Evaluation of Prevalence Data for Vascular Dementia

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The monetary cost of dementias worldwide in 2015 was $818 billion, and it will increase to over a trillion dollars by 2018 (Prince et al., 2015). Aging is the greatest risk factor for dementias, and the increasing percentage of the global population over age 65 will result in continued growth in this cost, as well as associated human impacts (Mayo Clinic, 2017). The World Health Organization (2017) indicated deaths due to dementias more than doubled between 2000 and 2015, making it the seventh leading cause of global deaths in 2015.

These impacts have provided support for many studies concerning the leading type of dementia, Alzheimer's disease (AD). However, prevalence and other data related to the second most predominate type, vascular dementia (VaD), are far less available (Gorlick et al., 2011). This paper reviews what information is available on the global prevalence of VaD by first discussing the health issue and defining a research strategy for finding current relevant data. Using that strategy, several applicable data sources or studies are reviewed, and their results and characteristics are described. The paper concludes with a discussion of how the identified prevalence data might be reported as well as potential needs for additional research.

Overview of VaD and Epidemiological Challenges

Dementia rates are growing in all regions of the world, primarily related to population aging (Rizzi, Rosset, & Roriz-Cruz, 2014). Neurologic conditions, including dementia, were estimated by the Global Burden of Disease 2010 Study as the third leading cause of years lived with disability at global level (Horton, 2012). Additionally, the number of people affected by dementia globally will approximately double every 20 years, from 46.8 million in 2015, to 74.7 million in 2030, and 131.5 million in 2050 (Prince et al., 2015).

While AD is the most predominate type of dementia worldwide with approximately 60% of cases, VaD is second at about 20-30%, with Lewy body, and frontotemporal dementia composing the remainder (Prince et al., 2012). However, robust prevalence data for VaD is lacking and inconsistent. This is partially attributed to the lack of methodological uniformity among studies and the utilization of different definitions for VaD (Rizzi et al., 2014).

Currently, there are multiple diagnostic criteria for dementia associated with vascular issues. Additionally, these multiple criteria are utilized inconsistently in VaD epidemiological studies to date (Prince et al., 2012). To address this issue for future studies, the American Heart Association (AHA) suggested future epidemiological studies utilize a common and more inclusive term, Vascular Cognitive Impairment (VCI), for vascular related dementias (Gorlick et al., 2011). The definition of VCI refers to the entire spectrum of vascular-related cognitive impairment, and includes the more severe cognitive and functional conditions typically associated with past VaD definitions plus other prodromal or milder conditions. As such, the definition of VCI proposed by the AHA is "A syndrome where there is evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain based on two factors: a demonstration of the presence of a cognitive disorder by neuropsychological testing, and a history of clinical stroke or presence of cerebrovascular disease (CVD) by neuroimaging that suggests a link between the cognitive disorder and the vascular disease" (Gorlick et al., 2011, p. 11).

Another attempt to refine, expand, and standardize the definition of VaD is included in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V). VaD is redefined in DSM-V as "a temporal relationship between a cerebrovascular event and onset of cognitive impairment, with memory loss usually secondary to impairment in frontal/executive

function" (Sinha, Bharath, & Chandra, 2015, p 2). Based upon this definition, the Alzheimer's Association (2014) estimates that approximately 20-30% of all dementias are VaD.

Although these new definitions of vascular related dementias are similar, they are not fully adopted across the healthcare industry. As such, most epidemiological studies to date have not used these common definitions, thus increasing the variance in prevalence rates. Additionally, VaD epidemiological studies over the last 30 years lack a common evaluation approach and consistent age or other population characteristics for population grouping. These factors increase the challenge of analyzing sources of VaD prevalence data (Rizzi et al., 2014).

