Community Dental Health (2018) **35,** 1–7
Received 23 May 2017; Accepted 17 December 2017

doi:10.1922/CDH_4200Hanindriyo07

Chronic Intra Oral Pain and Depressive Symptoms in Japanese Community-Dwelling Elderly: A Longitudinal Study

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***Objective*:** The incidence of major depressive disorder in the elderly ranges from 0.2 to 14.1/100 person-years, and the incidence of clinically relevant depressive symptoms is 6.8/100 person-years. This study aimed to assess the longitudinal relationship between chronic intra oral pain and depressive symptom in Japanese elderly. ***Basic research design*:** 3-year cohort study. ***Participants*:** 212 community-dwelling seniors (129 men, 83 women) aged 77 years residing in the city of Niigata, Japan in 2005. ***Interventions*:** At baseline, subjects were asked about chronic intra oral pain (tooth, gingival or denture pain), with response choices of "yes" or "no". Any type of pain, was counted as chronic intra oral pain. ***Main outcome measures*:** The General Health Questionnaire 30 (GHQ-30) was used to assess depression at follow up. The Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence was used to assess activities of daily living. ***Results*:** In multivariate logistic regression, baseline intra oral pain predicted depressive symptoms at follow up (Odds Ratio = 3.2, 95% CI = 1.32-7.81) after adjusting for serum HbA1c, creatinine and working life. ***Conclusions*:** Chronic intra oral pain increased the risk for the development of depressive symptoms in the elderly.

Key words*: orofacial pain; depressive symptom; elderly*

Introduction

Japanese society has a large and growing proportion of elderly people. In 2000, 22.7% of the population was aged 65 and older, increasing to 25.1% and 26.7% in 2013 and 2015, respectively (Statistics Bureau, 2014).

Depression is one of the major psychological disorders affecting the elderly due to experiencing negative life events such as physical illness or injury, death of a spouse, relocation, work-related difficulties, legal problems, deterioration of financial situation and unemployment (Takiguchi *et al*., 2016). According to international data, the incidence of major depressive disorder in the elderly ranges from 0.2 to 14.1/100 person-years, and the incidence of clinically relevant depressive symptoms is 6.8/100 person-years (Büchtemann *et al*., 2012). Functional impairment, cognitive impairment and smoking are predictors of depression in seniors (Weyerer *et al*., 2013), and low quality of life and chronic conditions such as angina, asthma, arthritis and nocturnal sleep problems, are also associated (Peltzer and Phaswana-Mafuya, 2013). Furthermore, a diagnosis of T2DM (type 2 diabetes melitus) increases the risk of incident depression and can contribute to a more severe disease (Semenkovich *et al*., 2015). Moreover, depression, anxiety and sleep disturbances are highly prevalent in patients with chronic kidney disease (Aggarwal *et al*., 2017).

Psychological stress is associated with oral dysfunction. Stress and depressive symptoms are predictors of dental caries (Hugo *et al*., 2012), and are associated with periodontal problems (Rosania *et al*., 2009). Conversely, cross-sectional and longitudinal studies have shown that chronic temporomandibular joint and facial pain are associated with depressive symptoms (Sipilä *et al*., 2013; Giannakopoulos *et al*., 2010). Our previous cross-sectional study showed that subjective and objective oral dryness, especially reduced unstimulated salivary flow rate (USFR) and mouth pain were associated with depressive symptoms in an elderly population (Takiguchi *et al*., 2016).

Furthermore, a previous study revealed that chronic general pain can cause depression, and that depression can also worsen chronic pain symptoms (Åkerblom *et al*., 2017). Therefore, oral pain as one form of chronic general pain may also be associated with depressive symptoms. However, only one longitudinal study has suggested that temporomandibular disorders with facial pain may increase depressive symptoms (Sipilä *et al*., 2013), and few studies have revealed that chronic intra oral pain increases depressive symptoms (Djernes, 2006). Thus, the aim of this study was to assess whether chronic oral pain increases the risk of depressive symptoms longitudinally.

Method

Participants

Participants were drawn from the Niigata Elderly study; a prospective community-based study to evaluate the relationship between individual general health and dental disease.

