Title:

Risk of Alzheimer's Disease in Relation to Diabetes: A Population-Based Cohort Study

Authors' names and affiliations:

Kai-Chen Wang[a,b], Lin-Chung Woung[c,d], Ming-Tsu Tsai[e,f], Chih-Ching Liu[g], Ying-Hwa Su[h], and Chung-Yi Li[i,j]

[a] Department of Neurology, Cheng-Hsin General Hospital, Taipei, TAIWAN
[b] Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, TAIWAN
[c] Department of Ophthalmology, Taipei City Hospital, Taipei, TAIWAN
[d] Department of Ophthalmology, National Taiwan University Hospital, Taipei, TAIWAN
[e] Department of Nursing, New Taipei County Hospital, Taipei, TAIWAN
[f] Department of Nursing, Oriental Institute of Technology, Taipei, TAIWAN
[g] Bureau of Health Promotion, Department of Health, Taipei, TAIWAN
[h] Department of Nursing, College of Medicine, National Cheng Kung University, Tainan, TAIWAN
[i] Department and Institute of Public Health, College of Medicine, National Cheng Kung University, Tainan, TAIWAN
[j] Department of Public Health, College of Public Health, China Medical University, Taichung, TAIWAN

Kai-Chen Wang and Lin-Chung Woung contributed equally to this work.

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Corresponding Author:

Chung-Yi Li, PhD

Department of Public Health
College of Medicine, National Cheng Kung University
NO. 1, University Rd., Tainan 701, TAIWAN
Tel. +886 6 2353 535, Fax +886 6 2359 033
E-mail cyli99@mail.ncku.edu.tw

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Abstract

Background/Aims: Detailed information on the age- and sex-specific relationships between diabetes and Alzheimer's disease (AD) is scarce. This study aims to prospectively investigate the age- and sex-specific incidence density and relative hazards of AD in relation to diabetes.

Methods: Totally 615,529 diabetic patients and 614,871 age- and sex-matched random controls were linked to the claim data from 2000-2008 to identify the first episode of primary or secondary diagnoses of AD. Incidence density (ID) was calculated under the Poisson assumption. We also assessed the age- and sex- specific risk of AD in relation to diabetes with the Cox proportional hazard regression models.

Results: Over nearly 9 years of follow-up, a total of 4,615 diabetic subjects developed AD, representing a cumulative incidence rate of 0.75% (n=3,873, 0.63% in controls). The overall ID of AD for diabetic men and women, respectively, were 0.82 and 1.15 per 1,000 person-years, which were higher than those for control men and women (0.63 and 0.89 per 1,000 person-years). Diabetic patients had a significantly higher hazard ratios (HRs) of AD (1.45; 95% Confidence Interval (CI), 1.38-1.52). Diabetic women ≥65 years had a higher HR (1.52; 95% CI, 1.42-1.62) than diabetic women <65 years (1.34, 95% CI, 1.15-1.56).

Conclusion: Diabetes may increase the risk of AD in both sexes and in all ages. Higher HR of AD was especially notable in older diabetic women.

Introduction

Alzheimer's disease (AD) is a devastating progressive neurodegenerative disease affecting more than 15 million people worldwide [1]. AD is characterized by neuronal loss associated with a progressive decline in memory and other cognitive functions, resulting in dementia. Clinically, AD is diagnosed according to the criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition [2].

Diabetes mellitus is characterized by hyperglycemia and is associated with pathological changes in numerous peripheral organs, such as the eyes, kidneys and peripheral nerves. In addition, diabetes affects the central nervous system. Learning disability and memory deficits are observed in people with long term diabetes [3]. Furthermore, subjects with diabetes have hippocampal and amygdala atrophy on brain imaging relative to non-diabetic subjects. The hippocampus and amygdala are responsible for such functions as memory and behavior and, are also found to be atrophied in AD [4]. Post-mortem studies of brains of diabetes with dementia often reveal the coexistence of both brain microvascular lesions and extensive amyloid plaque burden, a characteristic of AD [5]. Additionally, numerous animal studies provided possible explanations for the putative link between diabetes and AD. Data from most animal studies found that insulin deficiency may result in AD pathology including increased tau phosphorylation at multiple sites, increased tau cleavage, and greater neuronal and synaptic damage, even with increased amyloid β peptide production [6,7]. However, AD pathology is more severe in T2DM animal models exhibiting hyperinsulinemia and insulin resistance [7].

