Vascular Cognitive Impairment in Asia

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Edited by

Koji Abe and Tsong-Hai Lee

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IN MEMORIAM

SIMEON M. MARASIGAN, M.D.
1950-2020

Professor of Neurology and Psychiatry,
University of Santo Tomas, Manila, Philippines
Jose R. Reyes Memorial Medical Center, Manila, Philippines
St Luke's Medical Center, Quezon City, Philippines

Eight to ten hours by car north of Manila on the island of Luzon, is the province of Isabela. Dr. Simeon Mina Marasigan was born and raised in a small rural town in this province, one of four children, on April 21, 1950. After completing his primary and secondary studies, he moved to Manila to study in one of the biggest and oldest universities in the Philippines, the University of Santo Tomas. He completed his preparatory course in this institution to enter the Faculty of Medicine and Surgery. He obtained his diploma in medicine in 1975. He planned to go for further training with the intention of taking surgery as a specialty. However, after several long sessions in the operating room, it eventually dawned on him that the field of surgery was not his calling.

Like a bolt of lightning, he suddenly appeared during one of the busy days at the office of the Department of Neurology and Psychiatry. He came to us applying for a residency position after several months of being in limbo of what to do and trying to cope with the "trauma" he experienced in surgery. Mon, as we fondly called him, finished his residency in the Department of Neurology and Psychiatry, Faculty of Medicine and Surgery, University of Santo Tomas in 1982. He found satisfaction and fulfillment as a neuro-psych resident doctor. We were able to complete several research papers that were presented during the annual neurological meetings.

After his training, he was appointed as an Instructor, the entry level in the Department of Neurology and Psychiatry in the College of Medicine of

the University of Santo Tomas. Additionally, he received a teaching position in one of the medical schools outside Manila, traveling one day each week to teach neuroanatomy in that institution. During one of the Philippine Neurological Association's annual conferences, Prof. Miyoshi, a clinician and neuropathologist from Hyogo University in Japan, was invited to talk on dementia. Coincidentally, Prof. Miyoshi offered a fellowship program on dementia, and I told Mon to take this opportunity to study abroad. He spent one year under the tutelage of Prof. Miyoshi and was able to publish several papers during his training.

When he returned to the country, he resumed teaching and became very active in the residency program of the hospital and the undergraduate curriculum in the College of Medicine. Mon rose in rank from Instructor to Professor in the university, and was appointed as chairman of the department in 2007 and served for the next six years. During this period in 1989, I also invited him to be part of the staff of the Department of Neurology at the Dr. Jose R. Reyes Memorial Medical Center. His interest in teaching and patient care was further demonstrated and admired by the residents of this institution. Through his collaboration with the residents, several papers were produced, presented and published locally and internationally.

Extramurally, he was the past president of the Philippine Neurological Association in 1995 and subsequently became the president of the Philippine Psychiatric Association in 1999. In collaboration with other Asian countries, the ASEAN Neurological Association (ASNA) was formed through his leadership. He was the founding president of this organization in 1995. Likewise, he formed and was the founding president of the Dementia Society of the Philippines in 2002, and held the position for several years. Despite these accomplishments, his thirst for further learning was demonstrated when he went to the Alzheimer's Disease Center in Baylor College of Medicine for a preceptorship rotation.

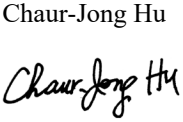
Dr. Marasigan has made a name for himself in the field of dementia, especially in Asia. He was very active in the Dementia Association in Asia, with close collaborations with Prof. Christopher Chen from Singapore and Prof. Koji Abe from Japan. Subsequently, the VasCog Asia Society was also formed with his support and participation. One of his most significant contributions before his death was establishing the VasCog Philippines, which was given recognition by the VasCog Asia Society during the last Asia Pacific Stroke Conference in Manila in 2019. He would often tell me that neurologists, especially those in the field of stroke, should be aware of the psychological and behavioral manifestations of stroke attributable to vascular dementia.

His interest in the future of residents after completing the residency program is quite palpable. He has inspired several young neurologists to train further on dementia in other institutions abroad through his recommendation. These dementia specialists are now back in the Philippines heading the memory and dementia clinics in other hospitals and institutions. The last scientific work that we collaborated on is a chapter in this book that we have written together with two younger colleagues on biomarkers in small vessel diseases.

