

Analysis of dental amalgam fillings on primary Sjögren's syndrome

A population-based case-control study in Taiwan

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Abstract

Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized by the inflammatory infiltrate and progressive dysfunction of salivary glands. Dental amalgam with mercury has been raised the public concerns regarding its purported mercury toxicity from dental amalgam to possible systemic inflammatory and immune reactions.

In this study, a nationwide population-based database was employed to investigate the association of amalgam filling (AMF) and the risk of pSS. A retrospective case-control study was sourced from the Taiwanese National Health Insurance Research Database (NHIRD) from 2000 to 2013. Case and control groups were matched by sex, age, urbanization level, monthly income, and comorbidities using the propensity score method with a 1:1 ratio. In this study, 5848 cases and 5848 controls were included.

The results demonstrated no statistically significant differences between AMF and pSS (odds ratio [OR]: 0.974, 95% confidence interval [CI]=0.904–1.049). In addition, pSS was also not associated with AMF for women (OR: 0.743, 95% CI=0.552–1.000) and men (OR: 1.006, 95% CI=0.670–1.509), respectively.

Taken together, evidence demonstrated that the association of AMF and pSS was inconsistent from this robust register databank.

Abbreviations: AMF = amalgam filling, CIs = confidence intervals, ICD-9-CM = International Classification of Diseases, ninth revision, Clinical Modification, LHID = Longitudinal Health Insurance Database, NHI = national health insurance, NHIRD = national health insurance research database, OR = odds ratio, pSS = primary Sjögren's syndrome, SS = Sjögren's syndrome.

Keywords: dental amalgam fillings, national health insurance research database, primary Sjögren's syndrome, Taiwan

1. Introduction

It has been a long time that dental amalgam has been used for caries restoration. Dental amalgam is composed of silver alloys and mercury. Previous studies have reported that mercury vapor could be released for dental amalgam.^[1,2] For the public health concern, to ban, phase-out, or phase down of dental amalgam is still under monitor and discussion.^[3]

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The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Sjögren syndrome (SS) is a chronic, inflammatory, and systemic autoimmune disease manifested by the dryness of mouth and eyes.^[4] Primary Sjögren syndrome (pSS) occurs alone with no other rheumatologic disease.^[5] People who have other rheumatologic diseases such as systemic lupus erythematosus or rheumatoid arthritis were recognized as secondary SS. The exact etiology and pathogenesis of pSS still remains unknown, the genetic predisposition, environmental triggers, autoantibodies, and pathological injury, are proposed to associate with pSS.^[6] Elevated antinuclear antibodies, autoantibodies anti-Ro/SSA and anti-La/SSB, are common in patients with SS.^[7]

Previously, mercury exposure was found to evoke antinuclear antibodies positivity among females of reproductive age.^[8] In addition, a review article reported that SS patients exposed to mercury were usually accompanying with Type IV allergy.^[9] The exposure to mercury was frequently linked to dental restorations. However, little is known about the impact of amalgam filling (AMF) on pSS. Therefore, the authors analyzed the risk of AMF for pSS from the National Health Insurance Research Database (NHIRD) by case control design in Taiwanese population.

2. Methods

2.1. Data source

The Longitudinal Health Insurance Database (LHID) 2010 was used for this case control study. This research database includes the details of all medical services utilized by the enrollees. The codes of disease diagnoses and treatment procedures are based on International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM). Under surveillance by Bureau of

National Health Insurance (NHI), the validation of LHID 2010 data is associated with public confidence. Many studies have been published from NHIRD represented the epidemiological profiles of Taiwanese population.^[10–12] This study was approved by the institutional review board of Chung Shan Medical University Hospital (CSMUH No. CS2-17086).

2.2. Study design

The flow chart of this case control study is shown in Figure 1. According to the European classification criteria for Sjögren syndrome in 2002,^[13] subjects who had at least three consensus diagnoses ICD-9-CM 710.2 were identified as pSS. In addition, patients with history of pSS, age less than 18 years old, incomplete medical records, or missing data were excluded. Moreover, we also excluded patients with autoimmune diseases such as systemic lupus erythematosus (ICD-9-CM 710.0), dermatomyositis (ICD-9-CM 710.3), polymyositis (ICD-9-CM 710.4), rheumatoid arthritis (ICD-9-CM 714), and ankylosing spondylitis (ICD-9-CM 720.0) to ensure the validity of the pSS diagnoses. The comparison subjects were selected from the random sample of general population.

