Association of Polypharmacy With Mild Cognitive Impairment and Cognitive Ability: A Nationwide Survey in Taiwan

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ABSTRACT

Background: Polypharmacy, defined as the concomitant use of 5 or more medications, has a documented negative association with cognitive impairment such as delirium and is associated, potentially, with a higher risk of dementia. However, whether polypharmacy contributes to increased risk of mild cognitive impairment (MCI) or decreased cognitive capacity requires further investigation. This nationwide population survey investigated the association among polypharmacy, MCI, and dementia.

Methods: Through random sampling based on the proportion of all Taiwan counties, subjects were recruited and received in-person interviews between December 2011 and March 2013. Demographic data and clinical information included medical histories, medication use, and mental status measured by the Taiwanese Mini-Mental State Examination (TMSE) and Clinical Dementia Rating (CDR). Data on lifestyle and habits were collected, and subjects were distributed to cognitively normal, MCI, or all-cause dementia groups based on criteria by the National Institute on Aging and the Alzheimer's Association.

Results: A total of 7,422 people aged 65 years or older were recruited. After adjustment for age, sex, body mass index, education, medical comorbidities, and lifestyle and habits, polypharmacy was associated with a 1.75-fold increased odds of MCI and 2.33-fold increased odds of dementia. Polypharmacy was associated with a 0.51-point decrease in TMSE scores ($P = .001$) and a 0.10-point increase in CDR score ($P < .001$). Additionally, for those without specific vascular comorbidities, polypharmacy had a greatly more negative impact on cognitive capacity.

Conclusions: Polypharmacy is common in the elderly and is associated with significantly lower cognitive capacity and higher risks of MCI and dementia, especially for persons without diabetes, hypertension, hyperlipidemia, or cerebrovascular diseases.

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Dementia is a progressive degenerative disease characterized by a cluster of clinical signs and symptoms such as memory impairment, disturbance in language, visuospatial deficit, and impairment in activities of daily living.[1] It is recognized as a public health priority by the World Health Organization. About 47 million people were living with dementia worldwide in 2015, and the annual global cost of dementia is estimated to be US $818 billion.[2] Although dementia cannot be cured and ultimately may lead to disability in patients and heavy burden to caregivers,[1,2] reducing risk of developing dementia takes on added importance in the absence of a disease-modifying treatment.

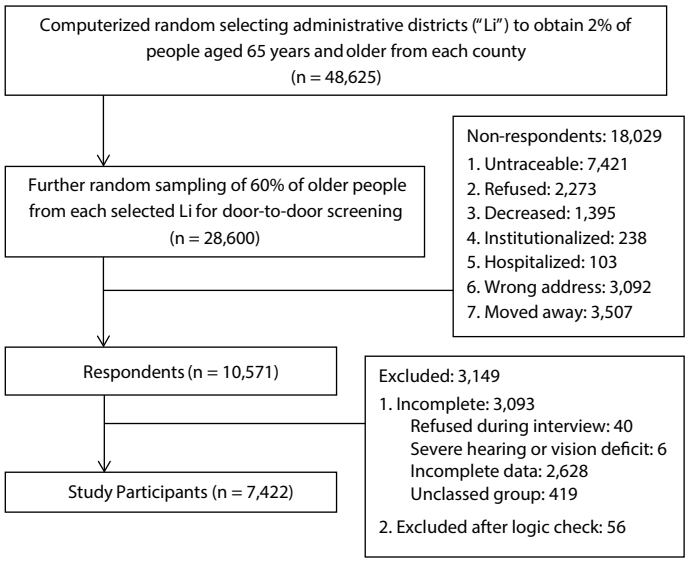
Mild cognitive impairment (MCI) often precedes dementia and is defined as impairment in at least 1 cognitive domain with the preservation of independence in functional abilities.[3–5] MCI is also identified as an important target for dementia prevention.[6,7] Several risk factors that influence the development of dementia or MCI have been identified from previous literature,[1,8,9] including vascular risk factors, lifestyle habits, apolipoprotein E genotype, and drug misuse. How to modify risk factors, increase the cognitive reserve, and thus delay or prevent subsequent dementia will become an important issue in aging societies.[1]

Polypharmacy, most commonly defined as taking 5 or more medications,[10–12] has been associated with a higher possibility of adverse drug reactions,[5,9] potentially causing cognitive dysfunction,[6,8,9,13] falls,[9,14,15] unplanned hospitalizations/outpatient visits,[16,17] and mortality.[18] Previous studies[8,10,11] have examined the relationship between polypharmacy and cognitive impairment, mostly focusing on the risk of dementia. A Finnish study[8] showed excessive polypharmacy was associated with increasing risk of dementia and negative impact on cognitive capacity as evaluated by

Clinical Points

- Polypharmacy was demonstrated to be associated with dementia, but was not well-proven to be associated with mild cognitive impairment (MCI).
- Polypharmacy showed a gradient association with MCI and dementia in the elderly.
- Physicians should try to persuade patients with a high risk of cognitive impairment to modify their lifestyle and habits and help them reduce polypharmacy.

Figure 1. Flowchart of the Enrollment of Study Participants



the Mini-Mental State Examination (MMSE) compared with the non-polypharmacy group. Using their respective national health insurance databases, studies in South Korea[10] and Taiwan[11] both found that elderly people taking 5 or more drugs had higher risk of dementia. However, similar research in MCI is rare. Oyarzun-Gonzalez et al[19] followed 572 participants and found polypharmacy was associated with an increased risk of MCI (OR = 1.95) and a decrease in MMSE scores, but these results were not statistically significant.