Mon Marasigan was a mentor, administrator, organizer, researcher, and an inspiration who will surely be missed by his students, colleagues, friends, his patients and, of course, by the VasCog Asia Society members.

Jose C. Navarro, MD, MSc
Koji Abe, MD, PhD
Tsong-Hai Lee, MD, PhD

Blessings from chapter contributors:

No.	Blessings	Signature
1		Yan-Jiang Wang
2	Thank you for your great contribution to VasCog Asia. We will further develop this society.	Toru Yamashita 
3		Koji Abe
4		Jose C. Navarro
5	Thank you for your contribution to	Vorapun Senanarong
6	VasCog Asia. We will follow your steps	Dong-Eog Kim
7	to make this society prosperous.	Paulus Anam Ong
8		Tsong-Hai Lee
9		Man Mohan Mehndiratta
10		
11	I shall always appreciate and remember your smile and great contribution to VasCog Asia.	Chaur-Jong Hu 

CHAPTER ONE

THE EPIDEMIOLOGY OF VASCULAR COGNITIVE IMPAIRMENT IN ASIA

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Introduction

Dementia is the leading cause of disability in the elderly population worldwide. According to World Health Organization (WHO) estimates, there were approximately 43.8 million dementia cases globally in 2016, an increase of 117% from the 20 million in 1990 (G. B. D. Dementia Collaborators 2019, 88-106). In 2005, a Delphi consensus study suggested that the prevalence of dementia in people over 60 years old was 3.9%, and the incidence was 7.5/1000 person-years worldwide. The total number of patients with all-cause dementia was 24 million in 2005, with an incidence of 4.6 million new cases each year. The number of people affected by dementia doubles every 20 years. It is estimated that there will be 81.1 million cases worldwide in 2040 (Ferri et al. 2005, 2112-7). The incidence of dementia increases significantly with age. The average annual incidence is approximately 4/1000 person-years for people aged 65–74 years, 32/1000 person-years for people aged 75–84 years and 76/1000 person-years for people over 85 years (Rajan et al. 2019, 1-7). Most dementia cases occur in people over the age of 75 years, who account for 81% of all patients with dementia (Alzheimer's Association 2020). The population aged over 80 years worldwide will increase from 120 million in 2012 to 391 million by

2050, and the number of dementia patients worldwide will increase from 36 million in 2010 to 115 million by 2050 (Prince et al. 2013, 63-75 e2). The *World Alzheimer Report 2018* estimated that the global number of people affected by dementia and related diseases in the world will triple and reach 50 million by 2050.

Asia has the largest prevalence of dementia patients in the world, with one-quarter of dementia patients worldwide currently living in East Asian countries (Prince et al. 2013, 63-75 e2). Major subtypes of dementia include Alzheimer's disease (AD), vascular cognitive impairment (VCI) or vascular dementia (VaD), Lewy body dementia (LBD), frontotemporal dementia (FTD) and Parkinson's disease dementia (PDD). VaD (a component of VCI) is the second largest subtype of dementia after AD. In recent years, important progress has been made in VCI research. In this chapter, we aim to review the incidence, prevalence and disease burden of VCI in Asia.

Definition of VCI and subtypes

The definition of VCI has undergone several revisions. Hachinski first introduced the concept of multi-infarct dementia (MID) in 1974 to describe a class of cognitive impairments caused by multiple sites of infarction in grey matter (Hachinski et al. 1974, 207-10). In the early 1990s, the diagnostic criteria represented by the Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) and the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) were proposed, and the term VaD began to be widely used (Chui et al. 1992, 473-80; Roman et al. 1993, 250-60). In 2003, O'Brien et al. proposed the term VCI to describe a type of cognitive impairment that has a cerebrovascular pathological basis or that is assumed to be caused by cerebrovascular disease. This term covers various vascular pathological changes that could cause cognitive impairment (Iadecola 2017, 17-42; Iadecola et al. 2019, 3326-44; O'Brien et al. 2003, 89-98; Roman et al. 1993, 250-60).