Potential confounders were including sex, age, urbanization level, socioeconomic status, and comorbidities. Diabetes mellitus (ICD-9-CM 250), hypertension (ICD-9-CM 401–405), hyperlipidemia (ICD-9-CM 272), coronary artery disease (ICD-9-CM 410–414), stroke (ICD-9-CM 430–438), alcoholism (ICD-9-CM 291, 303, 305.00–305.03, 571.1, 571.2, 571.3, 790.3, A215 and V11.3), obesity (ICD-9-CM 278), and tobacco use disorder (ICD-9-CM 305.1, 491.0, 491.2, 492.8, 496, 523.6, 649.0, 989.84, and V15.82) are recognized as comorbid diseases. We conditionally selected comparison subjects from the general population matched by sex, age, urbanization level, socioeconomic status, and comorbidities using the propensity score method at a 1:1 ratio for each case (Fig. 1).

2.3. AMF exposure assessment

The individuals with AMF from LHID 2010 were validated by NHI treatment codes for health insurance reimbursement qualification. Subjects who received AMF with NHI treatment codes 89001C, 89002C, 89003C, 89101C, 89102C, and 89103C were captured as the exposed group. As shown in Figure 1, potentially confounding factors were also identified and categorized.

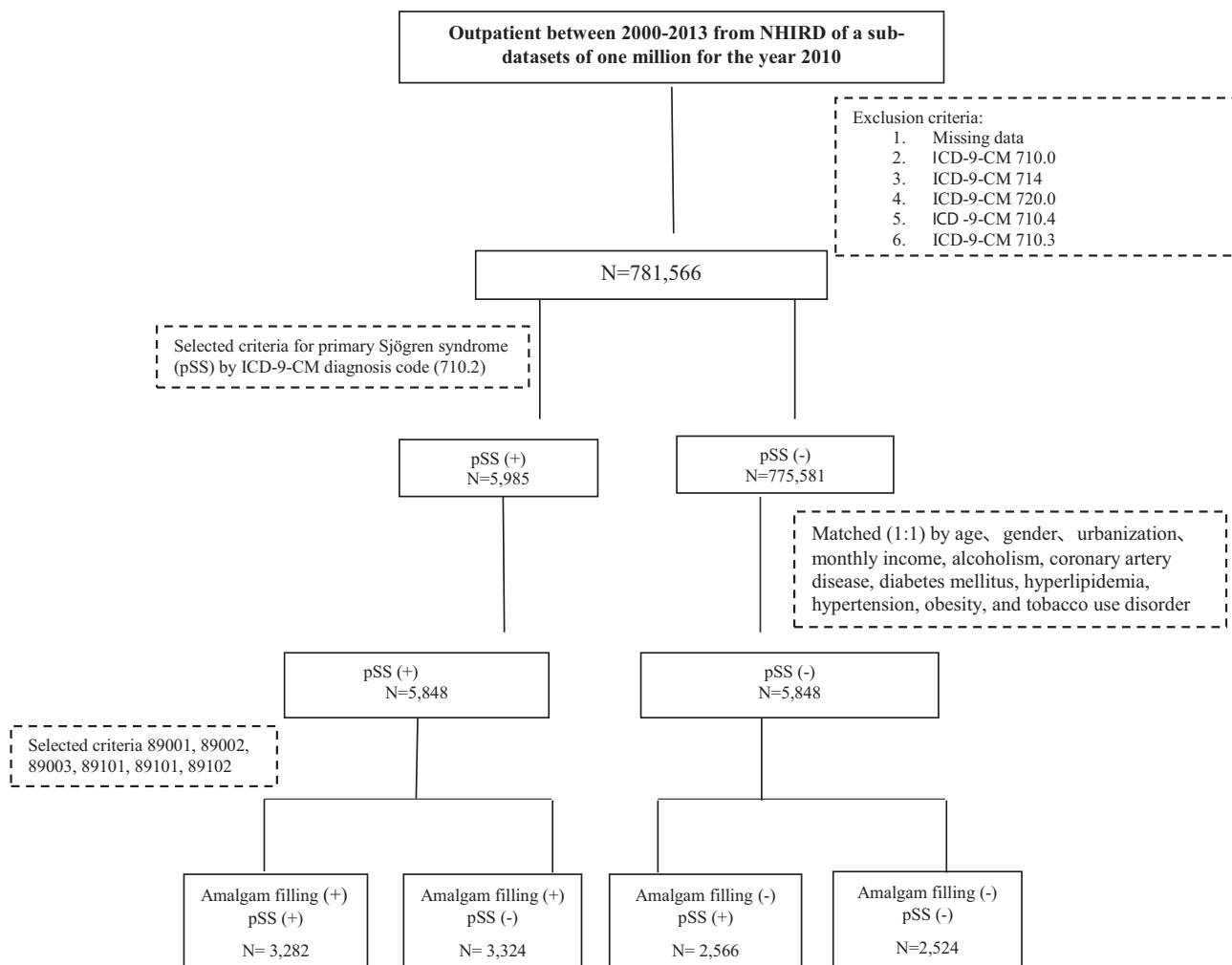


Figure 1. Flow chart used for selection of cases from the Longitudinal Health Insurance Database 2010.