To our best knowledge, no clinical reports have evaluated the effect of polypharmacy on the results of formal cognitive tests such as MMSE or Clinical Dementia Rating Scale (CDR) in Asia, and studies on the relationship of MCI with polypharmacy have been scarce. Using a nationwide population-based survey in Taiwan, we aimed to determine the association between polypharmacy and risk of MCI and dementia in individuals aged 65 years and older and the association between polypharmacy and cognitive capacity. We hypothesized individuals with polypharmacy would have a decrease in MMSE scores and an increase in CDR score.

METHODS

Source of Data

This nationwide population-based cross-sectional survey was performed between December 2011 and March 2013. Our target population was identified as residents aged 65 years and older in all 19 counties or cities in Taiwan. From the 2010 census data, we performed computerized multistage random sampling to achieve our nationally representative samples. According to addresses obtained from the Ministry of Health and Welfare of Taiwan and local city governments, our field interviewer would perform an in-person interview. The interrater reliability of the global CDR was good with a κ value of 0.671. Additionally, to promote the quality and reliability of the entered data, experienced supervisors would do logic checks for inconsistency and auditing.[20] The details of the sampling and home visit procedures are described elsewhere.[20–22] This study was approved by the ethics committee at the National Taiwan University Hospital. Written informed consent and permission for interview were received from all study participants or their main adult caregiver.

Measurements of Medical History and Cognitive and Functional Status

Interviews recorded brief demographic data, medical history, and current medication from each recruited participant, a knowledgeable informant who was a relative, and a principal caregiver providing at least 10 hours of direct care for the dementia participant per week. Drug name, frequency, and dosage were checked by our interviewers on the basis of prescriptions and drug containers at home. As in previous studies,[10–12] polypharmacy was defined as taking 5 or more medications, including prescription medication, over-the-counter medication, or Chinese medicine. From the recorded history, our interviewers could detect any mental decline or insidious change of personality and behavior from the baseline status and evaluate whether this decline made impacts on the ability to function or in the daily routine activity. The cognitive impairment could not be explained by delirium and major psychiatric disorders. The Taiwanese Mini-Mental State Examination (TMSE) and CDR were used to assess cognitive status.[23–26] Normal limits for TMSE results were defined as a score > 24 for literate elders and > 13 for illiterate elders.[26]

Diagnostic Criteria and Exclusion Criteria

Core clinical criteria recommended by National Institute on Aging and the Alzheimer's Association (NIA-AA) were used for diagnosis of all-cause dementia and MCI.[3,27] Participants diagnosed as not having dementia were without any conditions listed in the NIA-AA criteria for all-cause dementia, had a CDR score of 0, and had a TMSE score within normal limits after adjustment for education.[3,20,21] Participants who were difficult to diagnose would be reexamined and discussed by a consultant panel consisting of 4 experienced neurologists and 1 clinical

psychologist. Participants who did not fully meet the aforementioned criteria and whose diagnoses were still unclear after a discussion by the consultant panel were categorized in the unclassified group and excluded. Participants with incomplete data or possibly erroneous data were also excluded (Figure 1).

Covariates

Per our previous studies,[20–22] medical comorbidities such as asthma, cirrhosis, and cancer as well as life habits such as good sleep, afternoon nap habit, exercise, and social contact were assessed as the cognition-associated factors. Exercise was defined as physical activity of at least 20 minutes' duration that could make one sweat, ie, swimming, mountain climbing, jogging, exercise walking, dancing, and others. Social activity included attending religious activities; meeting friends, family, or others; and joining club or group activities. "Regular or sometimes" means the frequency was at least once per month. "Good sleep" was determined on the basis of having never complained about insomnia. "Afternoon nap habit" was defined as taking a nap in the afternoon daily. "Habits of" drinking tea, coffee, alcohol; chewing betel nut; or smoking were defined as consumption or use at least 3 times per week.

Statistical Analyses

Chi-square tests and independent *t* tests were used to compare categorical and continuous variables, respectively, between the polypharmacy and non-polypharmacy groups. The logistic regression was conducted to evaluate the association between covariates and MCI or dementia compared with the cognitively normal group. Odds ratio (OR) and its 95% CI were assessed. The linear regression analysis was performed to evaluate the association between covariates and TMSE or CDR score. Variables in the univariate analysis included polypharmacy, age, sex, education level, body mass index (BMI), dementia history in first-degree relatives, lifestyle and habits, and medical comorbidities. All variables with *P* values < .1 in the univariate analysis were included in the multivariate regression model. The variance inflation factor (VIF) and conditional index were used to measure collinearity among factors in the multivariable regression analysis. VIF > 10 or conditional index > 30 indicated collinearities among predictor variables. In addition, the correlation between numbers of medications taken and the risk of MCI/dementia as well as MMSE/CDR scores was also evaluated. Finally, subgroup analysis was conducted to evaluate the interaction between comorbidities and polypharmacy in the TMSE score. All statistical analyses were performed using SPSS version 21.0 for Windows (IBM, Armonk, New York). All tests were 2-tailed, and $P < .05$ was considered statistically significant.

