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FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

AGEING, SOCIAL SUPPORT AND COGNITIVE IMPAIRMENT

RICARDO JOÃO CORREIA DA CRUZ PAIS ANTUNES

TESE DE DOUTORAMENTO APRESENTADA
À FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO EM
SAÚDE PÚBLICA

Exmo. Senhor

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Doutor Valdemar Miguel Botelho Dos Santos Cardoso

Doutor Walter Friedrich Alfred Osswald

Ao abrigo do Art.º. 8º do Decreto-Lei nº. 388/70, fazem parte desta tese as seguintes publicações:

I. Pais R, Ruano L, Carvalho OP, Barros H. Global Cognitive Impairment Prevalence and Incidence in Community Dwelling Older Adults-A Systematic Review. Geriatrics (Basel). 2020 Oct 27;5(4):84. doi: 10.3390/geriatrics5040084. PMID: 33121002; PMCID: PMC7709591.

II. Pais R, Ruano L, Moreira C, Carvalho OP, Barros H. Prevalence and incidence of cognitive impairment in an elder Portuguese population (65-85 years old). BMC Geriatr. 2020 Nov 16;20(1):470. doi: 10.1186/s12877-020-01863-7. PMID: 33198643; PMCID: PMC7667782.

III. Ruano L, Araújo N, Branco M, Barreto R, Moreira S, Pais R, Cruz VT, Lunet N, Barros H. Prevalence and Causes of Cognitive Impairment and Dementia in a Population-Based Cohort From Northern Portugal. Am J Alzheimers Dis Other Demen. 2019 Feb;34(1):49-56. doi: 10.1177/1533317518813550. Epub 2018 Dec 4. PMID: 30514090.

IV. Pais R, Ruano L, Moreira C, Fraga S, Carvalho OP, Barros H. Social Support and Cognitive Impairment: Results from a Portuguese 4-Year Prospective Study. Int J Environ Res Public Health. 2021 Aug 22;18(16):8841. doi: 10.3390/ijerph18168841. PMID: 34444589.

Em cumprimento com o disposto no referido Decreto-Lei, declaro que participei ativamente na definição dos objetivos dos trabalhos que constituem esta tese, na aquisição dos dados dos estudos descritos nos artigos, e fui responsável pela análise dos dados, interpretação dos resultados e redação da versão inicial dos manuscritos I, II e IV. No manuscrito III colaborei na recolha de dados e revisão do manuscrito final.

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List of abbreviations

MMSE	Mini-Mental State Exam
MOCA	Montreal Cognitive Assessment
WHO	World Health Organization
AIC	Akaike's Information Criterion
HR	Hazard Ratio
CI	Cognitive Impairment
MCI	Mild Cognitive Impairment
CIND	Cognitive Impairment Not Dementia

ABSTRACT

The world population is experiencing one of the most remarkable social transformations in history, with people living longer than in any previous period. The currently observed increase in average life expectancy can be explained by the decrease in birth rates and increase in longevity. It is expected that the number of older people will continue to increase globally in the coming decades.

With this in mind, the World Health Organization recommends that countries change their social and public health policies to an older population.

The ageing of the population poses challenges due to older people greater vulnerability and fragility, which limit their quality of life.

To promote active ageing, one must consider that quality of life is an essential component of ageing and that multiple factors that include mental health and social relationships influence it.

Advancing age leads to a natural physical and cognitive decline. However, some develop a cognitive deficit characterized by changes in memory and learning that are higher than expected, taking into account their age and education, which interferes with their daily activities, being a risk for dementia and mortality.

Cognitive decline is an indicator of the frequency of vascular problems that can progress to Alzheimer's disease or other types of dementia, and it is essential to define prevention measures for this population.

The relationship between ageing and cognitive impairment needs further studies, and the information is sometimes contradictory. It is pertinent to know the epidemiological measures of cognitive impairment, identify risk groups and assess the effect of different sources of social support to improve public health policies.

In Portugal, studies on the prevalence of cognitive impairment are scarce, and, as far as we know, the incidence is unknown. In order to have a better understanding of cognitive impairment in our population and optimize our ability to intervene effectively and reduce the social vulnerabilities brought on by cognitive impairment, we have set out to elucidate its

determinants, as well as assessing the impact on the cognitive health of the dimensions of gender, education, marital status, retirement age as well as the impact of the social network.

We designed this study to describe the frequency and determinants of cognitive impairment in older people in an urban centre using a longitudinal approach to assess cognitive ability.

The following specific objectives were defined, which we describe together with individual methods and results.

1. To review the global prevalence and incidence of cognitive impairment and to derive prevalence and incidence estimates for this entity

We did a systematic review of the literature based on the Pubmed electronic database, in January 2019, with the terms "cognitive impairment", "prevalence", "incidence", and "elders". We did a second survey in which we added "Portugal" and "aged". We obtained 3690 articles that, after reviewing by a two-step process, resulted in 85 papers, of which 74 with prevalence data, 5 with incidence data and 6 with both frequencies. We checked the studies' quality with the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. We did the review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2009 Checklist.

The studies examined report that the global prevalence of cognitive impairment ranges from 5.1 to 41.0% (median = 19.0%; 25th percentile = 12.0%; 75th percentile = 24.90%). Europe is the region with the lowest median prevalence worldwide. At the global level few studies report incidence of cognitive impairment with reported estimates ranging from 22.0 to 215.0 per 1000 person-years (median = 56.50 per 1000 person-years; 25th percentile = 41.77; 75th percentile = 76.50).

2. To evaluate the prevalence and incidence of cognitive impairment in an older people population and to identify individual risk characteristics

We analysed data from the 1999-2004 evaluation of the EPIPorto cohort of 586 participants aged 65-85 years to determine the prevalence of cognitive impairment using the

Mini-Mental State Exam. We re-evaluated a total of 287 participants without baseline cognitive impairment after an average of 6.2 years (2005-2015) to assess the incidence of cognitive impairment. Participants presenting an MMSE score lower than the cut off scores adapted to the Portuguese population were considered to have cognitive impairment. In this study, we did not exclude cases of dementia.

In Portugal, we found that the overall prevalence was 15.5%, higher in women, increasing with age and decreasing with the number of schooling years. For 6.2 mean years of follow-up time, we observed that the incidence was 26.97 per 1000 person-years, higher in older participants and without schooling. Neither retirement nor marital status has a significant effect on cognitive impairment.

To assess the aetiology of cognitive impairment, we evaluated the data from the third follow-up, from 2013 to 2015, and we used a different methodological approach. We include participants older than 55 years (n = 730) in the study participants. We evaluated two steps, a screening phase with validated tests Mini-Mental State Exam and Montreal Cognitive Assessment, and a clinical evaluation by neurologists. The most common cause of mild cognitive impairment/dementia was vascular, followed by Alzheimer's disease. The prevalence of cognitive impairment was 9.3%, lower than the 15.5% found in the same cohort in the evaluation done between 1999 and 2004. We need to consider the different methodology of cognitive impairment assessment, the analysis of a younger sample in this follow-up stud, and between 1999 and 2015, the percentage of older people with no schooling decreased, and more years of schooling increased.

3. To evaluate the effect of different sources of social support on the risk of cognitive impairment

We analysed data from the 2005-2009 follow-up of the EPIPorto cohort study and selected participants aged 60 to 85 years old (n = 656). Between 2013-2015 we conducted a cognitive evaluation of 341 participants. We evaluated cognitive impairment using the Mini-Mental State Exam, with cut-off points adjusted by years of schooling validated for the Portuguese population. We assessed the social support perception with the Multidimensional Scale of Perceived Social Support. In this study, we did not exclude cases of dementia.

Social support from friends' impacts cognition, decreased the risk of cognitive impairment. The participants aged between 80 and 85 years or with fewer schooling years have a lower social support perception.

This study reports the global view of epidemiological data on cognitive impairment based on population studies' results and epidemiology measures of cognitive impairment evaluated by a longitudinal population-based survey. We conclude that the prevalence and incidence of cognitive impairment are lower in Europe than in other regions of the globe. In Portugal, we identify as risk groups for cognitive impairment women and older people with no education, and we also find that the risk increases with age. Postponing retirement age and marital status have no significant effect on cognitive impairment. In terms of social support, we report that social support from friends reduces the risk of cognitive impairment. Older participants and those with fewer years of schooling have a lower perception of cognitive impairment.

RESUMO

A população mundial está a viver uma das maiores transformações sociais da história com as pessoas a viverem mais anos do que em qualquer período anterior. Com o aumento da esperança média de vida, explicado pela diminuição das taxas de natalidade e aumento da longevidade, espera-se que o número de pessoas mais velhas continue a aumentar nas próximas décadas.

Tendo isto presente, a Organização Mundial da Saúde recomenda que os países adaptem as suas políticas sociais e de saúde publica para uma população mais velha.

O envelhecimento da população coloca vários desafios devido à maior vulnerabilidade e fragilidade das pessoas nessas idades que limitam a sua qualidade de vida.

Para promover o envelhecimento ativo devemos ter em consideração que a qualidade de vida é um componente essencial do envelhecimento e que é influenciada por múltiplos fatores que incluem a saúde mental e as relações sociais.

O avançar da idade leva a um declínio físico e cognitivo natural nos indivíduos, porém alguns desenvolvem défice cognitivo caraterizado por alterações de memória e de aprendizagem acima do esperado tendo em conta a idade e escolaridade e que interferem nas suas atividades de vida diária, sendo um risco para a demência e mortalidade.

O declínio cognitivo é um indicador frequente de problemas vasculares podendo evoluir para a doença de Alzheimer ou outros tipos de demência sendo essencial definir estratégias de prevenção para esta população.

A relação entre envelhecimento e défice cognitivo carece de mais estudos sendo que a informação por vezes é contraditória. É pertinente conhecer as medidas epidemiológicas do défice cognitivo, identificar grupos de risco e avaliar o efeito de diferentes fontes de apoio social de modo a melhorar as políticas de saúde publica.

Em Portugal, os estudos sobre a prevalência de défice cognitivo são escassos e, tanto quanto sabemos, a incidência é desconhecida. Também, os seus determinantes precisam ser analisados e devemos avaliar o impacto sobre a saúde cognitiva do género, educação, estado civil e adiar a idade de reforma. O impacto da rede de apoio social também precisa ser clarificado de modo a contribuir para a redução das vulnerabilidades sociais.

Projetámos este estudo para descrever a frequência e os determinantes do défice cognitivo em idosos num centro urbano, usando uma abordagem longitudinal para avaliar a capacidade cognitiva.

Foram definidos os seguintes objetivos específicos, que descrevemos em conjunto com os métodos e resultados de cada um.

1. Rever a prevalência global e incidência de défice cognitivo e determinar a estimativa de prevalência e incidência desta entidade.

Fizemos a revisão sistemática da literatura na base de dados eletrónica Pubmed, em janeiro de 2019, com os termos "cognitive impairment", "prevalence", "incidence" e "elders". Fizemos uma segunda pesquisa em que adicionámos "Portugal" e "aged". Obtivemos 3690 artigos que, após revisão por processo de duas etapas, obtivemos 85 artigos, sendo 74 com dados de prevalência, 5 com dados de incidência e 6 com ambas as frequências. Verificámos a qualidade dos estudos com a National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Fizemos a revisão de acordo com a lista de verificação de itens de 2009, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Os estudos que examinámos reportam que a prevalência de défice cognitivo varia de 5,1 a 41,0% (mediana = 19,0%; 25º percentil = 12,0%; 75º percentil = 24,90%). A Europa é a região com a menor mediana de prevalência mundial. A nível global, poucos estudos relatam dados de incidência sendo que esses estudos reportam valores que variam entre 22,0 e 215,0 por 1000 pessoas-ano (mediana = 56,50 por 1000 pessoas-ano; 25º percentil = 41,77; 75º percentil = 76,50).

2. Avaliar a prevalência e incidência de défice cognitivo numa população idosa e identificar as características individuais de risco

Analisámos os dados da avaliação de 1999-2004 da coorte EPIPorto composta por 586 participantes com idades entre 65-85 anos para determinar a prevalência de défice cognitivo utilizando o Mini-Mental State Exam. Reavaliámos um total de 287 participantes sem défice cognitivo, no *baseline*, após uma média de 6,2 anos (2005-2015) para avaliar a incidência de

défice cognitivo. Foi considerado que apresentavam défice cognitivo todos os participantes que apresentaram uma pontuação no teste cognitivo inferior aos pontos de corte adaptados para a população portuguesa. Neste estudo, não excluímos participantes com demência.

Em Portugal, constatou-se que a prevalência global de défice cognitivo foi de 15,5%, sendo mais elevada nas mulheres, aumentando com a idade e diminuindo com o número de anos de escolaridade.

Para a média de 6,2 anos de seguimento, a incidência foi de 26,97 por 1000 pessoas-ano, maior nos mais velhos e nas pessoas sem escolaridade. Nem a idade de reforma nem o estado civil têm um efeito significativo sobre o défice cognitivo.

Com o objetivo de determinar a etiologia de défice cognitivo avaliámos os dados do terceiro *follow-up*, de 2013 a 2015, e utilizámos uma abordagem metodológica diferente. Incluímos participantes com mais de 55 anos (n = 730) entre os participantes do estudo. Foram avaliados em duas etapas, uma fase de triagem com os testes validados Mini-Mental State Exam e Montreal Cognitive Assessment, e uma avaliação clínica por neurologistas. A causa mais comum de défice cognitivo ligeiro/demência foi vascular seguida por Doença de Alzheimer. A prevalência de défice cognitivo foi de 9,3%, inferior aos 15,5% encontrados na mesma coorte na avaliação feita entre 1999 e 2004. É necessário ter em conta que neste estudo a metodologia de avaliação de défice cognitivo foi diferente e a amostra era mais jovem. Além disso, entre 1999 e 2015, a percentagem de pessoas mais velhas sem escolaridade diminuiu e aumentaram os idosos com mais anos de escolaridade.

3. Avaliar o efeito de diferentes fontes de suporte social no risco de défice cognitivo

Analisámos os dados do *follow-up* de 2005-2008 do estudo de coorte EPIPorto e selecionamos participantes com idade entre 60 e 85 anos (n = 656). Entre 2013-2015 fizemos a reavaliação cognitiva de 341 participantes. Avaliámos o défice cognitivo através do Mini-Mental State Exam, com pontos de corte validados para a população portuguesa e ajustados para os anos de escolaridade. Avaliámos a perceção do suporte social com a Multidimensional Scale of Perceived Social Support. Neste estudo, não excluímos casos de demência.

Concluímos que o apoio social de amigos tem impacto no estado cognitivo diminuindo o risco de défice cognitivo. Os participantes com idade entre 80 e 85 anos ou com menor escolaridade apresentam menor perceção de suporte social.

Este estudo relata a visão global de dados epidemiológicos sobre défice cognitivo com base em resultados de estudos populacionais e medidas epidemiológicas de défice cognitivo avaliados por uma pesquisa longitudinal de base populacional. Concluímos que a prevalência e a incidência de défice cognitivo são menores na Europa do que em outras regiões do globo. Em Portugal, identifica-se como grupos de risco as mulheres e os idosos sem escolaridade e verifica-se que o risco aumenta com a idade. O adiamento da idade de reforma ou o estado civil não tem efeito significativo sobre o défice cognitivo. Em termos de apoio social, permite-nos relatar que o apoio social de amigos reduz o risco de défice cognitivo. Também, que os mais velhos ou os que têm menos anos de escolaridade têm menor perceção de suporte social.

1. INTRODUCTION

1.1. Ageing Population

The world is changing. In the 21st century, one of the biggest social transformations is population ageing, and soon there will be more older people than children, with more people living longer lives than ever before (1).

