin SF, Massoth DL. Temporomandibular disorders and chronic pain: disease or illness? J Prosthet Dent 1994;72:29-38.

25. Turner JA, Dworkin SF. Screening for psychosocial risk factors in patients with chronic orofacial pain: recent advances. J Am Dent Assoc 2004;135:1119-1125.

26. Dickens C, McGowan L, Dale S. Impact of depression on experimental pain perception: a systematic review of the literature with meta-analysis. Psychosom Med 2003;65:369-375.

27. Lautenbacher S, Spernal J, Schreiber W, Krieg JC. Relationship between clinical pain complaints and pain sensitivity in patients with depression and panic disorder. Psychosom Med 1999;61:822-827.

28. Dworkin SF, Sherman J, Mancl L, Ohrbach R, LeResche L, Truelove E. Reliability, validity, and clinical utility of the research diagnostic criteria for Temporomandibular Disorders Axis II Scales: depression, non-specific physical symptoms, and graded chronic pain. J Orofac Pain 2002;16:207-220.

29. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic

pain. Pain 1992;50:133-149.

30. Locker D, Leake JL, Hamilton M, Hicks T, Lee J, Main PA. The oral health status of older adults in four Ontario communities. J Can Dent Assoc 1991;57:727-732.

31. Macfarlane TV, Blinkhorn AS, Davies RM, Kincey J, Worthington HV. Oro-facial pain in the community: prevalence and associated impact. Community Dent Oral Epidemiol 2002;30:52-60.

32. Lindroth J, Schmidt JE, Carlson CR. A comparison between masticatory muscle pain patients and intracapsular pain patients on behavioral and psychosocial domains. J Orofac Pain 2002;16:277–283.

33. Schmitter M, Kress B, Ohlmann B, Henningsen P, Rammelsberg P. Psychosocial behaviour and health care utilization in patients suffering from temporomandibular disorders diagnosed on the basis of clinical findings and MRI examination. Eur J Pain 2005;9:243-250.

TABLES

Table 1. Comparisons in demographic characteristics between patients with and without depression at baseline in 2000-2001

Variables	Depression*			
	No ‡ N = 30197		Yes N = 7485	
	n	(%)	n	(%)
Sex				
Female	14529	(48.1)	4536	(60.6)
Male	15668	(51.9)	2949	(39.4)
Age, years				< 0.001
< 20	9240	(30.5)	363	(4.9)
20-39	10558	(35.0)	2307	(30.8)
40-59	6995	(23.2)	2672	(35.7)
≥ 60	3404	(11.3)	2143	(28.6)
Occupation				
White collar	16977	(56.2)	3440	(46.0)
Blue collar	9412	(31.2)	2675	(35.7)
Others†	3808	(12.6)	1370	(18.3)
Urbanization‡				
Low	3627	(12.1)	1007	(13.5)
Moderate	6337	(21.1)	1458	(19.6)
High	20092	(66.9)	4978	(66.9)
Region				
North	14215	(47.0)	3148	(42.1)
Central	6162	(20.4)	1534	(20.5)
South	7535	(25.0)	2104	(28.1)
East and Island	2284	(7.6)	699	(9.3)
Income				
<15,000	15164	(50.2)	3138	(41.9)
15,000-29,999	11257	(37.3)	3505	(46.8)
≥30,000	3776	(12.5)	842	(11.3)

Depression: ICD-9 codes:296.2, 296.3, 300.4 and 311

*Chi-square test, all p-values are less than 0.001

† Unemployed: retired and low income

‡ Urbanization: low = 1st and 2nd lowest quartile of population density, moderate = 3rd quartile of population density, high = 4th highest quartile of population density

Table 2. Comparisons of incidence of temporomandibular disorder between cohorts with and without depression by sociodemographic factor

Variables	Depression						
	No			Yes			
	Cases	Person-years	Rate†	Cases	Person-years	Rate†	Crude HR (95% CI)
All	533	229485	2.32	338	54872	6.16	2.64 (2.30-3.03)
Sex							
Female	319	110865	2.88	241	33785	7.13	2.49 (2.10-2.95)
Male	214	118619	1.80	97	21087	4.60	2.49 (1.95-3.18)
Age, years							
< 20	149	72808	2.05	15	2787	5.38	2.78 (1.63-4.73)
20-39	207	79699	2.60	109	17558	6.21	2.36 (1.86-2.99)
40-59	137	53806	2.55	123	20276	6.07	2.35 (1.84-3.01)
≥ 60	40	23172	1.73	91	14252	6.39	3.64 (2.50-5.30)
Occupation							
White collar	313	129644	2.41	172	25691	6.69	2.70 (2.23-3.26)
Blue collar	163	71273	2.29	105	19628	5.35	2.42 (1.89-3.10)
Others	57	28569	2.00	61	9553	6.39	3.15 (2.19-4.53)
Urbanization							
Low	57	27151	2.10	44	7138	6.16	2.93 (1.97-4.36)
Moderate	109	47877	2.28	74	10664	6.94	3.01 (2.23-4.07)
High	367	153372	2.39	219	36748	5.96	2.48 (2.09-2.94)
Region							
North	244	107867	2.26	141	23217	6.07	2.61 (2.11-3.23)
Central	110	46962	2.34	65	11327	5.74	2.39 (1.75-3.27)
South	145	57316	2.53	107	15253	7.02	2.84 (2.21-3.66)
East & Island	34	17332	1.96	25	5075	4.93	2.57 (1.54-4.32)
Income							
<15,000	260	116460	2.23	135	22391	6.03	2.70 (2.19-3.34)
15,000-29,999	196	83606	2.37	162	26066	6.21	2.65 (2.15-3.27)
≥30,000	77	29419	2.62	41	6415	6.39	2.35 (1.59-3.47)

† per 1,000 person-years

Table 3. Hazard ratio of temporomandibular disorder in association with depression in Cox proportional hazard models

Variables	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Depression			
No	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	2.64 (2.30-3.03)***	2.42 (2.09-2.81)***	2.21 (1.83-2.66)***

Model 1: unadjusted

Model 2: adjusted for age, sex

Model 3: adjusted for age, sex, area, occupation, urbanization, income and other psychiatric co-morbidity

***p <0.0001

Table 4. Sex- and age-specific hazard ratio of temporomandibular disorder associated with depression measured with multivariable Cox method

Variables	Depression	
	No†	Yes†
Sex*	HR (95% CI)	HR (95% CI)
Female	1.61 (1.36-1.92)***	3.54 (2.81-4.45)***
Male	1.00 (reference)	2.23 (1.70-2.94)***
Age, years†		
< 20	1.25 (0.87-1.81)	2.70 (1.48-4.94)**
20-39	1.55 (1.09-2.19)*	3.05 (2.10-4.45)***
40-59	1.49 (1.04-2.13)*	2.98 (2.05-4.33)***
≥ 60	1.00 (reference)	3.22 (2.20-4.73)***

† multivariable model including also area, occupation, urbanization, income and other psychiatric co-morbidity

*p <0.05; **P <0.01; ***p <0.0001