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Letters of invitation were sent to all people born in 1927 residing in the city of Niigata, Japan in 1998 (n = 4542). The invitations included a written explanation of the purpose of the study. After receiving the invitation, 81.4% (n = 3965) agreed to participate in the survey. Due to the availability of resources, examination appointments could only be arranged for 600 individuals. Preliminary participants were randomly selected by computer software to yield an approximately equal number of men (306) and women (294) who gave written informed consent; none of the participants required special assistance for their daily activities. In 2005, 391 of the original 600 participants (men: 207, women: 184 now aged 77) took part in a follow up (209 were lost during the 7 year interval). Participants taking medications were asked to provide their medication history, which was obtained from their pharmacies. To avoid effects from antidepressants, participants who were regular antidepressant users were excluded from the present analysis. Bromazepam and Etizolam were noted as being anxiolytics. Therefore, among the 391 participants, 179 participants were excluded due lack of data, having a General Health Questionnaire 30 (GHQ-30) score > 6 or being regular antidepressant users. Finally, data from 212 participants (men: 129, women: 83) who participated in all annual examinations from 2005 to 2008 were analyzed (Figure 1). The Ethics Committee of the Niigata University School of Dentistry approved this study and protected the rights of the participants.

Measurements

Subjective parameters

Structured interviews were used to assess subjective oral health status, depressive symptoms and activities of daily living (ADL). Subjective oral health status was assessed using four oral health events: chronic intra oral pain, subjective oral dryness, chewing difficulty, and total oral discomfort. To determine chronic intra oral pain, participants were asked about tooth, gingival or denture pain experienced over more than 1 month with response choices of "yes" or "no". Participants with at least one type of pain, were categorised as experiencing chronic intra oral pain. Questions regarding subjective oral dryness, chewing difficulty and total oral discomfort used "yes" or "no" response choices.

To assess depressive symptoms, we utilized the GHQ-30, which contains 30 questions reflecting mental state (e.g., depressive mood, sleeping problems, anxiety), social functioning and well-being, and coping abilities. Fifteen of the questions are negatively and 15 are positively worded. The GHQ-30 was scored in the Goldberg 0-0-1-1 format, where any response indicating deterioration from the usual was scored as 1. The total possible score on the GHQ-30 ranges from 0 to 30. For the Japanese version of the GHQ-30, a cut-off score of 7 yields the best sensitivity (92%) and specificity (85%) (Nakagawa and Daibou, 1985). Therefore, participants were categorized into a low GHQ-30 group (score <7) and a high group (score ≥7).

