

# 科技部補助

## 大專學生參與專題研究計畫研究成果報告

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\* 計 畫  
\* : 牙科銀粉充填與阿茲海默症的相關性研究  
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執行計畫學生： 孫以華  
學生計畫編號： NSC 102-2815-C-040-040-B  
研究期間： 102年07月01日至103年02月28日止，計8個月  
指導教授： 廖勇柏

處理方式： 本計畫可公開查詢

執行單位： 中山醫學大學公共衛生學系（所）

中華民國 103年03月31日

# 牙科銀粉充填與阿茲海默症的相關性研究

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## 摘要

### 目地

銀粉成分中的汞對阿茲海默症的影響尚未明確，因此本研究探討經過年齡調整後，台灣 65 歲以上的國民之銀粉充填的總次數、總面數、性別、社經地位、縣市別與罹患阿茲海默症之相關性。

### 材料與方法

本研究將利用「全民健康保險研究資料庫」之 2005 年與 2010 年 100 萬人承保抽樣歸人檔(LHID2005 與 LHID2010)進行分析，對象為 2010 年底具有台灣國籍，設有戶籍，年滿 65 歲以上之國人。全民健康保險研究資料庫中，牙科銀粉充填的處置代碼為 89001C、89002C、89003C、89101C、89102C、89103C；阿茲海默症的 ICD-9-CM 診斷代碼為 331.0。資料分析方面則使用 SAS software package (version 9.3; The SAS Institute Inc., Cary, NC) 統計套裝軟體來進行邏輯式迴歸分析方法(logistic regression analysis)，探討 2000 年至 2010 年間接受銀粉充填的次數、總面數、性別、社經地位(平均投保金額)、承保縣市與阿茲海默症間之相關性。

### 研究結果

65 歲以上的國人當中，有接受過銀粉充填的人相較於沒有的人，罹患阿茲海默症的危險性較高，勝算比為 1.105 (95% CI = 1.025-1.190)。若區分不同的性別，女性有接受銀粉充填的人相較於沒有的人，有顯著的勝算比 1.132 (95% CI = 1.022-1.254)；然而，男性則呈現非顯著的勝算比 1.07 (95% CI = 0.962-1.196)。

### 結論

有接受銀粉充填的女性相較於沒有的女性，對於罹患阿茲海默症有 1.132 倍顯著的勝算比；男性則呈現非顯著的結果。

### 關鍵詞

銀粉充填、阿茲海默症、全民健康保險研究資料庫

# **The Association of Dental Amalgam Fillings and Alzheimer's Disease: A Population-based Cross-sectional Study in Taiwan**

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## **Abstract**

**Aim:** To investigate the association of dental amalgam fillings and Alzheimer's disease in population aged 65 and older by using Taiwan's National Health Insurance Research Database (NHIRD), a large-scale population-based database.

**Materials and Methods:** The study utilizes the Longitudinal Health Insurance Database 2005 and 2010 (LHID 2005 and LHID 2010) to conduct the analysis, each of which contains the original claim data of 1,000,000 beneficiaries enrolled in year 2005 and 2010 randomly sampled from NHIRD. Objects are those who hold the nationality of Taiwan and were 65 years old and older in the end of 2010. Dental amalgam filling is coded as 89001C, 89002C, 89003C, 89101C, 89102C, or 89103C in NHIRD. Individuals with Alzheimer's disease were diagnosed using ICD-9-CM codes 331.0. Multiple logistic regression analysis was performed to make clear the association of dental amalgam fillings and Alzheimer's disease by calculating the odds ratio and 95% confidence interval.

**Results:** Among subjects aged 65 or older, those having non-zero amalgam filling times had higher risk of having Alzheimer's disease (OR = 1.105, 95% CI = 1.025-1.190) than those having zero filling times after adjusting for age, gender, insurance amount, and residential area. Further analysis for the risks in both genders showed that the odd ratio became 1.07 (95% CI = 0.962-1.196) in males while a significant odd ratio, 1.132 (95% CI = 1.022-1.254), was derived in females.

**Conclusions:** In females, after adjusting for age, insurance amount, and residential region, those having non-zero amalgam filling times were 1.132 times more likely to have Alzheimer's disease compared to those having zero amalgam filling times while a non-significant odd ratio was derived in males.