Table 1. Demographic Data of Study Participants in the Non-Polypharmacy Versus the Polypharmacy Group[a]

Variable	Non-Polypharmacy (n = 6,555)	Polypharmacy (n = 867)	*P* Value
TMSE score, mean ± SD	24.50 ± 5.29	23.47 ± 6.35	< .001
CDR score, mean ± SD	0.13 ± 0.30	0.29 ± 0.50	< .001
Cognitive status			< .001
Cognitively normal	5,156 (78.7)	532 (61.4)	< .001
MCI	1,052 (16.0)	214 (24.7)	< .001
Dementia	347 (5.3)	121 (14.0)	< .001
Male	3,209 (49.0)	453 (52.2)	.071
Age, mean ± SD, y	75.32 ± 6.32	77.59 ± 6.91	< .001
Age			< .001
65–74	3,353 (51.2)	328 (37.8)	
75–84	2,617 (39.9)	383 (44.2)	
≥ 85	585 (8.9)	156 (18.0)	
Education, y			.006
0	1,871 (28.5)	221 (25.5)	
1–6	3,059 (46.7)	384 (44.3)	
7–12	1,141 (17.4)	185 (21.3)	
> 12	484 (7.4)	77 (8.9)	
BMI, kg/m^2			< .001
≤ 18	173 (2.6)	34 (3.9)	
18 < BMI ≤ 24	3,426 (52.3)	358 (41.3)	
24 < BMI ≤ 30	2,672 (40.8)	409 (47.2)	
> 30	284 (4.3)	66 (7.6)	
Dementia history in first-degree relatives	203 (3.1)	37 (4.3)	.081
Head trauma	237 (3.6)	76 (8.8)	< .001
Lifestyle and habits			
Regular or sometimes exercise	4,599 (70.2)	567 (65.4)	.005
Regular or sometimes social activity	2,355 (35.9)	301 (34.7)	.498
Drinking tea	1,671 (25.5)	214 (24.7)	.619
Drinking coffee	721 (11.0)	93 (10.7)	.862
Smoking	638 (9.7)	59 (6.8)	.005
Drinking alcohol	427 (6.5)	46 (5.3)	.183
Chewing betel nut	68 (1.0)	6 (0.7)	.465
Good sleep	3,878 (59.2)	361 (41.6)	< .001
Afternoon nap	3,569 (54.4)	494 (57.0)	.168
Comorbidities			
Hypertension	3,050 (46.5)	688 (79.4)	< .001
Diabetes mellitus	1,183 (18.0)	370 (42.7)	< .001
Cerebrovascular disease	228 (3.5)	115 (13.3)	< .001
Hyperlipidemia	1,060 (16.2)	332 (38.3)	< .001
Cirrhosis	18 (0.3)	4 (0.5)	.316
Asthma	116 (1.8)	43 (5.0)	< .001
Cancer	267 (4.1)	61 (7.0)	< .001

[a]Values shown as n (%) unless otherwise noted.
Abbreviations: BMI = body mass index, CDR = Clinical Dementia Rating Scale, MCI = mild cognitive impairment, TMSE = Taiwanese Mini-Mental State Examination.

RESULTS

We interviewed 10,571 subjects and excluded 3,149 cases due to incomplete or possibly erroneous data. A total of 7,422 participants were analyzed in our study. Of these, 468 participants (6.3%) fulfilled the NIA-AA core clinical criteria for all-cause dementia. A total of 1,266 participants (17.1%) were classified with MCI, and 5,688 (76.6%) were cognitively normal (Figure 1). A total of 38.7% of participants with polypharmacy had cognitive impairment, namely MCI or dementia, compatible with previous studies.[11,28,29]

Compared with the non-polypharmacy group, subjects with polypharmacy had a significantly lower mean score on the TMSE (23.47 vs 24.50) and a significantly higher mean score on the CDR (0.29 vs 0.13). The polypharmacy group was older and more educated, had more head injuries, exercised less, smoked less, had poorer sleep,

Table 2. Comparison of Polypharmacy and Demographic Factors in Cognitively Normal Controls Versus Patients With MCI or Dementia by Univariate and Multivariable Logistic Regression[a]