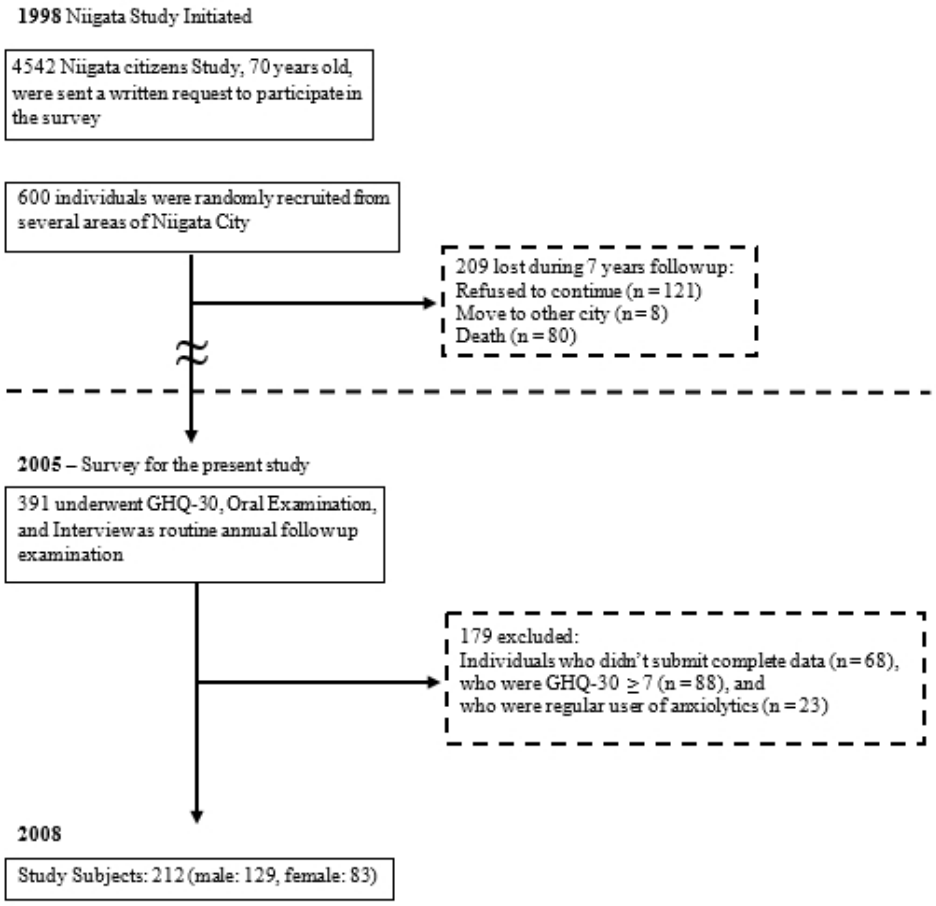

Figure 1. *Flow diagram of the study*

ADL are related to depressive symptoms (Wada *et al*., 2004). We adopted the Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG-Index), which is a multidimensional 13-item index (Table 1), to assess ADL. The TMIG-Index has three categories: instrumental self-maintenance, intellectual activity and social role. The response choices for each item were "yes (able to do)" or "no (unable to do)"; responses of "yes" were scored 1 and responses of "no" were scored 0. The total score was calculated as the sum of the 13 items, such that a higher score (maximum 13 points) would indicate greater competence (Koyano *et al*., 1991). Furthemore, to asses the working life, as an aspect of socioeconomic status, participants were asked whether they held a regular job with response choices of "yes" or "no".

Table 1. Questions on the TMIG index of competence subscales

Instrumental Self-Maintenance
Can you use public transport by yourself?
Are you able to shop for daily necessities?
Are you able to prepare meals by yourself?
Are you able to pay bills?
Can you handle your own banking?
Intellectual Activity
Are you able to fill out forms for your pension?
Do you read newspapers?
Do you read books or magazines?
Are you interested in news stories or programs dealing with health?
Social Role
Do you visit the homes of friends?
Are you sometimes called on for advice?
Are you able to visit sick friends?
Do you sometimes initiate conversations with young people?

Biological parameters

Dental examinations were carried out by four trained dentists at local community centers in Niigata City, using mouth mirrors incorporating light- and pressure-sensitive plastic periodontal probes set to give a constant probing force of 20 g with 1-mm intervals (Vivacare TPS Probe®, Schaan, Liechtenstein). Before and during the survey, inter-examiner reliability calibrations were conducted in an institution for seniors and at Niigata University. Kappa values were calculated based on the first calibration using four internationally recognized codes (sound, filled, decayed and bridge abutment), probing pocket depth (PPD) and clinical attachment level (CAL) in 18 volunteers. Kappas ranged from 0.60 to 0.79, from 0.80 to 0.95, 0.79 to 0.93 and 0.56 to 0.92 for crown caries, root caries, PPD and CAL, respectively.

All functioning teeth, except those partially erupted, were assessed, including crown and root conditions. Dental status including caries experience index (DMFT, decayed missing filled teeth) was assessed using the diagnostic criteria of the World Health Organization (2013). Periodontal condition was measured using mean PPD and CAL as well as the proportion of sites with PPD and CAL of ≥ 6 mm, measured at six sites per tooth and rounded to the nearest whole millimeter.

Blood sampling was performed with the participants in the supine position. Participants' HbA1c (glycated haemoglobin) and Creatinine levels were recorded as markers for diabetes and renal disease respectively, by a commercial laboratory (BML, Inc., Tokyo, Japan) under non-fasting conditions. Based on the threshold for diagnosing diabetes suggested by the World Health Organization (2011), participants with serum HbA1c concentration of < 6.5% were considered to have a favorable serum HbA1c profile, while those with a concentration of ≥ 6.5% were considered to have an unfavorable profile. Furthermore, participants with a serum creatinine concentration of 0.6 – 1.2 mg/dL and 0.5 – 1.1 mg/dL for male and female respectively (Verma *et al*. 2006), were considered to have a favorable serum creatinine profile, while those outside this range were considered to have an unfavourable profile.