**Keywords:** Amalgam filling, Alzheimer's disease, National Health Insurance Research Database

## **Introduction**

Dental amalgam, a material for filling prepared cavity after removing caries, consists of about 50% mercury [1]. Mercury vapor, as a matter of fact, has been proved to be toxic to central nerve system. In 2008, European Commission asserted that there is no evidence showing negative effects on human's central nerve system when applying amalgam filling according to previous studies. In 2009, similar statement has been made by American Dental Association [2, 3]. U.S. Food and Drug Administration, however, published an announcement in 2008 that mercury in amalgam can raise neural risk to children and pregnant women [4]. Some scientific experiments showed that amalgam restorations in oral cavity keep releasing human-absorbable mercury vapor [5-9]. Other studies pointed out a significant association between mercury concentration in urine or in blood and quantities of amalgam restoration or number of total faces in amalgam restoration [10-12]. Furthermore, the occupational studies on mercury exposure provided a strong association between mercury metal and the degeneration on nervous system [13].

Alzheimer's disease (AD) has been regarded as unsolved, irreversible, and incurable brain neuron degeneration. AD patients normally have difficulties in memorizing and thinking. Their behaviors change as the disease progresses. Eventually the disease leads to loss of control of body function in daily life [14-16]. Being the most common type of dementia, AD is most often diagnosed in individual aged 65 and older [17]. A document showed that there were 22.6 million AD patients worldwide in 2006. By 2050, a prediction is made that 1 in 85 people would suffer AD [18]. In the United States between 2000 and 2010, someone develops AD every 68 seconds and the proportion of deaths resulting from AD increased 68% while the proportion of other heart disease decreased [19]. Taiwan, with its rapid aging population, is predicted to have 3.5% of total population suffering from dementia by 2050 by Taiwan Alzheimer's Disease Association [20]. Alzheimer disease, the most common type of dementia, is going to be of critical importance in public health.

The Alzheimer's Association in U.S. claimed no relationship between silver dental fillings (known as amalgam filling) and AD [21]. However, the potential effect of amalgam on the development of AD remains uncertain [22, 23]. Increasing age is considered to be a great risk factor for AD [24, 25]. This study aims to investigate the association of dental amalgam fillings and AD in population aged 65 and older by using Taiwan's National Health Insurance Research Database (NHIRD), a large population database.

## **Materials and Methods**

The study utilizes the Longitudinal Health Insurance Database 2005 and 2010 (LHID 2005 and LHID 2010) to conduct the analysis, each of which contains the original claim data of 1,000,000 beneficiaries enrolled in year 2005 and 2010 randomly sampled from NHIRD. Objects are those who hold the nationality of Taiwan and were 65 years old and older in the end of 2010. The variables associated with those objects that are selected for model analysis include birthday, gender, insurance amount, etc. Dental amalgam filling is coded as 89001C, 89002C, 89003C, 89101C, 89102C, and 89103C in NHIRD, where 89001C indicates single-face amalgam restoration, 89002C indicates two-face amalgam restoration, and 89003C indicates three-face amalgam restoration. The other three codes 89101C, 89102C, and 89103C represent single-, two-, and three-face amalgam restoration in specific cases. Individuals with Alzheimer's disease were diagnosed using ICD-9-CM codes 331.0.

Data analysis was conducted by using SAS software package (version 9.3; The SAS Institute Inc., Cary, NC). Multiple logistic regression analysis was performed to make clear the association of dental amalgam fillings and AD by calculating the odds ratio and 95% confidence interval. In the analysis, the number of times and accumulated faces that a patient received amalgam fillings during 2001-2010 are regarded as independent variables while AD is considered as the dependent variable. Adjustments are made on age, gender, insurance amount, and residential region in an attempt to reveal a relatively direct association between amalgam fillings and AD.

## Results

A total of 207,587 beneficiaries aged 65 and over, consisting of 98,750 males (47.57%) and 108,837 females (52.43%), were identified from databases of LHID2005 and LHID2010 in the end of 2010 (figure 1). In males, there were 14,539 people (14.72%) having amalgam filling times larger than zero, among which were 401 patients (2.76%) diagnosed with AD; on the other hand, among those having zero filling times (84,211 people, 85.28%), 2,354 (2.8%) were diagnosed with AD. In females, there were 16,840 people (15.47%) having amalgam filling times larger than zero, among which were 459 patients (2.73%) diagnosed with AD; on the other hand, among those having zero filling times (91,997 people, 84.53%), 2,692 (2.93%) were diagnosed with AD.

