American Journal of Alzheimer's Disease & Other Dementias®
2019, Vol. 34(1) 49-56

DOI: 10.1177/1533317518813550
journals.sagepub.com/home/aja
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Prevalence and Causes of Cognitive Impairment and Dementia in a Population-Based Cohort From Northern Portugal

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Abstract

Background: Vascular disease may play an important role in the epidemiology of dementia in countries with high stroke incidence, such as Portugal. **Objective:** To assess the prevalence and etiology of cognitive impairment in a population-based cohort from Portugal. **Methods:** Individuals ≥55 years (n = 730) from the EPIPorto cohort were assessed using the Mini-Mental State Examination and the Montreal Cognitive Assessment. Those scoring below the age-/education-adjusted cutoff points were further evaluated to identify dementia or mild cognitive impairment (MCI) and to define its most common causes. **Results:** Thirty-six cases of MCI/dementia were identified, corresponding to adjusted prevalences of 4.1% for MCI and 1.3% for dementia. The most common cause of MCI/dementia was vascular (52.8%), followed by Alzheimer's disease (36.1%). **Conclusion:** These findings highlight the importance of vascular cognitive impairment in the epidemiology of dementia in Portugal and carry an important public health message regarding its prevention and management, possibly extending to other countries with a high-stroke burden.

Keywords

epidemiology, dementia, mild cognitive impairment, Alzheimer's disease, vascular dementia

Background

Cognitive impairment and dementia are increasingly frequent worldwide, impacting the quality of life of millions of patients and their families.[1] Dementia is estimated to affect 2% to 3% of individuals aged 70 to 75 years and 20% to 25% of those aged 85 years or more, globally.[1] In Western societies, the age-standardized prevalence among those older than 60 years has been estimated at 6% to 7%[2] and is expected to remain at this level in the next decades,[2] contributing to a greater number of cases in the population due to the demographic aging. Alzheimer's disease (AD) is the most frequent type of dementia in Western countries, while vascular cognitive impairment and dementia (VaD) is generally described as the second cause.[3]

Epidemiological data are needed to assess the potential for preventive interventions and resource distribution toward the most adequate health responses. The only published epidemiological study on the frequency of cognitive impairment and dementia in Portugal was performed in 2003, showing prevalences of 2.7% for dementia and 12.3% for all causes of cognitive impairment, including psychiatric and congenital disorders, in the population aged between 55 and 79 years.[4] Additional studies are needed to replicate these findings in different populations and to monitor their variation over time.

The present study aims to assess the prevalences of cognitive impairment and dementia in the EPIPorto population-based cohort and to identify their most frequent causes.

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Methods

Study Design and Protocol

EPIPorto is a population-based closed cohort assembled between 1999 and 2003 in the city of Porto, representative of dwellers ≥18 years (n = 2485).[5] Porto is the second largest urban center in Portugal, with a heterogeneous sociodemographic population that consisted of approximately 300 thousand inhabitants at the time.[5] Random digit dialing of landline telephones was used to select households. Then, within each household, a permanent resident aged at least 18 years was selected by simple random sampling.

The present study was based on the 2013 to 2015 reevaluation of the cohort. From 1126 cohort members aged ≥55 years, a total of 730 were evaluated (63.3% participation) in 2 steps, namely, a screening phase and a clinical evaluation. When comparing the screened and the nonscreened population, there were no significant differences in sex (38.3% men in nonparticipants vs 38.8% among participants; $P = .94$), while the nonscreened were older (mean difference in age, 7.8 years, 95% confidence interval [95% CI]: 6.8-8.8) and slightly less educated (mean difference in schooling, 1.6 years, 95% CI: 1.0-2.1). Concerning vascular risk factors, the prevalences of hypertension (43.1% vs 29.8%; $P < .01$) and diabetes (9.6% vs 4.3%; $P < .01$) were higher among nonparticipants, but there were no significant differences regarding the prevalence of dyslipidemia (44.2 in nonparticipants vs 39.6% in participants; $P < .001$).