In the last decades, we have witnessed a demographic change that affects almost every country, with lower birth rates associated with decreased mortality and an increased average life expectancy increasing the relative proportion of older people (2-4). In low- and middle-income countries, reducing childhood and childbirth mortality and mitigating infectious diseases increased life expectancy. In high-income countries, this increase in life expectancy is due to elders' living more years (5).

Population ageing is a sign of society's success and is positively associated with economic and social development. Worldwide there is a constellation of socioeconomic processes which impact the age balance, such as reduced child mortality, improved access to education, better employment opportunities, more gender equality, increased family planning, and improved reproductive health concomitant with the reduced birth rate. Advances in public health and medicine, and improved living conditions, have all contributed to people living longer. Together, declining fertility and increased longevity are causing changes in society's structure, decreasing the numbers of children and increasing the numbers of older people per adult (6).

The United Nations reports that by 2050, life expectancy at birth will exceed 80 years in Europe, North America, Latin America, and Oceania, close to 80 years in Asia, and approximately 70 years in Africa. Today, young people can expect to live at least 80 years everywhere globally, except in Africa (6).

The number of senior people will increase in the coming years more rapidly in Latin America, Asia and Africa than in the rest of the world. Although population ageing is a global phenomenon, we know this process is more advanced in some regions; it has started in

countries that have developed earlier and extended more recently to countries that developed later on. There is also a global tendency towards fertility declines (6).

Globally, the number of people who are over 80 is increasing faster than any other age group. Estimates project that, by 2050, the most aged population, people over 80 years, will have tripled to 434 million, compared to data from 2015 (6). Between 2030 and 2050, the percentage of senior people, 80 years or more, will increase from 14% to 20%. In 2015, in Europe, only one out of five seniors over 60 were over 80 years old; this ratio will increase to one in four by 2040.

In 2013 the United Nations reported that the world population percentage of people aged 60 years or older had increased from 9.2% to 11.7% since 1990; and expected this percentage to rise to 21.1% by 2050, which means more than double the 841 million senior people of 2013, *id est* over two thousand million people by 2050 (2).

The world will see a substantial increase in the population aged 60 or older from 2015 to 2030. The number of people aged over 60 in Europe was 147 million in 2000, and the United Nations estimates it will be 217 million in 2030. Similarly, in North America, the number of people aged 60 years or older has increased from 51 million, in 2000, to 75 million in 2015 and is estimated to reach 105 million by 2030. Despite the projections of substantial increases in the number of older persons living in Europe and North America, the growth will be slower than in other regions of the globe (6).

In Portugal, people aged over 65 increased 180.668 from 2012 to 2017. Portugal maintained a demographic ageing tendency due to the decrease in birth rates, an increase in longevity and the negative migratory flows until 2016. This migratory flow resulted in an average age increase of the resident population: from 42.7 in 2012 to 44.2 years in 2017 (7). The quotient between the number of people over 65 and below 14 years was 27.5% in 1961, and it increased exponentially to 153.2% in 2017 (8). Estimates of the Portuguese Statistics National Institute (INE) predicts that the population aged 65 and over will increase from 2.2 to 2.8 million people between 2017 and 2080. It will have reached its highest value by 2049, decreasing from that year onwards (7).

In Portugal, many older people live alone or with other older people, often playing the role of caregiver. Most have low education and low incomes, and a higher risk of poverty (9).

We can look at the ageing of the population from the perspective of the success of public health and social development policies, but it also poses numerous challenges since older people are more vulnerable to various health problems. Frailty increases with age and is related to lifelong events with results that can be negative in the ageing process (10).

In the last century, longevity was the marker of successful ageing, but currently, the focus of most studies has changed to “active ageing”, that is, the number of years spent without illness or disability. The quality of life is considered an essential component of ageing, along with the number of years of life (10).

The World Health Organization defines the quality of life as a perception of living, taking into consideration the cultural and social context of the individual, which include the physical and mental health, level of independence, social relationships and social support (1, 11).

Quantifiably, ageing increases the risk of illness, frailty, and dementia, limits older people's quality of life. Studying population ageing would help the definition of health measures that promote health and ensure an increase in the quality of life of older people.

Health-related quality of life in older people has multiple factors that include emotional well-being, cognitive functional status, quality of close interpersonal relationships, participation and enjoyment in social activities (12) and the results of studies on those factors should be highlighted and used to increase older people's quality of life.

1.2. Ageing and Social Support

With the increase in average life expectancy, one of the pertinent questions arises of whether a longer life results in increased years lived in good health or, on the other hand, if these years increase morbidity and translate into proportionately more years spent being dependent and disabled (13). There is a growing fear that a longer life will contribute to individual vulnerability, which will impact society's structure, especially in the countries' social, health, and economic systems. For this increase in longevity to be sustainable, it is essential to ensure that older people enjoy good health and live in a supportive environment (14).

During their lifetime, all individuals have a wide variety of social relationships with different engagement groups such as family, friends, neighbours, co-workers and others thus, benefiting from the positive psychosocial aspects of support, affection and social belonging (15).

Activities like playing sports, participation in cultural activities, tourism, further education, carrying out voluntary activities, and socialising with family and friends provide a means for senior people to remain active and connected, positively impacting their health and wellbeing (16). Rich social relationships may increase cognitive and physical activity, prevent low mood, and positively impact health (17, 18). On the contrary, social isolation is a risk factor for cognitive decline, negatively impacting health (19).

Social support is inserted in the individual's social network and presupposes daily exchange between people, financial, emotional and advisory assistance (17, 20).

Research suggests that relationships improve quality of life as individuals get older and are essential for health and longer life, reducing stress (15).

The support given by social networks is related to better health outcomes, namely concerning the lower risk of mortality, lower disease burden and slower functional decline (20).

More aged people are more inclined to live in rural areas characterised by lower services, increasing social exclusion. Also, a member of the couple's death causes senior people to live alone, which is particularly true for women (16).

Cultural differences affect how social support influences health. For example, in Asian societies, interactions with friends have less impact on well-being than in Western societies (20). In some societies, there is greater family integration and proximity between different generations of the same family, who often live in the same house, compared to other societies where greater physical distance is the norm.

The impact of social support on health may vary, depending on the source of support and whether it comes from family, friends, neighbours or others (17).

Married people with better quality marriages have greater life satisfaction and fewer health problems than unmarried people. On the contrary, marriages with higher levels of conflict have a nefarious health effect (15).

The relationship between parents and children has a significant effect on wellbeing and health. Parents report well-being when their children give them emotional support and affection, and trust for support tasks (15).

Some studies suggest that relationship satisfaction increases as children leave home or retirement time is reached because it allows couples to share more leisure time (15).

Friends are an essential social support source that shares life experiences and often came from the same community (15). Some studies point out that support from friends and neighbours is associated with less functional decline, even in the absence of family support, essential for those who live alone (20).

1.3. Ageing, Cognition and Cognitive Impairment

The World Health Organization (WHO) recommends adapting health systems to serve a proportionately senior population, their health concerns, and increase the sense of wellbeing in advanced ages. Understanding the levels and trends of disease prevalence and severity is key to understanding ageing implications, especially Alzheimer's disease and other dementias which are causes of disability. Globally, by 2013, people spent an average of 9 years of their lives struggling with illnesses. Additionally, since this population group requires and needs more health care, services, and technologies, the population's overall ageing and relative proportion of older people create additional pressures in existing health care systems.

Ageing leads to muscle and cognitive functional change, but this process does not occur in all biological functions at the same time nor in all people alike. As one ages, the senses decline in acuity, a concomitant decrease in muscle strength, and a gradual decline in vital organ functions and cognitive performance (21).

For a long time, cognitive decline was considered physiological, natural and attributed to the ageing process. Actually, we know that some individuals present cognitive deficits above and beyond those expected for their age, losing autonomy or functionality, mostly due to underlying pathologies. This cognitive decline is a frequent indicator of vascular problems or Alzheimer's disease, for example (22).

The healthy ageing process is associated with both physiological and cognitive ability changes. In some people, their brain cells suffer increased oxidative, metabolic and ionic

stress associated with pathologies, inducing the accumulation of proteins, nucleic acids and lipids, leading to neurodegenerative disease. The most common of these diseases is Alzheimer's disease, which affects memory and other cognitive abilities, and for which there is currently no available treatment capable of stopping or reversing it (23). In Alzheimer disease, anatomical, morphological and chemical alterations are observed in the brain, including cortical and subcortical atrophy, synaptic degeneration, decreased blood flow and changes in neurotransmitters such as serotonin, acetylcholine and dopamine. These changes affect functions ranging from mood regulation, memory recall and learning.

Performance in neurocognitive tests negatively correlates with age, but the decline is far from uniform across individuals. Ageing is a natural and gradual process, accompanied by several cognitive functioning changes, which are unexpectedly high in some individuals (24). Cognitive decline is associated with health factors and lifestyle, and cardiovascular risk factors affect it (24).

The brain is an organ with an individual genetic inheritance. Environmental factors influence its functioning (25) and may increase or decrease neurodegenerative disease probability (26).

Genetic mutation and environmental factors, such as physical and mental inactivity, high-calorie consumption, and exposure to toxic agents, may trigger neural death. Low-calorie consumption, antioxidants and folic acid, coupled with physical exercise, are protective life habits and contribute to adapting the nervous system to ageing.

The functions most affected by advancing age are attention, memory recall, perceptual and spatial capacity, executive functions, processing speed, and response time (24). Memory decline without functional loss is standard (27). Some senior people have complaints of memory loss but do not reach the criteria for the diagnosis of dementia (28).

Memories are not chemical modifications that occur at the molecular level but instead changes in neural circuitry. The hippocampus has an essential role in the process of memory retention and retrieval. Some mental illnesses disrupt the effective recovery of memories resulting in progressive memory loss (29).

The number of non-communicable diseases and disabilities increases with living longer (2), but there is a need to know more about cognitive function and ageing (3, 4).

In older people, the most common form of dementia is Alzheimer's disease, which is the fourth leading cause of death above 65 years of age, and the prevalence increases

exponentially with age after 65 years, rising from 4 to 10% of the population to 20 to 40% at 85 years of age (26).

The process of transition from healthy ageing to Alzheimer's disease is called mild cognitive impairment, with a conversion rate of 8 to 15% of cases/year for Alzheimer's disease, with some evolving to other forms of dementia or showing a benign form of mild cognitive impairment (26, 30).

Cognitive impairment ranges from mild deficits that are not detected clinically to dementia (31). Its characterized by difficulties with memory, learning, and the ability to concentrate on a task, higher than would be expected, taking into account the age and educational level of the individual (32-35) and with an impact on the activities of daily living of the older people individual (36).

Cognitive impairment is a major cause of disability and care dependency in ageing societies (37, 38) and is an example of common geriatric syndromes that impact occupational health (39, 40). It is also a risk factor for dementia and mortality in older people (41-43).

To define the level of cognitive impairment and its impact on daily activity, we should take into account that individuals with this disorder have deficits in at least two areas of cognitive functioning: memory disorders (e.g., learning or recalling recent memories); executive functioning (e.g. reasoning); the speed of information processing (e.g. concentration, data analysis); perception (e.g. integrating visual information with motor activities); or language (e.g. word-finding difficulty). Neuropsychological tests must substantiate such changes. The cognitive deficits must cause discomfort or interfere with social or occupational life, and the cognitive disturbance should not meet the criteria for delirium, dementia or other mental disorder (44).

Table 1 – Definitions of Cognitive Impairment

American Psychiatric Association, 2002 (44)
Mild neurocognitive disorder describes a degree of cognitive decline beyond normal ageing with an impact on cognitive function. The individual, a close relative, or other knowledgeable informants, such as a friend, colleague, or clinician, observe these symptoms or detected them through objective testing

American Psychological Association, 2021 (45)

Cognitive impairment is any impairment in perceptual, learning, memory, linguistic, or thinking abilities.

Centers for Disease Control and Prevention, 2011 (46)

Cognitive impairment is when a person has trouble remembering, learning new things, concentrating, or making decisions that affect their everyday life. Cognitive impairment ranges from mild to severe. With mild impairment, people may begin to notice changes in cognitive functions but still do their everyday activities.

Folstein et al., 1985 (47)

Cognitive impairment is a diminished capacity to know the world.

Petersen et al., 2014 (48)

Cognitive changes beyond normal ageing do not capture by any clinical definition.

It is essential to define prevention and treatment strategies adequate for cognitive impairment because individuals with cognitive impairment are at high risk for developing Alzheimer's disease and other dementias (49, 50). It also has a negative social impact, and it is associated with other pathologies (51).

Public health and clinical care policy need epidemiological measures of cognitive impairment and its relation to comorbidities and sociodemographic factors to define the importance of primary and secondary prevention measures within the health system. It is important to identify groups at risk of developing cognitive changes at early stages in order to allow us to determine the best times and types of intervention strategies to prevent initial cognitive impairment and either stop or delay its progression towards dementia once established (30).

Global reports on epidemiological data on cognitive impairment make possible the aggregation of information and knowledge across the world's regions.

In Europe, the prevalence of cognitive impairment is estimated between 5.1 and 24.5% (52-65), whereas in North America, the estimated cognitive impairment prevalence ranges

from 14.1 to 28.3% (34, 66-71). In Portugal, three previously published studies report a prevalence of 9.3% (72), 9.6% (58) or 12.0% (73).

Fewer reports addressed cognitive impairment incidence (42, 74). The incidence of cognitive impairment ranges from 56.5 to 76.8 per 1000 person-years in Europe (59, 75, 76) and 41.8 to 65.4 per 1000 person-years in North America (77-79). In Portugal, as far as we know, the incidence is unknown.

Studies consider risk factors for cognitive impairment: age, sex, genetic factors, low education and cardiovascular outcomes (42, 80-86). Other studies report that individuals with instrumental disabilities in daily living activities are more likely to develop cognitive impairment, increasing likelihood with a greater degree of disability (87-90).

Older people often take several medications for health conditions that may have cognitive side effects and interact with cognition and memory. Medications used to treat mental illnesses such as schizophrenia, bipolar disorder, or depression have a detrimental effect on memory and cognition; given the effect of improvement in these diseases, there is also an improvement in cognitive functioning when adequately used, but they can have a detrimental impact when misused (91).

Some studies also refer to the importance of work status and profession in cognitive impairment onset and progression (92).

In many countries, the percentage of senior people is growing faster than people within the working-age limits. Therefore, to maintain the viability of current social protection systems, many governments increase the full retirement age (3, 93, 94), which will increase the number of senior workers in the future (39, 95, 96) and make it more common for people to work in their late 60s and even their early 70s (97). Workers, employers and government have to face the prospect of having workers in their sixties (39), which increases the need to understand older people's physical and cognitive decline. Retirement is a direct transition at a minimum age from full employment to a condition in which the individual is inactive, and most of his/her income consists of pension benefits. For countries, mainly in Europe and North America, the retirement age is 65 years of age (2). In the OECD countries, in 2007, the average worker left the workforce before being 64 and could expect 18-22 years of retirement (98). In Portugal, the expectation is that women will live a mean of 19.3 years after retirement, and men will live 14.6 years (99). In Portugal, the retirement age is 66 years (100), but it is possible to postpone the retirement age up to 70 years old (101, 102).

The timing of retirement can impact physical and emotional health, but health effects are not well-understood, and reports are contradictory. Whereas some studies report that the individuals who retire earlier experience stress reduction and more opportunities for leisure and exercise (103), others report that early retirees have self-perceived poor health (104). Some reports speculate that later retirement may provide higher financial income (104, 105) and that people live longer lives and experience a delay in cognitive decline and a more extended period before diabetes onset and stroke (106). Overall, retirement transitions appear to have more benefits if they occur at the expected right time or later, but this impact may be transitory and disappear after a few years, as soon protection afforded by exposition to the benefits of work disappear (107).