With an aging population, the prevalence of diabetes and AD will continue to rise in the coming decades [8], thus posing a major public health problem. The findings from several

cross-sectional studies suggest that diabetes and AD may be inter-related [9, 10]. Several longitudinal studies have also found an association between a history of diabetes and dementia; however, these studies were limited by a relatively short follow-up period, a substantial loss of subjects to follow-up, and / or a small sample size [11]. Hence, the purported link between diabetes and AD is yet to be confirmed by investigations controlling for the methodological concerns in earlier studies. The objective of this study was to verify, using a large population-based cohort study design, the putative association between diabetes and the risk of AD.

Materials and Methods

Data sources

The Department of Health in Taiwan reformed health insurance in 1995. By the end of 1996, around 96% of the Taiwanese population had enrolled in the National Health Insurance (NHI) program [12] and the Bureau of National Health Insurance (BNHI) had contracted with 97% of hospitals and 90% of clinics [13]. To verify the accuracy of claim data, the BNHI performs quarterly expert reviews on a random sample of every 50-100 ambulatory and inpatient claims in each hospital and clinic. False reports of diagnosis result in a severe penalty from the BNHI. With the ethical approval from the National Health Research Institutes, we obtained data for the current analysis from ambulatory care claims, all inpatient claims, and the updated registry for beneficiaries from the year 2000 to 2008. With each individual personal identification number (PIN), all NHI datasets could be interlinked.

Study design, cohorts, and co-morbidities

This was a population-based cohort study from 2000 to 2008. Diabetic ambulatory care claim records included those patients coded with diabetes-related diagnoses: either International Classification of Disease- 9th version (ICD-9): 250 or A-code: A181. An individual was classified as being a diabetic patient if he or she had an initial diabetes-related diagnosis at any time in 2000, and was then diagnosed one or more times within the following 12 months. The first and last outpatient visits within one year were required to be > 30 days apart to avoid accidental inclusion of miscoded patients [14]. To detect newly diagnosed AD, we excluded patients who sought treatment in hospitals or ambulatory care visits for AD (ICD-9: 331.0) from 1997 to the first ambulatory care appearance in 2000 from our diabetic group. In total, 615,532 diabetic patients

were identified in 2000. Control group subjects were selected from all beneficiaries insured in 2000 who did not have diabetes or AD between 1997 and 2000. A total of 614,871 age- and sex-matched control individuals were thus randomly selected.

Once the study subjects were identified, we searched the claims regarding ambulatory care visits and hospitalization for the selected comorbidities including cerebrovascular disease (ICD-9: 430–432, 433–438), cardiovascular disease (ICD-9: 393–398, 410–414, 420–429, 440–449, 451–459; ICD-9 procedure codes: 36.0, 36.01, 36.02, 36.05, 36.06, 36.1, 36.10–36.19, 391), hypertension (ICD-9: 401–405), and hyperlipidemia (ICD-9: 272.0–272.4). We counted these comorbidities only when dates of first-time diagnosis during the study period (2000-2008) were noted at a time prior to the date of encountering study end-points (i.e., AD) or the date of censoring.

Data linkage and statistical analysis

With the unique personal identification number, we linked study subjects in both diabetic and control groups to the claim data in years from 2000 to 2008 to identify the first episode of primary or secondary diagnoses of AD. The index date for each study subject was the date of his / her first ambulatory care visit for diabetes in 2000. The date of encountering AD was the first day of ambulatory care or hospitalization with primary or secondary diagnoses of AD following the index date. The study period was from 1 January 2000 to 31 December 2008, a 9-year period.