With the deepened understanding of VCI, updated guidelines and diagnostic standards exist; for example, the consensus standard *Vascular Cognitive Impairment Harmonization Standards* released by the National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network (NINDS-CSN) in 2006 (Hachinski et al. 2006, 2220-41), the scientific statement *Vascular Contributions to Cognitive Impairment and Dementia* released by the American Heart Association/American Stroke

Association (AHA/ASA) in 2011 (Gorelick et al. 2011, 2672-713), the *DSM-V* released by the American Psychiatric Association in 2013 and *Diagnostic Criteria for Vascular Cognitive Disorders* issued by VAS-COG in 2014 (Sachdev et al. 2014, 206-18). The latest diagnostic standard is the *Guidelines from the Vascular Impairment of Cognition Classification Consensus Study* (VICCCS 2017), which provides a clearer explanation of the classification and diagnosis of VCI (Skrobot et al. 2018, 280-92). These guidelines define VCI as a type of cognitive impairment syndrome with evidence of clinical stroke or subclinical vascular brain injury, with at least one cognitive domain impaired. Compared with earlier diagnostic criteria, such as NINDS-AIREN, the VICCCS standard does not require the presence of a certain impairment of memory function or any specific cognitive function domain. Impairment of any cognitive domain can meet the VICCCS standard of cognitive impairment. According to the VICCCS standard, VCI can be divided into mild cognitive impairment and major cognitive impairment (or follow the old name of VaD) by the severity of the cognitive impairment. The determination of severity is mainly based on whether cognitive impairment affects independent living ability. Major VCI is further divided into post-stroke dementia (PSD) and non-post-stroke dementia. Non-post-stroke dementia can be identified by neurological imaging or pathological examination, including subcortical ischaemic vascular dementia (SIVaD), multi-infarct dementia (MID) and mixed dementia (MixD). These classifications are not absolute or exclusive of each other, as VCI patients are likely to have multiple vascular pathological changes (Skrobot et al. 2018, 280-92).

Following these diagnostic guidelines, a series of epidemiological studies were conducted on VCI or VaD in Asia during the past two decades. This chapter aims to discuss the incidence, prevalence, economic burden, disease burden and trends of VCI and VaD in Asia.

Incidence of VCI

There have been several incidence studies of VCI in Asia, and most conducted during the past two decades chose VaD as the research object. The currently available studies on VaD were mainly conducted in East Asia (Table 1). In 2007, a community-based cohort study in Beijing estimated that the incidences of dementia and VaD in the Chinese population over 60 years old are approximately 9.0/1000 and 3.2/1000 person-years, respectively (Li et al. 2007, 73-9). Another multicentre epidemiological study conducted

in Beijing, Xi'an, Shanghai and Chengdu in 2016 yielded similar findings, suggesting that the incidences of dementia and VaD in people over 65 years of age are approximately 12.14/1000 and 3.13/1000 person-years, respectively (Yuan et al. 2016, 262-71). A systematic review of epidemiological studies from 1990 to 2010 estimated that the incidences of dementia and VaD are 9.87/1000 and 2.42/1000 person-years, respectively, in people over 60 years of age (Chan et al. 2013, 2016-23). The Hisayama study, which was a prospective cohort study of cerebrocardiovascular diseases conducted in the general Japanese population, reported follow-up data from 1985 to 2002 and found that the incidences of dementia and VaD in the population over 65 years were 32.3/1000 and 9.5/1000 person-years, respectively (Matsui et al. 2009, 366-70). The report of another two cohorts in 2017 suggested that the incidences of dementia and VaD were 25.9/1000 and 9.3/1000 person-years, respectively, between 1988 and 1998 and 41.6/1000 and 10.6/1000 person-years, respectively, between 2002 and 2012 in a Japanese community (Ohara et al. 2017, 1925-32). Incidence studies in other regions of Asia are lacking.