	MCI vs Cognitively Normal				Dementia vs Cognitively Normal			
Variable	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Polypharmacy	1.97 (1.66 to 2.34)	**<.001**	1.75 (1.44 to 2.12)	**<.001**	3.65 (3.08 to 4.32)	**<.001**	2.33 (1.74 to 3.11)	**<.001**
Male	0.63 (0.56 to 0.71)	**<.001**	0.86 (0.74 to 1.00)	**.045**	0.55 (0.48 to 0.64)	**<.001**	0.82 (0.64 to 1.06)	.138
Age, y		**<.001**				**<.001**		
65–74	1.00 (reference group)		1.00 (reference group)		1.00 (reference group)		1.00 (reference group)	
75–84	1.83 (1.60 to 2.09)	**<.001**	1.64 (1.43 to 1.89)	**<.001**	3.13 (2.44 to 4.02)	**<.001**	2.73 (2.09 to 3.57)	**<.001**
≥85	3.25 (2.66 to 3.96)	**<.001**	3.08 (2.48 to 3.82)	**<.001**	13.90 (10.57 to 18.27)	**<.001**	12.08 (8.80 to 16.58)	**<.001**
Education, y		**<.001**				**<.001**		
0	1.00 (reference group)		1.00 (reference group)		1.00 (reference group)		1.00 (reference group)	
1–6	0.38 (0.33 to 0.43)	**<.001**	0.45 (0.39 to 0.52)	**<.001**	0.34 (0.28 to 0.42)	**<.001**	0.56 (0.44 to 0.73)	**<.001**
7–12	0.26 (0.21 to 0.31)	**<.001**	0.33 (0.27 to 0.41)	**<.001**	0.19 (0.14 to 0.27)	**<.001**	0.31 (0.21 to 0.47)	**<.001**
>12	0.23 (0.17 to 0.31)	**<.001**	0.31 (0.23 to 0.43)	**<.001**	0.21 (0.13 to 0.34)	**<.001**	0.37 (0.21 to 0.65)	**.001**
BMI, kg/m^2		.126				**.021**		
≤18	1.00 (reference group)				1.00 (reference group)		1.00 (reference group)	
18<BMI≤24	0.71 (0.50 to 1.00)	.052			0.69 (0.42 to 1.13)	.136	0.89 (0.50 to 1.60)	.703
24<BMI≤30	0.78 (0.55 to 1.11)	.172			0.53 (0.32 to 0.88)	**.014**	0.75 (0.41 to 1.36)	.341
>30	0.82 (0.53 to 1.26)	.365			0.64 (0.33 to 1.21)	.170	0.76 (0.36 to 1.62)	.479
Dementia history in first-degree relatives	0.82 (0.57 to 1.18)	.294			0.21 (0.19 to 0.25)	**<.001**	0.73 (0.34 to 1.56)	.412
Head trauma	1.36 (1.01 to 1.81)	**.039**	1.33 (0.97 to 1.82)	.073	2.52 (1.93 to 3.29)	**<.001**	2.59 (1.70 to 3.94)	**<.001**
Lifestyle and habits								
Regular or sometimes exercise	0.48 (0.43 to 0.55)	**<.001**	0.61 (0.53 to 0.70)	**<.001**	0.14 (0.12 to 0.16)	**<.001**	0.25 (0.20 to 0.32)	**<.001**
Regular or sometimes social activity	0.60 (0.53 to 0.69)	**<.001**	0.81 (0.70 to 0.94)	**.005**	0.23 (0.19 to 0.29)	**<.001**	0.62 (0.47 to 0.82)	**.001**
Good sleep	0.54 (0.48 to 0.61)	**<.001**	0.65 (0.57 to 0.74)	**<.001**	0.46 (0.40 to 0.53)	**<.001**	0.67 (0.54 to 0.84)	**.001**
Afternoon nap	0.91 (0.80 to 1.02)	.111			1.19 (1.03 to 1.37)	**.017**	0.92 (0.74 to 1.16)	.495
Drinking tea	0.51 (0.44 to 0.60)	**<.001**	0.71 (0.60 to 0.84)	**<.001**	0.22 (0.17 to 0.28)	**<.001**	0.32 (0.22 to 0.47)	**<.001**
Drinking coffee	0.50 (0.40 to 0.64)	**<.001**	0.76 (0.59 to 0.97)	**.029**	0.19 (0.12 to 0.28)	**<.001**	0.60 (0.35 to 1.03)	.062
Smoking	0.93 (0.76 to 1.15)	.512			0.38 (0.27 to 0.53)	**<.001**	0.63 (0.37 to 1.05)	.077
Drinking alcohol	0.75 (0.57 to 0.98)	**.033**	1.15 (0.86 to 1.54)	.362	0.28 (0.18 to 0.45)	**<.001**	0.86 (0.44 to 1.68)	.664
Chewing betel nut	1.62 (0.96 to 2.75)	.073	2.38 (1.34 to 4.21)	**.003**	0.46 (0.17 to 1.27)	.135		
Comorbidities								
Hypertension	1.15 (1.02 to 1.30)	**.023**	0.99 (0.87 to 1.13)	.891	1.41 (1.22 to 1.62)	**<.001**	0.81 (0.64 to 1.03)	.083
Diabetes mellitus	1.14 (0.98 to 1.32)	.088	1.01 (0.86 to 1.20)	.862	1.91 (1.63 to 2.23)	**<.001**	1.76 (1.36 to 2.27)	**<.001**
Cerebrovascular disease	2.41 (1.86 to 3.12)	**<.001**	2.20 (1.66 to 2.91)	**<.001**	7.98 (6.41 to 9.93)	**<.001**	4.34 (2.98 to 6.31)	**<.001**
Hyperlipidemia	1.13 (0.98 to 1.32)	.102			0.95 (0.78 to 1.16)	.641		
Cirrhosis	2.63 (1.03 to 6.69)	**.042**	2.49 (0.95 to 6.54)	.065	3.08 (1.15 to 8.21)	**.025**	3.60 (0.77 to 16.89)	.104
Asthma	1.56 (1.06 to 2.28)	**.024**	1.31 (0.87 to 1.98)	.197	2.27 (1.55 to 3.31)	**<.001**	1.82 (0.99 to 3.35)	.053
Cancer	0.86 (0.63 to 1.18)	.362			1.43 (1.07 to 1.92)	**.017**	0.92 (0.56 to 1.52)	.750

[a]*P* values shown in boldface indicate statistical significance.
Abbreviations: BMI = body mass index, MCI = mild cognitive impairment, OR = odds ratio.

and had a higher risk of 4 vascular risk factors, asthma, and cancer (all comparisons were significant; see Table 1). The most common classifications of medications used in the polypharmacy group were cardiovascular drugs, gastrointestinal drugs, psychotropic agents, antidiabetic drugs, and antihyperlipidemic drugs. After adjustment, polypharmacy showed an increased risk of MCI and dementia (OR = 1.75; 95% CI, 1.44 to 2.12; $P < .001$; OR = 2.33; 95% CI, 1.74 to 3.11; $P < .001$, respectively) (Table 2).