Literature Search Strategy

Given the epidemiological issues, the search strategy for relevant VaD prevalence literature included a multi-tiered approach. First, multiple databases (PubMed, Ovid, Cochrane, EMBASE, and Google Scholar) were initially searched using the terms "Dementia and Epidemiology" present in any searchable field for English only articles for the last 5 years. Regional descriptors were not included since the intent is to examine VaD data globally. The search returned 11,727 entries and was thus further reduced by limiting the search to the title or subject field, resulting in 76 entries. A second search using the same databases and parameters but with the terms "vascular dementia and epidemiology" resulted in 1 entry. A third search with the same databases and parameters using the terms "vascular dementia and prevalence", revealed 6 entries. The third search was modified to include years from 2000 and beyond, resulting in 16 entries. Titles and abstracts from the superset of all title/subject searches were examined for relevance and 21 documents were downloaded for in-depth analysis based upon relevance. Seven additional studies were discovered by examination of primary sources cited in the selected documents. Finally, 3 final sources were identified from a review of 3 relevant

websites including the US Administration on Aging, the US HealthyPeople 2020 program, and the Alzheimer's Association.

From the list of 31 reviewed sources, 22 were excluded based on (a) lack of VaD prevalence data; (b) data from research prior to 2000; (c) a very small sample size or geographic focus, such as a survey conducted in only one city in one country; (d) lack of supporting data, and; (e) lack of strong statistical or process approaches in the methods. Two exception were made. First, several meta-analyses were included that utilized some data prior to 2000, but only if most studies included in the meta-analysis were from 2000 or later. Additionally, one large study with only overall dementia prevalence was included since it included high quality global data. All the final selected nine reports were either meta-analyses or primary research studies.

Most of the exclusions were due to the use of data obtained prior to 2000. This issue was also highlighted by the large global meta-analysis reviews which indicated that only approximately 30% of the dementia prevalence studies over the last 37 years were conducted since 2000 (Prince et al., 2015). The majority, especially in developed nations, were conducted in the 1990's, but the reason is not clear. The other primary reasons for exclusion were the use of a small sample size or a sample from a limited area within a country. Both issues would limit the ability of the research to represent the overall population of a country or region.

Results from Literature Search

Appendix A provides summary information for the nine selected research articles, with the meta-analyses listed first followed by the individual studies. At an overall level, most of the nine studies provided a consistent linkage of age to the prevalence of VaD and overall dementia, despite definitional and methodological differences. Excluding the early onset dementia (EoD) analysis, the studies indicated a VaD prevalence range of 0.7% to 2.5%, primarily varying by

age, with some differences by region. In a similar manner, overall dementia ranged from 2.4% to 13.9%, again primarily varying based on the age grouping used in the study. Overall dementia prevalence is included to help evaluate the percentage of overall dementia attributable to VaD. This amount ranged from 15.6% to 40.0% in the nine studies, with lower percentages of dementia caused by VaD occurring in the US, Europe, and Korea. Differences in overall dementia prevalence rates by multi-country region are also present, with Asia (excluding Japan), Southern Africa, and Eastern Europe having lower rates. The global meta-analysis effort did not normalize and report VaD prevalence across multi-country regions, so that level of VaD prevalence is not identifiable other than by approximation from the VaD percentage range found across other studies.

Based on an in-depth examination of the studies, the quantitative meta-analyses provided the highest quality data since these reviews benefitted from a larger amount of consolidated data and robust statistical and other processes to normalize the results. In addition to the meta-analyses, the Sekita et al. (2010) Japanese study provided more extensive data than other individual studies. The four different meta-analyses and the Japanese studies are examined in more detail, while summaries of the other 5 articles are included in appendix A.

The most comprehensive meta-analysis with VaD data is the Chinese study (Zhang et al., 2012). It included over 100,000 participants across 48 studies from 1980-2010 and reported VaD, AD, and overall dementia prevalence by time and region. This analysis showed the percentage of dementia from VaD and its prevalence decreased from 2006-2010, a finding that is similar for many Asian regions. Overall dementia prevalence in China increased from 1980-2005 but was flat from 2006-2010, with a lower dementia incidence rate offsetting an increased duration of the disease over the last 5 years. Finally, the prevalence of overall dementia and

VaD was higher in urban areas, with an assumed link to the Westernization of diets in those areas. The detail provided to show these differences was a major area of strength of the study, as was the size of its combined sample. However, the meta-analysis provided few details on its statistical analysis process and no measures of homogeneity for the included studies.