According to the available data, the overall incidence of VaD in the Chinese population is similar to that in the rest of the world, but the incidence is relatively higher in the Japanese population. The incidence of VaD in people over 65 years old in Western countries, for example the United States, Canada and Italy, is approximately 1.8–3.3/1000 person-years, and there has been a downward trend in recent years (Hebert et al. 2000, 1487-93; Ravaglia et al. 2005, 1525-30; Ruitenberg et al. 2001, 575-80). According to data from the Hisayama study, which was conducted in the Fukuoka metropolitan area in two cohorts of people of the same age, the incidence of VaD was 9.3/1000 person-years in 1988 and 10.6/1000 person-years in 2002, with no significant change between the two time periods. However, these incidences in the Japanese population are significantly higher than those in the Western population. Although advances have been achieved in the control of vascular risk factors in recent years, age-related diseases such as metabolic syndrome might have offset these protective factors. This may explain the high incidence of VaD in the Japanese population. In addition, whether genetic factors cause a higher incidence of VaD in the Japanese population remains to be investigated (Ohara et al. 2017, 1925-32).

Table 1. Incidence of dementia, AD and VaD (/1000 person-years) in Asia

Cities	Dementia	AD	VaD	Age	References
Beijing and other cities	12.14	8.2	3.13	≥ 65 y	(Yuan et al. 2016, 262-71)
Beijing	9.0	5.4	3.2	≥ 60 y	(Li et al. 2007, 73-9)
Beijing and other cities	9.87	6.25	2.42	≥ 60 y	(Chan et al. 2013, 2016-23)
Taipei	12.8	5.4	4.1	≥ 65 y	(Liu et al. 1998, 1572-9)
Fukuoka	25.9–41.6	14.6–28.2	9.3–10.6	≥ 65 y	(Ohara et al. 2017, 1925-32)
Fukuoka	32.3	14.6	9.5	≥ 65 y	(Matsui et al. 2009, 366-70)

Prevalence of VCI

A series of prevalence surveys aimed at VCI have been conducted in different regions of Asia over the past 20 years. Overall, the prevalence of VaD is between 0.6% and 4.2% for people over 65 years old in Asia, with VaD cases accounting for approximately 15–40% of all cases of dementia (Table 2). Among the general population over 65 years old, the lowest reported prevalence was 0.6% in a community survey in Ragama (De Silva et al. 2003, 711-5), and the highest was 4.2% in a multicentre population survey of seven regions, including Tsukuba, Sendai, Joetsu, and so on (Ikejima et al. 2012, 120-3). In recent years, several large-scale epidemiological studies have been conducted in East Asia. Two multicentre population surveys conducted in five regions (Changchun, Beijing, Zhengzhou, Guiyang and Guangzhou) in 2005 and four regions (Beijing, Xian, Shanghai

Table 2. Prevalence of dementia, AD and VaD (%) in the elderly population of Asia

Cities	Dementia	AD	VaD	VaD/Total (%)	Number of subjects	Age	References
Changchun and other cities	5.14	3.21	1.50	29.2	10,276	≥ 65 y	(Jia et al. 2014, 1-9)
Beijing and other cities	2.8	1.6	0.8	25.5	87,761	≥ 60 y	(Dong et al. 2007, 619-24)
Beijing and other cities	3.0	1.9	0.9	30.9	105,866	≥ 60 y	(Zhang et al. 2012, 1333-7)
Ji County	7.7	5.4	1.7	22.1	5,578	≥ 60 y	(Ji et al. 2015, 294-302)
Shanghai	2.99	2.16	0.62	20.7	15,910	≥ 55 y	(Zhao et al. 2010, 151-8)
Beijing and other cities	4.6	3.5	1.1	27.6	34,807	≥ 65 y	(Zhang et al. 2005, 447-53)
Shanghai	5.0	3.6	0.8	16.0	3,141	≥ 60 y	(Ding et al. 2014, 114-22)
Beijing	2.51	1.38	0.94	37.5	1,593	≥ 60 y	(Li et al. 2007, 73-9)
Hong Kong	6.1	3.6	2.2	36.1	1,034	≥ 70 y	(Chiu et al. 1998, 1002-9)
Hong Kong	19.4	14.3	4.3	22.2	737	≥ 60 y	(Lam et al. 2008, 135-48)
Tsukuba and other counties	22.5	15.2	4.2	18.7	3,394	≥ 65 y	(Ikejima et al. 2012, 120-3)