1.4. Unanswered questions

The quality of life in older people becomes more pertinent with the increase in average life expectancy due to the concern that the increase of life years may lead to increased frailty and morbidity. In order to ensure sustainable longevity, older people must be in good health and live in a supportive environment (13, 14).

The World Health Organization (WHO) recommends adapting health systems to serve a proportionately senior population, their health concerns, and increase the sense of wellbeing in advanced ages. Understanding the levels and trends of disease prevalence and severity is key to understanding ageing implications, especially Alzheimer's disease and other dementias which are causes of disability. Globally, by 2013, people spent an average of 9 years of their lives struggling with illnesses. In countries with a shorter average life expectancy, people have proportionately more loss of healthy years of life than in other countries.

Whereas the scientific community focuses on understanding the mechanisms of cognitive diseases, such as Dementia or Alzheimer's disease, it is equally essential to develop effective preventive measures and interventions that will help delay the onset, and possibly even reverse, the symptoms of cognitive impairment.

An essential aspect of public health is disseminating and creating guidelines for specific health contexts. Cognitive impairment and 'awareness' of some nosological entities that may

include a cognitive decline in its spectrum should be a pressing issue to help promote prevention and development of treatment strategies.

Knowledge regarding the global epidemiology state of cognitive impairment worldwide carries the ability to know the current state of affairs and predict its evolution. However, studies on the prevalence of cognitive impairment are scarce in Portugal, and there are no studies on the incidence.

Population ageing puts social and health systems under pressure, and as such, it is essential to identify groups at risk and define appropriate public health policies to prevent cognitive decline. Some studies addressed the determinants of gender, marital status, retirement age (40), but the results are contradictory. There is a lack of information, and further research is needed.

A better understanding of social function's impact on cognitive decline could help identify areas to improve support and decrease social vulnerabilities (108).

The research should study the longitudinal effect of multiple social ties on health, especially on the early cognitive decline (108, 109) to identify areas of improvement and focus the resources to improve the quality of life at older ages. The longitudinal effect of social support on cognitive impairment is still unclear especially distinguishing the different sources of support.

To achieve those goals, we fulfil this study expecting to contribute to the global scientific knowledge on this subject, focusing on Portugal, hoping that it makes it possible to improve public health policy.

2. AIMS

This study describes the frequency and determinants of cognitive impairment in the older people in an urban, more aged Portuguese population using longitudinal approaches to evaluate cognitive performance.

The specific objectives of this thesis were:

1. To review the global epidemiological data on cognitive impairment and to derive prevalence and incidence estimates of this entity - Paper I
2. To evaluate the prevalence and incidence of cognitive impairment in an older people population and to identify personal risk characteristics- Paper II and Paper III
3. To evaluate the effect of different sources of social support on the risk of cognitive impairment - Paper IV

3. RESEARCH DESIGN AND METHODS

3.1. Setting

The EPIPorto study is a cohort study of adults gathered to assess Porto's non-institutionalised population's health determinants, an urban centre in Portugal's northwest, with about 300,000 inhabitants (110-112).

Porto's inhabitants, aged 18 to 92 years, were selected using random digit dialling of landline telephones. After identifying a household, characterised permanent adult residents according to age and gender, selected one adult by simple random sampling and invited them to visit the Department of Hygiene and Epidemiology of University of Porto Medical School for an interview and examination. If there was a refusal, substitution was not allowed.

The recruitment baseline occurred between January 1999 and December 2003. The proportion of participation was 70%, and the final sample size was 2485 individuals. The first follow-up assessment occurred between 2005 and 2008, and the second follow-up assessment of the cohort occurred between 2013 and 2015.

We did several research studies based on the EPIPorto cohort study. With the support and collaboration of a multidisciplinary team that collected data throughout the different evaluation phases.

The studies' specific methods will be detailed in-depth in the following sections, but a brief overview follows.

In Paper I, we conducted a systematic review of the literature based on the PubMed® electronic database. Research done on January 4, 2019, with the terms "cognitive impairment", "prevalence", "incidence" and "elders". We added the terms "Portugal" and "aged" to the second research. We deleted the duplicates. We verified references using a two-step process according to defined exclusion criteria. Of 3690 potentially relevant articles, 3394 were deleted in step one, based on the title and/or abstract, and 211 in step two after reading the articles' entire text. We included 85 articles in the systematic review, 74 with prevalence

data, 5 with incidence data and 6 with both frequencies.

We assessed the quality of the studies included in the systematic review using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, evaluating the internal validity, the risk of bias and the general quality of each study. Of the selected papers, 77 had an overall rating of "good", and eight were rated "fair", and none were rated "poor". Therefore, no papers were excluded from the analysis. We did the review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2009 Checklist (PRISMA).

In Paper II, we analysed data from the 1999-2004 evaluation of the EPIPorto cohort of participants aged 65-85 years (586) to determine the prevalence of cognitive impairment with the Mini-Mental State Exam (MMSE). We re-evaluated a total of 287 participants without baseline cognitive impairment after an average of 6.2 years (2005-2015) to assess the incidence of cognitive impairment. Participants with cognitive impairment had an MMSE score lower than the cut off scores adapted to the Portuguese population (113). In this study, we did not exclude cases of dementia.

In Paper III, we analysed data from the third follow-up, from 2013 to 2015, of the EPIPorto cohort participants to report the prevalence and causes of cognitive impairment and dementia in the population. We include participants older than 55 years (n = 730) in the study participants. We evaluated in two steps, a screening phase and a clinical evaluation. We use the screening tests Portuguese validated versions of the Mini-Mental State Examination (MMSE) (113) and Montreal Cognitive Assessment (MOCA) (114) to determine cognitive impairment and assessed by a neurologist the individual identified with possible cognitive impairment.

In Paper IV, we analysed data from the 2005-2008 follow-up of the EPIPorto cohort study and selected participants aged 60 to 85 years old (n=656). Between 2013-2015 we did the cognitive evaluation of 341 participants. We evaluated cognitive impairment using the Mini-Mental State Exam (MMSE), with cut-off scores adjusted for the Portuguese population(113). We evaluated the social support perception with the Multidimensional Scale of Perceived Social Support (115). In this study, we did not exclude cases of dementia.

3.2. Methodology

In the three waves of evaluation, all participants were invited to visit the Department of Hygiene and Epidemiology of the University of Porto Medical School for an interview and physical examination. Trained interviewers using similarly structured questionnaires and the same physical examination procedures collected the information regarding self-reported data on social-demographic (years of education, age, gender, marital status, professional status), past personal and family medical conditions, and behavioural characteristics.

A more detailed description of the study variables follows.

3.2.1. Social-Demographic Characteristics

Trained interviewers collected information on personal characteristics using structured questionnaires and did a physical examination.

Education

The education was recorded as completed years of schooling.

Marital Status

The marital status was registered as married, living together, divorced, single or widowed. For data analysis, we categorised the marital status into two groups: married or cohabiting and not married (divorced, single or widowed).

Professional Status

Subjects reported their actual professional status as upper, intermediate, specialised non-manual, specialised manual, semi-skilled or unskilled (categorised has work) and others, no profession, unemployment (categorised has retired), housewives.

Physical Examination

The physical examination was performed at the Department of Hygiene and Epidemiology during the morning by a trained team of interviewers comprised of nutritionists, biochemists, pharmacists, nurses and physicians.

Cognitive Impairment

The cognitive impairment was evaluated with the MMSE, one of the most used tests for cognitive impairment research. The MMSE is the most cited small-sized scale used for dementia and cognitive impairment assessment (116, 117) and is a thought reliable and valid test for cognitive impairment (112, 118, 119). It detects intellectual impairment and quantifies cognitive function but has lower sensibility, especially in frontal executive functions evaluation (120, 121).

It was validated for the Portuguese population in 1994 by Guerreiro et al., who established cut-off values according to schooling years (122). More recently, Morgado et al. updated cut-off values to reflect educational progress in Portugal (113). As such, we use the Mini-Mental State Exam (MMSE) with cut-off points adjusted by years of schooling validated for the Portuguese population: 22 for 0-2 years; 24 for 3-6 years and 27 for seven or more years of schooling (113).

For Paper III, we use the validated Portuguese version of Montreal Cognitive Assessment (MOCA)(114) cumulatively. We considered cognitively impaired participants with age- and education- adjusted defined as 1.5 standard deviations below the normative sample's average. Those were selected for evaluation by a neurologist using a standardised clinical protocol that consisted of an interview and clinical evaluation. A close family member accompanied the participants to ensure the presence and impact of cognitive impairment in daily living activities. The neurologists analyse their clinical records results of imaging and laboratory tests in three hospitals in Porto. A diagnosis of mild cognitive impairment was made based on the results of this systematic assessment.

Social Support Perception

We evaluated the social support perception with the Multidimensional Scale of Perceived Social Support, a 12-item scale of perceived social support from family and friends. Each item

scored 1-7; the total sum of all 12 items is a possible range of 7-84. The highest scores suggest a high level of social support (115).

3.3. Statistical Analysis

We performed the statistical analyses using SPSS® version 21, R statistical software or Stata version 11.2.

We described data as a mean and standard deviation. We tested the differences among the variables using the Chi-Square test, Test-t for independent samples or the Mann-Whitney as appropriate. Losses to follow-up were compared to participants in the follow-up using the Chi-Square test or Test-t for independent samples as appropriate.

On Paper I, to explore the papers selected in the systematic review, we divided data into more homogeneous groups to analyse the within-group comparisons with Kruskal-Wallis for independent samples and the median quartiles using Tukey's Hinges method, due to the wide variance of reported prevalence and incidence estimates. We reported Prevalence as a percentage and incidence as cases per 1000 person-years, and the median (25-75 percentile) for both.

Paper II and III were devoted to analysing the epidemiology of cognitive impairment and its determinants, and we did the Crude incident rates' appraisal has the quotient of the number of events by person-years at risk for the total sample. We calculated the time at risk as the time in years between the two evaluations for subjects who remained free of cognitive impairment. For those who experienced cognitive impairment was given by the midpoint of the two evaluations.

We used the Poisson generalised linear models to compute relative risks (RR) and respective 95% confidence intervals to quantify the associations between professional status and cognitive impairment incidence. Crude sex- age- and education- RR was estimated considering the interaction documented in previous studies. The log of the variable follow-up time was the offset. We estimated the survival curves in the baseline professional status setting using the Kaplan-Meier estimator and compared them by the log-rank test. The Cumulative

Incidence Functions were estimated in the competing risks setting using the R Libraries (123) and Gray's test for equality across groups.

On Paper IV, in which the purpose was to study the effect of different sources of social support on the risk of cognitive impairment, we used Cox proportional hazards regression models to estimate the hazard ratios (HRs) with the backward stepwise conditional LR method to select the most suitable model and used Akaike's Information Criterion (AIC) model selection to distinguish among the set of possible models. We complied with the model assumptions about proportional risks. We did the normality testing using the Skewness test and performed Test-t for independent samples or Oneway Anova as applicable. To compare variable means, we use the General Linear Model with Bonferroni comparison.

3.4. Ethical Consideration

The Ethics Committee, "Comissão de Ética para a Saúde" of Hospital de São João, approved the study and also the Portuguese Data Protection Authority. Researchers made procedures in order to guarantee data confidentiality and protection. All participants received an explanation of the study's purpose and design and gave their written informed consent in the evaluation. They have also allowed access to their electronic clinical records and referral of the diagnosis and investigation plan to the general practitioner.

4. WORLD DATA

4.1. Paper I: Global Cognitive Impairment Prevalence and Incidence in Community Dwelling Older Adults - a systematic review.

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Keywords: Epidemiology; Cognitive impairment; Prevalence; Incidence.

geriatrics

MDPI

Review

Global Cognitive Impairment Prevalence and Incidence in Community Dwelling Older Adults—A Systematic Review

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Abstract: (1) Background: We proposed to review worldwide estimates of cognitive impairment prevalence and incidence in adults older than 50 years of age living in the community. (2) Methods: Systematic searches were performed in January 2019 using MEDLINE/PubMed. Articles were selected if they referred to cognitive impairment, prevalence, incidence, elders, and population or community-based studies. Analysis, aggregated by different methodologic features, was performed. (3) Results: Prevalence (80 studies) ranged between 5.1% and 41% with a median of 19.0% (25th percentile = 12.0%; 75th percentile = 24.90%). Incidence (11 studies) ranged from 22 to 76.8 per 1000 person-years with a median of 53.97 per 1000 person-years (25th percentile = 39.0; 75th percentile = 68.19). No statistically significant effects were found except for inclusion age. (4) Conclusion: We propose that the homogenization and clarification of the definition of what constitutes cognitive impairment are essential to refine the epidemiological understanding of this entity. The results of this review reinforce the importance of adherence to standardized cut-off scores for cognitive tests to promote study comparability.

Keywords: epidemiology; cognitive impairment; prevalence; incidence

1. Introduction

The size of the elderly population is increasing worldwide. The United Nations project that this increase will intensify in the coming decades, mostly due to the rise in average life expectancy. The number of elderly people in the world (more than 60 years old) will increase by 56% in the next 15 years and the "oldest old" (more than 80 years old) will triple in number by 2050 [1]. This rapid demographic ageing will increase the prevalence of disease and disability, with a particular emphasis expected for the impairment of cognitive functions [2].

Loss of memory, learning difficulties and a decrease in the ability to concentrate on a task characterizes cognitive impairment in the elderly [3]. This ranges from mild deficits, which are not clinically detectable, to dementia [4]. There are many different etiologies of cognitive impairment, ranging from vascular conditions to neuronal degeneration and stroke. Cognitive impairment leads to a decrease in the life quality of elders and increases the risk of dementia and mortality [5,6]. Additionally,

it has significant social consequences, resulting in the loss of autonomy and independence and leading to an increased need for permanent caregivers and assistance by health services [7,8].

There is a scarcity of studies reporting the prevalence of cognitive impairment at a given time point, as well as of the incidence of newly diagnosed cases. Both of these measures help to identify disease trends within a population, giving information not only on how common the condition is but also at what speed new cases are emerging. This information is essential to assess the overall burden of disease and to develop hypotheses regarding the causes and factors that increase the risk of disease. Good quality scientific data on cognitive impairment are needed, both to identify groups at risk of developing cognitive changes at an early stage and to identify the optimum time at which to implement preventive and corrective measures. A better understanding of cognitive impairment and its lifetime course is needed to define and implement strategies to both prevent initial cognitive impairment and either stop or delay its progression towards dementia once established. In 2015, the COSMIC studies (Cohort Studies of Memory in an International Consortium) was published, which used data from cohort studies in several countries around the world, applied uniform criteria to harmonize data, and reported the prevalence of cognitive impairment [9]. Our systematic review complements the COSMID study as it includes information on the prevalence as well as incidence of cognitive impairment by considering the latest studies published after 2015, and it includes information from Portugal.

The free-form research question we used to drive this research was "What is the worldwide cognitive impairment prevalence and incidence in older adults, as reported by observational studies?" The PICO structure to our research question was as follows: Population—older adults; Intervention—observational studies; Comparison—worldwide; Outcome—prevalence and incidence of cognitive impairment. Our objective was to review the global epidemiological data on cognitive impairment and to derive prevalence and incidence estimates for this nosological entity.