Screening was performed using the Portuguese validated versions of the Mini-Mental State Examination (MMSE)[6] and the Montreal Cognitive Assessment (MoCA)[7] tests; the Beck Depression Inventory,[8] and other instruments and questionnaires were also used during this evaluation which aimed to assess the current health status and sociodemographic determinants. Participants who scored below the validated cutoff points for the Portuguese population in either of the cognitive screening tests (MMSE: 22 for 0-2 years; 24 for 3-6 years and 27 for ≥7 years of schooling[6]; MoCA: age- and education-adjusted defined as 1.5 standard deviation [SD] below the mean of the normative sample[7]) were selected for the clinical evaluation. This comprised a clinical interview and examination, performed by a trained neurologist using a standard clinical protocol, including the clinical assessment of higher cognitive functions, a complete anamnesis and the standardized search for memory complaints using the Portuguese version of the Subjective Memory Complaints Scale.[9] Participants were asked to bring a close relative or other surrogate to assess the presence and impact of cognitive impairment in daily activities. The clinical records of all participants selected for the clinical examination were reviewed to identify any previously established diagnoses of neurological or psychiatric disorders as well as results from brain imaging and relevant laboratory results. This search was performed in the 3 public hospitals of Porto (*Hospital de São João*, *Hospital de Santo António*, and *Hospital Magalhães Lemos*). Based on the clinical evaluation results, the results from the cognitive screening tests and the clinical records, participants were classified by a neurologist as having (1) no psychiatric or neurologic affection; (2) depression or anxiety; (3) static/reversible cognitive impairment; and (4) progressive cognitive impairment, further classified as mild cognitive impairment (MCI) or dementia. Mild cognitive impairment was defined as the presence of subjective cognitive complaints over a period of at least 6 months, reported by the patient or family members, in the presence of impairment according to the MoCA test (1.5 SDs or more below age- and education-adjusted norms), without clinical depression and without impairment in daily activities.[10] Dementia was considered present when participants fulfilled the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-V*) definition for major neurocognitive disorder[11] (significant cognitive impairment in at least one cognitive domain representing a significant decline from a previous level of functioning that interferes with independence in everyday activities). The probable etiology was defined by the neurologist who performed the neurological assessment, using all clinical, imaging, and laboratory data retrieved from health records, based on the *DSM-V* criteria for each nosological entity.[11] When a new diagnosis was established during this clinical assessment, the neurologist wrote a letter to the participant's general practitioner, providing all clinical information, and recommending an investigation and management plan, including complementary studies (that were later retrieved for etiological diagnosis). In the individuals who did not participate in the clinical evaluation, any relevant diagnoses identified in the clinical records search that were established by neurologists or psychiatrists and complied with the previously defined criteria were also included in the estimates.