Table 1 gives the demographics of subjects with and without AD. The mean age of AD group surpassed significantly that of non-AD group ( $79.36 \pm 7.14$  vs.  $74.87 \pm 6.89$ ,  $p < 0.001$ ). Gender distributions of AD and non-AD group show no significant difference based on NHIRD, in which the percentage of females was higher in Alzheimer group (53.35%) than in non-Alzheimer group (52.40%). Distribution of whether subjects accepting amalgam fillings in these two groups were also showing no significant difference. Subjects in AD and non-AD group were categorized into four levels according to insurance amount in an attempt to explore how socioeconomic status can associate with AD. The percentages of subjects occupying these four levels in AD group were 41.86% for dependent group, 25.70% for insurance amount between 1-20,000, 31.59% for insurance amount between 20,001-40,000, and 0.85% for insurance amount  $>40,000$ ; in non-AD group were 42.02%, 21.95%, 34.65%, and 1.38%, respectively. Distributions according to insurance amount, an index reflecting income, were significantly different among AD and non-AD groups. In the distribution of residential region, both groups had relatively high prevalence in central and southern Taiwan, exclusive of Taipei (region 1).

Among subjects aged 65 or older, those having non-zero amalgam filling times had higher risk of having Alzheimer's disease (OR = 1.105, 95% CI = 1.025-1.190) than those having zero filling times after adjusting for age, gender, insurance amount, and residential area (table 2). Advanced analysis was performed for exploring the risks in both genders. The odd ratio became 1.07 (95% CI = 0.962-1.196) in males while a significant odd ratio, 1.132 (95% CI = 1.022-1.254), was derived in females (table 3).

## Discussion

The study is the first study to investigate the association between dental amalgam fillings and Alzheimer's disease using large-scale population-based Taiwan's National Health Insurance Research Database. In females, after adjusting for age, insurance amount, and residential region, those having non-zero amalgam filling times were 1.132 times more likely to have Alzheimer's disease compared to those having zero amalgam filling times while a non-significant odd ratio was derived in males.

Since when National Health Insurance was launched in Taiwan, it had covered 97% of Taiwan's population by 2001 and 99% by 2009 [26, 27]. The NHI has been responsible for the payment of Amalgam filling operations since 2004. In fact, the number of times that a patient of age 65 years or older received amalgam fillings during 2001-2010 is not equivalent to the actual times in his or her lifetime and can possibly be underestimated. However, with regard to the long history of amalgam filling application, those who received more times of amalgam fillings during 2001- 2010 are believed to have willingness or tendency that is not lower than those who received fewer times of amalgam fillings. Therefore, even though the NHIRD cannot provide causal relationship between exact number of filling times and AD, the variables designed in the study, the number of filling times during 2001-2010, can still represent the tendency of total number of times during a patient's life. The same assumption was made for accumulated faces. Accumulated faces are sum of number of faces each amalgam filling has completed according to the operation codes 89001C, 89002C, 89003C, 89101C, 89102C, and 89103C in NHIRD. As a result of the above assumption, the study utilizes the large population-based NHIRD during 2001-2010 in an attempt to provide a cross-sectional point of view for investigating this controversial issue in dental history.

Population aged 65 and older were selected in the study for the reason that late-onset Alzheimer's disease is often diagnosed among older people which implies accumulation effect resulted from certain possible risk factors. Early-onset and familial occurrence of Alzheimer's disease, both of which account for a small part of disease incidence, are beyond our discussion.

A study has shown that lower income predicted risk of incident AD [28]. Therefore, insurance amount was adjusted in this study.

Environmental pollutions such as heavy metal contaminations in ground water contribute to varying levels of dietary mercury. A study conducted by Chung Shan Medical School indicates that mercury concentration is higher in the western costal townships [29]. Thus, residential region is selected for adjustment in the multiple logistic regression analysis in order to even out the influence.

Bruxism, a rhythmic or spasmodic grinding of the teeth other than chewing and typically occurring during sleep, may account for the result that females having amalgam fillings were 1.132 times more likely to have Alzheimer's disease compared to those who don't have. A study revealed that higher levels of mercury exposure can occur in individuals who chew gum or show bruxism [30]. Moreover, frequent bruxism was significantly positively associated with severe stress experience (Odds ratio = 5.00; 95% CI = 2.84-8.82) and female gender (Odds ratio = 2.26; 95% CI = 1.43-3.55) [31]. Therefore, material other than amalgam can be a possible choice when doctors have female patients with the needs of cavity fillings.