2. Materials and Methods

We conducted a systematic search of the PubMed electronic database on 4 January 2019. We did not seek unpublished data. We considered all studies published until 4th January 2019 for the analysis. The search details were "cognitive impairment"[All Fields] AND (("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms])) AND (elders[All Fields] OR older[All Fields]). For the first evaluation, we imported a total of 3645 references to Endnote. In order to increase the information for Portugal, we conducted a second related search on the same day. The search details were "cognitive impairment"[All Fields] AND (("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms])) AND (elders[All Fields] OR older[All Fields] OR ("aged"[MeSH Terms] OR "aged"[All Fields])) AND ("portugal"[MeSH Terms] OR "portugal"[All Fields]). A total of 53 references were imported and added to the database. We did not limit the search results by the language of publication. We eliminated duplicates (8 references).

References were verified using a two-step process. For the first step, articles were selected based on information available in the title and/or abstract. The full text of the selected articles was read in the second step to determine the agreement of each article with the adopted criteria. We included reports with epidemiological data on cognitive impairment (CI), mild cognitive impairment (MCI) and cognitive impairment not dementia (CIND). These terms are used differentially but overlap to some extent and there was no standard rule that would allow us to draw a clear distinction between them, therefore they were assumed to refer broadly to the same entity and treated as such.

The exclusion criteria were as follows: non-original full-length articles (e.g., a systematic review, guidelines, meta-analysis, review, comment, editorial, note, meeting abstract); case-reports; non-human/in vitro; non-elderly population (studies conducted in populations described as consisting exclusively or partially of children, adolescents or adults); language (papers not written in English,

Spanish, French or Portuguese were excluded); treatment/intervention/diagnostic studies; no data on cognitive impairment (studies that did not report prevalence or incidence of cognitive impairment); cognitive impairment in specific subgroups, such as patients with dementia, depression, HIV and Parkinson's disease; studies including the oldest old only (over 85 years old); institutionalized participants in hospitals, clinics or nursing homes (to obtain data for older people present in the general population and not report on a special population).

We collected data regarding the participants' age, sample size, diagnostic methods used, world region, and estimates of prevalence and/or incidence of cognitive impairment. We provide Supplementary Material with the characteristics of the cohort studies.

We assessed the quality of the studies included using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [10], categorized as >80% yes = "Good", 60–80% yes = "Fair", and <60% yes = "Poor" to assess the internal validity and risk of bias for each study and the overall quality. We took into account the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 Checklist (Table S4) and the Quality Assessment tool from the NHLBI to verify methodological quality and the quality of the included studies (Table S3).

Tables with the results of the Quality Assessment Tool and the score from the PRISMA 2009 Checklist are available as Supplementary Material.

2.1. Statistical Analysis

The included studies differed in several parameters such as participant inclusion age, sample size, diagnostic methods used and world region (Europe, Asia, North America, South America and Australia). Due to the large variance of reported prevalence and incidence estimates, we divided data into more homogeneous groups, and within-group comparisons were made with Kruskal–Wallis for independent samples test and the median quartiles using Tukey's Hinges method. We used non-parametric statistical techniques due to the asymmetrical distribution of the sample. The statistical analyses were performed using SPSS® version 21. Prevalence was reported as a percentage and incidence is reported in cases per 1000 person-years, while the median (25–75 percentile) are reported for both.

2.2. Data Analysis

For prevalence data, we subdivided papers into three groups according to inclusion age: (1) participants aged from 50 to 59 years (mean = 52.93 years; SD = 2.50 years)—14 papers; (2) participants aged from 60 to 69 years old (mean = 63.28 years; SD = 2.49 years)—57 papers; and (3) participants aged 70 years or older (mean = 75.11 years; SD = 3.02 years)—9 papers. Regarding sample size, 26 studies had fewer than 1000 participants (mean = 504.19 participants; SD = 222.12 participants); 22 had between 1001 and 2500 participants (mean = 1695.82 participants; SD = 408.78 participants); 18 had between 2501 and 5000 participants (mean = 3614.33 participants; SD = 519.19 participants) and 14 studies had more than 5000 participants (mean = 7314.50 participants; SD = 1682.56 participants). According to the diagnostic method used to identify cognitive impairment, 9 studies accounted for the presence of cognitive complaints by either the patient or family, the absence of dementia and a neurological evaluation; 62 used only standard neurological tests to determine cognitive impairment (including but not restricted to Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MOCA), and the Short Portable Mental Status Questionnaire); and 8 simultaneously used both of the previously described methods. We analyzed data by world region: 25 studies in Europe; 13 studies in North America; 3 studies in South America; 35 studies in Asia; 2 studies in Africa; and 2 studies in Australia (Table S1).

To estimate the incidence of cognitive impairment, we divided the papers according to the same criteria: people aged: 50–59 years (mean = 55.33 years; SD = 0.58 years)—3 papers; 60–69 years old (mean = 64.50 years; SD = 2.38 years)—4 papers; ≥70 years (mean = 73.75 years; SD =

2.87 years)—4 papers. In terms of sample size, 2 studies had fewer than 1000 participants (mean = 608.50 participants; SD = 215.60 participants); 5 studies had 1001–2500 participants (mean = 1701.80 participants; SD = 479.51 participants); 3 studies had 2501–5000 participants (mean = 3102 participants; SD = 698.69 participants); and one study included 7166 participants. As for the diagnostic method used to identify cognitive impairment, three studies accounted for the presence of a patient or family report of cognitive complaints, the absence of dementia and a neurological evaluation; five studies used validated neurological tests; and three studies used both of the previously described methods. There were five studies carried out in both Europe and North America, and one was carried out in Asia (Table S2).

3. Results

Of the 3690 potentially relevant articles found, 296 were selected based on the information present in the title and/or abstract (step 1); after reading the full text, 85 were selected as relevant (step 2). Of these, 74 papers provided information only on cognitive impairment prevalence, 5 papers only provided information on cognitive impairment incidence and 6 papers provided information for both parameters (Figure 1). The quality assessment tool from the NHLBI was used to assess the methodological quality of the included studies; 77 studies had an overall rating of "good", eight were rated "fair" and none were rated "poor". Based on these findings, no papers were excluded from the analysis.

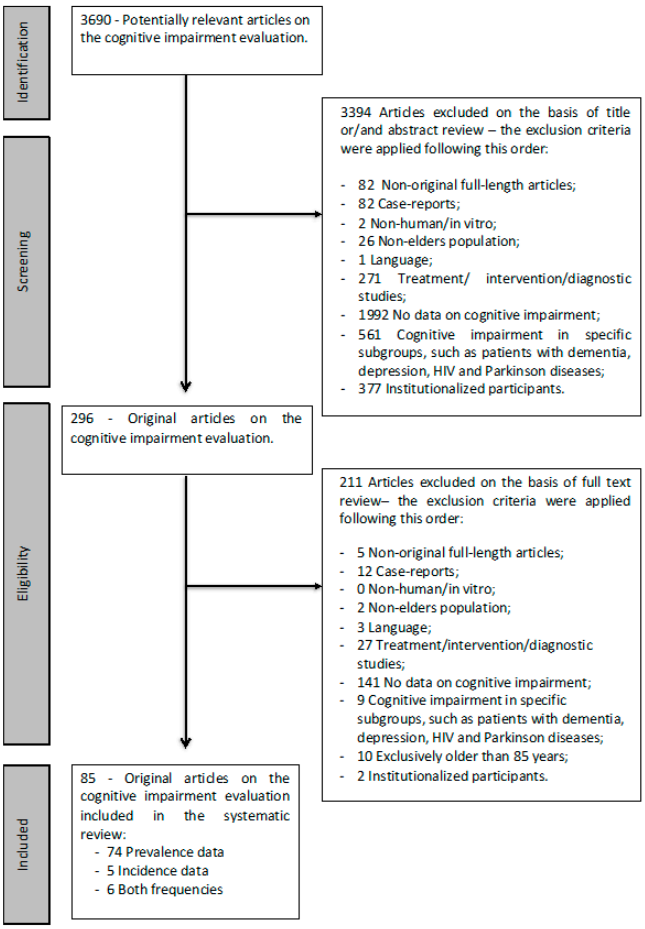

Figure 1. Flow chart summary of the literature search.

3.1. Prevalence of Cognitive Impairment

The prevalence of cognitive impairment (CI) reported in the 80 studies [11–90] ranged from 5.1% to 41.0% (median = 19.0%; 25th percentile = 12.0%; 75th percentile = 24.90%) (Table 1 and Figure 2).

Figure 2. Prevalence of cognitive impairment reported by published papers, which are grouped by world region (95% confidence intervals were obtained from papers or calculated from the data presented).

Table 1. Summary of the prevalence of cognitive impairment reported by 80 studies included in analysis.

	Number of Papers	With Cognitive Impairment Median (25–75 Percentile)	*p* Value
Inclusion Age			
50–59	15	12.0 (9.60–17.65)	0.062
60–69	57	20.10 (14.20–24.70)	
≥70	9	19.0 (15.0–29.90)	
Participants Number			
<1001	26	22.75 (14.90–31.40)	0.386
1001–2500	22	15.95 (11.60–28.50)	
2501–5000	18	13.75 (9.60–21.30)	
>5000	14	20.24 (18.80–24.10)	
Diagnostic Method			
Neurologist evaluation	9	15.40 (11.30–23.40)	0.737
Neurological tests	62	18.90 (12.20–24.70)	
Neurologist evaluation and tests	8	21.30 (12.0–28.90)	
Region			
Europe	25	12.10 (9.94–23.90)	0.110
North America	13	20.10 (19.0–24.70)	
South America	3	34.0 (29.15–35.75)	
Asia	35	19.44 (13.25–25.55)	
Africa	2	25.70 (18.40–33.0)	
Australia	2	20.50 (7.70–33.30)	

Legend: median expressed in percentage.

Grouping papers according to inclusion age (50–59 years old, 60–69 year old, and ≥70 years old), the reported prevalence ranges from 6.5% to 34% (median = 12%; 25th percentile = 9.6%; 75th percentile = 17.65%) in the first group [17,19,20,23–26,41,57,60–62,75,81], 5.1% to 37.5% (median = 20.1%; 25th percentile = 14.2%; 75th percentile = 24.7%) in the second group [11–16,21,22,28,30–40,42,44–46,49–56,59,63–74,76–80,82–89] and from 11.6% to 41% (Med = 19%; 25th percentile = 15%; 75th percentile = 29.90%) in the last group [18,27,29,34,43,47,48,58,90].

When grouping and analyzing the effect of sample size, we divided the studies into four groups based on the number of participants they had (<1001, 1001–2500, 2501–5000 and >5000). The reported prevalence in the first group ranged from 5.3% to 37.5% (median = 22.75%; 25th percentile = 14.9%; 75th percentile = 31.4%) [11,14,20,22,24,30,32,33,40,41,49,53,55,58,64,68,72,75,78–80,85–88,90], from 7.7% to 41% in the second group (median = 15.95%; 25th percentile = 11.60%; 75th percentile = 28.50%) [16,18,19,23,27,28,34,37,38,45,50,51,56,57,59,60,62,63,67,69,77,84,89], from 6.5% to 32.7% in the third group (Med = 13.75%; 25th percentile = 9.60%; 75th percentile = 21.30%) [12,13,15,17,25,26,29,35,42,44,46–48,61,66,71,81], and from 5.1% to 27% (median = 20.24%; 25th percentile = 18.8%; 75th percentile = 24.1%) in the last group [21,31,36,39,43,54,65,70,73,74,76,82,83].

Regarding cognitive impairment diagnostic methods, in the presence of cognitive complaints, the absence of dementia and with a neurological evaluation, the prevalence of cognitive impairment (CI) was from 9.6% to 33% (median = 15.4%; 25th percentile = 11.3%; 75th percentile = 23.4%) [17,19,20,25,29,37,65,80,88]. When only standardized neurological tests were used (MMSE, MOCA, Short Portable Mental Questionnaire, etc.), the prevalence of CI ranged from 5.1% to 41% (median = 18.9%; 25th percentile = 12.2%; 75th percentile = 24.7%) [11–16,18,21–23,26,28,30–34,36,38–53,55,58–61,63,64,66,67,

69,70,75–79,81–87,89,90]. When both methods (neurologist evaluation, patient or family complaints and standardized neurologic tests) were used, the estimated prevalence of CI ranged from 10.7% to 34% (median = 21.30%; 25th percentile = 12.0%; 75th percentile = 28.90%) [24,27,35,56,57,62,71–74].

With regard to the world region where data were collected, in Europe the prevalence of cognitive impairment ranges from 5.1% to 41% (median = 12.1%; 25th percentile = 9.94%; 75th percentile = 23.9%) [11–35]; in North America, it ranged from 7.1% to 28.3% (median = 20.1%; 25th percentile = 19%; 75th percentile = 24.70%) [36–48]; in South America, it ranged from 24.3% to 37.5% (median = 34%; 25th percentile = 29.15%; 75th percentile = 35.75%) [49–51]. In Asia the prevalence ranges from 6.5% to 37% (median = 19.44%; 25th percentile = 13.25%; 75th percentile = 25.55%) [52–86]. In Africa, CI prevalence ranged from 18.4% to 33% (median = 25.7%; 25th percentile = 18.4%; 75th percentile = 33%) [87,88] and in Australia from 7.7% to 33.3% (median = 20.5%; 25th percentile = 7.7%; 75th percentile = 33.3%) [89,90]. No statistically significant differences within groups were found in the reported CI prevalence when grouping papers according to any of these variables.

3.2. Incidence of Cognitive Impairment

The incidence of cognitive impairment reported by the 11 included studies [15,26,28,39,60,91–95] ranged from 22 to 215 per 1000 person-years, with a median incidence of 56.50 per 1000 person-years (25th percentile = 41.77; 75th percentile = 76.50) (Table 2 and Figure 3).

Table 2. Summary of cognitive impairment incidence as reported by the 11 studies included.

	Studies	With Cognitive Impairment Median (25–75 Percentile)	*p* Value
Inclusion Age			
50–59	3	30.70 (26.35–36.24)	0.035 *
60–69	4	71.11 (58.44–145.98)	
≥70	4	58.45 (51.84–68.45)	
Participants Number			
<1001	2	51.09 (41.77–60.40)	0.693
1001–2500	5	56.50 (41.19–76.50)	
2501–5000	3	51.45 (41.08–58.44)	
>5000	1	215	
Diagnostic Method			
Neurologist evaluation	3	76.50 (59.14–145.75)	0.737
Neurological tests	5	51.45 (30.70–60.40)	
Neurologist evaluation and tests	3	56.50 (51.82–60.96)	
Region			
Europe	5	56.50 (51.45–76.50)	0.285
North America	5	60.40 (47.19–65.42)	
Asia	1	22	

(* significant at $p < 0.05$). Legend: median expressed in per 1000 person-years.

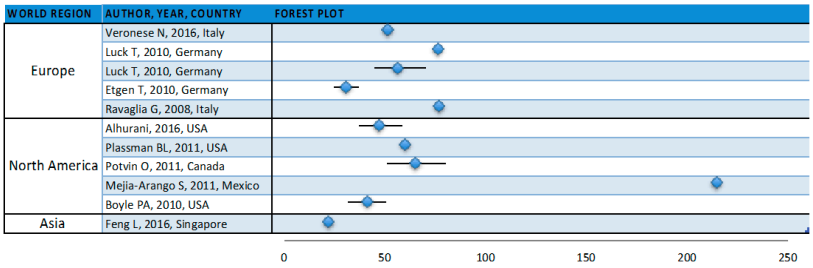

Figure 3. Incidence of cognitive impairment reported by the 11 included studies, which are grouped by world region (the 95% confidence intervals were obtained from papers or calculated with the data presented).

