ORIGINAL ARTICLE

Association between polypharmacy and dementia in older people: A population-based case–control study in Taiwan

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Aim: The aim of the present study was to investigate whether polypharmacy correlates with the risk of dementia in older people.

Methods: From representative claims data established from the National Health Insurance with a population coverage rate of 99% in Taiwan, we identified 7135 newly diagnosed patients with dementia in 2000–2008 and 2 8540 randomly selected controls without dementia, both aged ≥65 years. The daily use of prescribed drugs in the past 2 years was compared between cases and controls, controlling for demographic characters and comorbidities.

Results: The incidence of dementia increased with the number of medications used and age. Cases were older than controls, predominant with women and more likely to use five or more drugs daily (44.0% *vs* 32.0%, $P < 0.0001$). Multivariate logistic regression analysis showed that, compared with participants using zero to one drug, the odds ratios (OR) of dementia were 1.28 (95% confidence interval [CI] 1.18–1.38) for those using two to four drugs, 1.34 (95% CI 1.23–1.46) for those using five to nine drugs and 1.56 (95% CI 1.38–1.76) for those using 10 or more drugs. Cerebrovascular disease (OR 3.19), diabetes mellitus (OR 1.23), chronic kidney disease (OR 1.21) and hypertension (OR 1.08) were significant comorbidities predicting the risk of dementia. There was significant interaction between cerebrovascular disease and the number of medications used in the dementia risk.

Conclusions: The risk of dementia increases steadily with the number of medications used and age in older people in Taiwan. Cerebrovascular disease, diabetes mellitus, chronic kidney disease and hypertension might also correlate with the risk of dementia. **Geriatr Gerontol Int 2011; ••: ••–••.**

Keywords: cerebrovascular disease, chronic kidney disease, dementia, diabetes mellitus, polypharmacy.

Introduction

Polypharmacy, concurrently with multiple medications, is a well-established risk factor for adverse drug reactions (ADR) in older people.[1,2] Larson *et al.* found a significant association between the number of

medications used and ADR.[1] Compared with patients using zero to one drug, the relative odds of ADR increased from 2.7 (95% CI 0.9–7.8) for patients using two to three drugs, to 13.7 (95% CI 3.6–51.9) for those using six or more drugs.[1] du Souich has reported that serious ADR is an issue secondary to drug–drug interactions frequently found in older people with polypharmacy.[3]

The population aged ≥65 years in Taiwan increased from 7.0% in 1993 to 10.4% in 2008.[4] Previous studies have shown that the prevalence of dementia ranged from 2.5 to 4.4% among older people in Taiwan.[5–7] Dementia is regarded as a growing public health issue that causes a great socioeconomic burden as a result of the high cost of care and the negative impact on quality of life.[8–11]

Although the pathogenesis of dementia remains unclear, some epidemiological studies have shown that the ADR account for 2–12% of dementia-like cases.[1,12,13] As polypharmacy is a well-known risk factor for ADR in older people, and ADR can lead to dementia-like status, we make a hypothesis that older people with polypharmacy might be at an elevated risk of dementia.

To our knowledge, the clinical association between polypharmacy and dementia using a population-based study has not yet been investigated for an Asian population. In the present study, we used the claims data of the National Health Insurance of Taiwan to investigate the relationship between polypharmacy and dementia in older people.

Materials and methods

Study population

This was a population-based case–control study using data from the Taiwan National Health Insurance Database. This insurance program began in March 1995 and has covered more than 99% of the entire population of 23 million people in Taiwan by the end of 2008.[14] We obtained the claims data of 1996–2008 from the National Health Research Institutes in Taiwan, consisting of registries and claims reported by contracted health-care providers. The insurance program details were addressed in previous studies.[15–17]