Table 3 shows the association between TMSE score and lifestyle factors, medical comorbidities, and other demographic factors in univariate and multivariable analyses. Our results indicated that participants with polypharmacy had a mean 0.51-point decrease on TMSE score. Regarding the impact of lifestyle and habits on TMSE scores in multivariable analysis, there were significantly enhancing effects if participants regularly or sometimes exercised (β = 1.21; 95% CI, 0.98 to 1.44), regularly or sometimes had social activities (β = 0.60, 95% CI; 0.38 to 0.82), and had habits of drinking tea (β = 0.78; 95% CI, 0.53 to 1.03), drinking coffee (β = 0.40; 0.07 to 0.73), or drinking alcohol (β = 0.43; 95% CI, 0.00 to 0.86). There was no influence on TMSE scores in chewing betel nut or afternoon naps in the univariate model or smoking in the multivariable model. There were negative effects if participants had comorbid diabetes mellitus (β = −0.41; 95% CI, −0.67 to −0.16) or cerebrovascular disease (β = −2.20; 95% CI, −2.69 to −1.71), a positive effect with hyperlipidemia (β = 0.63; 95% CI, 0.36 to 0.90), and no effect with hypertension, asthma, cirrhosis, or cancer. Table 3 also demonstrates the association between CDR score and lifestyle factors, medical comorbidities. and other demographic factors. Participants with polypharmacy

Table 3. Association of TMSE and CDR Scores With Polypharmacy and Demographic Factors by Univariate and Multivariable Linear Regression[a]

	TMSE: Univariate		TMSE: Multivariable Model		CDR: Univariate Model		CDR: Multivariable Model	
Variable	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Polypharmacy	−1.03 (−1.42 to 0.65)	**<.001**	−0.51 (−0.84 to −0.18)	**.003**	0.16 (0.14 to 0.18)	**<.001**	0.10 (0.08 to 0.12)	**<.001**
Male	2.38 (2.14 to 2.62)	**<.001**	0.68 (0.45 to 0.92)	**<.001**	−0.06 (−0.07 to −0.04)	**<.001**	−0.02 (−0.03 to 0.00)	**.026**
Age, y		**<.001**				**<.001**		
65–74	0.00 (reference group)		0.00 (reference group)		0.00 (reference group)			
75–84	−1.90 (−2.15 to −1.64)	**<.001**	−1.19 (−1.41 to −0.97)	**<.001**	0.08 (0.07 to 0.10)	**<.001**	0.06 (0.05 to 0.08)	**<.001**
≥85	−4.69 (−5.10 to −4.27)	**<.001**	−3.76 (−4.12 to −3.40)	**<.001**	0.28 (0.26 to 0.31)	**<.001**	0.23 (0.21 to 0.25)	**<.001**
Education, y		**<.001**				**<.001**		
0	0.00 (reference group)		0.00 (reference group)		0.00 (reference group)			
1–6	4.86 (4.60 to 5.12)	**<.001**	3.94 (3.68 to 4.20)	**<.001**	−0.13 (−0.15 to −0.12)	**<.001**	−0.09 (−0.10 to −0.07)	**<.001**
7–12	6.95 (6.62 to 7.27)	**<.001**	5.75 (5.42 to 6.07)	**<.001**	−0.16 (−0.19 to −0.14)	**<.001**	−0.10 (−0.12 to −0.08)	**<.001**
>12	7.23 (6.79 to 7.67)	**<.001**	5.97 (5.52 to 6.42)	**<.001**	−0.16 (−0.19 to −0.13)	**<.001**	−0.10 (−0.13 to −0.07)	**<.001**
BMI, kg/m^2		**<.001**				.414		
≤18	0.00 (reference group)		0.00 (reference group)		0.00 (reference group)			
18<BMI≤24	0.53 (−0.23 to 1.29)	.174	−0.16 (−0.79 to 0.46)	.605	−0.04 (−0.08 to 0.01)	.129		
24<BMI≤30	1.05 (0.29 to 1.81)	**.007**	0.12 (−0.51 to 0.75)	.706	−0.04 (−0.09 to 0.01)	.094		
>30	0.43 (−0.50 to 1.37)	.361	−0.06 (−0.83 to 0.71)	.875	−0.04 (−0.10 to 0.02)	.177		
Dementia history in first-degree relatives	1.54 (0.85 to 2.24)	**<.001**	0.51 (−0.06 to 1.08)	.079	−0.04 (−0.08 to 0.01)	.085	−0.02 (−0.05 to 0.02)	.426
Head trauma	−1.32 (−1.93 to −0.71)	**<.001**	−1.42 (−1.93 to −0.92)	**<.001**	0.17 (0.13 to 0.21)	**<.001**	0.15 (0.11 to 0.18)	**<.001**
Lifestyle and habits								
Regular or sometimes exercise	2.67 (2.41 to 2.93)	**<.001**	1.21 (0.98 to 1.44)	**<.001**	−0.16 (−0.18 to −0.15)	**<.001**	−0.11 (−0.13 to −0.10)	**<.001**
Regular or sometimes social activity	1.96 (1.71 to 2.22)	**<.001**	0.60 (0.38 to 0.82)	**<.001**	−0.08 (−0.10 to −0.07)	**<.001**	−0.03 (−0.04 to −0.01)	**.001**
Good sleep	1.20 (0.96 to 1.45)	**<.001**	0.36 (0.15 to 0.57)	**.001**	−0.07 (−0.09 to −0.06)	**<.001**	−0.04 (−0.05 to −0.02)	**<.001**
Afternoon nap	−0.10 (−0.35 to 0.15)	.436			0.00 (−0.01 to 0.02)	.912		
Drinking tea	2.41 (2.14 to 2.69)	**<.001**	0.78 (0.53 to 1.03)	**<.001**	−0.10 (−0.11 to −0.08)	**<.001**	−0.04 (−0.06 to −0.03)	**<.001**
Drinking coffee	2.27 (1.88 to 2.67)	**<.001**	0.40 (0.07 to 0.73)	**.019**	−0.08 (−0.10 to −0.05)	**<.001**	−0.02 (−0.04 to 0.01)	.127
Smoking	1.31 (0.89 to 1.74)	**<.001**	0.06 (−0.31 to 0.43)	.752	−0.04 (−0.07 to −0.01)	**.002**	0.00 (−0.03 to 0.02)	.939
Drinking alcohol	2.14 (1.64 to 2.65)	**<.001**	0.43 (0.00 to 0.86)	**.049**	−0.06 (−0.10 to −0.03)	**<.001**	0.00 (−0.02 to 0.03)	.758
Chewing betel nut	0.61 (−0.63 to 1.86)	.336			0.00 (−0.08 to 0.07)	.898		
Comorbidities								
Hypertension	−0.09 (−0.34 to 0.15)	.459			0.02 (0.01 to 0.04)	**.002**	−0.01 (−0.02 to 0.00)	.198
Diabetes mellitus	−0.58 (−0.88 to −0.27)	**<.001**	−0.41 (−0.67 to −0.16)	**.002**	0.04 (0.03 to 0.06)	**<.001**	0.02 (0.00 to 0.03)	.053
Cerebrovascular disease	−2.83 (−3.42 to −2.25)	**<.001**	−2.20 (−2.69 to −1.71)	**<.001**	0.27 (0.23 to 0.30)	**<.001**	0.21 (0.18 to 0.24)	**<.001**
Hyperlipidemia	0.83 (0.51 to 1.15)	**<.001**	0.63 (0.36 to 0.90)	**<.001**	0.00 (−0.02 to 0.02)	.800		
Cirrhosis	−0.38 (−2.66 to 1.89)	.741			0.13 (−0.01 to 0.27)	.075	0.10 (−0.03 to 0.23)	.124
Asthma	−0.83 (−1.68 to 0.03)	.058	−0.46 (−1.16 to 0.24)	.198	0.05 (0.00 to 0.10)	.064	0.00 (−0.04 to 0.05)	.896
Cancer	0.17 (−0.44 to 0.77)	.591			0.00 (−0.04 to 0.03)	.912		