Grouping papers according to the age of the participants (50–59 years old, 60–69 years old, and ≥70 years old) yielded incidence estimates ranging from 22 to 41.77 per 1000 person-years (median = 30.7 per 1000 person-years (25th percentile = 26.35; 75th percentile = 36.24) in the first group [26,60,95], from 51.45 to 215 per 1000 person-years (median = 71.11 per 1000 person-years (25th percentile = 58.44; 75th percentile = 145.98) in the second group [15,28,39,96] and from 47.19 to 76.50 per 1000 person-years (median = 58.45 per 1000 person-years (25th percentile = 51.84; 75th percentile = 68.45) in the last group [91–94]. Statistically significant differences were found in the incidence of CI across age categories ($p = 0.035$).

Taking into account the number of participants included in the studies (<1001, 1001–2500, 2501–5000 and >5000), the reported CI incidence ranged from 41.77 to 60.4 per 1000 person-years (median = 51.09 per 1000 person-years (25th percentile = 41.77; 75th percentile = 60.40) for group 1 [94,95], from 22 to 76.8 (median = 56.50 per 1000 person-years (25th percentile = 47.19; 75th percentile = 76.50) for group 2 [28,60,91–93], from 30.70 to 65.42 (median = 51.45 per 1000 person-years (25th percentile = 41.08; 75th percentile = 58.44) for group 3 [15,26,44,96] and the only study with more than 5000 participants reported an incidence of 215 cases per 1000 person-years. No statistically significant differences were found between the groups.

According to the cognitive impairment diagnostic methodology used, studies that evaluated the presence of cognitive complaints and the absence of dementia, and included a neurological evaluation, reported a CI incidence ranging from 41.77 to 215 per 1000 person-years (median = 76.5 per 1000 person-years (25th percentile = 59.14; 75th percentile = 145.75) [91,92,94]. The studies that used neurological tests (MMSE, MOCA, Short Portable Mental Questionnaire) reported an incidence from 22 to 76.80 per 1000 person-years (median = 51.45 per 1000 person-years (25th percentile = 30.7; 75th percentile = 60.4) [15,26,28,60,96]. The studies that used both methods reported a CI incidence ranging from 47.9 to 65.42 per 1000 person-years (median = 56.50 per 1000 person-years (25th percentile = 51.82; 75th percentile = 60.96) [39,93,95]. There were no statistically significant differences among these groups.

In Europe, the incidence of cognitive impairment ranges from 30.70 to 76.50 per 1000 person-years (median = 56.5 per 1000 person-years (25th percentile = 51.45; 75th percentile = 76.5) [15,26,28,91,92]. In North America, this ranged from 41.8 to 215 per 1000 person-years (median = 60.4 per 1000 person-years (25th percentile = 47.19; 75th percentile = 65.42) [39,93–96] and in Singapore the incidence was reported as 22 per 1000 person-years [60]. We did not find statistically significant differences among groups.

One study reported an incidence of 215 per 1000 person-years, which is 11.85 standard deviations over the mean of the other ten studies. Excluding that study from the data analysis changes the reported median incidence to 53.97 per 1000 person-years (25th percentile = 39.0; 75th percentile = 68.19). In the group of participants with the minimum inclusion age (60–69 years old), the median incidence was 65.42 per 1000 person-years (25th percentile = 58.44; 75th percentile = 71.11), statistically significant differences were found within the group ($p = 0.05$). In the group of studies that evaluated the presence of cognitive complaints, the absence of dementia included a neurological evaluation, the

median incidence was 59.14 per 1000 person-years (25th percentile = 41.77; 75th percentile =76.50), and we did not find statistically significant differences within the group. In the group of studies from North America, the median incidence was 53.80 per 1000 person-years (25th percentile = 44.48; 75th percentile = 62.91), and we did not find statistically significant differences within the group.

4. Discussion

4.1. Methodological Considerations

Our objective was to review the global epidemiological data to derive prevalence and incidence estimates for cognitive impairment. We included reports with three different constructs: cognitive impairment (CI), mild cognitive impairment (MCI) and cognitive impairment not dementia (CIND). Besides the different names, we could not distinguish consistently between them, so all were assumed to refer broadly to the same entity and were treated as such.

We expected a significant degree of heterogeneity among studies, so data were aggregated by age group, study sample size, diagnostic methods used, and world region.

Despite all the studies having elderly people as the study focus, the minimum inclusion age for participants diverged greatly between studies and could bias the results. For example, higher estimates of cognitive impairment could be a result of a more elderly sample, as several different studies reported an increase in cognitive impairment prevalence with increasing age [17,20,45,92]. In our study, we found that in terms of the incidence of cognitive impairment, studies that had an inclusion age starting at 60 years had a median incidence higher than those with an inclusion age over 70 years old, and the difference was statistically significant. The lower incidence at higher ages might imply that the rate of conversion from healthy cognition to cognitive impairment might reach a plateau at some point after 60 but before 70 years of age, considering that cognitive impairment is a milder form of decline that, at older ages, can progress to dementia.

Regarding the sample size of the studies, the main objective was to compare the results of studies with hundreds of participants to others with thousands of participants, and we found no significant quantitative differences among these.

While there were no statistically significant differences regarding the method used to identify cases of cognitive impairment, for studies of the prevalence of cognitive impairment, the median prevalence of cognitive impairment was higher for the method that used a neurological evaluation paired with neurological tests. With regard to studies on the incidence of cognitive impairment, the median was higher for neurological evaluations. In the future, we aim to further explore the optimum methods to identify cognitive impairment and develop recommendations that will lead to a better and more accurate diagnosis [97].

We aggregated data by world region to examine the geographic differences that may influence the epidemiology. In terms of the prevalence of cognitive impairment, there were no statistically significant differences. However, in terms of incidence of cognitive impairment, in Europe it was lower than in North America; this could be due to cultural or genetic effects, or a combination of both, with an impact on cognitive impairment severity and progression [9].

Regarding cognitive impairment incidence studies, the Mejia-Arango [39] study from Mexico reports an incidence that is 11.85 standard deviations above the mean of the other ten studies (Figure 3). Although the median is not greatly affected by outliers, this study alone increases the median reported incidence from 53.97 per 1000 person-years (without) to 56.50 per 1000 person-years (with). Several procedural characteristics set this study apart. Briefly, it was the only study that used a version of the Cross-Cultural Cognitive Examination (CCCE) as a cognitive decline screening approach, which might point to a culturally diverse background of the participants. To those unable to complete the questionnaire due to limitations of language or health, a brief version of the informant questionnaire of Cognitive Decline in the Elderly (IQCODE) was applied. Additionally, 32.70% of the participants in the study were illiterate, and education years have a meaningful impact on cognitive impairment

frequency [28,88]. The high cultural heterogeneity implicit in this choice of instruments and reported illiteracy prevalence raises doubts over whether this incidence estimate is valid for Mexicans in general or highly influenced by a specific sub-population within Mexico. Due to its methodological particularities and high incidence estimate, we analyzed all of the incidence variables excluding the Mejia-Arango paper; however, there were no statistically significant differences within groups with or without it.

4.2. Future Directions

The ability to rely on tests to identify the incipient cases of cognitive impairment with high accuracy (sensitivity and specificity) is crucial for population studies and population interventions, as it is both impractical and cost-prohibitive to have a specialist neurological assessment of large numbers of unaffected individuals. We believe that our results highlight the need for the development of a consensus regarding the best initial markers of cognitive impairment, the development of more reliable tests to detect incipient cognitive impairment cases, both with better reliability and more universally applied cut-off points that account for the factors known to influence cognitive declines such as age and education. Equally, to examine age-related cognitive decline, studies should restrict the inclusion age to 60 years old, as this is the threshold for older people as defined by the WHO [1]. We expect that the implementation of these measures would lead to a more reliable and valid diagnosis of cognitive impairment and a more accurate global view of the prevalence and incidence of cognitive impairment in older people, which is fundamental to the delineation of public health measures aimed at this risk group. Results from this systematic review may inform public health decisions through accurate regional estimates of cognitive impairment for the definition of adequate measures regarding modifiable risk factors, particularly in people over 60 years old. Detection and treatment of diabetes and hypertension, reduction in levels of obesity, smoking cessation, increased physical activity, and better education should be public health priorities. We also provide some suggestions for methodologies on further cognitive impairment studies, as there are significantly different social and economic structures in different world regions, and even in different countries within the same world region, it would be essential to conduct studies aimed explicitly at understanding cognitive impairment in the specific region.

4.3. Strengths and Limitations

The strengths of this study were its global view of the epidemiological data and the use of studies which reported on the general population, while excluding those that reported on people within the healthcare system or with a diagnosed underlying disease etiology. There are some methodological limitations and a risk of different types of bias associated with this study. Among these, we should mention publication bias, the selective reporting of data within studies and the incomplete retrieval of research. To try to reduce the risk of other biases, we aggregated papers into more methodologically homogeneous groups and compared the reported data within each group. By not restricting the initial search by publication language, we have an estimate of the size of our language bias. By only including reports written in Portuguese, English, Spanish or French, we excluded four studies. Reporting bias in published studies due to the selective reporting of subgroups of a population or the exclusion of non-significant outcomes measured by the study is a possibility that should be borne in mind. Additionally, we did not consider data on cognitive impairment etiology, as the main objective of this study was to review worldwide estimates of the prevalence and incidence of cognitive impairment in older adults regardless of etiology. Another limitation was that there was no pairwise review.

5. Conclusions

This systematic review reports that the global prevalence of cognitive impairment ranged from 5.1% to 41% with a median of 19.0%. The incidence of cognitive impairment ranged from 22 to 76.8 per 1000 person-years, with a median of 53.97 per 1000 person-years. We did not find statistically

significant effects besides participant age in the studies sampled. For future studies, we propose the homogenization of the definition of cognitive impairment and the importance of the standardized cut-off scores of cognitive tests to compare different studies.

Supplementary Materials: The following are available online at http://www.mdpi.com/2308-3417/5/4/84/s1, Supplemental Table S1: Cognitive Impairment Crude Prevalence, Supplemental Table S2: Cognitive Impairment Crude Incidence, Supplemental Table S3: Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies; Supplemental Table S4: PRISMA 2009 checklist.

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5. PORTUGUESE DATA

5.1. Paper II: Prevalence and incidence of cognitive impairment in an elder Portuguese population (65-85 years old)

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Keywords: Cognitive impairment, Prevalence, Incidence, Population-based cohort, EPIPorto

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RESEARCH ARTICLE Open Access

Prevalence and incidence of cognitive impairment in an elder Portuguese population (65–85 years old)

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Abstract

Background: The increase in average life expectancy increases the risk of illness and frailty in the elderly, especially in the cognitive arena. This study has the objective to estimate the prevalence and incidence of cognitive impairment, in a representative sample of 65 to 85 years old followed for a mean period of 6-years.

Methods: Subjects aged 65–85 years ($n = 586$) were screened at baseline (1999–2004) to estimate the prevalence of cognitive impairment using the Mini-Mental State Examination. A total of 287 individuals with a normal MMSE at baseline were reassessed after 6.2 mean years (± 4.30 years) to evaluate the incidence of cognitive impairment, defined as scoring below the age and education-adjusted MMSE cut-off points adapted for the Portuguese population. We did not exclude Dementia.

Results: The baseline prevalence of cognitive impairment was 15.5% (95% CI: 12.7–18.7). Higher in women (18.9%; 95% CI: 14.9–23.3), that in men (10.4%; 95% CI: 6.7–15.1). Increased with age and was highest for participants without any schooling. The overall incidence rate was 26.97 per 1000 person-years; higher in women (33.8 per 1000 person-years) than in men (18.0 per 1000 person-years). Higher for the oldest participants and those with no schooling. Taking the standard European population, we estimated a prevalence of 16.5% and an incidence of 34.4 per 1000 person-years.

Conclusion: The prevalence of cognitive impairment in Portugal is within the estimated interval for the European population, and the incidence is lower than for the majority of the European countries. Women, senior and elders without education have a higher risk of cognitive impairment. In our sample, neither employment nor marital status has a significant effect on cognitive impairment.

Keywords: Cognitive impairment, Prevalence, Incidence, Population-based cohort, EPIPorto

Background

The ageing of the world population is a demographic trend that will intensify in the coming decades. Eurostat projects that by 2050 Portugal will be the European country with the highest percentage of people aged 55 years or more (47%) [1]. The growing number of older people poses health challenges such as increasing the prevalence of disease and disability in the elders, especially the burden of cognitive dysfunctions [2]. Cognitive impairment increases the risk of dementia and mortality in the elders [3, 4]. It is characterised by individuals having more difficulties with memory, learning, and the ability to focus on a task, than would be normally expected for the individual's age and educational level [5]. It ranges from mild deficits that are not clinically detectable to dementia [5]. It has a social impact and is associated with other pathologies, such as

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Alzheimer or Dementia [6, 7]. Age, sex and level of education are considered risk factors for cognitive impairment [4]. Continued professional activities may be protective against cognitive decline [8] however there is a lack of information about the impact on cognitive function of postponement of retirement age. Also, changing demographics characteristics added to a higher divorce rate increases the number of older people living alone, especially women, which traditionally already presented with an increased risk of cognitive decline [1, 9, 10].

Reports on the prevalence and incidence of cognitive impairment, as well as its relation with comorbidities and sociodemographic factors, are essential for public health and clinical care policy. They are necessary to allow primary and secondary prevention measures within the healthcare system.

In Europe, published studies report the prevalence of cognitive impairment to be between 5.1 and 24.5% [11–16], whereas in North America, the estimated cognitive impairment prevalence ranges from 13.8 to 28.3% [17–19]. In Europe reports that used the Mini-Mental State Exam for cognitive impairment evaluation in samples with the same age characteristics as ours estimated cognitive impairment prevalence between 7.7 and 33.1% [12, 16, 20]. The incidence of cognitive impairment ranges from 56.5 to 76.8 per 1000 person-years in Europe [16, 20, 21] and from 41.8 to 65.4 per 1000 person-years, in North America [22–24] In Portugal, previously published studies report a prevalence of cognitive impairment ranging from 9.3 to 12.0% [10, 25, 26] and as far as we know, the incidence is unknown.

Methods

Aim

This study aims to estimate the prevalence and incidence of cognitive impairment after 6.2 mean year's follow-up assessed using the Mini-Mental State Exam (MMSE) in a cohort of city dwellers from Porto, Portugal, aged 65 to 85 years old, and to evaluate the impact of age, sex, schooling, retirement and civil status in cognitive function. For the main variables of interest, we hypothesize that cognitive impairment prevalence and incidence are similar to other European countries.

Study population

The EPIPorto cohort study design and methodology have been published previously [27, 28]. In brief, between 1999 and 2004, we assembled a representative sample of community dwellers of Porto, an urban centre in the northwest of Portugal, with approximately 300,000 inhabitants at the time. We selected Households by random digit dialling of landline telephones. Within each household, selected by simple random sampling a permanent resident aged 18 years or more and not replaced refusals. The proportion of participation was 70%, and the final sample size was 2485 individuals. Of the 633 participants with age between 65 and 85 years old, 586 completed the assessment at baseline. The follow-up evaluation took place in two waves, part of the participants ($N = 221$) were evaluated during the first follow-up, between 2005 and 2008, and the others were evaluated only on the second follow-up ($N = 66$), between 2013 and 2015 (Fig. 1).