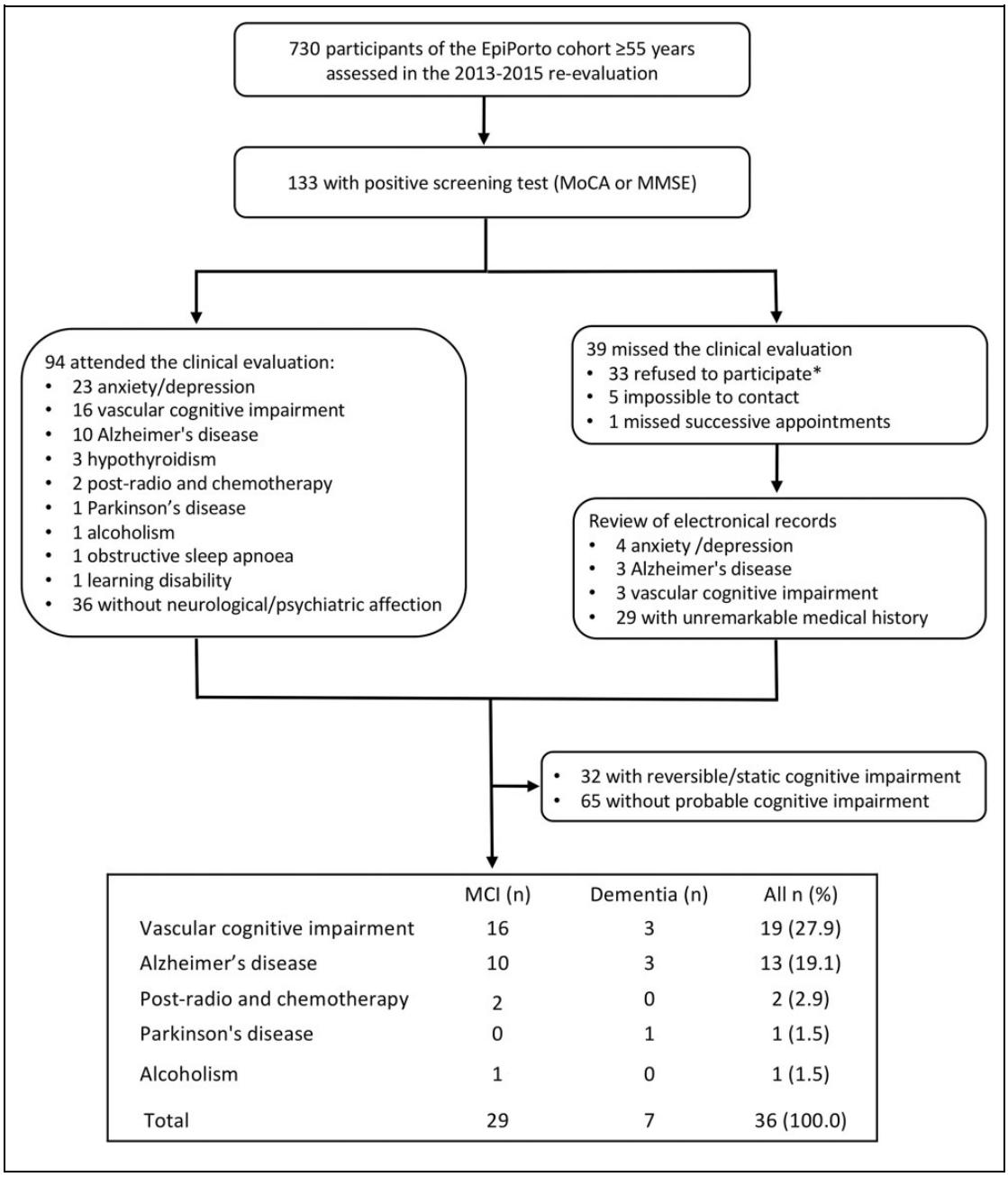
Figure 1 depicts the flow of participants through the steps of the study. From the 730 participants screened, 133 (18.2%) presented a score suggestive of a possible cognitive impairment. Among the latter, 94 were evaluated by a neurologist to confirm and classify the cognitive impairment, while a clinical evaluation could not be performed in 39 participants who were classified regarding the presence of cognitive impairment using data from clinical records alone.

Ethical Issues

All participants provided written consent, and specifically allowed access to their electronic clinical records, and referral of the diagnosis and investigation plan to their general practitioner, with the possibility to opt out of any of the study procedures. In cases of cognitive impairment, written consent was also obtained from a valid surrogate. The study was approved by the institutional ethics committee and by the national data protection authority.

Statistical Analysis

Comparisons of continuous variables between sample groups were performed using the Student *t* test or the Mann-Whitney



	MCI (n)	Dementia (n)	All n (%)
Vascular cognitive impairment	16	3	19 (27.9)
Alzheimer's disease	10	3	13 (19.1)
Post-radio and chemotherapy	2	0	2 (2.9)
Parkinson's disease	0	1	1 (1.5)
Alcoholism	1	0	1 (1.5)
Total	29	7	36 (100.0)

Figure 1. Flowchart of participants through the steps of the study and final results on the frequency of mild cognitive impairment (MCI) and dementia.