Unlike the Chinese study, the Prince et al. (2015) review did not include the prevalence data for different types of dementias, but it contains the largest and most current set of data. Over 640,000 participants across 276 studies were included, covering most regions of the world. The analysis also reported chronological information revealing trends by region over time. Since 2009, dementia prevalence increased in Asia and most developing nations, while it decreased in Western Europe and North America. However, because of the overall aging of the World population, the actual number of people affected by dementias increased in all regions and is expected to continue to double every 20 years across all areas. Due to challenges in examining the data, the study did not provide rationale for the differences in regional prevalence chronology. It did note that while people are living longer with dementia, the increased effects of that on prevalence were offset by lower incident rates in more developed nations. The overall scope of the meta-analysis was a major strength in the study as was its detail regarding study selection and statistical methods and measures. In terms of dementia sub-type information, a major weakness was the absence of any VaD or AD prevalence data. While a rough approximation of the range of AD or VaD prevalence could be produced using relative percentage information from other studies, the result would be a very wide range given the variance in VaD percentages in other studies.

The European meta-analysis was also well-done but had fewer included studies. The review included 2,346 participants across 11 studies (Lobo et al., 2000). As a strength, it

reported gender and age group sub-populations for VaD, AD, and overall dementia prevalence. This information showed an increase in prevalence of all dementias with age as well as the dominance of AD at 54% of all cases and VaD at 16%. The data also revealed variances among gender and region in terms of VaD prevalence, but the data did not provide meaningful rationale for this. In addition to the smaller size, the major weakness of the European meta-analysis was the age of the included studies, but a more recent European study was not available. The European meta-analysis also lacked statistical details to verify its quantitative approach.

Similar to the European review, the African meta-analysis only included 11 studies, but it covered over 11,000 participants (George-Carey et al., 2012). The review provided robust data for larger Western African countries, but a weakness was the lack of studies for Eastern areas. The prevalence of overall dementia and VaD was higher than previous estimates, though still below more developed regions/nations. The researchers believe the prevalence in Africa will continue to increase due to increasing life expectancies. They further noted a lack of studies as a weakness in their analysis and suggested significant additional research was thus needed. An additional weakness was the lack of statistical sophistication in the quantitative meta-analysis. To determine age prevalence and overall disease burden, a simple meta-regression analysis of the data from the different studies was used versus a more robust normalization approach.

Although not a meta-analysis, the Sekita (2010) Japanese study provided a very thorough analysis and the ability to examine trends over time for a sample from the same geographic area. By utilizing an area and sample with similar attributes to the overall Japanese population, this study provided a good approximation of Japanese national prevalence. The study showed that overall dementia prevalence increased strongly from 1985 to 2005, while VaD prevalence increased only modestly, resulting in a material drop in the relative percentage of VaD dementia.

While the study was strong overall with very good statistical analysis and reporting, its weaknesses did include variation in participation rates over the years, making chronological comparison more difficult. Additionally, it was focused in one geographic region, although robust efforts were included to assure relative demographics to the overall Japanese population.

Summary

The currently available overall dementia and VaD prevalence data helps show the major importance of the issue. While studies to date suffer from inconsistency in disease definitions and methods, even the research with lower VaD prevalence rates demonstrates a huge number of affected people. This fact provides the justification for increased focus and future analysis. To be effective, these future studies should (a) utilize the new standardized DSM-V dementia definitions, (b) include analysis and data for overall dementia, AD, and VaD, (c) include consistent population subgroups, and; (d) utilize standard methods such as the "Updated Guidelines for Evaluating Public Health Surveillance Systems" from the CDC (CDC, 2001).

Prior to the completion of future studies, robust meta-analysis and current, well-executed national studies can be used to report VaD prevalence. To normalize these studies and show the linkage of age and VaD prevalence data, scatterplots graphing age and VaD prevalence could be utilized. A "best-fit" line in the scatter-plot could be calculated to show the most likely global VaD prevalence by age, since most of the variance across studies was based on age group. A simple example of this with partial data from the studies in this analysis is shown in Appendix B. Showing the variance across geographic regions would be more difficult, since many of the current regional studies have different age groupings. However, multiple bar graphs could be utilized to show VaD prevalence by region, per age grouping. These approaches would help demonstrate VaD prevalence and help justify future more consistent VaD data.