Criteria and definition

Individuals aged 65 years and older with newly diagnosed dementia in outpatient clinics in 2000–2008 were identified as cases, according to International Classification of Diseases 9th Revision Clinical Modification (ICD-9 290.0, 290.1, 290.2, 290.3, 290.4, 294.1 and 331.0). Controls were also aged 65 years and older, randomly selected from those without dementia in a ratio of 1 : 4 (cases *vs* controls). Individuals with other major

psychiatric diseases (ICD-9 291–293 and 295–298) were excluded from the present study. The other medical conditions potentially associated with dementia were included as covariates, such as obesity (ICD-9 278.00 and 278.01), diabetes mellitus (ICD-9 250), hypertension (ICD-9 401–405), cerebrovascular disease (ICD-9 430–438), hyperlipidemia (ICD-9 272.0, 272.1, 272.2, 272.3 and 272.4) and chronic kidney disease (ICD-9 585, 586, 588.8 and 588.9).

We collected each study subject's medication history for 2 years before the date at which the subject was identified. We estimated the average daily use of prescribed drugs by calculating the total number of prescribed drugs in 2 years divided by 730 days. The prescribed drugs included oral, topical and injection medicines. The following was the estimating equation:

The average daily use of prescribed drugs = {[(1 type of drug) × (using days)] + [(2 types of drug) × (using days)] + [(3 types of drug) × (using days)] + [(4 types of drug) × (using days) + . . . + [(10 or more types of drug) × (using days)]} / 730 days.[15] We have previously defined the daily average use of five or more drugs as polypharmacy.[15]

Statistical analysis

Data analysis first calculated the incidence rates of dementia by the number of medications used and age group (65–74 years, 75–84 years, and 85 years and older), and followed by cases and controls comparison. Distributions of dementia and several types of comorbidities were presented by the number of medications. We also carried out the receiver–operator characteristic analysis and presented a plot. Cases and controls were compared for demographic status, number of medications used and comorbidities, and tested with the χ^2-test. Univariate unconditional logistic regression analysis was applied to calculate the crude odds ratios (OR) and 95% confidence intervals (CI) for the association between potential risk factors and dementia. Significant factors found in the univariate analysis were included in the multivariate unconditional logistic regression analysis. Further analysis measured the interaction between cerebrovascular disease and the number of medications associated with the risk of dementia. We used SAS software (version 9.1, SAS Institute, Cary, NC, USA) to analyze data with a two-sided test significance level of 0.05.

Ethical approval

All identifications in the insurance reimbursement claims data were scrambled to secure patient privacy for public access. The present study was exempt from full review by the institution review board.
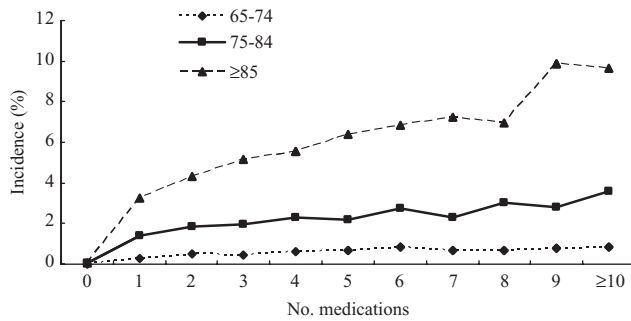
Figure 1 Age-specific rate of newly diagnosed dementia by number of medications and age among population aged 65 years and older in Taiwan, 2000–2008.

Results

Retrospective characteristics of the study population

We identified 7135 newly diagnosed cases of dementia from the sub-dataset of insurance claims in 2000–2008. Figure 1 shows the distribution of average annual incidence of dementia markedly increased with age and the number of medications in three age groups (65–74 years, 75–84 years and >85 years). The incidence rates among those using five drugs were 0.7%, 2.16% and 6.39%, respectively. Among subjects aged 85 years and older, the incidence of dementia increased from 3.27% for those using one drug to as high as 9.65% for those using 10 or more drugs.

Table 1 compares the distribution of demographic characteristics, medications and other medical conditions between dementia cases and controls. Cases had a higher proportion of women and were older than controls (both $P < 0.0001$). Dementia cases were more prevalent with comorbidities than controls, including diabetes, hypertension, hyperlipidemia, cerebrovascular disease and chronic kidney disease. More than half of the study subjects lived in urbanized areas with no statistical difference in population densities between cases and controls ($P = 0.334$).