Fukuoka	6.8–11.3	1.5–7.2	1.5–2.4	-	6,983	≥ 65 y	(Ohara et al. 2017, 1925-32)
Fukuoka	4.4–8.3	1.1–3.8	1.5–2.5	-	5,079	≥ 65 y	(Sekita et al. 2010, 319-25)
Tajiri	8.5	7.2	1.3	15.3	1,654	≥ 65 y	(Meguro et al. 2002, 1109-14)
Ama-Cho	11.8	7.5	1.8	15.3	884	≥ 65 y	(Wada-Isoe et al. 2009, 101-6)
Seoul and other cites	8.1	5.7	2.0	24.7	6,141	≥ 65 y	(Kim et al. 2011, 281-91)
Seongnam	5.2	3.9	0.9	17.3	714	≥ 65 y	(Jhoo et al. 2008, 270-6)
Yonchon County	7.1	4.2	2.4	33.8	1,037	≥ 65 y	(Suh et al. 2003, 606-12)
Seoul and other cites	9.2	5.7	2.1	22.8	17,703	≥ 65 y	(Kim et al. 2014, 903-12)
Kerala	2.9	1.6	1.1	37.9	1,934	≥ 65 y	(Shaji et al. 2005, 136-40)
Chiang Mai	2.35	1.76	0.29	12.3	1,492	≥ 45 y	(Wangtongkum et al. 2008, 1685-90)
Ragama	3.98	2.85	0.6	15.1	703	≥ 65 y	(De Silva et al. 2003, 711-5)
Singapore	1.6	0.9	0.7	43.8	14,817	≥ 50 y	(Sahadevan et al. 2008, 2061-8)

and Chengdu) in 2014 reported similar VaD prevalence among community residents over 65 years old, approximately 1.5% (Jia et al. 2014, 1-9) and 1.1% (Zhang et al. 2005, 447-53), respectively. Three systematic reviews analysed epidemiological studies of dementia and suggested that the prevalence of VaD in people over 60 years of age was 0.6% (Dong et al. 2007, 619-24), 0.9% (Zhang et al. 2012, 1333-7), and 1.09% (Zhu et al. 2019, 578) in people over 55 years of age. The long-term Hisayama study reported a VaD prevalence of 1.5–2.5% in Fukuoka (Ohara et al. 2017, 1925-32; Sekita et al. 2010, 319-25). The results of a random Korean population survey conducted in 15 districts were similar to those in the Hisayama study, with a VaD prevalence of 2.0% (Kim et al. 2011, 281-91). Similarly, an epidemiological meta-analysis reported that the prevalence of VaD was approximately 2.1% in the Korean population between 1990 and 2013 (Kim et al. 2014, 903-12).

The prevalence of VaD in Asia and other regions of the world is impacted by similar factors, such as age, sex and vascular risk factors, as reflected in studies with analysis stratified by demographic data. However, the available data also show several particular epidemiological characteristics of VaD in Asia.

Firstly, there are large differences in the prevalence of VaD among different regions in Asia. Studies in Kerala, Singapore and Ragama have shown that the prevalence of VaD in the elderly population over 65 years old is between 0.6% and 1.7%. However, studies in Japanese and Korean populations reported a higher prevalence of up to 4.2%, with most ranging from 2% to 2.5%. Secondly, the overall prevalence of VaD is higher in Asia than in Western countries. The prevalence of VaD in people over 65 years is approximately 0.6–4.2% in Asia, which is higher than the 1.0–1.6% in Europe (Lobo et al. 2000, S4-9; Ott et al. 1995, 970-3). This is supported by several interracial epidemiological studies that suggest that VaD is more common in Asia (Jorm and Jolley 1998, 728-33; Mayeda et al. 2016, 216-24; Mehta and Yeo 2017, 72-83). However, in some regions of Asia (for example South Asia), the prevalence of VaD in the population over 65 was estimated to be approximately 0.6–1.7%, which is similar to that in Western countries. Thirdly, the proportion of patients with VaD is higher, while the ratio of AD cases/VaD cases is lower in Asia than in Western countries. VaD is currently considered to be the second leading cause of dementia after AD in North America and Europe, accounting for approximately 15–20% of all cases of dementia (Lobo et al. 2000, S4-9; Rizzi et al. 2014, 908915). In contrast, the proportion of VaD in Asia has been reported to be approximately 30% (Chan et al. 2013, 2016-23; Jhoo et al. 2008, 270-6). A

community survey in Kerala even showed that VaD accounted for as high as 37.9% of cases among people with dementia over 65 years of age (Shaji et al. 2005, 136-40). Several earlier community surveys in the Japanese population, such as the 1992 Okinawa study (Ogura et al. 1995, 373-80), the 1996 Hiroshima study (Yamada et al. 1999, 189-95) and the 1998 Tajiri study (Meguro et al. 2002, 1109-14; Meguro et al. 2004, 3-10), all reported lower AD/VaD ratios than those reported for other regions of the world: 1.85, 1.85 and 3.33, respectively. However, the Ama-Cho study (2008) showed that the ratio was 4.12 (Wada-Isoe et al. 2009, 101-6), which was close to that in Europe and the United States.