Data collection and definition of variables

Trained interviewers performed a face-to-face questionnaire which collected data on sociodemographic and behavioural characteristics [29] and administered the Mini-Mental State Exam (MMSE) at the beginning of each interview [30]. Education was recorded as completed years of schooling and further categorized into three groups: zero years, one to 9 years and more than 10 years of schooling. Civil status was categorized in two groups: married or living together, and not-married (divorced, single or widowed). Professional status was considered to be either working (participants employed), retired (considering retirement as a direct transition between a situation of full employment and a situation where the individual is entirely inactive and where most of his resources consist of pension benefits), or housewives. There were no unemployed participants. Cognitive impairment was evaluated using the MMSE [30], with cut-off points adjusted by years of schooling validated for the Portuguese population: 22 for 0–2 years; 24 for 3–6 years and 27 for seven or more years of schooling [31]. Subjects with an MMSE score below the age and education adjusted cut-off point were considered to have cognitive impairment. The MMSE is the most cited small-sized scale used for dementia and cognitive impairment assessment and is thought to be a reliable and valid test for cognitive impairment [30, 32].

Prevalence evaluation

At the baseline evaluation, 633 participants were aged 65 to 85 years old, but we excluded 47 subjects due to missing information on the Mini-Mental State Exam (MMSE). The final sub-sample was 586 participants (Table 1) with 71.95 years (± 4.84 SD) mean age; 355 were women (60.6%); 57 (9.7%) had no education, 432 (73.7%) had one to 9 years of education, and 97 (16.6%) had more than 10 years (16.6%) of schooling; 350 (59.7%) were married or living in civil union; 464 (79.2) were retired.

Incidence evaluation

There were two follow-up evaluations where the participants completed a questionnaire and had a physical examination. The first follow-up was between 2005 and

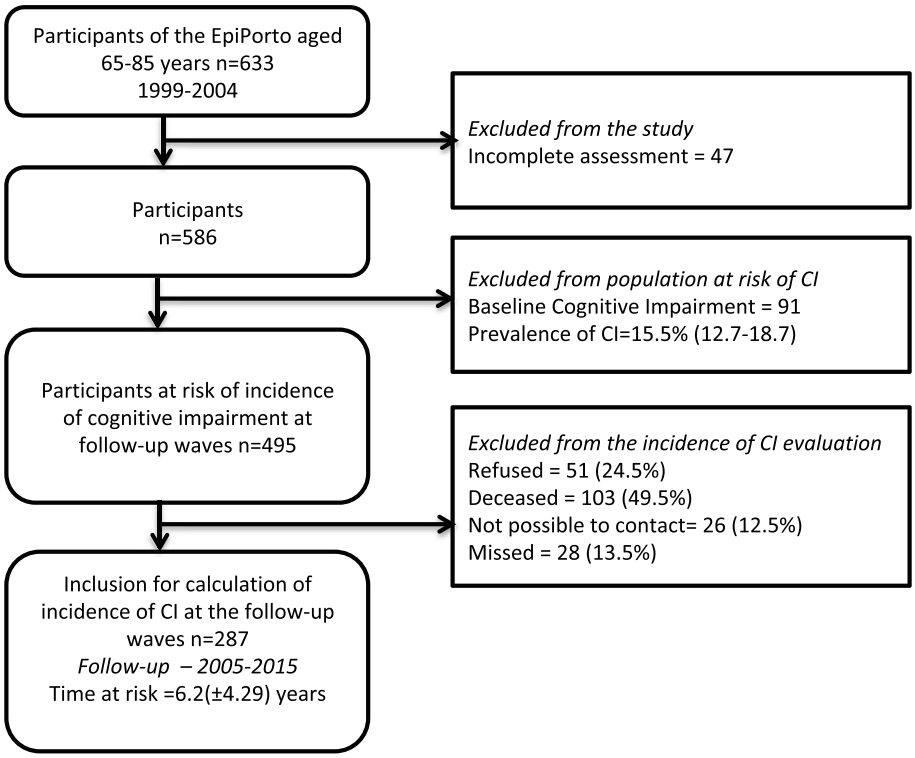

Fig. 1 Flow-chart of participants through the steps of the study and final results on the frequency of cognitive impairment

Table 1 Socio-demographic characteristics of participants

Characteristic	Baseline	Follow-up	Lost to follow-up	*P* value
N	586	287	208	
Sex				
Female	355 (60.6)	169 (58.9)	119 (57.2)	0.709
Male	231 (39.4)	118 (41.1)	89 (42.8)	
Age (years)				
[65–69]	216 (36.9)	125 (43.6)	67 (32.2)	0.010*
[70–74]	200 (34.1)	100 (34.8)	70 (33.7)	
[75–79]	120 (20.5)	46 (16.0)	50 (24.0)	
[80–85]	50 (8.5)	16 (5.6)	21 (10.1)	
Education				
0	57 (9.7)	17 (5.9)	14 (6.7)	0.751
[1–9]	432 (73.7)	219 (76.3)	162 (77.9)	
≥ 10	97 (16.6)	51 (17.8)	32 (15.4)	
Marital Status				
Married/Civil Union	350 (59.7)	180 (62.7)	118 (56.7)	0.179
Single, divorced, widower	236 (40.3)	107 (37.3)	90 (43.3)	
Employment Status				
Work	50 (8.5)	26 (9.1)	18 (8.7)	0.626
Retired	464 (79.2)	233 (81.2)	164 (78.8)	
Housewives	71 (12.1)	28 (9.8)	26 (12.5)	

Legend: Data are *n* (%); *P*-value compares follow-up to lost to follow up, obtained with Chi-square test
*Significant at $p < 0.05$

2008 and the second follow-up between 2013 and 2015. Some participants were evaluated only during the 1st or the 2nd follow-up. Of the initial 586 eligible participants, there were overall 208 losses with 103 (49.5%) deaths, 51 (24.5%) refusals, 26 (12.5%) were not possible to contact and 28 (13.5%) missed without justification. We re-evaluated a total of 287 participants (mean follow-up of 6.2 years, SD 4.30 years). There were no significant differences regarding sex, education, civil status or employment status between follow up participants and those lost to follow-up (Table 1). However, participants lost to follow-up were older (72.58 vs 71.09 mean age in years).

Competing risk model

During the follow-up, in the disease/death process, often more than one type of event plays a role. We are interested as the first event a diagnosis of cognitive impairment. However, death may prevent the event of interest from occurring, because the person died before the diagnosis of cognitive impairment. Therefore, death is a competing risk of cognitive impairment and may substantially change the risk of disease diagnosis. Death substantially reduces the probability of being diagnosed with cognitive impairment, and hence is treated as a competing risk event when calculating cognitive impairment incidence [33, 34]. Ignoring death as a competing risk or treat it as no informative censored observations will lead to a bias in the standard methods for estimate the probability of the event [35] such as the Kaplan-Meier estimate [36]. The assumption of independence of the time to event and the censoring distributions is violated and then violates one of the fundamental assumptions of the Kaplan-Meier estimator. We considered the time of event as the time from entering in the cohort to the first event, cognitive impairment or death, during the follow-up.

The cumulative incidence function (CIF) allows for estimation of the incidence of the occurrence of an event while taking competing risk into account [37, 38]. This allows one to estimate incidence in a population where all competing events must be accounted for in clinical decision making. It denotes the probability of experiencing the *kth* event before time t and before the occurrence of a different type of event, i.e., for instance, the probability of experience death before 70 years old, before the occurrence of the cognitive impairment. The CIF has the desirable property that the sum of the CIF estimates of the incidence of each of the individual outcomes will equal the CIF estimates of the incidence of the composite outcome consisting of all of the competing events [39].

We performed the competing risks analysis to the 495 participants at risk of incidence of cognitive impairment, excluding those 105 that refused to participate, missed or were impossible to contact along all period of the follow-up. From these 390, 103 died before cognitive impairment diagnosis, 48 were diagnosed with cognitive impairment and 239 were still alive without cognitive impairment diagnosis.

Statistical analysis

We assessed differences in the prepositions using the Chi-Square test. Losses to follow-up were compared to participants in the follow-up using the Chi-Square test. Calculated crude incident rates dividing the number of events by total number of person-years at risk. Counted time at risk as the time in years between the baseline evaluation and the last follow-up that each participant attended and taking into consideration the full length of time for subjects who remained free of cognitive impairment, and estimate time of onset of cognitive impairment being set to the midpoint between the baseline and follow-up observation waves for those participants who did develop the disease. Poisson generalized linear models were used to determine confidence intervals, with Log of time at risk as to the offset. We tested the possible interaction of each explanatory variable with age, sex, education and retirement status was tested. Sex-, age-, education- and education- adjusted OR and RR were estimated. Standardized prevalent and incident rates were calculated for the Portuguese population using data from the last census, in 2011 [40], and for European population using data from the standard European population, 2013 [41]. The CIFs were estimated in R using the cuminc function in the *cmprsk* R [42] package which uses the cumulative incidence function introduced by Kalbfleisch and Prentice [38].We used the Gray's test [43] for equality of CIFs across groups. We assessed differences in the MMSE mean score reduction of participants with and without cognitive impairment with T-test for independent samples. The remaining statistical analyses were performed using SPSS® version 21. We include the Box Plot of the Mini-Mental State Examination score of the population at baseline evaluation and of the participants with or without cognitive impairment at the follow-up evaluation as Supplementary material (Figure S1).

Results

Prevalence evaluation

The crude prevalence of cognitive impairment was 15.5% (95% CI: 12.7–18.7) at baseline. The standardized prevalence rate for the Portuguese population was 16.9% and for the standard European population was 16.5%. Prevalence was lower in men (10.4%; 95% CI: 6.7–15.1) than in women (18.9; 95% CI: 14.9–23.3), with the odds of presenting cognitive impairment, adjusted for age and education, of 0.95 (95% CI: 0.89–1.01).

The prevalence of cognitive impairment increases with age, being higher at 80–85 years than 65–69 years (26.0; 95% CI: 17.3–40.2 vs 11.1; 95% CI: 9.3–17.2), with the odds for cognitive impairment, adjusted for sex and education, being 1.14 higher.

The cognitive impairment prevalence is higher for participants with zero years of schooling (45.6; 95% CI: 32.4–59.3) and slightly higher for participants with more than 10 years than for participants with one to 9 years (14.4; 95% CI 8.1–23.0 vs 11.8; 95% CI 8.9–15.2) with statistically significant differences.

Not-married participants had a higher prevalence of cognitive impairment (16.5; 95% CI: 12.0–21.9 vs 14.9; 95% CI: 11.3–19.0), but the difference was not statistically significant after adjustment for age and education.

Retired participants had a higher prevalence of cognitive impairment than the working participants (14.4; 95% CI: 11.4–18.0 vs 12.0; 95% CI: 4.6–24.3) and housewives have the highest prevalence (23.9; 95% CI: 14.6–35.5) but without statistically significant differences. (Table 2).

Incidence evaluation

During the study protocol, 48 individuals developed cognitive impairment, an incidence rate of 26.97 per 1000 person-years (95% CI: 20.3–35.8). The standardized incidence rate using the Portuguese population was 35.7 per 1000 person-years and using the standard European population was 34.4 per 1000 person-years.

The incidence of cognitive impairment was higher in women (33.8 per 1000 person-years; 95% CI: 24.2–47.4) than men (18.0 per 1000 person-years; 95% CI: 10.7–30.5) and increasing with age at 80–85 years old (66.0 per 1000 person-years; 95% CI: 27.5–158.7) vs 65–69 years old (21.1 per 1000 person-years; 95% CI: 13.5–33.1).

As observed on baseline prevalence, the incidence is higher for participants with zero years of schooling (126.4; 95% CI: 68.0–234.8) and almost the same for participants with 1 to 9 years and more than 10 years (21.6; 95% CI: 15.0–31.0 vs 25.3; 95% CI 13.2–48.7).

Not married participants have a higher incidence rate of cognitive impairment (32.5; 95% CI: 21.4–49.4 vs 23.6; 95% CI: 16.1–34.6), but the difference did not reveal statistically significant differences after adjusting for age and education.

Retired participants have a higher incidence of cognitive impairment than working participants (30.0; 95% CI: 21.3–37.9 vs 18.1; 95% CI: 6.8–48.3) but without statistically significant differences. (Table 3).

Table 2 Observed prevalence of cognitive impairment by socio-demographic characteristics

Characteristics	n	Prev. % (95% CI)	*p*-value	OR (95% CI) Adjusted
Sex				
Female	67	18.9 (14.9–23.3)	0.006*	1 [reference][a]
Male	24	10.4 (6.7–15.1)		0.95 (0.89–1.01)
Age (years)				
[65–69]	24	11.1 (9.3–17.2)	0.026*	1 [reference][b]
[70–74]	30	15.0 (11.0–21.1)		1.03 (0.97–1.10)
[75–79]	24	20.0 (13.3–28.3)		1.10 (1.02–1.19)
[80–85]	13	26.0 (17.3–40.2)		1.14 (1.03–1.27)
Education				
0	26	45.6 (32.4–59.3)	0.000*	1 [reference][c]
[1–9]	51	11.8 (8.9–15.2)		0.72 (0.66–0.80)
≥ 10	14	14.4 (8.1–23.0)		0.74 (0.67–0.84)
Marital Status				
Married/Civil Union	52	14.9 (11.3–19.0)	0.584	1 [reference][d]
Single, divorced, widower	39	16.5 (12.0–21.9)		0.96 (0.90–1.02)
Employment Status				
Work	6	12.0 (4.6–24.3)	0.471	1 [reference][a]
Retired	67	14.4 (11.4–18.0)		99.6 (0.90–1.10)
Housewives	17	23.9 (14.6–35.5)		1.07 (0.94–1.22)

Legend: *Prev* Prevalence, *OR* odds ratio. 95% CI: 95% confidence interval
[a]adjusted for age and education
[b]adjusted for sex and education
[c]adjusted for sex and age
[d]adjusted for sex, age and education
* Significant at $p < 0.05$

Table 3 Observed incidence of cognitive impairment by socio-demographic characteristics

Characteristics	n	Incidence (95% CI) per 1000 person-years	*p*-value	RR (95% CI) Adjusted
Sex				
Female	34	33.8 (24.2–47.4)	0.084	1 [reference][a]
Male	14	18.0 (10.7–30.5)		0.66 (0.35–1.27)
Age (years)				
[65–69]	19	21.1 (13.5–33.1)	0.142	1 [reference][b]
[70–74]	16	25.8 (15.8–42.2)		1.29 (0.66–2.52)
[75–79]	8	43.5 (21.7–86.9)		2.20 (0.96–5.05)
[80–85]	5	66.0 (27.5–158.7)		2.01 (0.72–5.58)
Education				
0	10	126.4 (68.0–234.8)	0.005*	1 [reference][c]
[1–9]	29	21.6 (15.0–31.0)		0.21 (0.10–0.47)
≥ 10	9	25.3 (13.2–48.7)		0.25 (0.10–0.65)
Marital Status				
Married/Civil Union	26	23.6 (16.1–34.6)	0.296	1 [reference][d]
Single, divorced, widower	22	32.5 (21.4–49.4)		1.03 (0.55–1.93)
Employment Status				
Work	4	18.1 (6.8–48.3)	0.911	1 [reference][a]
Retired	40	30.0 (21.3–37.9)		1.30 (0.44–3.79)
Housewives	4	22.3 (24.2–47.4)		0.79 (0.19–3.31)

Legend: *RR* relative risk. 95%, *CI* 95% confidence interval
[a]adjusted for age and education
[b]adjusted for education and sex
[c]adjusted for age and sex
[d]adjusted for sex, age and education
*Significant at $p < 0.05$