The proportion of polypharmacy (≥5 drugs) was significantly higher in dementia cases (44.0%) than in controls (32.0%) ($P < 0.001$; Table 2). Compared with the first year, polypharmacy users increased by 5.6% in the dementia cases and 2.8% in the controls in the second year (data not shown). Subjects with obesity, diabetes, hypertension, hyperlipidemia, cerebrovascular disease or chronic kidney disease also were more likely to be polypharmacy users than subjects without those respective diseases ($P < 0.0001$).

Estimated risk of dementia and associated factors

Table 3 shows the multivariate unconditional logistic regression analysis for the risk of dementia associated with sex, age, number of medications, obesity, diabetes, hypertension, hyperlipidemia, cerebrovascular disease and chronic kidney disease. The risk of dementia increased with age. Women were at higher risk than men to be associated with dementia. Cerebrovascular disease (OR 3.19, 95% CI 3.01–3.38), diabetes mellitus (OR 1.23, 95% CI 1.16–1.32), chronic kidney disease (OR 1.21, 95% CI 1.10–1.33) and hypertension (OR 1.08, 95% CI 1.01–1.17) were independent comorbidities significantly associated with dementia. There was an obvious relationship between number of medications and dementia. When compared with subjects using zero to one drug, the adjusted OR of dementia were 1.28 (95% CI 1.18–1.38) for subjects using two to four drugs, 1.34 (95% CI 1.23–1.46) for those using five to nine drugs and 1.56 (95% CI 1.38–1.76) for those using 10 or more drugs. Further data analysis considered the number of medications as a continuous variable in the multivariate regression analysis. The results showed that per drug used increased 3% of dementia risk (OR = 1.03, 95% CI 1.02–1.04; data not shown).

Table 4 shows the synergistic interactions between cerebrovascular disease and the number of medications associated with dementia, using patients with zero to one drug, and with and without cerebrovascular disease separately as the reference group. The OR of dementia increased, from 1.12 (95% CI 1.01–1.25) for those with cerebrovascular disease and using two to four drugs, to 1.16 (95% CI 1.03–1.29) for those with cerebrovascular disease and using five to nine drugs, and 1.38 (95% CI 1.19–1.59) for those with cerebrovascular disease and using 10 or more drugs. Among patients without cerebrovascular disease, those taking multiple drugs had a greater risk of dementia. The OR increased from 1.41 (95% CI 1.26–1.57) for those taking two to four drugs, to 1.57 (95% CI 1.39–1.78) for those taking five to nine drugs, and 1.79 (95% CI 1.44–2.21) for those taking 10 drugs or more. However, the prevalence of dementia was much higher in patients with cerebrovascular disease than in those without the disease (32.3% *vs* 11.4%).

Discussion

Although the real cause of dementia remains to be explored, many known risk factors have been investigated. Meador suggests that, in addition to acute toxic effects, drugs might also act as the primary cause of dementia.[18] Studies have claimed that drug-induced dementia accounts for 2–12% of all dementia cases.[1,12,13]

To date, there is still not a consensus definition for polypharmacy. Two available definitions for polypharmacy have been addressed. The first one is the use of drugs not clinically indicated, representing unnecessary or inappropriate medications.[19–21] The other definition is the concurrent use of multiple drugs, but how many

Table 1 Comparison by sociodemographic factors and other medical conditions between dementia cases and controls in Taiwan, 2000–2008