U test, depending on whether the distribution of the values was a bell-shaped curve or not, respectively. For categorical variables, the Pearson χ^2 test or the Fisher exact test were used.

The age-standardized prevalences of MCI and dementia were computed using the direct method. Data from the last census, in 2011, of the Portuguese population were used as the standard populations for the city of Porto and for the population of Portugal. For the European population, the European Standard Population 2013 was used.

The statistical analysis was performed using Stata version 11.2 (StataCorp 2009, Stata Statistical Software: Release 11, College Station, Texas: StataCorp LP).

Results

From the 94 participants assessed in the clinical evaluation, cognitive impairment was confirmed in 58. In the 39 participants who did not undergo a clinical evaluation, the review of electronical records resulted in a diagnosis in 10 cases, while the others had an unremarkable medical history. In all, a total of 68 participants (47 women and 21 men) were classified as having cognitive impairment (Figure 1).

Regarding the distribution of the scores of the 2 screening tests used (Figure 2), the MoCA scores presented a nearly normal distribution for all participants and, as expected, a shift

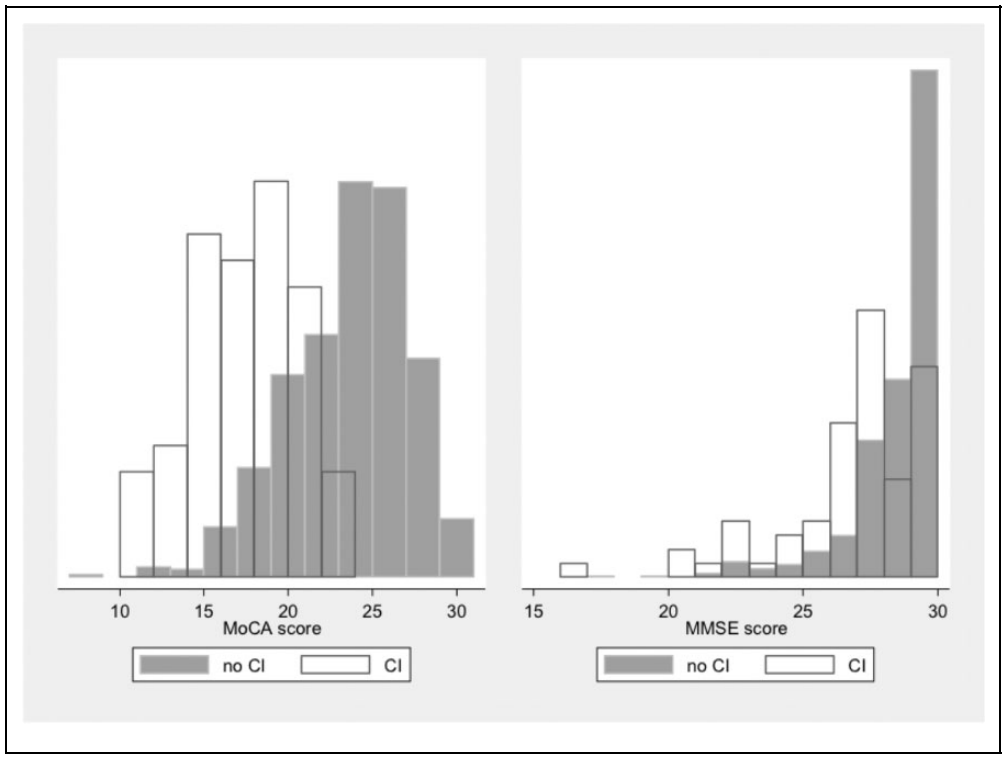


Figure 2. Distribution of the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) scores for participants with and without cognitive impairment.

to the left was observed in those with cognitive impairment. For the MMSE, the distribution of the scores was asymmetric and suggested a ceiling effect, with most of the results equal to the maximum value of the test. Although a shift to the left was seen among participants with a psychiatric or a neurologic affection in relation to participants without these conditions, a considerable proportion of the MMSE scores were at the maximum value, and there was a substantial overlap in the scores between cognitively affected participants and the remaining participants.