The geographic area of each member's NHI unit, either the location of employment or residential area, was grouped into 1 of 4 geographic areas (North, Central, South, or East) and 1 of 3 urbanization levels (metropolis, satellite city / town, or rural) according to the National Statistics of Regional Standard Classification [15]. The age- and sex-specific incidence of AD was calculated

with person-years as the denominator under the Poisson assumption. To assess the independent effects of diabetic status on the risk of AD, Cox proportional hazard regression model analysis was performed, with adjustments for age, sex, insurance premium, selected comorbidities, geographic area, and urbanization status. The latter two geographic variables were adjusted for possible geographic variations in health care accessibility and quality in Taiwan [16].

Subjects who died in hospital and did not have AD listed as one of the discharge diagnoses were censored in the survival analysis; the date of censorship was the date of death. If a study subject was not diagnosed with AD at an inpatient or outpatient setting, the date of censorship was either the date of their last withdrawal from NHI or the study end date. All statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC). A P value < 0.05 was considered statistically significant.

Results

With the age- and sex-matched selection of control subjects, the age and sex distributions between diabetic and control groups were very similar. The sample contained slightly more females (51.9%) than males (48.1%) and comprised approximately 40% elderly (≥ 65 years) subjects in each groups. The mean insurance premium was slightly lower in the diabetic group than in the control group. While there was no marked difference in living or working geographic areas between the two groups, diabetic patients tended to reside or work in urbanized regions. The prevalence rates of selected comorbidities including cerebrovascular disease (48.6% vs 30.4%), cardiovascular disease (81.6% vs 65.0%), hypertension (89.6% vs 62.1%), and hyperlipidemia (74.2% vs 38.2%) were higher in the diabetic group compared with the control group (Table 1).

Over nearly 9 years of follow-up, a total of 4,615 diabetic subjects developed AD, representing a cumulative incidence rate (CIR) of 0.75%. The corresponding figure for control subjects was 0.63% (3,873/614,871). The overall incidence density (ID) was also higher in the diabetic group (0.99 per 1,000 patient-years) than in the control group (0.77 per 1,000 patient-years). Sex-stratified analysis revealed that women had a higher overall incidence of AD than women, regardless of diabetic status (diabetic women / men: 1.15 / 0.82 per 1,000 patient-years; control women / men: 0.89 / 0.63 per 1,000 patient-years). The overall incidence of AD was higher in subjects aged ≥ 65 years compared with subjects aged < 65 years, regardless of sex or diabetic status. Diabetic women had the highest sex-age-specific overall incidence of AD (2.47 per 1,000 person-years; Table 2).

After controlling for potential socio-demographic, geographic, and clinical confounders, diabetic patients were found to have a significantly increased adjusted hazard ratio (AHR) of developing AD (1.45, 95% confidence interval (CI) 1.38-1.52). Women with diabetes had a higher

AHR (1.48, 95% CI 1.39-1.57) than men with diabetes (1.40, 95% CI 1.30-1.51). While there was no difference in the age-specific AHR between elderly men and younger man, the AHR tended to be higher in elderly diabetic women (1.52, 95% CI 1.42-1.62) compared with younger diabetic women (1.34, 95% CI 1.15-1.56).

In addition to diabetes, certain sociodemographic and geographic factors, and comorbidities were found to be associated with a significantly increased hazard for AD (Table 3). Subjects aged $\geq$ 65 years were 7 times more likely to develop AD than subject aged $\leq$ 65 years. Being female (AHR=1.31, 95% CI 1.25-1.37) and having a higher insurance premium (AHR=1.25, 95% CI 1.18-1.32) were also significantly ($P<0.05$) associated with an increased AHR for AD. The AHR for AD varied with geographic location. Subjects who resided or worked in southern Taiwan had higher AHRs (1.92, 95% CI 1.62-2.28) than subjects who resided or worked in Eastern Taiwan (a relatively remote area). Cerebrovascular disease (AHR=1.74, 95% CI 1.66-1.82), cardiovascular disease (AHR=1.09, 95% CI 1.03-1.15), and hypertension (AHR=1.38, 95% CI 1.30-1.48) were all associated with significantly increased AHR for AD respectively. Subjects with hyperlipidemia had a significantly reduced AHR for AD (0.69, 95% CI 0.66-0.72).