The crude cumulative incidences of cognitive impairment and death in the overall sample are described in Fig. 2, along with the incidence of the composite outcome of all-cause of failure (death or cognitive impairment). The cumulative incidence of all-cause failure is equal to the sum of the cumulative incidences of the 2 cause-specific failures. Although the cumulative incidence of death before the cognitive impairment exceeded that of cognitive impairment diagnosis at each point in time, the incidence of cognitive impairment was not negligible in this population. In the group analysis by sex, the cumulative incidence curves for women and men were statistically different for cognitive impairment before death (*P*-value 0.0008), and for death before cognitive impairment (*P*-value 0.0004). The estimated CIFs for each cause of failure by sex displayed in Fig. 3 presented notable differences. In women, from 73 years old to 80 years old, the cumulative incidence of cognitive impairment is higher that its competitive event, while for the men, the incidence of death before cognitive impairment is higher in all points in time when compared to the cognitive impairment diagnosis, following the same trend as when analysing the whole sample. The estimates of death before cognitive impairment diagnosis

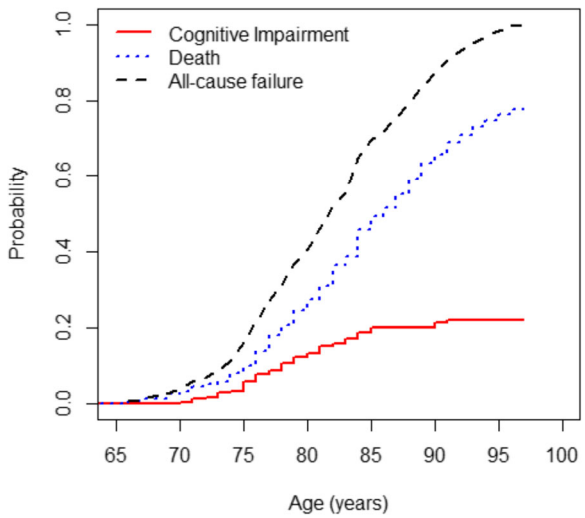

Fig. 2 Cumulative incidence functions. The solid line shows the cumulative incidence of cognitive impairment. The dotted line shows the competing risk event, i.e. death occurring prior to the cognitive impairment. The dashed line shows the cumulative incidence function of all-cause failure, i.e. the sum of the cumulative incidences of the 2 cause-specific failures

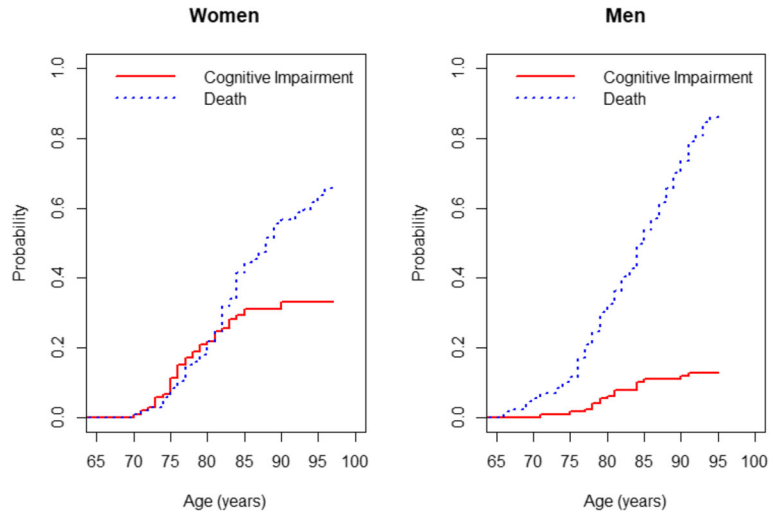

Fig. 3 Cumulative incidence functions by sex. Left panel: The solid line shows the cumulative incidence of cognitive impairment, for women. Right panel: The dotted line shows the competing risk event, i.e. death occurring prior to the cognitive impairment, for Men

of the women exceeds the estimates of cognitive impairment diagnosis in the point's time after 80 years old. The slope of the curves are quite similar in women and men until 70 years – 75 years old, however, in the men it can be observed a higher probability of death before cognitive impairment than in the women.

Participants with cognitive impairment had an average MMSE score reduction of 5.33 (SD 3.64), while participants without cognitive impairment had an average of 0.44 reduction (SD = 1.84) ($p = 0.000$) over the time at risk of 6.2 mean years (± 4.30 years).

Discussion

In this urban population with 65 to 85 years, the prevalence of cognitive impairment was 15.5%. It was higher in women, in not-married participants, and retired participants, it increased with age and decreased with education years.

Previous studies with Portuguese population samples reported a prevalence of cognitive impairment between 9.3 and 12.0% [10, 25, 26] using younger participants, over 50 years old on the first study and over 55 years old on the other two. Both the studies which used the MMSE as a screening test, Nunes et al. [25] and Ruano et al. [26] complemented the results with a neurologist evaluation. It is worth to point out that Ruano et al. [26] report the 2015 prevalence for the EpiPorto cohort with the present study focusing on the period from 1999 to 2004 and that only in the current study was the incidence of cognitive impairment in this population ascertained (1999–2015).

The prevalence estimate found in our study is within the estimated interval for the European population using ascertainment approaches similar to ours [9, 20].

As previously reported cognitive impairment prevalence was higher in women than in men [9, 10, 44], with studies pointing out hormonal causes, namely the loss of estrogens in women, to justify this difference [45]. It increased in frequency with increasing age between the ages of 65 and 85 years, which is in accordance to other studies that associated ageing with cognitive decline and dementia [9, 10, 44, 46] and it is associated with low levels of education, possibly due to the higher cognitive reserve of the ones with more years of education [9, 44, 47]. Participants without schooling have a higher prevalence of cognitive impairment than participants with at least some schooling. Participants with more than 10 years of schooling have a higher prevalence of cognitive impairment compared with those between one and 9 years of schooling. However, this may be attributable to their higher mean age and presence of more participants with 80–85 years old (13.4% vs 6.9%). When we determined the odds ratio, adjusted for sex and age, the risk is almost the same (0.72 vs 0.74) between both groups and statistically different for the group without any schooling. It was also slightly higher for not-married participants [9, 44, 48] despite not reaching statistical significance and we did not find differences between retired and non-retired participants (Table 2).

For 6.2 mean years of follow-up time, we observed that the incidence rate of cognitive impairment was 26.97 per 1000 person-years. The standardized incident rate for the Portuguese population was 35.7 and for the standard European population was 34.4 per 1000 person-years. The cognitive impairment incidence we found in our sample is lower than estimates for other European countries [20, 21, 49] and North America, [22, 23] however this might be due to the older populations and different cognitive impairment definitions used in these studies.

In concordance with other studies [22, 24, 49, 50], we also observed a trend towards increased incidence with older age, and higher in women albeit without reaching statistical significance. These findings were also achieved when considering death as a competing risk of cognitive impairment.

Participants with zero years of schooling have a higher incidence of cognitive impairment than the ones with schooling, which is in concordance to the impact of education years reported in previous findings [20, 51].

Non-married participants have a non-significant trend towards a higher incidence of cognitive impairment, which could be explained by the memory and cognition stimulation of the married participants [52].. For employment status, we observe that retired participants have a trend towards a higher incidence of cognitive impairment than the ones which are still working, after adjusting for age and education, which may indicate a protective effect of working, as described before [8, 53]. It would be interesting to conduct further work to try to determine if indeed working has a protective effect on cognitive decline or if other social dimensions involved in being employed mediates this effect.

The average MMSE score reduction is higher in participants with cognitive impairment compared with other participants, which demonstrates a more pronounced cognitive loss on the first ones that must be taken into account when defining preventive measures in the Health System.

A previous study [26] has found that one of the major causes of cognitive impairment in this population stems from vascular disease, as such we suggest that help managing blood pressure and an increase in physical activity, if targeted to these groups, could lead to significant public health improvements.

In Portugal, in the period under analysis, from 1999 to 2015, the demographic characteristics of the population over 65 years old changed and, according to PORDATA, the percentage of older people increased from 15.9 to 20.5% [54], and the number of people without education decreased by 36.7% and those with higher education, increased by 247.7% [55]. The increased education may have contributed to the decrease in the prevalence of cognitive impairment from 15.5 to 9.3% [26], despite some methodological differences in the two studies in the EpiPorto cohort discussed above. The increase in schooling will mitigate the effect of increasing average life expectancy, but it should be taken other measures because by 2050, Portugal will be one of the European countries with a higher percentage of older people and with the highest old-age dependency ratio.

The main strengths of our study are the population-based cohort and the long-term prospective study design as well as the use of MMSE published cut-off points adjusted for education. This study provides an estimate of the prevalence and incidence of cognitive impairment in an elder western European cohort providing essential data to target public health strategies accurately.

Some methodological limitations may have overestimated the results, namely the inability to diagnose dementia, meaning that we could not exclude participants with dementia from the study, which may have overestimated the prevalence of cognitive impairment at baseline. Mortality as a competing risk may have overestimated the incidence of cognitive impairment. Participants lost-to-follow-up where older and with lower mean MMSE scores than the participants and this could have underestimated the incidence calculations.

Conclusion

This study reports a prevalence of cognitive impairment of 15.5% and an incidence of 26.97 per 1000 person-years in a cohort of city dwellers from Porto, Portugal, aged 65 to 85 years old. Women and elders without schooling have a higher risk of developing cognitive impairment, and this risk increases with ageing. This study highlights the need to develop preventive health measures targeted to these groups to help maintain brain health with ageing. In our study we found that neither retirement nor marital status have a significant effect on cognitive impairment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-020-01863-7.

Additional file 1: Figure S1. Box Plot of the Mini-Mental State Examination score of the population at baseline evaluation and participants with or without cognitive impairment at the follow-up evaluation.

Abbreviations

MMSE: Mini-Mental State Examination; CIF: Cumulative incidence function; OR: Odds ratio; RR: Relative Risk

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Not applicable.

Authors' contributions

All authors contributed to the study conception and design. Material preparation and data collection: RP. Statistical analysis: RP, CM. Writing - review and editing: RP, LR, CM, OC, HB. Supervision: HB. RP wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in agreement with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ethics committee of Hospital de São João approved the study. All individual participants received an explanation on the purpose and design of the study and gave their written informed consent in the evaluation. In participants with cognitive impairment, written consent was also sought from a valid surrogate.

Consent for publication
Not Applicable.

Competing interests
The authors declare that they have no competing of interest and certify responsibility for the manuscript.

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Publisher's Note

5.2. Paper III: Prevalence and causes of cognitive impairment and dementia in a population based cohort from Northern Portugal

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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.

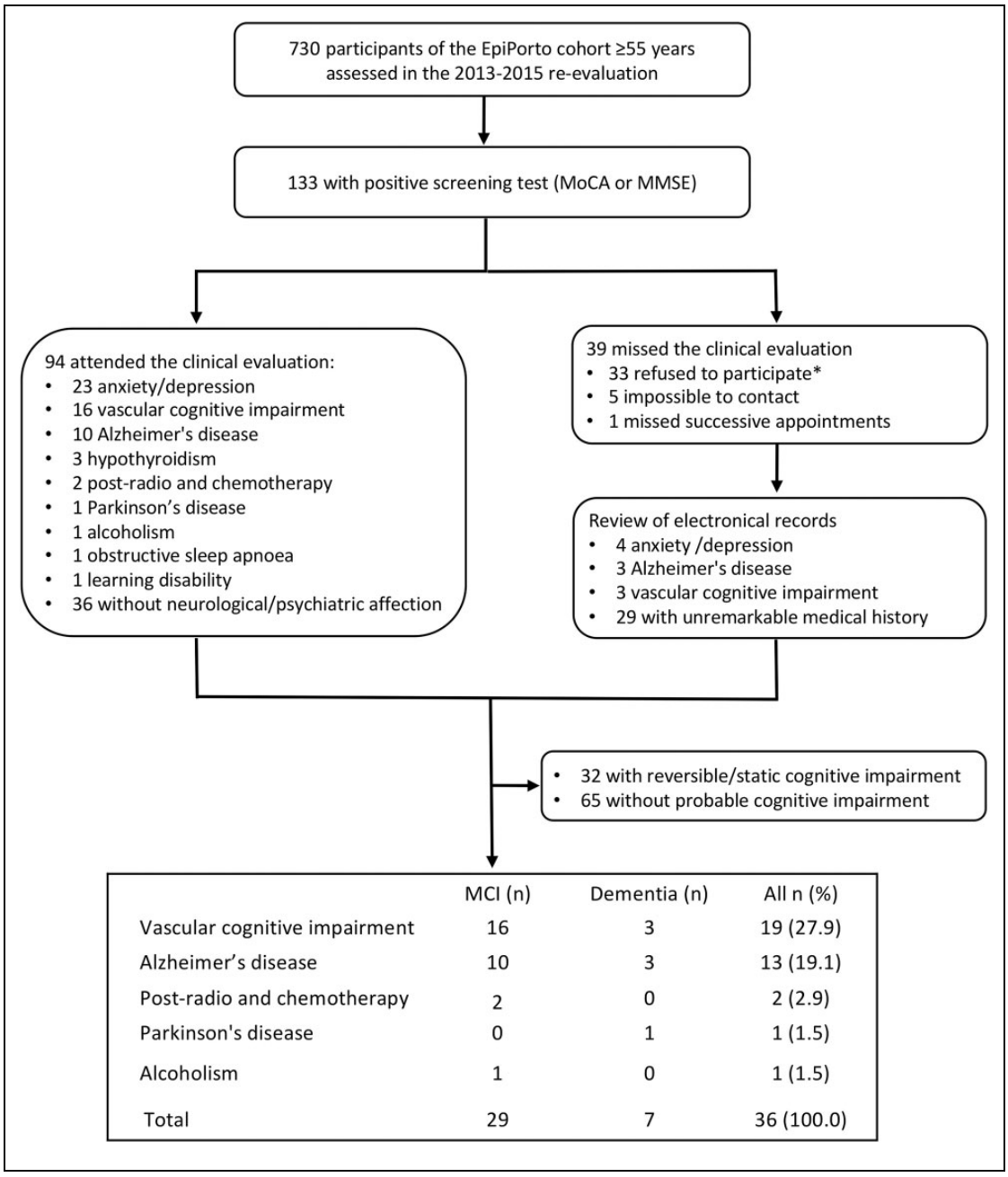
Figure 1 depicts the flow of participants through the steps of the study. From the 730 participants screened, 133 (18.2%) presented a score suggestive of a possible cognitive impairment. Among the latter, 94 were evaluated by a neurologist to confirm and classify the cognitive impairment, while a clinical 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

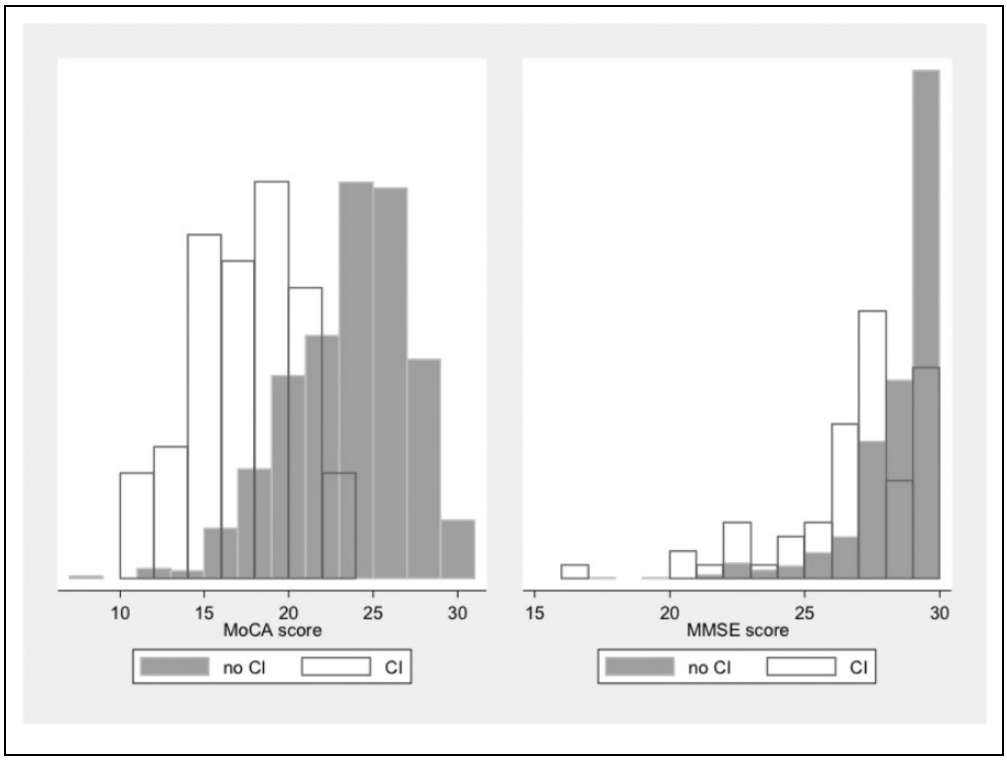


Figure 2. Distribution of the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) scores for participants with and without cognitive impairment.