The prevalence of VaD is likely to be affected by many factors, including socioeconomic level, geographical environment, culture, education level and genetics. At present, there is little VaD epidemiological data in Asia. It is uncertain how much these factors contribute to the difference in prevalence of VaD among different regions in the world. More epidemiological research needs to be carried out in Asia.

The existing studies above have revealed the epidemiological characteristics of VCI in Asia. However, research designs and methods, such as diagnostic criteria, epidemiological sampling methods and screening methods vary among previous studies, resulting in large variations in the reported incidence and prevalence of VCI. In addition, demographic differences such as race, culture, age structure of the population, natural mortality and socioeconomic characteristics are all sources of variation in the prevalence of VCI (Kasai et al. 2010, 667-78). Therefore, it is necessary to adopt a standardized and consistent research methodology to obtain accurate epidemiological data of VCI in Asia.

Economic burden

Dementia places a huge burden on patients and their caregivers, as well as on social health care capabilities. With the rapid increase in the elderly population, dementia has become the main cause of disability in this demographic (Alzheimer's Association 2020). The global burden of disease study has shown that disability-adjusted life years (DALYs) from dementia account for approximately 10.4% of all neurological diseases, ranking third on average globally (stroke 42.2%, migraine 16.3% and meningitis 7.9%) (G. B. D. Neurology Collaborators 2019, 459-80). A global cost of illness (COI) study published in 2017 revised the estimates in the *World Alzheimer Report* of 2010 and showed that there were 46 million dementia patients

worldwide, and a total of $817.9 billion in costs were generated annually, which was roughly equivalent to Indonesia's gross domestic product (GDP) in 2015 (Wimo et al. 2017, 1-7). By 2030, patients with dementia are expected to incur up to $2 trillion in costs annually (Alzheimer's Disease International 2018).

Low- and middle-income countries face a greater burden of dementia-related diseases than high-income countries. There were an estimated 17 million VCI/VaD patients globally in 2010 (Wimo et al. 2013, 1-11 e3), which cost up to $200 billion annually, and many dementia patients live in developing countries (G. B. D. Study Collaborators 2015, 743-800). It is worth noting that more than half of people with dementia live in low-income countries, and the costs incurred by these countries account for only 13% of the global costs. In low- and middle-income countries, dementia-related costs account for only approximately 0.2–0.5% of the GDP, lower than the 1.4% of the GDP accounted for in high-income countries (Wimo et al. 2017, 1-7). The majority of countries in Asia are low- and middle-income countries. It is estimated that Asia has approximately 49% of the total dementia patients in the world. Due to the lack of data on the economic burden of VCI/VaD, this article refers to research data on the economic burden of dementia in Asian countries and regions.

A multicentre study based on a Chinese population published in 2017 surveyed 3,098 patients with dementia and their caregivers and showed that the average annual cost of a single patient was estimated to be approximately $19,144. The total national cost of dementia was approximately $167.74 billion, of which direct medical expenses (such as outpatient expenses) accounted for 32.5%, direct non-medical expenses (such as nursing equipment) accounted for approximately 15.6% and indirect expenses (such as patient or caregiver loss of work due to illness) accounted for approximately 51.9%. The economic burden of dementia accounted for approximately 1.47% of China's GDP in that year, which was higher than the world average (1.09%). This study also predicted that by 2050, domestic dementia-related costs would reach $1.89 trillion, and worldwide costs would reach $9.12 trillion (Jia et al. 2018, 483-91).