Table 1
Demographic characteristics of selected subjects in this study.

	Total (N = 11,696)		pSS (n = 5848)		Non-pSS (n = 5848)		P value
	Population	%	Population	%	Population	%	
Age	58.27 ± 17.23		58.32 ± 16.94		58.21 ± 17.5		.234
Age groups							.168
18–29	656	5.61%	306	5.23%	350	5.98%	
30–39	1282	10.96%	640	10.94%	642	10.98%	
40–49	1635	13.98%	817	13.97%	818	13.99%	
50–59	2372	20.28%	1193	20.40%	1179	20.16%	
60–69	2367	20.24%	1208	20.66%	1159	19.82%	
70–79	1997	17.07%	1015	17.36%	982	16.79%	
>80	1387	11.86%	669	11.44%	718	12.28%	
Gender							.868
Female	8456	72.30%	4223	72.21%	4233	72.38%	
Male	3240	27.70%	1625	27.79%	1615	27.62%	
Urbanization							.499
Urban	7252	62.00%	3590	61.39%	3662	62.62%	
Suburban	3535	30.22%	1816	31.05%	1719	29.39%	
Rural	909	7.77%	442	7.56%	467	7.99%	
Comorbid diseases							
Alcoholism	99	0.85%	52	0.89%	47	0.80%	.597
Coronary artery disease	2468	21.10%	1239	21.19%	1229	21.02%	.810
Diabetes mellitus	797	6.81%	405	6.93%	392	6.70%	.669
Hyperlipidemia	422	3.61%	216	3.69%	206	3.52%	.798
Hypertension	5791	49.51%	2880	49.25%	2911	49.78%	.250
Obesity	15	0.13%	7	0.12%	8	0.14%	.801
Tobacco use disorder	2732	23.36%	1371	23.44%	1361	23.27%	.879
Monthly income							.994
<NT\$ 20,000	8891	76.02%	4434	75.82%	4457	76.21%	
NT\$ 20,000~40,000	1860	15.90%	952	16.28%	908	15.53%	
>NT\$ 40,000	945	8.08%	462	7.90%	483	8.26%	

pSS = primary Sjögren syndrome.

2.4. Statistical analysis

All statistical analyses were performed using SPSS version 18 for Windows (SPSS, Chicago, IL, USA). Statistical analyses were performed using Student *t* test for continuous variables and the Chi-Squared test for categorical variables. The odds ratio (OR) between case and control groups was analyzed by the Chi-Squared test. A multivariate logistic regression model was performed for subgroup analysis. All results are presented as ORs and 95% confidence intervals (CIs). Adjustments were made for age, gender, income, region, and comorbidities. Statistical significance was set at $P < .05$.

3. Results

As shown in Table 1, we identified 5848 newly diagnosed patients with pSS as cases and 5848 matched non-pSS patients from general population as controls. The mean age was 58.32 ± 16.94 years for cases and 58.21 ± 17.5 years for controls. The

female to male ratio was about 2.6:1. Demographic characteristics, including age, gender, urbanization, region, monthly income, and comorbidities, were not significantly different between the cases and control groups.

As shown in Table 2, no statistically significant difference was observed between AMF and pSS (adjusted OR: 0.974, 95% CI = 0.904–1.049) was observed. In addition, pSS was not associated with AMF regardless of gender (Tables 3 and 4).

The adjusted OR of AMF for female pSS patients was 0.937 (95% CI = 0.858–1.024) compared with non-AMF. Individuals. The adjusted OR of AMF for male pSS patients was 1.085 (95% CI = 0.943–1.249) for non-AMF subjects.

4. Discussion

To the best of our knowledge, this case-control study is the first to use nationwide, population-based longitudinal administrative data to examine the association between AMF and pSS. The

Table 2
Odds ratio for amalgam filling of those with a diagnosis of primary Sjögren syndrome.

	pSS (n = 5848)		Non-pSS (n = 5848)	
	No. of patients	%	No. of patients	%
AMF	3282	56.12%	3324	56.84%
Non-AMF	2566	43.88%	2524	43.16%
OR (95% CI)	0.971 (0.903–1.045)		1.00	
Adjusted OR (95% CI)	0.974 (0.904–1.049)		1.00	

AMF = amalgam filling, CI = confidence interval, OR = odds ratio, pSS = primary Sjögren syndrome. Adjustment by age, gender, urbanization, monthly income, and comorbidities.