Discussion

The findings from our population-based study indicate that diabetes is associated with an increased risk of AD. Older female diabetes tended to have the highest relative risk of developing AD. The absolute risk of AD was found to be related to age in both diabetic and control subjects.

A common feature of AD and diabetes is amyloid deposition in target organs; Aβ and tau in AD brains, and amylin in pancreatic islets of type 2 diabetes [17]. Biochemical analysis supports a link between AD and insulin dysfunction [18]. An impaired insulin response in the brain [1], which may accelerate neurofibrillary tangles formation, has been proposed to increase the risk of AD in patients with diabetes [17]. In animal models, Takeda et al. explored the insulin action and its resistance in the development of cognitive impairment by cross-mated double transgenic models of AD and DM [19]. They found that diabetes may accelerate the cerebrovascular inflammation but would not increase Aβ levels. This report supports that AD may be related to cerebraovacular dysfunction [20] and neuroinflammation [21]. It also supports our finding that cerebrovascular disease, cardiovascular disease, and hypertension were all significantly associated with an increased hazard of AD. Despite the existence of a plausible mechanism to explain the link between diabetes and AD, controversy remains [3, 9, 10], primarily because of a lack of large-scale epidemiology data to substantiate the purported association. The findings from our large cohort study provide support for the proposed link between diabetes and AD. Specifically, our findings suggest that patients with diabetes are 1.45-fold more likely than non-diabetics to develop AD. And this relative risk estimate is similar to previous findings (1.3- to 2.4-fold) reported [22].

We also found that the absolute risk of AD increased with age in both diabetic and control subjects. It is well known that the incidence of AD increases exponentially with age to at least 90

years of age [23]. Age is a key risk factor for AD because the function of critical brain areas, such as the hippocampus, decreases with age [24]. Aging-related atherosclerosis is also considered to contribute to the pathogenesis of AD [25]. As arteries stiffen and lymph drainage is impaired [26], the drainage of amyloid-beta protein is also impaired, leading to deposition in the brain parenchyma and consequent AD [27]. Women had slightly higher HRs for AD compared to men. Gender is a well-established risk factor for AD, especially in older ages [28, 29]. The overall relative risk estimate for AD in woman subjects is comparable with those reported in earlier studies [29], suggesting that there is little ethnic variation with regards to the link between gender and AD.

Our study tended to suggest an effect-modification by age on the relationship between diabetes and AD in women, but not so in men. Several studies have found an increased risk of AD in men with low serum levels of testosterone, which is the primary source of plasma estradiol in men. Because testicular secretion of testosterone never completely stops, serum estrogen levels are higher in elderly males than in postmenopausal women [30] Additionally, insulin resistance and the compensatory hyperinsulinemia provoke increased androgen synthesis at the expense of decreased estrogen production [31]. Hence, while healthy premenopausal women enjoy the defensive effect of estrogens, older women with profound estrogen deficiency may confer a higher risk of AD. These may partly explain that there is no difference between older and younger men regarding to the relative risk of AD, and why older female diabetic patients are more easily at an increased risk of developing AD compared to the non-diabetic women of similar ages.

Diabetes is a complex metabolic disorder, which is closely associated with other vascular risk factors such as cerebrovascular disease [27], cardiovascular disease [32], and hypertension [33]. Vascular risk factors have been linked to the development of AD, which contributes to the deposition of amyloid-β protein in the brain [34]. Our results are consistent with previous findings

that most vascular risk factors, except for hyperlipidemia, are associated with an increased risk of AD [8]. Results from epidemiologic studies examining the relationship between serum cholesterol levels and the risk of AD have been inconsistent [35-38]. The role of cholesterol as a susceptibility factor or a protective agent in neurodegeneration and, more generally, in amyloid-induced cytotoxicity remains controversial [39].