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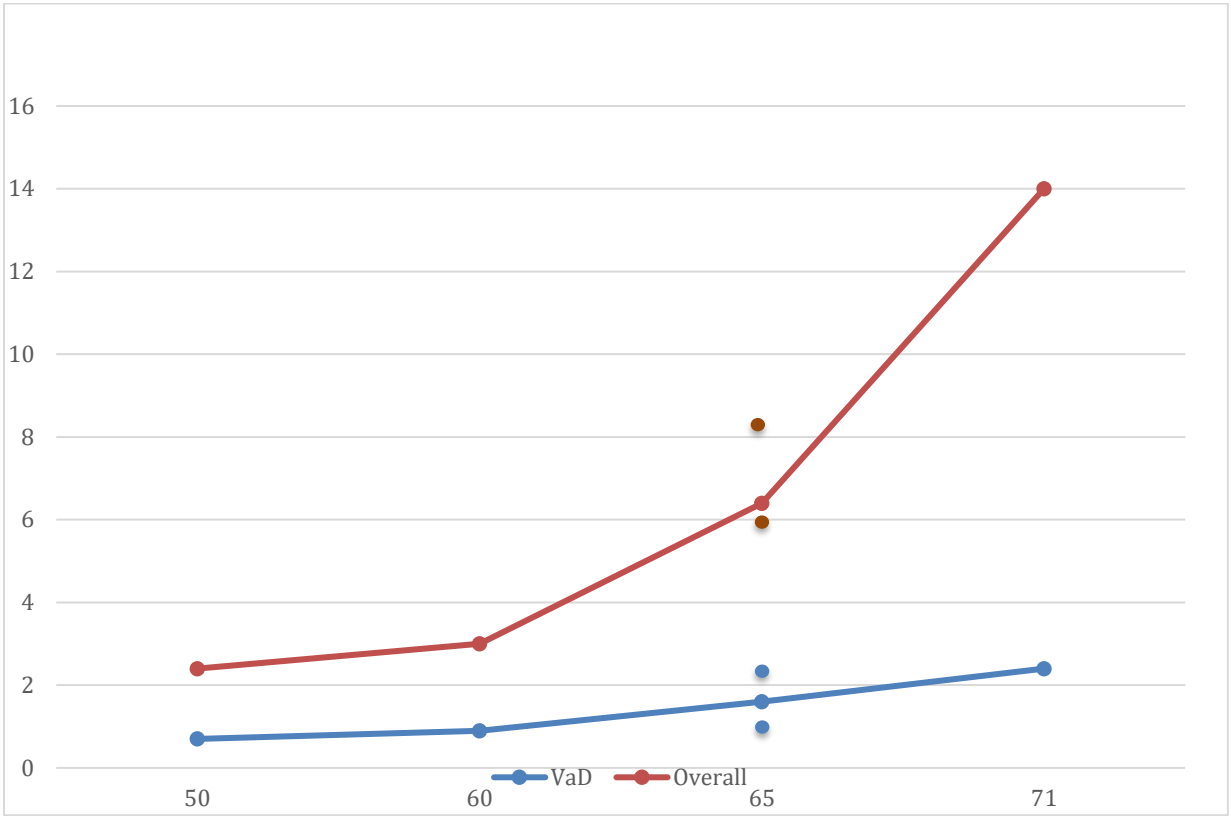
Appendix A
Sources of Dementia Prevalence Data