Table 3
Odds ratio for females with a diagnosis of primary Sjögren syndrome with amalgam filling.

	Female (n=8,487)			
	pSS (n=4249)		Non-pSS (n=4238)	
	No. of patients	%	No. of patients	%
AMF	2379	55.99%	2459	58.02%
Non-AMF	1844	43.40%	1774	41.86%
OR (95% CI)	0.931 (0.854–1.015)		1.00	
Adjusted OR (95% CI)	0.937 (0.858–1.024)		1.00	

AMF = amalgam filling, CI = confidence interval, OR = odds ratio, pSS = primary Sjögren syndrome. Adjustment by age, gender, urbanization, monthly income, and comorbidities.

Table 4
Odds ratio for males with a diagnosis of primary Sjögren syndrome with amalgam filling.

	Male (n=3227)			
	pSS (n=1608)		Non-pSS (n=1619)	
	No. of patients	%	No. of patients	%
AMF	903	56.16%	865	53.43%
Non-AMF	722	44.90%	750	46.32%
OR (95% CI)	1.084 (0.944–1.245)		1.00	
Adjusted OR (95% CI)	1.085 (0.943–1.249)		1.00	

AMF = amalgam filling, CI = confidence interval, OR = odds ratio, pSS = primary Sjögren syndrome. Adjustment by age, gender, urbanization, monthly income, and comorbidities.

findings show that people with AMF were not at a higher risk of pSS in Taiwanese population.

Contrarily, some reports suggested possible links between dental amalgam exposure and Sjögren's syndrome could be via systemic autoimmune and inflammatory reactions.^[14–16] However, these studies without appropriate control groups may result in the inconsistent linking mercury toxicity from dental amalgam to cause pSS. As the NHIRD represents the whole population, the use of health insurance claims could minimize recall bias typical of case-control studies and enhance clinical significance.

Dysfunction of salivary glands is the main symptom in pSS patients. Studies have shown that pSS patients face a high risk of developing dental caries due to xerostomia.^[17,18] Recently, Chuang et al^[19] reported that the risk of dental caries was significantly higher in patients with pSS from Taiwanese NHIRD. Taken together, it could be explained that SS is associated with high risk of caries, therefore, amalgam is a material of choice for people with high susceptibility to dental caries.

In Taiwan, SS is one of the catastrophic illness covered under the NHI program. However, patients with minor manifestations of dry mouth and eye might not have a catastrophic illness certificate of SS. In this study, only patients with at least three consensus diagnoses (ICD-9-CM 710.0) were captured. Diagnosed pSS patients before a history of AMF were also excluded. Moreover, to ensure the accurate diagnosis of pSS, patients who had systemic lupus erythematosus, dermatomyositis, polymyositis, rheumatoid arthritis, and ankylosing spondylitis were excluded. The validity of the AMF was also identified by treatment codes of the NHI system for health insurance reimbursement qualification. Therefore, the results of this nationwide registry-based study could have significance meaningful.

However, there are some possible limitations to the current study. First, the lack of laboratory data is an inherent limitation of the NHIRD. Second, information on individual behaviors, lifestyle factors, and the subtypes of SS are unavailable from the

database. Third, NHIRD does not provide data on other teeth metal restorations. Fourth, it is hard to monitor the actual mercury vapor leached from amalgam restoration. Whether mercury in the etiology of pSS occurrence released by amalgam cannot be directly obtained in this study. The evaluation of changes of mercury level in blood or saliva from newly restored amalgam is required to verify the cause relationship. Finally, the weakness of propensity matching methodology nature which does not account for unmeasured confounders in this study should be taken into consideration. In addition, this is a case-control study, and the effect of AMF on pSS over time could not be estimated, a cohort study design is required in the future.^[20]

5. Conclusions

This population-based case-control study preliminarily proposed that AMF was not associated with pSS. However, approximately 50% of dental amalgam is elemental mercury by weight, it is still a public concern for continuing use of dental amalgam or not. Thus, the cause-effect relationship and pathophysiology are still necessary to further investigations.

Author contributions

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Supervision: Hui-Chieh Yu, Yu-Chao Chang.

Validation: Yu-Chao Chang.

Writing – review & editing: Yu-Chao Chang.

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