Unexpectedly, we noted an inverse association between hyperlipldemia and risk of AD. There are still some debates regarding whether statins may reduce the risk of AD [40]. Based on a cross-sectional sample of nearly 5 thousands elderly participants (355 cases of prevalent dementia (200 with AD)), Zandi et al. found that statin use was inversely and significantly associated with prevalence of dementia (adjusted odds ratio, 0.44) [41]. After this sample was followed for 3 years, Zandi et al. identified 185 cases of incident dementia (104 with AD) among 3308 survivors at risk; and statin use at baseline did not significantly predict incidence of dementia or AD (adjusted HR for dementia and AD was both at 1.19) [41]. Additionally, two recent randomized controlled trials also reported that statin had no benefit on the progression of symptoms in individuals with mild to moderate AD despite significant lowering of cholesterol [42, 43]. On the other hand, The Rotterdam Study, a population-based study with some 7 thousands participants and a mean of 9 years of follow-up, found that compared with never use of cholesterol-lowering drugs, statin use was associated with a decreased risk of AD (HR 0.57, 95% CI 0.37-0.90), but non-statin cholesterol-lowering drug use was not (HR 1.05, 95% CI 0.45 to 2.44) [44].

In addition to cholesterol-lowering drugs, some medications used to treat diabetes were also found beneficial in neuropathological outcomes in AD patients. Beeri et al. found that diabetic patients with concomitant use of both insulin and any oral antidiabetic medications were at substantially lower neuritic plaque density [45]. In a mouse model of Alzheimer's disease. McClean

et al. demonstrated that liraglutide, a novel long-lasting incretin hormone glucagon-like peptide-1(GLP-1) analogs, prevents key neurodegenerative developments found in Alzheimer's disease [46]. Recently, Hamilton et al. used mouse models of diabetes to demonstrate that GLP-1 mimetics show promise as a treatment for neurodegenerative diseases such as Alzheimer's disease, because these novel drugs may cross the blood-brain barrier and increase neuroneogenesis [47]. Due to a lack of prescriptions data available in our study, we are unable to assess whether or to what extent the medications used to treat diabetes or Alzheimer's disease may have confounded the study findings.

In addition to demographic and clinical risk factors, we also noted that socioeconomic background was associated with the risk of AD. In keeping with findings from a previous report [48], we found that higher insurance premiums (and supposedly higher income) were associated with a lower risk of AD. Different lifestyle factors including education, occupation, and leisure activities have been increasingly recognized as factors that may affect the development of AD [49]. The decreased risk of AD among individuals with better socioeconomic backgrounds might be related to a better brain reserve against brain damage [50].

We noted regional differences in the risk of AD. Specifically, diabetic subjects living or working in southern and northern Taiwan had higher relative risks of AD compared with their eastern and western counterparts. It is not clear what underlies such geographic variation in the risk of AD. Given that there is a higher density of medical centers in northern and southern Taiwan, the increased risk of AD in these areas may simply reflect the fact that the inhabitants have more ready access to medical consulting and are thus more likely to be diagnosed than inhabitants in other areas. Further studies are needed to examine this possibility.

Our study had several methodological strengths. First, follow-up was based on the linkage of study subjects' PINs. This approach limited loss to follow-up. Response rates were also high and recall bias was limited in the cohort studies. Second, the longitudinal records of a large sample of geographically dispersed patients were easily obtained because we used insurance claims data to obtain data. Including a large number of study subjects also allowed us to perform stratified analyses according to certain variables of interest such as age and sex.

There are several limitations to our study. First, we were unable to differentiate between type 1 and type 2 diabetes. Given that only 1.8% of diabetics in Taiwan have type 1 diabetes [51], the majority of patients in our study likely had type 2 diabetes. Second, as NHI claim data were only available from 1997 onwards, we were not able to determine the exact duration of diabetes for each study patient, limiting our ability to assess the relationship between the timing of diabetes onset and AD. Third, due to limited variables in the claim data, we were unable to adjust for a number of known clinical and environmental risk factors for AD.