| | Dementia | | | | *P*-value |
| | No (*n* = 2 8540) | | Yes (*n* = 7135) | | |
	n	(%)	*n*	(%)	
Age (years) (mean ± SD)	76.46 ± 5.72		78.92 ± 6.84		<0.0001
Sex					<0.0001
Female	13 520	(47.4)	3614	(50.6)	
Male	15 020	(52.6)	3521	(49.4)	
Age group (years)					<0.0001
65–74	12 875	(45.1)	2143	(30.0)	
75–84	13 290	(46.6)	3610	(50.6)	
≥85	2 375	(8.3)	1382	(19.4)	
Urbanization					0.334
Low	1 796	(6.3)	419	(5.9)	
Moderate	10 949	(38.4)	2719	(38.1)	
High	15 795	(55.3)	3997	(56.0)	
No. medications					<0.0001
0–1	9 356	(32.8)	1455	(20.4)	
2–4	10 047	(35.2)	2542	(35.6)	
5–9	7 531	(26.4)	2458	(34.5)	
≥10	1 606	(5.6)	680	(9.5)	
Obesity					0.2166
No	28 342	(99.3)	7095	(99.4)	
Yes	198	(0.7)	40	(0.6)	
Diabetes mellitus					<0.0001
No	21 355	(74.8)	4778	(67.0)	
Yes	7 185	(25.2)	2357	(33.0)	
Hypertension					<0.0001
No	9 494	(33.3)	1541	(21.6)	
Yes	19 046	(66.7)	5594	(78.4)	
Hyperlipidemia					0.0155
No	20 260	(71.0)	4961	(69.5)	
Yes	8 280	(29.0)	2174	(30.5)	
Cerebrovascular disease					<0.0001
No	18 576	(65.1)	2390	(33.5)	
Yes	9 964	(34.9)	4745	(66.5)	
Chronic kidney disease					<0.0001
No	26 437	(92.6)	6320	(88.6)	
Yes	2 103	(7.4)	815	(11.4)	

drugs remains unsettled. Because of the natural limitations of a case–control study, recall bias of the number of medications used daily by each patient was possible. Therefore, we used a new equation to measure the average daily use of prescribed drugs by the subject, which was designed in our previous study.[15] In the present study, the estimated risk of dementia increased markedly as the average daily number of medications increased. The OR of dementia were 1.28 for subjects using two to four drugs daily, 1.34 for subjects using five to nine drugs daily and 1.56 for subjects using 10 drugs or more daily, compared with subjects using one drug or less (Table 3). Some other studies have defined the daily use of five or more drugs as polypharmacy.[22–24] However, our analysis of the receiver–operator curve showed that dementia might significantly increase for those who took 2.86 drugs (data not shown). We further used patients taking zero to two drugs as a reference and found that OR of dementia were 1.12 for subjects using three to four drugs daily, 1.18 for subjects using five to nine drugs daily and 1.38 for subjects using 10 drugs or more daily.

Table 2 Proportional distribution of medication by dementia and other medical conditions in Taiwan, 2000–2008

	No. medications							
	0–1		2–4		5–9		≥10	
	n	(%)	n	(%)	n	(%)	n	(%)
Dementia								
No	9 356	(32.8)	10 047	(35.2)	7531	(26.4)	1606	(5.6)
Yes	1 455	(20.4)	2 542	(35.6)	2458	(34.5)	680	(9.5)
Obesity								
No	10 782	(30.4)	12 503	(35.3)	9903	(28.0)	2249	(6.3)
Yes	29	(12.2)	86	(36.1)	86	(36.1)	37	(15.6)
Diabetes mellitus								
No	9 905	(37.9)	9 569	(36.6)	5710	(21.9)	949	(3.6)
Yes	906	(9.5)	3 020	(31.7)	4279	(44.8)	1337	(14.0)
Hypertension								
No	6 672	(60.5)	3 242	(29.4)	999	(9.0)	122	(1.1)
Yes	4 139	(16.8)	9 347	(37.9)	8990	(36.5)	2164	(8.8)
Hyperlipidemia								
No	9 679	(38.4)	8 875	(35.2)	5616	(22.3)	1051	(4.1)
Yes	1 132	(10.9)	3 714	(35.5)	4373	(41.8)	1235	(11.8)
Cerebrovascular disease								
No	8 453	(40.3)	7 399	(35.3)	4336	(20.7)	778	(3.7)
Yes	2 358	(16.0)	5 190	(35.3)	5653	(38.4)	1508	(10.3)
Chronic kidney disease								
No	10 461	(31.9)	11 699	(35.7)	8733	(26.7)	1864	(5.7)
Yes	350	(12.0)	890	(30.5)	1256	(43.0)	422	(14.5)

All $P < 0.0001$.