[a]*P* values shown in boldface indicate statistical significance.
Abbreviations: BMI = body mass index, CDR = Clinical Dementia Rating Scale, TMSE = Taiwanese Mini-Mental State Examination.

would have a 0.10-point increase in CDR score. Regarding the impact of lifestyle and habits on CDR scores in multivariable analysis, only the following habits revealed positive effects: regular or sometimes exercise (β = −0.11; 95% CI, −0.13 to −0.10), regular or sometimes social activity (β = −0.03; 95% CI, −0.04 to −0.01), good sleep (β = −0.04; 95% CI, −0.05 to −0.02), and drinking tea (β = −0.04; 95% CI, −0.06 to −0.03). Only participants with cerebrovascular disease would have a significant (0.21-point) increase in CDR score. The VIF and conditional index among confounding factors showed there was no collinearity in all models. Regarding the analysis for the number of medications taken, we found a dose-dependent relationship, which means that the more drugs that were used, the higher the risks of MCI or dementia to which the individual was exposed and the lower the cognitive scores that were found (*P* values for trend: risk of MCI: $P < .001$; risk of dementia: $P < .001$; decreasing MMSE score: $P < .001$; increasing CDR score: $P < .001$; see Supplementary Table 1).

Finally, in subgroup analyses (Table 4), polypharmacy had different effects on TMSE score in different groups. For example, polypharmacy had a significant negative effect on TMSE score in patients without diabetes ($P < .001$), but there was no significant effect in patients with diabetes ($P = .994$). Polypharmacy had a slightly larger impact on TMSE score in patients without hypertension (OR = −0.92; 95% CI, −1.61 to −0.22, $P = .009$) than in those with hypertension (OR = −0.42; 95% CI, −0.81 to −0.04; $P = .030$).

DISCUSSION

Our nationwide population-based cross-sectional study was the largest epidemiologic study to demonstrate that

Table 4. Subgroup Analyses for Polypharmacy and TMSE Score in Patients With or Without Specific Comorbidity

		TMSE Score[b]	
Polypharmacy	n	β (95% CI)	*P* Value
Overall	7,422	−0.54 (−0.87 to −0.20)	**.002**
Subgroup			
Hypertension			
Yes	3,738	−0.42 (−0.81 to −0.04)	**.030**
No	3,684	−0.92 (−1.61 to −0.22)	**.009**
Diabetes mellitus			
Yes	1,553	0.03 (−0.58 to 0.57)	.994
No	5,869	−0.82 (−1.24 to −0.40)	**<.001**
Cerebrovascular disease			
Yes	343	−1.32 (−2.78 to 0.15)	.078
No	7,079	−0.40 (−0.75 to −0.05)	**.024**
Hyperlipidemia			
Yes	1,392	−0.39 (−0.94 to 0.16)	.160
No	6,030	−0.62 (−1.04 to −0.20)	**.004**

[a]*P* values shown in boldface indicate statistical significance.
[b]Adjusted by sex, age, education, body mass index, dementia history in first-degree relatives, head trauma, lifestyle and habits, and comorbidities.
Abbreviation: TMSE = Taiwanese Mini-Mental State Examination.

polypharmacy was associated with significantly higher risk of MCI and also confirmed the result of a higher risk of dementia with polypharmacy noted in previous literature. For those patients without hypertension (or diabetes, cerebrovascular disease, or hyperlipidemia), polypharmacy is potentially a more important concern in relation to cognitive impairment. Regarding daily lifestyle and medical comorbidities, our preliminary results suggested education, exercise or social activity at least once per month, drinking tea, and having good sleep might have beneficial effects for cognitive capacity. Age, polypharmacy, head injury, and cerebrovascular disease were associated with declined cognitive capacity.