The prevalences of all causes of cognitive impairment, including static and reversible etiologies, were 9.3% (7.5% in men and 10.5% in women), 10.3% when standardized for the Porto population, 9.6% for the Portuguese population, and 9.8% for the European standard population.

In 32 (47%) participants, cognitive impairment was attributed to a static or reversible affection, the most common being anxiety/depression (n = 27) followed by hypothyroidism (n = 3), with 1 case of learning disability and one of obstructive sleep apnoea.

A total of 36 cases of cognitive impairment due to MCI or dementia were identified, corresponding to prevalences of 4.0% (5.3% in men and 3.1% in women) for MCI and 1.0% (0.4% in men and 1.3% in women) for dementia (Supplementary Table). The age-standardized prevalences were 4.1% for MCI and 1.3% for dementia, when using both the standard populations of Porto and Portugal. When standardizing these results for the European population, the estimates were 4.0% and 1.0%. A probable diagnosis of AD was established in 13 (36.1%) cases, whereas 19 (52.8%) were diagnosis with probable VaD. One patient presented dementia in the context of Parkinson disease. There were 2 cases with a clear history of progressive MCI after radiotherapy and chemotherapy treatments for cancer and 1 patient with MCI due to chronic alcoholism. Using the education-adjusted MMSE cutoff points, only 17.7% of participants later classified with MCI and dementia were correctly identified as positive in the screening strategy. Using the predefined 1.5 SD age- and education-adjusted cutoff points of the MoCA test, we identified 97.1% of participants with MCI and dementia, while using the age- and education-adjusted 2.0 SD cutoff points resulted in 61.8% being identified. Among the participants selected in the screening step by scoring below the 1.5 SD cutoff points, the frequency in which MCI and dementia were not confirmed was 77.1%.

The sociodemographic characteristics of participants with MCI and dementia in comparison with those having no cognitive impairment are presented in Table 1. The former were significantly older and less educated and presented lower scores for the MoCA and MMSE screening tests.

Discussion

In this study, we identified age- and sex-standardized prevalences of 1.3% for dementia and 4.1% for MCI, with VaD contributing to an important number of these cases.

Table 1. Sociodemographic Characteristics of Participants.

	General Population, No CI		MCI and Dementia		
	No.	% or (p25-p75)	No.	% or (p25-p75)	*P* Value
Sex					
Women	402	60.7	20	55.6	.537
Men	260	39.3	16	44.4	
Age, years	66.0	(62.0-73.0)	71.5	(65.5-78.0)	.007
Age-group					
55-64	262	39.6	8	22.2	.037
65-74	270	40.8	14	38.9	.822
75-84	108	16.3	12	33.3	.020
≥85	22	3.3	2	5.6	.354
Education, years	9.0	(4.0-13.0)	6.0	(4.0-10.0)	.037
Education					
<12	453	68.4	31	86.1	.025
≥12	209	31.6	5	13.9	
MoCA score	24.0	(21.0-26.0)	17.0	(15.0-19.0)	<.001
MMSE score	29.0	(27.0-29.0)	27.0	(26.0-28.0)	<.001

Abbreviations: CI, cognitive impairment; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