Polypharmacy has been regarded as a risk factor of ADR in older people. Nguyen *et al.* have found, in a geriatric nursing home study, residents using nine medications or more were 2.33-fold (95% CI 1.54–3.52) more likely than controls to experience an ADR.[25] One longitudinal study in Sweden showed that older people using five or more drugs were 2.6-fold (95% CI 1.1–6.1) more likely to have a dementia-like state in approximately 3 years of follow up than those not using drugs.[26]

In the present study, we reviewed the medication history of each subject for 2 years before the date at which dementia was diagnosed. That is, use of polypharmacy preceded the diagnosis of dementia. In the present study, drug-related dementia was increasingly identified as the number of medications increased, particularly in older people. This appears as an obvious relationship between the number of medications and dementia, strongly supporting the hypothesis that polypharmacy is significantly related to the risk of dementia in older people.

Epidemiological studies have consistently shown a strong association between age and dementia.[27–30] The present study also showed the OR of dementia increased to 3.01 for people aged 85 years or more, compared with the younger group. Further analysis

showed that the daily use of medications also increased with age. However, it is not clear whether there was a higher risk of dementia for the older group mainly because of polypharmacy or other factors corresponding to age.

In the present study, women were at an elevated risk of dementia (OR 1.12). However, epidemiological studies regarding the role of sex in association with dementia have shown conflicting results. A large Italian population study found sex is not associated with dementia risk for older people.[28] In contrast, a Spanish study showed women are more likely to have dementia than men.[29] Thus, the geographic variation of dementia between men and women might be dependent on the population characteristics.

Epidemiological studies have consistently reported the association between dementia and comorbidities, particularly diabetes mellitus,[31–35] hypertension[34,35] and cerebrovascular disease.[29,30,33] In the present study, the higher proportion of cerebrovascular disease in subjects with dementia and a strong association with cerebrovascular disease (OR 3.19) show that cerebrovascular disease is associated with dementia. Nearly half of the patients with cerebrovascular disease were users of five and more drugs. Our data showed that polypharmacy

Table 3 Crude and adjusted odds ratios and 95% confidence intervals of dementia and associated factors in Taiwan, 2000–2008

Variable	Univariate		Multivariate	
	OR	(95% CI)	OR	(95% CI)
Sex				
Female	1.13	(1.07–1.19)	1.12	(1.06–1.19)
Male	1.00	(Reference)	1.00	(Reference)
Age group (years)				
65–74	1.00	(Reference)	1.00	(Reference)
75–84	1.65	(1.55–1.75)	1.44	(1.35–1.53)
≥85	3.64	(3.36–3.95)	3.01	(2.76–3.27)
Urbanization				
Low	1.00	(Reference)	1.00	(Reference)
Moderate	1.07	(0.95–1.20)	1.09	(0.97–1.23)
High	1.10	(0.99–1.24)	1.11	(0.99–1.25)
No. medications				
0–1	1.00	(Reference)	1.00	(Reference)
2–4	1.63	(1.52–1.75)	1.28	(1.18–1.38)
5–9	2.10	(1.95–2.25)	1.34	(1.23–1.46)
≥10	2.72	(2.45–3.03)	1.56	(1.38–1.76)
Obesity				
No	1.27	(0.91–1.79)	1.44	(1.01–2.06)
Yes	1.00	(Reference)	1.00	(Reference)
Diabetes mellitus				
No	1.00	(Reference)	1.00	(Reference)
Yes	1.43	(1.35–1.51)	1.23	(1.16–1.32)
Hypertension				
No	1.00	(Reference)	1.00	(Reference)
Yes	1.71	(1.61–1.82)	1.08	(1.01–1.17)
Hyperlipidemia				
No	1.00	(Reference)	1.00	(Reference)
Yes	1.04	(0.98–1.10)	0.80	(0.75–0.85)
Cerebrovascular disease				
No	1.00	(Reference)	1.00	(Reference)
Yes	3.61	(3.41–3.81)	3.19	(3.01–3.38)
Chronic kidney disease				
No	1.00	(Reference)	1.00	(Reference)
Yes	1.59	(1.46–1.73)	1.21	(1.10–1.33)