More recent studies found that a higher percentage of MCI patients may progress to dementia or Alzheimer's disease,[4,7,29] even for those MCI individuals that revert to cognitively normal in the follow-up period, emphasizing the importance of studying MCI.[7] The only previous study, by Oyarzun-Gonzalez et al,[19] found polypharmacy was associated with a nonsignificantly increased risk of MCI (OR = 1.95; 95% CI, 0.4 to 9.43) and nonsignificant decrease in MMSE score (β ± SE = 0.11 ± 0.09 decrease, $P = .23$). The authors considered that their results may have been influenced by a relatively small sample and relatively healthy recruited participants. Compared to a previous study,[30] our percentage of polypharmacy was lower, which may have been contributed to by several factors. First, this was a national health insurance register study with very highly coverage rate, having comprehensively and compulsively reviewed medical records. But some medical behaviors such as doctor shopping, even for the same diagnosis in different facilities on the same day, may provide the opportunity to potentially overestimate the percentage of polypharmacy if it is merely evaluated from the claims data. Additionally, some divergence between the number of medications prescribed and actually taken by patients might be expected, especially in the condition of more prescriptions.[31] Also, the definition of study outcome in the study by Lu and colleagues[30] was the baseline percentage of polypharmacy through 1 year of observation, but we calculated it after 1 home-visit. The final contributing factor was that for those patients who lived in the institution or hospital, usually those with moderate-to-severe physical illnesses, their family at home tended to prefer to refuse to join in our study when contacted. Therefore, the percentage of polypharmacy may be underestimated, but even then our results still demonstrated a significant clinical impact of polypharmacy on cognitive impairment. Differing from previous studies utilizing reimbursement claims data and based solely on prescription records,[10,11,30] our evaluations included actual daily-taken medications in the container, Chinese herbs and medications participants paid for themselves from drug stores, which may better reflect actual administration of medications of participants. Through detailed nationwide random sampling, our results were directly representative of the whole country via a large sample size and a wide age range of the study population (≥ 65 years old). In our findings, approximately 26% of elderly individuals with dementia were identified as receiving polypharmacy, which was a higher prevalence than the in the non-dementia (MCI + cognitively normal) population (11%). We further demonstrated that the prevalence of polypharmacy increased with the severity of cognitive impairment (9% of cognitively normal participants, 17% of those with MCI, and 26% of those with dementia).

Some studies[10,11,32] have reported a higher risk of dementia in patients with polypharmacy. A Finnish cohort study[8] composed of 294 individuals aged 75 years and older in a single community demonstrated declined cognitive capacity as measured by the MMSE in the excessive polypharmacy group (ie, those who took 10 or more medications). Our study also found a negative impact of polypharmacy on CDR score. Additionally, population-based case-control studies using data from the South Korean[10] and Taiwanese[11] national health insurance databases reported a higher risk of dementia for those taking 5 to 9 medications (OR = 2.64 in Korean study and 1.34 in the Taiwanese study) compared with the reference group. Given the door-to-door and in-person evaluation design in our study, we could further evaluate the confounding effects of education, lifestyle and habits, BMI, and family history in the analysis of polypharmacy and cognitive impairment, which was hardly possible to obtain in the register studies. Another recent (Japanese) study[31] conducted in an urban community also found the association between polypharmacy (≥ 6 prescribed medications) and cognitive impairment (MMSE score < 24), although the definitions of polypharmacy and cognitive impairment were different from those in our study. The Japanese study had several similarities with ours, such as cross-sectional design, factors of several vascular comorbidities, and in-person interview for data collection. Conversely, our study used a national population-based survey and further evaluated the risk of specific cognitive disorders, estimated the cognitive association for several life habits, and provided

the potential changes in cognitive capacity as measured by the MMSE or CDR for all variables. Our study suggested a higher likelihood of MCI and dementia occurrences in an aged population with polypharmacy, which should alert practicing physicians to take into consideration the safety of drug overuse in the elderly.

Cognitive impairment resulting from polypharmacy has been commonly documented in association with adverse drug effects and inappropriate medication use,[28,32,33] such as use of anticholinergics, benzodiazepines, or H_2-receptor antagonists,[10,32] especially for the elderly with age-related decreases in metabolic rates. Drugs that easily cross the blood-brain barrier might have a higher risk of brain toxicity due to age-related poor metabolic rate and higher concentrations of central nervous system drugs.[34] We hypothesized that the cumulative effect of inappropriate medication use, including longer duration and more types of medication, might gradually damage the cognitive function or reserve, which may explain our finding of increased prevalence of polypharmacy in patients more severe cognitive impairment. As they age, patients indeed might have increased comorbid physical diseases, and the rates of diseases requiring medications might be higher.[8,21,28,35]Also of note from our previous study,[21] the MCI and dementia groups had significantly higher mean numbers of comorbidities (1.51 and 1.73, respectively) than did the cognitively normal group (1.29). Disease itself might be the direct reason for developing dementia and was the main reason associated with increased number of prescribed medications.[10,11] In the search for the exact mechanism of developing cognitive impairment or dementia, the contribution among potentially inappropriate medications, comorbidities, and anticholinergic burden should be investigated in the future.