In the previous MCI and dementia survey in a Portuguese population, the prevalence of dementia was higher at 2.7%.[4] This could be explained by the higher socioeconomic and educational level and the younger average age of the population of the city of Porto. Indeed, the study conducted in 2003 found a prevalence of 1.6% for dementia when including participants from the urban setting alone. When considering only the cognitive impairment cases with no dementia due to neurological causes, the prevalences of MCI were 3.9% for the urban and 4.3% in the rural populations, also in line with our current observations. Both studies report lower overall prevalences of dementia and MCI in Portugal than usually described for Western Europe, where the average prevalence, standardized for the European population, ranges from 1.6% in the 60 to 64 years age-group to 24.7% in 85 to 89, with 6.9% for those ≥60 years.[12] When looking more closely at the regional context of Mediterranean countries, the prevalence of dementia in Italy ranges from a minimum of 5.9%[13] (for a sample with an age range of 65-97 years) to a maximum of 28.4%% (for a sample with age ≥75 years),[14] while in Spain the dementia prevalence ranges from a minimum of 5.9%[15] to a maximum of 14.9%[16] in populations aged ≥65 years. Several factors could explain the observed differences in prevalence. Regarding environmental factors, there is evidence that the consumption of omega-3 and omega-6 acids, particularly in fatty fish, is associated with a reduced risk of dementia and AD.[17] Portugal is the country with the highest seafood consumption in Europe, higher than in Italy or Spain, particularly concerning fatty fish.[18] A similar scenario is observed in Japan, where the consumption of fish is also very high,[19] and AD prevalence is low.[20] Another additional factor that may contribute to the lower prevalences of dementia and AD is the seemingly lower prevalence of carriers and homozygous for the ϵ4 allele of the APOE gene in Portugal when compared to other European countries, with the only prevalence estimate being 9.8%[21] compared to the 12.7% European average.[22]

We found 2 cases of progressive cognitive impairment related to postradiotherapy and chemotherapy. It is known that patients undergoing certain forms of cancer chemotherapy may develop cognitive impairment ("chemo-brain"), and postradio cognitive impairment has been reported even in cases where such therapy was not directed to areas of the brain.[23] In a study performed in the same setting of Northern Portugal, the incidence of cognitive impairment at 1 year after diagnosis was estimated to be 8.1% in women with breast cancer.[24] Since the incidence of most types of cancer increases with age, similar to cognitive impairment and dementia, and taking into account the life expectancy increase in high-income countries, cancer-related cognitive decline may truly become a public health issue. More investigation in this field is needed in order to determine the types of cancer and therapeutic agents more likely to cause this effect as well as means of prevention and treatment.

The main cause of MCI and dementia identified in this study was vascular cognitive impairment (52.8% for VaD vs 36.1% for AD). The only previous study performed in Portugal also showed a high prevalence of VaD, equal to that of AD (38.7%)[4] as a cause of dementia, and adding the reported prevalences of all vascular causes accounted to 48% of cognitive impairment.[4] Taken as a whole, the present results emphasize the role of vascular disease in the epidemiology of MCI and dementia in the Portuguese population. It is interesting to note that these findings are different from the results of studies performed in other Southern European populations.[20,25] A study aiming to assess the incidence and subtypes of dementia in 3 elderly people (age 65 years and older) populations of central Spain revealed that most participants had AD (71.4%), while only 11.2% had VaD.[26] An Italian study on the prevalence of clinically diagnosed dementing disorders among individuals older than age 59 found prevalences of 2.6% for AD and 2.2% for multi-infarct dementia.[27] Another Italian study, performed with individuals aged 65 to 84, showed that AD was the most common type of dementia (53%), while VaD accounted for 27% of the overall number of cases.[28] Although the younger age of participants enrolled in the present study could contribute to a lower prevalence of AD in relation to VaD, these findings are not surprising if we consider that Portugal presents a considerably higher incidence of stroke than other similar Western European regions,[29] and cerebrovascular disease is the main cause of death, unlike Spain or Italy, where the main cause of death is ischemic heart disease.[30]

An explanation for such a high risk of cerebrovascular disease and vascular dementia in Portugal is lacking. The prevalence of hypertension, a major risk factor for stroke and VaD,[31] is high (42.2%)[32] but within the figures reported in other European countries. However, it is estimated that the percentage of nonmedicated younger patients with hypertension and the

percentage of patients under monotherapy are far above the European average.[33] This may help explain the high frequency of VaD in Portugal. Another possible explanation is the high prevalence of atrial fibrillation and the reduced frequency of anticoagulant therapy utilization in the Portuguese population.[34]