Table 4 Interaction between cerebrovascular disease and number of medications associated with dementia in Taiwan, 2000–2008

Cerebrovascular disease	No. medications			
	0–1 drug	2–4 drugs	5–9 drugs	≥10 drugs
	n/N	*n/N*	*n/N*	*n/N*
	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)
No	754/7699	903/6496	608/3728	125/653
	1.00 (reference)	1.41 (1.26–1.57)	1.57 (1.39–1.78)	1.79 (1.44–2.21)
Yes	701/1657	1639/3551	1850/3803	555/953
	1.00 (reference)	1.12 (1.01–1.25)	1.16 (1.03–1.29)	1.38 (1.19–1.59)

Adjusted for sex, age, obesity, diabetes mellitus, hypertension, hyperlipidemia and chronic kidney disease. CI, confidence interval; *n*, number of dementia cases; N, sample size; OR, odds ratio.

interacts with cerebrovascular disease and further increases the risk of dementia. The OR of dementia increased for 38% for patients with both cerebrovascular disease and using ≥10 drugs, compared with patients with cerebrovascular disease and using zero to one drug. The present study shows a dose–response relationship between polypharmacy and dementia among patients without cerebrovascular disease.

In addition, we found dementia also has a significant association with chronic kidney disease (OR 1.21). Only limited studies have explored this relationship. The REGARDS Study has suggested that impaired renal function is associated with a dementia-like state for USA adults after adjustment for cardiovascular risk factors.[36] Two other studies carried out by Elias *et al*. and by Etgen *et al*. also showed a similar trend.[37,38] Madero *et al*. have reviewed several studies on dementia and concluded that patients in all stages of chronic kidney disease are at an elevated risk of dementia with a significant impact on their quality of life.[39] Therefore, early detection of dementia in the early course for patients with chronic kidney disease is highly recommended.

The topic is fascinating and original. The present pilot study has the strength of using a representative population to identify a large number of cases for a nested case–control observation, as a national electronic medical record offers significant power to assess these relationships. A risk factor reported in the present study, but not found elsewhere, is polypharmacy. The risk of dementia increases with the number of medications. Thus, we emphasize that polypharmacy might correlate with the risk of dementia. A cross-sectional study by Doraiswamy *et al*.[40] has reported that 61% of patients with Alzheimer's disease had three or more coexisting medical conditions. From a clinical view, our data also support the concept that cerebrovascular disease, diabetes mellitus, chronic kidney disease and hypertension are significantly related to the risk of dementia.

There are limitations to the present study. First, there were a small number of patients with Alzheimer's disease identified in the data analysis. How much the early stages of dementia could have contributed to the excessive use of medications was not clear. Confirmation of the risk variation of dementia subtypes associated with polypharmacy should be encouraged. Second, the other potential risk factors of dementia, such as genetic factors, smoking, education level, homocysteine level, folate level, environmental factors, family history of dementia and non-prescription drugs were not specifically analyzed separately because of the inherent limitation of insurance data.

Third, use of drugs without clinical indication could also act as a risk factor for dementia, but it is not clearly differentiated by this dataset. Fourth, interpretation of these results should be done very carefully, as dementia is really related to pre-existing comorbidities, particularly cardiovascular diseases, which if optimally managed will need polypharmacy. Thus, further well-designed prospective studies are needed to confirm the association between polypharmacy and ADR in older people, and to explore whether minimizing the number of medications used might prevent ADR and further reduce the risk of dementia.

We conclude that the present study has shown that polypharmacy might correlate with the risk of dementia in older people in Taiwan. Cerebrovascular disease, diabetes mellitus, chronic kidney disease and hypertension are also significantly related to the risk of dementia. Cerebrovascular disease might interact with polypharmacy and further increase the dementia risk.

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Disclosure statement

The authors disclose no conflicts of interest.

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