Statistical analysis

Initially, Pearson correlation analysis described the correlations between the subjective and clinical measures of oral health. Subsequently, chi-square tests were performed to test the relationships between subjective oral health status, blood values and general conditions at baseline with GHQ-30 scores at the 2008 follow-up. Finally, all independent variables with a signifant relationship with GHQ-30 in bivariate analyses were tested in a multivariate logistic regression model to evaluate the relationship between subjective oral health status at baseline and GHQ-30 scores at the 2008 follow-up, controlling for serum HbA1c, serum creatinine and working life at baseline as confounders (Semenkovich *et al*. 2015; Aggarwal *et al*. 2017; Peltzer and Phaswana-Mafuya 2013). Analyses were performed using SPSS for Windows software (ver. 22.0 IBM, SPSS). Statistical significance was set at $p < 0.05$.

Results

Table 2 shows the characteristics of the participants. Most were male. At baseline, all 212 participants had low GHQ-30 scores. After 3 years, 27 were categorized into the high GHQ-30 group. Forty-eight complained of intra oral pain at baseline, and 197 complained of oral dryness.

The correlations between between the subjective and clinical measures of oral health are shown in Table 3. Positive correlations were found between mean PPD, mean CAL, percentage of sites with PPD ≥ 6 mm and percentage of sites with CAL ≥ 6 mm, and complaints of chewing difficulty at baseline. Chronic intra oral pain at baseline was correlated with percentage of sites with PPD ≥ 6 mm. An inverse correlation was found between FT (Filled teeth) and complaint of chewing difficulty at baseline.

The descriptive characteristics of participants at the 2008 follow up are presented by GHQ-30 score in Table 4. Chronic intra oral pain at baseline was related to high GHQ-30 scores. The proportion of participants with chronic intra oral pain at baseline was more dominant in the high GHQ-30 score group compared with the low GHQ-30 score group. However, there were no significant differences between GHQ-30 score groups and other variables included in the analysis.

The multivariate logistic regression analysis is presented in Table 5. Baseline intra oral pain predicted greater depressive symptoms as indicated by GHQ-30 scores at the 2008 follow-up (Odds Ratio = 3.2, 95% CI = 1.32-7.81), after adjusting for serum HbA1c, creatinine and working life.

Discussion

To our knowledge, this is the first longitudinal study elucidating the relationship between chronic intra oral pain and depressive symptoms in an elderly population. Experience of chronic intra oral pain at baseline increased the risk of having depressive symptoms 3 years later by 3.2 times compared to participants without baseline pain. This finding was in line with several previous studies showing that pain and depression are highly correlated (Maneeton *et al*., 2013; Åkerblom *et al*., 2017). Furthermore, mouth pain has been shown to have a substantial detrimental impact on ADL, psychological distress level and quality of life (Luo *et al*., 2007; Wan *et al*., 2012). Moreover, idiopathic oral pain and depressive symptoms have also been shown to be correlated in Brazilian seniors (Saintrain *et al*., 2013).

Previous research has provided evidence of a central pain modulation system that can either dampen or amplify peripheral nociceptive signals (Bair *et al*., 2008). Monoamine neurotransmitter such as serotonin, norepinephrine and dopamine play a vital role in the occurence and development of pain (Sheng *et al*., 2017). Chronic pain has been shown to have the potential to significantly damage dopamine activity in the limbic midbrain area (Taylor *et al*., 2016).

Table 2. Characteristics of the 212 participants

	Category	*n*
Gender	Male	129
	Female	83
The GHQ-30 score at follow up	≥ 7	27
	< 7	185
Complaint of chronic intra oral pain at baseline	Yes	48
	No	164
Complaint of subjective oral dryness at baseline	Yes	197
	No	15
Complaint of chewing difficulty at baseline	Yes	25
	No	187
Complaint of total oral discomforts at baseline	Yes	46
	No	166
Total score of TMIG-Index subscales at baseline	< 13	98
	13	114
Smoking habit at baseline	Yes	24
	No	188
Working life	Worker	47
	Non-worker	165
Blood serum HbA1c[1]	Favorable	184
	Unfavorable	10
Blood serum Creatinine[2]	Favorable	185
	Unfavorable	10

	Mean ± SD
DMFT	23.08 ± 5.50
DT	0.42 ± 0.92
MT	12.20 ± 9.37
FT	10.46 ± 6.71
PT	16.27 ± 9.73
Mean PPD	2.23 ± 0.55
Mean CAL	3.50 ± 1.05
% sites with PPD ≥ 6 mm	2.22 ± 4.68
% sites with CAL ≥ 6 mm	10.05 ± 15.58