## **Conclusion**

In females, after adjusting for age, insurance amount, and residential region, those having non-zero amalgam filling times were 1.132 times more likely to have Alzheimer's disease compared to those having zero amalgam filling times while a non-significant odd ratio was derived in males. It is recommended that when female patient is subject to the need of amalgam fillings, concerns shall be made on whether patient has bruxism or unusual oral habits that have potent to facilitate mercury vapor release.

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Table 1. Baseline characteristics of study subjects

Variable	Alzheimer's disease (n= 5,906)		Non- Alzheimer's disease (n=201,681)		<i>p</i> -value
	No.	%	No.	%	
Age (year)	79.36 ± 7.14		74.87 ± 6.89		<.0001
Sex					0.1496
Male	2,755	46.65	95,995	47.60	
Female	3,151	53.35	105,686	52.40	
Insurance amount					<.0001
0 (Dependent)	2,472	41.86	84,740	42.02	
1- 20,000	1,518	25.70	44,260	21.95	
20,001-40,000	1,866	31.59	69,890	34.65	
>40,000	50	0.85	2,791	1.38	
Region					<.0001
Area 1(Taipei)	1,659	28.09	65,573	32.51	
Area 2 (Northern)	868	14.70	26,761	13.27	
Area 3 (Central)	1256	21.27	36,693	18.19	
Area 4 (Southern)	1,247	21.11	34,690	17.20	
Area 5 (Kao-Ping)	739	12.51	32,141	15.94	
Area 6 (Eastern)	137	2.32	5,823	2.89	
Amalgam filling					0.2274
None	5046	85.44	171,162	84.87	
Yes	860	14.56	30,519	15.13	

Age was mean ± S.E

Table 2. Logistic regression model of factors with Alzheimer's disease in patients with Amalgam fillings

Variable	Logistic regression model	
	OR	95%CI
<b>Amalgam fillings</b>		
None	1.000	-
Yes	1.105	1.025-1.190
Age	1.087	1.083-1.090
<b>Sex</b>		
Female	1.031	0.976-1.088
Male	1.000	-
<b>Insurance amount</b>		
0 (Dependent)	1.374	1.287-1.466
1-20,000	1.287	1.195-1.386
20,001-40,000	1.000	-
>40,000	1.175	0.883-1.565
<b>Region</b>		
Area 1 (Taipei)	0.735	0.675-0.800
Area 2 (Northern)	1.000	-
Area 3 (Central)	1.127	1.032-1.232
Area 4 (Southern)	1.226	1.120-1.341
Area 5 (Kao-Ping)	0.734	0.672-0.821
Area 6 (Eastern)	0.732	0.609-0.880

Odds ratio was adjusted for age, sex, insurance amount, and geographical region.

Table 3. Logistic regression model of factors with Alzheimer's disease in both genders

Variable	Logistic regression model			
	Male		Female	
	OR	95%CI	OR	95%CI
<b>Amalgam Fillings</b>				
None	1.00	-	1.00	-
Yes	1.07	0.962-1.196	1.132	1.022-1.254
Age	1.09	1.084-1.096	1.085	1.080-1.090
<b>Insurance amount</b>				
0 (Dependent)	1.278	1.156-1.413	1.455	1.335-1.585
1-20,000	1.162	1.052-1.284	1.452	1.297 -1.625
20,001-40,000	1.00	-	1.00	-
>40,000	0.945	0.656-1.360	1.770	1.113-2.815
<b>Region</b>				
<sup>1</sup> Area 1	0.838	0.740-0.950	0.650	0.579-0.730
<sup>2</sup> Area 2	1.00	-	1.00	-
<sup>3</sup> Area 3	1.302	1.142-1.484	0.991	0.878-1.118
<sup>4</sup> Area 4	1.409	1.234-1.610	1.087	0.963-1.228
<sup>5</sup> Area 5	0.801	0.692-0.929	0.695	0.606-0.796
<sup>6</sup> Area 6	0.881	0.685-1.134	0.611	0.466-0.800

Odds ratio was adjusted for age, insurance amount, and geographical region.