Another epidemiological survey completed in Shandong showed that dementia-related annual costs increased from $900 million in 1990 to $47 billion in 2010 and predicted that these costs would exceed $69 billion by 2020 and $114 billion by 2030. In addition, 81.3–94.4% of the total costs were from informal care, which accounted for the highest proportion of costs (Xu et al. 2017, 18-26).

According to a survey conducted in the dementia clinic in Taipei, treatment for patients with mild, moderate or severe dementia costs approximately $14,609, $20,463 and $29,398 per year, respectively. Informal care expenditures borne by family members accounted for the highest proportion of costs, representing approximately 40% of costs across subgroups of dementia with differing severity (Ku et al. 2016, e0148779). Community research studied the burden of dementia in 2007–2008 in 100,802 randomly selected subjects in Kolkata and revealed that the total years of life lost (YLL) was 47.13/100,000 and the years lived with disability (YLD) ranged from 1.87/100,000 to 16.95/100,000 depending on the clinical severity of dementia. The overall disability adjusted life years (DALYs) lost per 100,000 cases related to dementia during the year 2007–2008 were 74.19 (Banerjee et al. 2017, 605-14).

A Japanese population-based analysis of disease expenditure showed that between 2002 and 2014, the total socioeconomic burden of dementia increased by 2.06–2.27 times, from $184–242 billion per year to $379–551 billion per year, of which informal care accounted for 37.7–57.2% of the total expenditure. In the context of increased ageing, a series of measures aimed at reducing the disease expenditure of patients with dementia have been introduced into Japanese communities in recent years. In response to campaigns promoting self-care by the healthy elderly and earlier diagnosis of dementia, as well as shifting nursing care from in-facilities to in-home and in-community (so-called ‘deinstitutionalization’), the average cost per patient was reduced by 0.82–0.91 times (Hanaoka et al. 2019, 231-7).

Previous studies did not investigate the specific economic burden of VCI. Patients with VCI are likely to have more admissions and hence may have higher disease-related costs than patients with other subtypes of dementia (Hill et al. 2005, 43-50).

Disease burden

A multicentre case-control study conducted in seven cities, including Chongqing, Chengdu, Guangzhou, Fuzhou, Lanzhou, Wuhan and Shenyang, showed that dementia patients have more comorbidities than non-dementia patients, and the Charlson Comorbidity Index (CCI) was higher in dementia patients. The mean CCI of all patients in this study was 3.0 ± 1.9; the CCI of VaD patients was 3.4 ± 1.8, which was significantly higher than the 3.0 ± 2.1 of AD patients ($P < 0.01$). VaD patients still had a high CCI after adjustment for age and sex, suggesting that VaD patients have more

comorbidities than those with other subtypes of dementia. Among VaD patients, the most common comorbidities included cerebrovascular diseases, hypertension, diabetes, hemiplegia, myocardial infarction and chronic lung disease (Wang et al. 2017, 703-10). In addition, 4.3% of VaD patients in this study had cancer, which is higher than the five-year cancer prevalence rate in East Asia (0.56%) (Bray et al. 2013, 1133-45).

Another case-control study conducted in Beijing reviewed data of 34,888 inpatients from 2002 to 2012 and showed that neurological and respiratory diseases were the most common coexisting diseases in patients with dementia over 60 years of age. Moreover, patients with dementia had longer hospital stays than those without dementia. Based on this study, VaD patients had more comorbidities of neurological diseases (26.9%), cardiovascular diseases (23.8%) and endocrine and metabolic diseases (10.9%) than those with other subtypes of dementia (Li et al. 2013, 393-401).

A cross-sectional survey of people in Taipei showed that among the general population over 65 years of age, both the average number of comorbidities and the CCI were higher in the mild cognitive impairment and dementia groups than in the control group. The numbers of patients who suffered at least three comorbidities were greater in the MCI and dementia groups than in the control group (MCI 20.9%, dementia 27.3% and control 15%). The comorbidities associated with MCI and dementia included hypertension, diabetes mellitus, cerebrovascular diseases, cirrhosis and asthma, with hypertension and diabetes mellitus being the most common (Chen et al. 2017, e0175475).