Determining whether there is a link between diabetes and AD is of great clinical and public health importance, as such information may provide crucial information for implementing AD prevention strategies, particularly in areas with aging populations such as Taiwan. Although the current study was based on a fairly large cohort, future studies should further remove potential confounding by known vascular and environmental risk factors for AD and determine the relationship between timing of diabetes onset and risk of AD in order to enhance evidence for the link between diabetes and AD. Our finding that elderly subjects with diabetes had a greater risk of AD suggests that older individuals with diabetes, who are vulnerable to AD, should be treated aggressively.

Conclusion

The findings from our national population-based cohort study provide support for there being a link between diabetes and AD, particularly in elderly women with diabetes. We suggest that diabetic patients should undergo routine mental and cognitive examinations to facilitate early detection and treatment of AD. Older diabetic women and their families should be made aware of the increased risk of AD and other risk factors for AD should be avoided as far as possible.

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1 **Table 1.** Characteristics of the study subjects

Variables [1]	Control group		Diabetic group	
	n	%	n	%
Age (years)				
<65	366427	59.6	366967	59.6
>=65	248444	40.4	248562	40.4
Mean age (±SD) [2]	60.0±12.8		60.1±12.7	
Sex				
Male	295563	48.1	295566	48.1
Female	319308	51.9	319310	51.9
Insurance premium (NTD) [2]				
Dependent	156296	25.4	169761	27.6
<Median (19,200)	135948	22.1	137408	22.3
>=Median	322627	52.5	308363	50.1
Mean premium (±SD) [3]	20142.6±15269.4		19307.7± 14454.7	
Geographic area				
Northern	269239	44.2	269920	44.4
Central	151693	25.0	141321	23.2
Southern	168995	27.8	178627	29.4
Eastern	17938	3.0	17944	3.0
Urbanization status				
Metropolis	243808	39.8	255467	42.0
Satellite city/town	163515	26.8	159687	26.2
Rural area	202343	33.2	193949	31.8
Co-morbidities				
Cerebrovascular disease				
No	428246	69.6	316627	51.4
Yes	186625	30.4	298905	48.6
Cardiovascular disease				
No	215104	35.0	113509	18.4
Yes	399767	65.0	502023	81.6

Hypertension				
No	233171	37.9	80400	13.1
Yes	381700	62.1	535132	89.6
Hyperlipidemia				
No	379843	61.8	158950	25.8
Yes	235028	38.2	456582	74.2
Total	614871	100.0	615532	100.0

[1] Inconsistency between total population and population summed for individual variable was due to missing information.

[2] SD=Standard deviation; NTD=New Taiwan Dollars.

[3] The dependent insurers werenot included.

Table 2. Overall and age- and sex-specific incidence densities and relative hazards of Alzheimer's disease in the diabetic and control groups

Variables[1]	Control group			Diabetic group			HR[2] (95% CI[2]) in association with diabetic group	AHR[2] (95% CI[2]) in association with diabetic group
	No. of patients	No. of events	ID[2,3] (per 1,000 patient-years) (95% CI[2])	No. of patients	No. of events	ID[2,3] (per 1,000 patient-years) (95% CI[2])		
Men								
<65	182436	233	0.15 (0.15-0.16)	182436	365	0.25 (0.25-0.26)	1.71 (1.45-2.01)	1.40 (1.16-1.68)[4]
>=65	113127	1270	1.53 (1.52-1.53)	113129	1433	1.92 (1.92-1.93)	1.28 (1.19-1.38)	1.41 (1.30-1.53)[4]
Total	295563	1503	0.63 (0.62-0.63)	295566	1798	0.82 (0.81-0.82)	1.31 (1.22-1.41)	1.40 (1.30-1.51)[5]
Women								
<65	183991	347	0.22 (0.21-0.22)	183990	514	0.34 (0.33-0.34)	1.61 (1.40-1.84)	1.34 (1.15-1.56)[4]
>=65	135317	2023	1.91 (1.91-1.92)	135318	2303	2.47 (2.46-2.47)	1.32 (1.25-1.41)	1.52 (1.42-1.62)[4]
Total	319308	2370	0.89 (0.88-0.89)	319310	2817	1.15 (1.15-1.16)	1.31 (1.24-1.39)	1.48 (1.39-1.57)[5]
Overall	614871	3873	0.77 (0.76-0.77)	615532	4615	0.99 (0.99-1.00)	1.31 (1.26-1.37)	1.45 (1.38-1.52)[6]