[1] Missing data for 18 subjects
[2] Missing data for 17 subjects
GHQ-30, General Health Questionnaire-30; TMIG, Tokyo Metropolitan Institute of Gerontology Index of Competence; DMFT, Decayed missing filled teeth; DT, Decayed teeth; MT, Missing teeth; FT, Filled teeth; PT, Present teeth; PPD, Probing pocket depth; CAL, Clinical attachment level

Table 3. Correlations between subjective complaints of oral health and clinical indicators at baseline

		Chewing difficulty	*Total oral discomfort*	*Oral dryness*	*Chronic intra oral pain*
DMFT	r	0.05	0.03	-0.04	-0.01
	p- value	0.46	0.69	0.57	0.98
DT	r	-0.05	0.10	-0.02	0.04
	p- value	0.43	0.15	0.82	0.58
MT	r	0.13	0.04	0.01	-0.04
	p- value	0.05	0.55	0.86	0.52
FT	r	-0.14	-0.05	-0.04	0.05
	p- value	0.04	0.49	0.50	0.45
PT	r	-0.13	-0.04	-0.01	0.04
	p- value	0.05	0.53	0.91	0.56
Mean PPD	r	0.18	0.09	0.05	0.07
	p- value	0.01	0.23	0.51	0.31
Mean CAL	r	0.18	0.14	0.01	0.13
	p- value	0.01	0.06	0.88	0.08
% sites with PPD ≥ 6 mm	r	0.16	0.07	0.06	0.15
	p- value	0.03	0.36	0.41	0.04
% sites with CAL ≥ 6 mm	r	0.15	0.08	0.04	0.12
	p- value	0.03	0.24	0.63	0.11

DMFT, Decayed missing filled teeth; DT, Decayed teeth; MT, Missing teeth; FT, Filled teeth; PT, Present teeth; PPD, Probing pocket depth; CAL, Clinical attachement level; r, Pearson's correlation coefficient

Table 4. Baseline characteristics by follow up GHQ-30 score

		GHQ-30 Score				*p-value*[1]
		Low		*High*		
		n (%)		*n (%)*		
Subjective oral health status						
Chronic intra oral pain	No	148	(80)	16	(59.3)	0.016
	Yes	37	(20)	11	(40.7)	
Subjective oral dryness	No	14	(7.6)	1	(3.7)	0.465
	Yes	171	(92.4)	26	(92.3)	
Chewing difficulty	No	163	(88.1)	24	(88.9)	0.906
	Yes	22	(11.9)	3	(11.1)	
Total oral discomfort	No	147	(79.5)	19	(70.4)	0.284
	Yes	38	(20.5)	8	(29.6)	
Blood serum						
HbA1c[2]	Favorable	160	(95.2)	24	(92.3)	0.529
	Unfavorable	8	(4.8)	2	(7.7)	
Creatinine[3]	Favorable	160	(94.7)	25	(96.2)	0.750
	Unfavorable	9	(5.3)	1	(3.8)	
General condition						
Gender	Male	114	(61.6)	15	(55.6)	0.546
	Female	71	(38.4)	12	(44.4)	
TMIG Index score	13	102	(55.1)	12	(44.4)	0.298
	<13	83	(44.9)	15	(55.6)	
Working life	Worker	146	(78.9)	19	(70.4)	0.318
	Non-worker	39	(21.1)	8	(29.6)	
Smoking habit	No	164	(88.6)	24	(88.9)	0.971
	Yes	21	(11.4)	3	(11.1)	

[1] x^2 test

[2] Missing data for 18 subjects

[3] Missing data for 17 subjects

GHQ-30, General Health Questionnaire-30; HbA1c, Glycated haemoglobin; TMIG, Tokyo Metropolitan Institute of Gerontology Index of Competence

Table 5. Logistic regression model for predictors of depression at follow up among 212 Japanese elders

Independent Variable	Dependent Variable GHQ-30 Score Group (0/1)[1]				
	(0/1)%	OR	95% CI		
Complaint of chronic intra oral pain at baseline[2]	(77.4/22.6)	3.2	1.32	-	7.81
Serum HbA1c at baseline[3]	(94.8/5.2)	2.1	0.39	-	10.98
Serum creatinine at baseline[3]	(94.8/5.2)	0.5	0.05	-	4.67
Working life[4]	(77.8/22.2)	1.9	0.76	-	5.01