Only a few regions in the world present a higher prevalence of VaD than AD, namely, Japan and the Middle East.[20] Among developed countries, Japan seems to have the lowest prevalences of dementia in general and of AD in particular.[20] Most VaD cases in Japan are due to multiple lacunar infarcts or small-vessel disease, while VaD secondary to large cortical infarcts represent a minor percentage. This is probably due to a higher incidence of lacunar stroke in Japan compared to European countries, where thromboembolism plays a major role in stroke etiology.[35] A previous epidemiological study showed that lacunar infarcts represented 39.1% of the total number of ischemic infarcts in a Portuguese population.[36] This is a high percentage compared to the results of other European studies, where the prevalence is heterogeneous but does not reach 30% in any study.[37] Since cerebral small-vessel disease is the most prevalent vascular lesion associated with vascular cognitive impairment,[38] the high prevalence of lacunar stroke in Portugal and Japan may, at least in part, explain the burden of vascular dementia in both countries.

We cannot discard that the erosion in participation in the EPIPorto cohort contributed to an underestimation of the prevalence of dementia and MCI, as participants with cognitive impairment could be less prone to participate in the cohort reassessment. This is supported by the older age and slightly less education of participants not assessed in the cohort reevaluation. Furthermore, while the prevalence of MCI and dementia generally increases for each age group, this study did not observe a doubling of prevalence by each 5 years found in many dementia surveys.[39] Interestingly, this effect was also not observed in the only previous study performed in the Portuguese population.[4] However, the small number of cases in each age-group probably precludes any meaningful conclusion regarding the comparison of different age stratum in the present study. Additionally, and although a complete revision of electronic medical records for relevant diagnoses was performed, there could be some missed cases in the participants who did not undergo the clinical evaluation, particularly for MCI.

The study design overestimates the sensitivity of MMSE and MoCA for MCI and dementia, as the test scores were also used to classify participants resulting in verification bias. Nevertheless, the frequency of those with MCI and dementia correctly identified by the education-adjusted cutoff points of the MMSE was very low in this sample. This frequency was still less than desirable for the most widely used 2.0 SD cutoff point of the MoCA test but high for the 1.5 SD cutoff point. However, and based on estimates from this sample, a screening strategy based on the 1.5 SD MoCA cutoff point would result in a considerably high number of individuals with a positive screening not having MCI or dementia (77.1%). These results indicate that there is a need for better tools to screen for these conditions in the Portuguese population.

In conclusion, the results of this study highlight the importance of VaD in the epidemiology of cognitive impairment in Portugal and carry an important public health message regarding the potential for its prevention and management. Indeed, measures of primary prevention, such as the promotion of healthy diet, regular practice of exercise, have the potential to avert a great part of the dementia epidemic in Portugal and other countries with a higher burden of cerebrovascular disease. Of particular potential, and a suitable target for public health programs, are the lack of awareness, control, and compliance with the treatment of hypertension.[40] Furthermore, directed multidomain interventions, involving changes in diet, exercise, cognitive training, and control of vascular risk factors, could prevent further cognitive deterioration in patients with early and presymptomatic vascular cognitive impairment.[41] It is important that coordinated efforts are directed to implement such measures to lessen the burden on patients, families, and society.

Acknowledgments

The authors gratefully acknowledge the participants enrolled in EPIPorto for their kindness, and all members of the research team for their enthusiasm and perseverance.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research project was financed by the *Programa Operacional Competitividade e Internacionalização* (POCI) (POCI-01-0145-FEDER-016867), the *Programa Operacional Regional do Norte 2014/2020* (NORTE 2020) (NORTE-01-0145-FEDER-000003) and by the *Fundação para a Ciência e a Tecnologia*, in the context of the Epidemiology Research Unit—*Instituto de Saúde Pública da Universidade do Porto* (EPIUnit) (POCI-01-0145-FEDER-006862; FCT UID/DTP/04750/2013), and the PhD Grant SFRH/BD/119390/2016 (Natália Araújo), co-funded by the FCT and the POCH/FSE Program.

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Supplemental Material

Supplemental material for this article is available online.

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