[1] Inconsistency between total population and population summed for individual variable was due to missing information.

[2] ID= incidence density; CI= confidence interval; HR= hazard ratio; AHR= adjusted hazard ratio.

[3] Based on Poisson assumption.

[4] Based on Cox proportional hazard regression with adjustment for all variables, except for age and sex.

[5] Based on Cox proportional hazard regression with adjustment for all variables, except for sex.

[6] Based on Cox proportional hazard regression with adjustment for age, sex, insurance premium, geographic area, urbanization status, cerebrovascular disease, cardiovascular disease, hypertension, hyperlipidemia, and status of diabetes.

Table 3. Relative hazards of Alzheimer's disease in relation to diabetes and various covariates

Variables	No. of patients[1]	No. of events	Crude HR[2]	95% CI[2]	Adjusted HR[2,3]	95% CI[2]
Diabetes						
No	614871	3873	1.00		1.00	
Yes	615532	4615	1.31[4]	1.26-1.37	1.45[4]	1.38-1.52
Age (years)						
<65	733394	1459	1.00		1.00	
>=65	497006	7029	8.58[4]	8.10-9.07	7.49[4]	7.05-7.97
Sex						
Male	591129	3301	1.00		1.00	
Female	638618	5187	1.40[4]	1.34-1.47	1.31[4]	1.25-1.37
Insurance premium (NTD)						
Dependent	326057	3315	1.67[4]	1.58-1.77	1.15[4]	1.08-1.23
<Median (19,200)	273356	2071	2.23[4]	2.12-2.34	1.25[4]	1.18-1.32
>=Median	630990	3102	1.00		1.00	
Geographic area						
Northern	539159	4005	1.75[4]	1.49-2.07	1.86[4]	1.56-2.21
Central	293014	1710	1.39[4]	1.17-1.64	1.47[4]	1.24-1.75
Southern	347622	2540	1.75[4]	1.48-2.07	1.92[4]	1.62-2.28
Eastern	35882	146	1.00		1.00	
Urbanization status						

Metropolis	499275	3679	1.10[4]	1.04-1.15	1.03	0.97-1.10
Satellite city/town	323202	2129	0.99	0.93-1.05	0.91	0.85-0.97
Rural area	396292	2602	1.00		1.00	
Co-morbidities						
Cerebrovascular disease						
No	744873	3256	1.00		1.00	
Yes	485530	5232	2.73[4]	2.62-2.86	1.74[4]	1.66-1.82
Cardiovascular disease						
No	328613	1721	1.00		1.00	
Yes	901790	6767	1.50[4]	1.42-1.58	1.09[4]	1.03-1.15
Hypertension						
No	313571	1373	1.00		1.00	
Yes	916832	7115	1.85[4]	1.75-1.96	1.38[4]	1.30-1.48
Hyperlipidemia						
No	538793	4022	1.00		1.00	
Yes	691610	4466	0.80[4]	0.76-0.83	0.69[4]	0.66-0.72
Total	1230403	8488				

[1] Inconsistency between total population and population summed for individual variable was due to missing information.

[2] HR= hazard ratio; CI=confidence interval.

[3] Estimated from the Cox proportional hazard model with all variables listed in Table 3 included in the regression equation.

[4] P<0.05.