In our subanalyses, participants without hypertension (or diabetes, cerebrovascular disease, or hyperlipidemia) had a significantly larger decline in cognitive capacity with polypharmacy, but almost no significant decline when having these diseases. This finding was also mentioned in the Korean population-based study[10] in which, compared with in patients without specific comorbidities, polypharmacy contributed less (even losing statistical significance) to the risk of dementia in patients with specific comorbidities. Lai et al,[11] in their subanalysis, found that in patients with polypharmacy, those without cerebrovascular disease had a higher risk of dementia than those with cerebrovascular disease; meanwhile, the dementia risk in the former group increased greatly along with the increasing number of medications compared with the latter group. We may find that for those patients without hypertension (or diabetes, cerebrovascular disease, or hyperlipidemia), polypharmacy causes greater damage to cognitive capacity. To maintain or enhance patients' cognitive capacity, clinicians should pay more attention to reducing or at least keeping the same the number of prescribed medications. This study was the first to provide evidence of greatly declined MMSE scores due to the impact of polypharmacy in those elderly patients without specific comorbidity.

Cognitive capacity may be positively or negatively affected by lifestyle and habits, comorbidities, and other demographic factors. Patients with higher brain reserve may be able to tolerate more neuropathology and not show any decline in cognitive and functional status, preventing or delaying the onset of dementia, compared with those without this kind of brain reserve or resilience.[1,36] On the basis of our results of enhanced TMSE and declined CDR scores, we confirmed the findings in previous studies[1,37,38] of late-life cognitive reserve–enhancing factors, including physical activity and social activity. In clinical practice, physicians could intuitively persuade patients with high risk of subsequent MCI or dementia to adjust their lifestyle and habits. Additionally, we also provided the evidence for other potentially cognitive reserve–enhancing factors, such as good sleep, drinking tea, and drinking coffee. Although similar findings were noted by previous studies,[39,40] further larger scale cohort studies with longer follow-up periods and focus on the apolipoprotein E genotype would be required to confirm our findings.

This study had several limitations. First, we did not differentiate the subtypes of MCI and dementia in our study groups. Hence, whether there were specific risk factors or protective factors for different subtypes of cognitive impairment could not be investigated. Second, the possibility of misdiagnosis, misclassification of comorbidities, and erroneous recording of medications cannot be completely excluded. We had logical check processes and a consultant panel to deal with the difficult cases, and our research nurse would ask for prescriptions, drug containers, or medical documentation to confirm the prescribed drugs, thus yielding improved diagnostic validity and correctness for recording. Third, some factors such as the exact duration of disease or habits, severity of comorbidities, details of the frequency and specifics of lifestyle and habits, previously received treatment for specific comorbidities, duration of medication use by participants, specific drugs, and potential inappropriate medication use were unavailable in the database and thus we could not assess their effects. Fourth, as a limitation of cross-sectional research, causality between polypharmacy and cognitive impairment (or MMSE or CDR scores) cannot be confirmed in this study and requires further longitudinal cohort studies or case-control studies to replicate. Finally, as mentioned before, the percentage of polypharmacy may be underestimated due to difficulty in contacting those patients who lived in the institution or hospital.

In conclusion, through the in-person interviewing of a national survey, this study is the largest to reveal that polypharmacy might induce a higher risk of MCI and have greater negative impact for elderly patients (aged ≥ 65 years) without hypertension, diabetes mellitus, cerebrovascular disease, or hyperlipidemia. Physicians should pay more attention to arranging cognitive evaluation and should suggest evidence-based interventions such as healthy lifestyle and stopping inappropriate medications for those patients with polypharmacy.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

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Supplementary Material

Article Title: Association of Polypharmacy With Mild Cognitive Impairment and Cognitive Ability: A Nationwide Survey in Taiwan

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List of Supplementary Material for the article

1. **Table 1** The correlation between number of medications use and the risk of MCI/dementia as well as MMSE/CDR scores

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Supplementary Table 1: The correlation between number of medications use and the risk of MCI/dementia as well as MMSE/CDR scores

Number of medications use	MCI v.s. Cognitively Normal		Dementia v.s. Cognitively Normal		TMSE Multivariable model		CDR Multivariable model	
	Adjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value
0 drug	1.00 (Ref. group)		1.00 (Ref. group)		0.00 (Ref. group)		0.00 (Ref. group)	
1 drug	1.15 (0.95 to 1.40)	0.158	1.18 (0.82 to 1.68)	0.370	-0.34 (-0.64 to -0.05)	0.023	0.02 (0.00 to 0.04)	0.109
2 drugs	1.24 (0.99 to 1.56)	0.066	1.57 (1.06 to 2.33)	0.025	-0.57 (-0.92 to -0.22)	0.002	0.03 (0.01 to 0.05)	0.013
3 drugs	1.35 (1.03 to 1.77)	0.030	2.26 (1.46 to 3.49)	<0.001	-0.34 (-0.76 to 0.08)	0.116	0.04 (0.01 to 0.07)	0.007
4 drugs	1.73 (1.29 to 2.31)	<0.001	2.12 (1.28 to 3.54)	0.004	-0.59 (-1.07 to -0.11)	0.016	0.08 (0.04 to 0.11)	<0.001
≥5 drugs	2.20 (1.71 to 2.84)	<0.001	3.88 (2.60 to 5.78)	<0.001	-0.92 (-1.33 to -0.51)	<0.001	0.13 (0.11 to 0.16)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001

MCI: minimal cognitive impairment; OR: odds ratio; CI: confidence interval; TMSE: Taiwanese Mental State Examination; CDR: Clinical Dementia Rating Scale.

Adjusting age, sex, education level, body mass index, dementia history in first degree relatives, Life style and habits, and medical comorbidities.