Source	Design	Reported Dementia Prevalence	Strengths/Weaknesses
Zhang et al. (2012).	• Chinese study • Meta-analysis of 48 studies, over 100,000 participants • Studies included from 1980-2011	• VaD, 0.9%, age >= 60: (95% CI=0.6-1.1) • Overall, 3.0%, age >= 60: (95% CI = 2.4-3.9) • 30.0% of overall dementia from VaD	• Large meta-analysis over time and multiple regions • Reported data is 2010 but is also compared to 1990 meta-analysis to show trends • Absence of detail on statistical methods and measures
Prince et al. (2015).	• Global Study • Meta-analysis of 276 studies grouped into 8 Global Regions, over 640,000 participants • Studies included from 1980-2015	• All data are % for overall dementia, age >= 60 • Australasia, 6.7% • Asia-Pacific, 7.0% • Other Asia, 4.4% • North America, 6.4% • Other Americas, 6.3% • Western Europe, 6.9% • Eastern Europe, 4.4% • North Africa, 6.0% • Other Africa, 3.4%	• Latest and most comprehensive meta-analysis of global dementia • Only includes prevalence data for overall dementia and not sub-types • VaD could be inferred to a degree from other studies describing VaD percent of overall total as 15-40%
George-Carey et al. (2012).	• African study • Meta-analysis of 10 studies, over 10,000 participants • Studies included from 1983-2011	• VaD, 0.7%, age > 50: CI calculated but not reported • Overall, 2.4%, age > 50: CI calculated but not reported • 29.2% of overall dementia from VaD	• Meta-analysis with good coverage of Western Africa but very limited in Eastern Africa • Smaller size relative to some meta-analyses but most studies were from 2002-2009 • Robust, well-defined search strategy but a less sophisticated quantitative meta-analysis
Lobo et al. (2000).	• European Study • Meta-analysis of 11 studies across East and West Europe, 2346 participants • Studies included from 1990's	• VaD, 1.6%, age >= 65: CI not reported • Overall, 6.4%, age >= 65: CI not reported • 15.6% of overall dementia from VaD	• Large geographic region meta-analysis • Not all areas in Europe, primarily Eastern Europe, included • Smaller size relative to some meta-analyses and older data • Lack of statistical detail
Sekita et al. (2010)	• Japanese Study • Neuropsychological testing and surveys of 1711 participants • Surveys in 1985, 1992, 1998, 2005	• Data from 2005 survey • VaD, 2.5%, age >= 65: (95%CI = 1.7–3.2) • Overall 8.3%, age >= 65: (95%CI = 7.0-9.5) • 30.1% of overall dementia from VaD	• Very thorough statistical analysis and detail • Sample analyzed to ensure representation of overall Japanese population • Includes trend data as well as male/female breakdown

Source	Design	Reported Dementia Prevalence	Strengths/Weaknesses
Ikejima et al. (2014)	• Japanese Study • Survey of EOD diagnosis in 12,747 medical institutions covering a 9-million-person area, 2,469 participants • Survey in 2007	• VaD, 0.019%, age 18-64: CI calculated but not reported • Overall, 0.052%, age 18-64: CI calculated but not reported • 36.5% of overall dementia from VaD	• Very thorough statistical analysis and detail • Large sample size representing a comprehensive portion of the country • Provide data on less studied age group
Plassman et al. (2007).	• Cross-US study • Survey of 856 participants obtained from 22,000 pool based on specific attributes • Survey in 2003	• VaD, 2.4%, age >= 71: (95%CI = 1.4–3.5) • Overall, 13.9%, age >= 71: (95%CI 11.4–16.4) • 17.3% of overall dementia from VaD	• Large initial dataset • Potential for selection bias but rigor used to reduce risk • Included age stratification over 71 (71-79,80-90, 90+), but no ages <71
Jhoo et al. (2008).	• Korean study • Survey of 1,118 participants in urban population • Survey in 2006	• VaD, 1.0%, age >= 65: (95% CI = 0.3-1.8) • Overall, 6.3%, age >= 65: (95% CI = 4.5-8.1) • 15.8% of overall dementia from VaD	• Good statistical process and detail • Relatively smaller sample size and limited geography • Sample did not include institutionalized elders, but this is a small relative number in Korea
Molero, Pino-Ramírez, & Maestre. (2007).	• Venezuelan Study • Clinical data evaluation of 2,438 participants, obtained from larger pool based on specific attributes • Survey in 2003	• VaD, 1.9%, age >= 55 (95%CI =1.4–2.4) • Overall 7.4%, age >= 55 (95% CI = 6.4–8.5) • 26% of overall dementia from VaD	• Large initial dataset, no selection bias • Includes a wider range of ages than most surveys • Specific and age standardized to one country • Older than some studies

Appendix B
Prevalence of VaD and Overall Dementia by Age Group



Data from Prince, Molero, and Ikejima studies excluded for better example of potential visual effect