GHQ-30, General Health Questionnaire-30; HbA1c, Glycated haemoglobin; TMIG, Tokyo Metropolitan Institute of Gerontology Index of Competence

[1] 0, GHQ-30 score < 7; 1, GHQ-30 score ≥ 7

[2] 0, No; 1, Yes

[3] 0, Favorable; 1, Unfavorable

[4] 0, No job; 1, Have a job

The reactivity of the dopamine system, in particular the dopamine receptor D2, as a protein that is known to be involved in the occurrence and development of depression (Glantz *et al*. 2010), has been observed to be reduced in patients with chronic pain (Martikainen *et al*., 2015). Thus, the dysregulation in these neurotransmitters may explain the association between chronic oral pain and depression.

Participants' subjective description of chronic intra oral pain was correlated with the proportion of sites with PPD ≥ 6 mm. This finding is justifiable as a PPD of more than 6 mm is evidence of periodontitis. Chronic pain, which is described as dull aching and long standing, can be caused by the spread of inflammation such as periodontitis or swelling (Mishra *et al*., 2017). Furthermore, the inverse correlation between FT and chewing difficulty at baseline showed a considerable accuracy of the participants' subjective description for their oral health status.

We used the GHQ-30 as an indicator of depression since it is one of the major psychological indicators of depression and methods of measuring depressive symptoms. The reliability coefficient between mental health as diagnosed by a psychiatrist and mental health as determined by the GHQ-60 (the original version of the GHQ) is 0.95. Scores of the GHQ-30 and GHQ-60 are significantly correlated (Nakagawa and Daibou, 1985); thus, the GHQ-30 is a valid method of assessing depressive symptoms.

We excluded participants with baseline GHQ-30 scores >6 to assure that no participants were experiencing depressive symptoms at the initial stage of the study. Therefore, any event of a high GHQ-30 score at follow up is an incident case and could be the result of some condition existing during the study period.

A low ADL score is a major factor associated with depressive symptoms (Wada *et al*., 2004). Therefore, we utilized the TMIG-Index to minimize confounding by physical and cognitive impairment. In this study, 53.8% of the 212 participants had the maximum TMIG-Index score, indicating high competence in ADL (Table 2). However, our study found an insignificant association between ADL and depression. This might be explained by the fact that only 7.1% of the participants who had depressive symptoms, also had low ADL (TMIG-Index < 13). Japan's Cabinet Office has reported that Japan has a large proportion of elderly people living alone, and that they are more likely than those in other countries to rely on family than neighbors when they are sick (Cabinet Office Government of Japan, 2017). An association has been identified between lack of social and family support and development of non-communicable chronic diseases in elderly people (Huang *et al*., 2015), and it was also reported that inadequate social capital is associated with a decline in ADLs and death (Imamura *et al*. 2016). Therefore, the mental health of Japanese elderly might have been more prone to living circumstances and marital status than ADL *per se* (Nakamura *et al*., 2017).

Recent systematic reviews reported that women had a higher risk for depression than men (Büchtemann *et al*., 2012; Djernes, 2006). Previous studies concluded that physical and socio-economic conditions were associated with depressive symptoms among female senior citizens (Jang *et al*., 2011; Back and Lee, 2011). Although there was no significant association found between sex and depressive symptoms at follow up, the predominance of male participants showed that a considerable proportion of females were excluded due to the existence of high GHQ-30 scores in 2005.

This study had some limitations. First, the participants needed to come to the local community centers for examinations. For this reason, those with severe psychological or physical disorders may have been excluded. If these people were included, other oral factors may have been shown to be associated with depressive symptoms. Furthermore, our sample of the Japanese elderly population, may have unique socio-cultural characteristics. Therefore, a future study with a larger and varied population settings of would enhance the generalizability of the findings. Second, we did not have any information about general chronic pain. Hence, we could not assess the effect of general chronic pain on depressive symptoms. Finally, there was a lack of information on important negative life events such as decline of income or death of a spouse. Such events may have a negative impact on depressive symptoms.

Conclusion

Results from the present study suggest that chronic oral pain increased the risk of developing depressive symptoms in an elderly population.

Acknowledgements

The authors declare that they have no conflict of interests. This study was supported by a Grant-in-Aid from the Ministry of Health and Welfare of Japan (H10-Iryo-001). We are profoundly grateful to the study participants for their assistance.

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