<sup>1</sup> Area 1 (Taipei) : Taipei City and County, Yilan County, Keelung City, Kinmen County, and Lienhiang County)

<sup>2</sup> Area 2 (Northern) : Taoyuan County, Hsinchu County, Miaoli County, and Hsinchu City

<sup>3</sup> Area 3 (Central) : Taichung City, Taichung County, Changhua County, and Nantou County

<sup>4</sup> Area 4 (Southern) : Tainan City and County, Chiayi City and County, Yunlin County

<sup>5</sup> Area 5 (Kao-Ping) : Kaohsiung City and County, Pingtung County, Penghu County

<sup>6</sup> Area 6 (Eastern) : Hualin and Taitung County

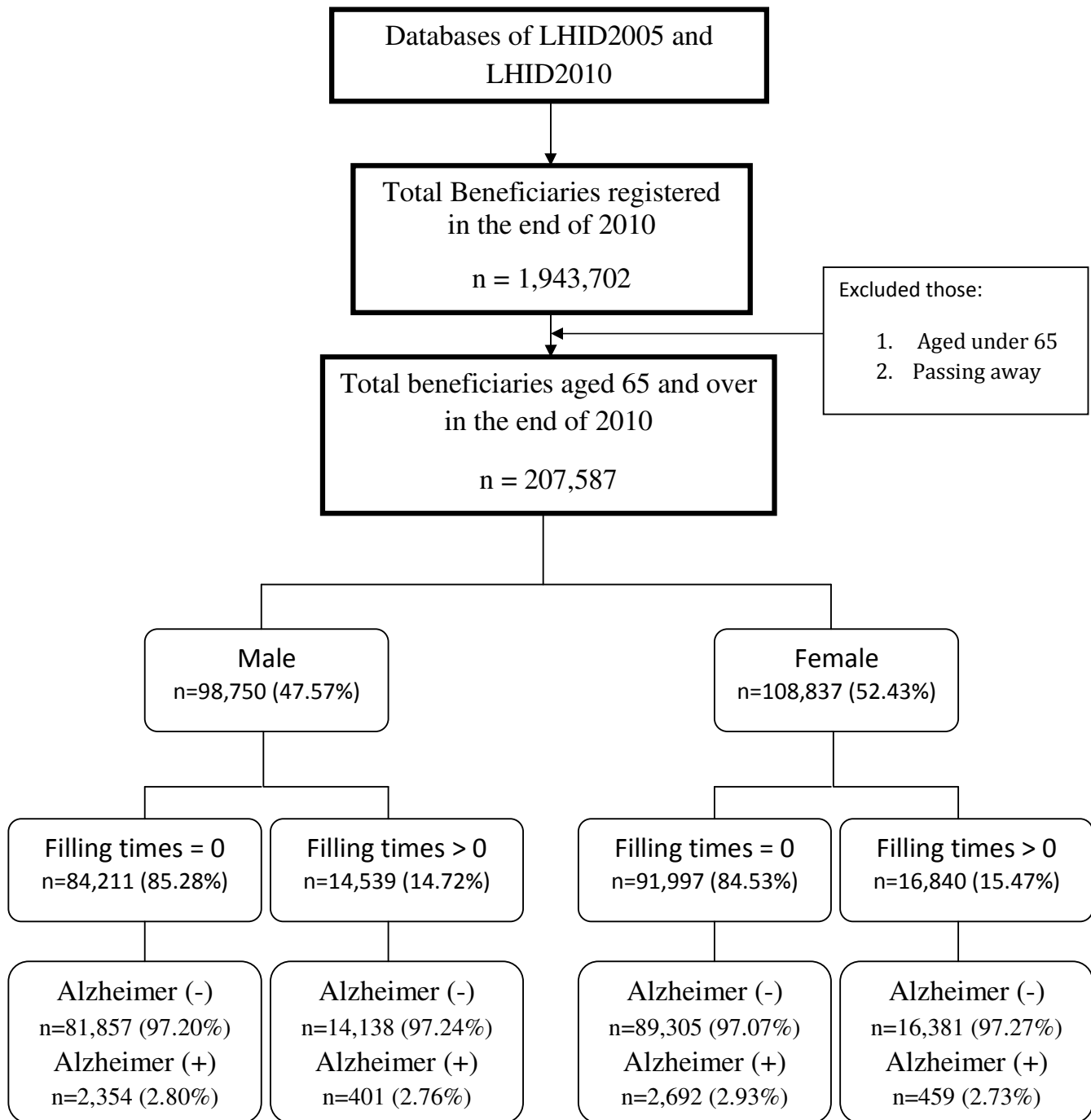


Figure1. Flow chart showing the procedures involved in the calculation of numbers of Alzheimer from 2000-2010