Some dementia comorbidity studies have shown similar conclusions in East Asia. Clinical Research for Dementia of South Korea (CREDOS) started a longitudinal hospital-based registry study of dementia patients. It was found that hypertension (48.9%), anaemia (23.9%) and diabetes mellitus (22.3%) were the most common comorbidities in patients with dementia included in the cohort (Park et al. 2011, 1219-26). A small outpatient observational study conducted in Tokyo showed that 38.9% of 113 patients with AD had three or more coexisting diseases. Specifically, 48% of patients with AD had lipid abnormalities, 42% had hypertension and 19% had diabetes mellitus (Sakurai et al. 2010, 216-7).

In general, the average CCI of patients with dementia is approximately 2, but the quantity and category of common comorbidities vary across different regions. These findings suggest that people with dementia, including VCI, are more likely to have multiple chronic diseases, such as diabetes, hypertension, chronic lung disease, heart disease and inflammatory

diseases. Cardio-cerebrovascular diseases are more closely related to VaD than to other dementia subtypes, which further aggravates the disease burden of VaD patients. Due to the complex nature of comorbidities, more attention needs to be taken to generate an individualized, specific and comprehensive approach for VCI/VaD care.

Perspectives on the epidemiology of VCI in Asia

Mostly owing to better education, improvements in living conditions and advances in medical practice, the prevalence and incidence of dementia have remained steady or decreased over the past 30 years (Wu et al. 2017, 327-39). The life expectancy of dementia patients has been increasing. The Neuropathology Group of the Medical Research Council cognitive function and ageing study (MRC-CFAS) reported a statistically significant decrease in the prevalence of dementia between 1993 and 2011 (Matthews et al. 2013, 1405-12; Matthews et al. 2016, 11398). Similar results have been reported in other prospective studies, such as the Framingham heart study (2016), Rotterdam study (2012) and Einstein ageing study (2017). These studies suggested that the prevalence and incidence of AD and other subtypes of dementia in high-income Western countries declined by 20% to 50% during the last 30 years (Ahmadi-Abhari et al. 2017, j2856; Cerasuolo et al. 2017, 1081-8; Choi et al. 2018, S29-S37; Crimmins et al. 2018, S20-S8; Derby et al. 2017, 1345-51; Hall et al. 2009, 227-33; Langa et al. 2017, 51-8; Qiu et al. 2013, 1888-94; Rocca et al. 2011, 80-93; Satizabal et al. 2016, 523-32; Schrijvers et al. 2012, 1456-63; Wiberg et al. 2013, 2627-34; Wimo et al. 2016, 387-96; Wu et al. 2017, 327-39). In addition to the constant improvements in education and living conditions, intensive control of cardiovascular risk factors is a key reason for such decreases.

The declining trend observed in Western high-income countries represents a positive sign that dementia is preventable. However, with the continued ageing of the population, the numbers of cases of AD and other subtypes of dementia are increasing. Compared with the relatively optimistic situation in developed regions and countries, the situation surrounding dementia in low- and middle-income regions and countries remains concerning. Most countries and regions in Asia are developing and have a higher risk for dementia than other areas of the world. According to the Delphi study, 71% of people in developing countries will have dementia by 2040. The number of patients with dementia will be double that in 2001 in developed countries, while it will triple in developing countries (Ferri et

al. 2005, 2112-7). The *World Alzheimer Report 2015* estimated that there were approximately 9.8 million and 22.9 million patients with dementia in East Asia and all of Asia, representing almost a quarter and a half of the worldwide cases, respectively. It is also predicted that the number of people with dementia will increase by 223–264% in low- and middle-income countries by 2050, accounting for 68% of the global dementia burden (Prince et al. 2013, 63-75 e2). The situation in high-income countries, such as Japan or South Korea, is also serious (Dodge et al. 2012, 1-11; Kim et al. 2011, 281-91; Okamura et al. 2013, 111-8; Sekita et al. 2010, 319-25; Wu et al. 2015, 793-801). Currently, there is no obvious evidence suggesting that the prevalence and incidence of dementia will decrease in Asia in the near future (Choi et al. 2018, S29-S37; Crimmins et al. 2018, S20-S8; Freedman et al. 2018, S48-S56; Langa 2015, 34; Larson et al. 2013, 2275-7; Loef and Walach 2013, E51-5; Rajan et al. 2019, 1-7; Rocca et al. 2011, 80-93; Sheffield and Peek 2011, 274-83; Weuve et al. 2018, S73-S81).

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