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.

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Supplemental Material

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6. SOCIAL SUPPORT AND COGNITIVE IMPAIRMENT

6.1. Paper IV: Social Support and cognitive impairment: results from a Portuguese 4-year prospective study

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Keywords: social support; cognitive impairment

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Social Support and Cognitive Impairment: Results from a Portuguese 4-Year Prospective Study

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Abstract: (1) Background: In an ageing society, social relationships may benefit cognitive performance with an impact on the health of older people. This study aims to estimate the effect of different social support sources on the risk of cognitive impairment in a sample of older Portuguese people. (2) Methods: From the Portuguese EpiPorto cohort study, we followed a sample of participants with 60 to 85 years (N = 656) between 2009 and 2015 (4.63 mean years of follow-up). The participants' perception of social support from family, friends and significant others was evaluated. Cox's regression models were used to investigate the association between this and sociodemographic variables. (3) Results: It was found that social support from friends reduces the risk of cognitive impairment. Men, participants aged 60 to 64 and those not married have a lower risk of cognitive impairment after adjusting for other variables. Participants between 80 and 85 years old (p = 0.021), those with less than four years of education ($p < 0.001$), and those with cognitive impairment (p = 0.007) have perception of less social support from friends. (4) Conclusions: A social support network from friends reduces the risk of cognitive impairment for older people.

Keywords: social support; cognitive impairment; older people; risk

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1. Introduction

The increases in life expectancy we observe nowadays did not come with a proportionate increase in quality of life, as the risk of disease, disability and dementia also increases with increasing age [1]. This fact highlights the importance of quality of life in later life.

Cognitive function is an essential indicator of overall well-being in older ages. Lower scores on measures of cognitive function are associated with increased frailty and limitations to daily life activities [2,3]. Although changes in cognitive function such as recollection, familiarity, and false recognition are typical with normative cognitive ageing, cognitive decline is not a part of healthy ageing [4]. Cognitive impairment is characterised by more difficulty than expected for an individual's age and education with memory or concentration while performing a task of everyday living or when learning new things [5]. It ranges in severity between deficits which are not clinically detected to clinically diagnosed dementia [6]. It is likely to appear prior to other disease diagnoses conducted, such as Alzheimer's disease or dementia [7,8].

Cognitive impairment is a risk factor for dementia and mortality [9,10] as it increases dependency on others and contributes to individual vulnerability [11]. Social support can be a protective factor delaying cognitive decline among older people. Social support

comprises the perception of care and assistance given within the individual social network, and it may be seen as care, financial assistance, gift-giving, counselling, or emotional assurance [12,13]. Individuals who have a variety of social relationships with family, friends, neighbours, and co-workers giving them a sense of support and affection [14] and who are involved in several social activities, such as sports and cultural activities, providing them with the sense of belonging are likely to have better health and well-being [15]. Social support is also related to better health outcomes [13,14]. Previous studies have shown that social support has a positive impact on cognition later in life and on the overall quality of life and mental health [16,17]. Insufficient social support may be a risk factor for cognitive decline, possibly due to fewer positive relationships and fewer social activities resulting in less brain stimulation and a higher risk of depression [18]. The stress-buffering hypothesis states that social support can act as a buffer against stressful life events by reducing adverse physiological stress reactions [19]. Therefore, engaging in socially and emotionally supportive environments decreases physiological reactivity and may protect against cognitive decline [20].

Research on the longitudinal impact of social support on the incidence of cognitive impairment remains unclear. A better understanding of the connection between cognitive impairment and social networks will identify areas for investing more resources and for significantly improving the quality of life at older ages [21]. Therefore, it is important to determine whether better quality marriages result in greater life satisfaction and fewer health problems, if the relationship between parents and children increases emotional support, or whether friends and neighbours are an essential source of social support for older adults [14].

The purpose of this study is to estimate the effects of different sources of social support on the risk of cognitive impairment in a population-based sample with participants over 60 years of age. It is hypothesised that higher social support from family, friends, or significant others would decrease the risks of cognitive impairment.

2. Materials and Methods

2.1. Study Population

The present research study is based on the data from the EpiPorto cohort study. The design and methodology have been published previously [22,23]. The study protocol comprised detailed information on interviewing procedures [24]. Briefly, participants were initially contacted by letter and later by telephone in order to schedule an interview. On the appointment day, the study's objective was explained and any concerns were clarified [25]. In 2009, 656 participants aged 60 to 85 took part in the study. Among the individuals evaluated at baseline, 16 (2.5%) were not eligible for the present study due to missing information on MMSE, and 86 (13.1%) had cognitive impairment and were excluded. The follow-up evaluation was between 2013 and 2015, and the participants were recalled for cognitive evaluation. About 213 individuals did not attend the follow-up evaluation procedure: 53 (24.9%) had died; it was impossible to contact 150 (70.4%); 10 (4.7%) refused to participate (Figure 1). There was no significant difference between the baseline data of the 341 participants and the 213 lost regarding gender or marital status. Nevertheless, participants lost in the follow-up were older ($p < 0.001$) and were less educated ($p = 0.029$) (Table 1). Among these 341 participants, 57.5% were women, 62.7% were aged between 60 and 69, most of them had 0–4 years of education (43.1%), and 70.1% were married or cohabiting.

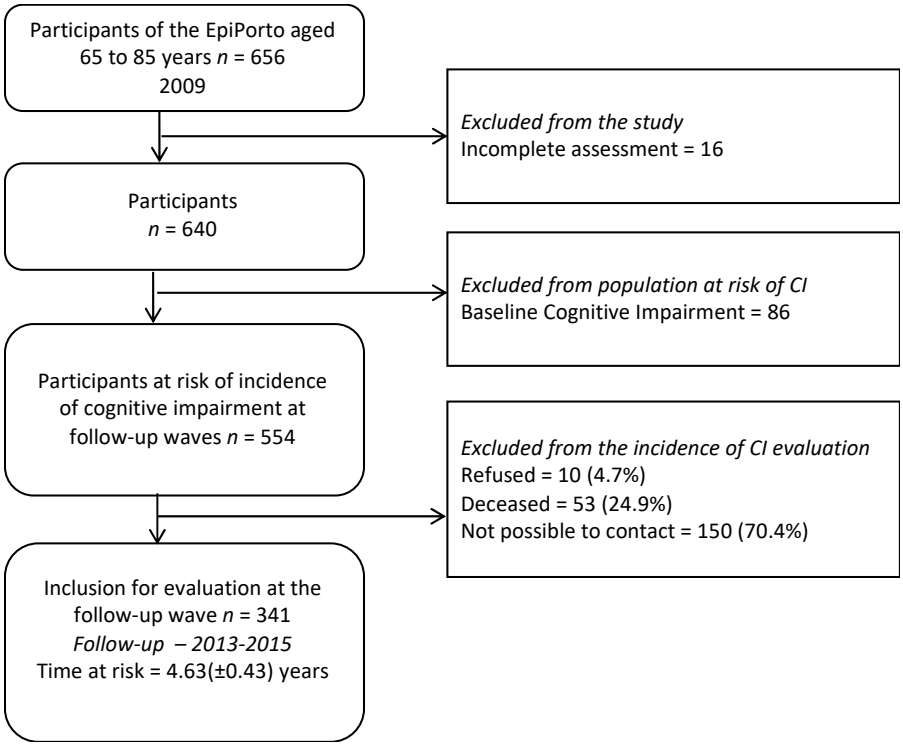

Figure 1. The flowchart of the study sample from 2009 to 2015. Note: "CI" refers to cognitive impairment; "Refused" refers to the participant who did not agree to participate in the follow-up surveys; "Deceased" refers to the participant who had passed away at the time of the follow-up surveys; "Not possible to contact" refers to the participants who could not be contacted for the follow-up surveys.

Table 1. Sociodemographic characteristics of participants.

Characteristic	Follow-Up	Lost to Follow-Up	*p*-Value
N	341	213	
Gender			
Female	196 (57.5)	133 (62.4)	0.247
Male	145 (42.5)	80 (37.6)	
Age (Years)			
60–64	114 (33.4)	30 (14.1)	<0.001
65–69	100 (29.3)	40 (18.8)	
70–74	71 (20.8)	44 (38.3)	
75–79	36 (10.6)	55 (25.8)	
80–85	20 (5.9)	44 (20.7)	
Education			
0–4	147 (43.1)	116 (54.7)	0.029
5–9	82 (24.0)	40 (18.9)	
≥10	112 (32.8)	56 (26.4)	
Marital Status			
Married/Cohabiting	239 (70.1)	133 (62.4)	0.062
Divorced, Separated, Widower, Single	102 (29.9)	80 (37.6)	

Note: Data are *n* (%); *p*-value compares follow-up to lost to follow up, obtained with Chi-square test.

2.2. Data Collection and Definition of Variables

Trained interviewers collected information on sociodemographic characteristics using structured questionnaires.

Education was recorded as completed years of schooling and further categorised into three groups: 0–4 years of education, between 5 and 9 years, and more than 10 years.

We categorised marital status into two groups: the married or cohabiting and the others (divorced, separated, widowed, or single).

We evaluated cognitive impairment using the Mini-Mental State Exam (MMSE), with cut-off points adjusted to the years of education and validated for the Portuguese population: 22 for 0–2 years; 24 for 3–6 years; and 27 for seven or more years of education [26]. Subjects would have cognitive impairment if they had an MMSE score below the age and education adjusted cut-off point.

The social support perception was assessed with the Multidimensional Scale of Perceived Social Support, which is a 12-item scale of perceived social support from family and friends. Each item scored 1 to 7, the total sum of all 12 items was a wide range from 7 to 84. The highest scores suggest high levels of social support [27].

2.3. Statistical Analysis

The follow-up participants were compared to losses to follow-up by using the Chi-Square test. We used the Cox proportional hazards regression models to estimate the hazard ratios (HR) and 95% confidence intervals of the association of the sociodemographic variables with cognitive impairment incidence. We used the backward stepwise conditional LR method to select the most suitable model and used Akaike's information criterion (AIC) model selection to distinguish among the set of possible models describing the relationship between age; gender; education; marital status; social support from family, friends, or from other significant people; and cognitive impairment. The best-fit model, carrying 100% of the cumulative model weight included the variables of age, gender, marital status, and social support from friends. The Omnibus Test of Model Coefficients was statistically significant ($p < 0.001$). We complied with the model assumptions with respect to proportional risks.

We performed normality testing of social support from friends using the Skewness test; thus, we used parametric tests to compare the mean of perception of social support from friends in each variable of the study (Test-t for independent samples or One-way Anova if applicable).

The mean of social support from friends, family, and other significant people in participants with and without cognitive impairment was compared by using the General Linear Model with Bonferroni comparison, adjusted for age, sex, and marital status. Data are presented as mean and standard deviation (SD). Statistical analyses were performed with SPSS® version 21 (IBM, New York, NY, USA).

3. Results

Three hundred forty-one participants completed the follow-up evaluation (mean follow-up of 4.63 years ± 0.43 years) of whom 297 (87.1%) maintained normal cognitive status and 44 (12.9%) had developed cognitive impairment.

The hazard ratio of men who possessed cognitive impairment was 63% which was lower when compared to women (HR = 0.370, 95% CI = 0.184–0.744). Participants 70 to 74 years old had a hazard ratio of having cognitive impairment 229.9% higher than participants who were aged 60 to 64 years old. Furthermore, participants 75 to 79 years old had a hazard ratio of 212.8% higher. The hazard ratio for the divorced or separated and the widowed or the single for having cognitive impairments was 60.2% lower when compared to married participants (HR = 0.398, 95% CI = 0.186–0.852). The increase in social support from friends reduces the hazard ratio of cognitive impairment by 23% (Table 2).

Table 2. The multivariable Cox analysis of gender, age, marital status, and social support on cognitive impairment.

Characteristics	HR (95% CI)
Gender	
Female	Reference
Male	0.370 (0.184–0.744)
Age	
60–64	Reference
65–69	0.857 (0.321–2287)
70–74	3.299 (1.383–7.868)
75–79	3.128 (1.097–8.922)
80–85	1.013 (0.205–5.005)
Social Support	
Friends	0.770 (0.635–0.933)
Marital Status	
Married/Cohabiting	Reference
Divorced, Separated, Widower, Single	0.398 (0.186–0.852)

Note: HR, hazard ratio; 95% CI, 95% confidence interval.

No significant differences for the perception of social support from friends were observed concerning gender or marital status, except for age and education. Participants more than 80 years old had a lower perception of social support from friends than participants with 60 to 64 (mean = 4.087; SD = 1.288 vs. mean= 4.882; SD = 1.625, $p = 0.021$), and participants with fewer years of education had a lower perception of social support from friends (mean = 4.450, SD = 1.544 vs. mean = 5.257, SD = 1.167; $p < 0.001$) (Table 3).

Table 3. Perception of social support from friends mean (±SD) according to sociodemographic variables.

Characteristics	Social Support Perception	*p*-Value
Gender		
Female	4.805 (1.476)	0.694 (a)
Male	4.866 (1.342)	
Age		
60–64	4.882 (1.288)	0.021 (b)
65–69	4.790 (1.454)	
70–74	4.736 (1.552)	
75–79	5.382 (1.155)	
80–85	4.087 (1.625)	
Education		
0–4	4.450 (1.544)	<0.001 (b)
5–9	4.927 (1.333)	
≥10	5.257 (1.167)	
Marital Status		
Married/Cohabiting	4.747 (1.395)	0.095 (a)
Divorced, Separated, Widower, Single	5.027 (1.463)	

Note: Data are means (±SD); *p*-value compares mean between groups, obtained with (a) Independent samples *t*-test; (b) One-way ANOVA test.

A lower perception of social support is associated with cognitive impairment (mean = 5.038, SD = 0.624; $p = 0.007$), specifically social support from friends (mean = 4.413, SD = 0.885; $p = 0.015$) or social support from significant others (mean = 5.517, SD = 0.657; $p = 0.017$) adjusted for sex, age, and marital status (Table 4).

Table 4. Perception of social support mean (±SD) according to cognitive status.

Social Support	NCI	CI	*p*-Value [a]
Family	5.529 (0.294)	5.180 (0.734)	0.071
Friends	4.979 (0.353)	4.413 (0.885)	0.015
Other Significant	5.593 (0.262)	5.517 (0.657)	0.017
Total	5.483 (0.25)	5.038 (0.624)	0.007

Note: [a] adjusted for sex, age, and marital status; NCI: no cognitive impairment; CI: cognitive impairment; *p*-value obtained with the General Linear Model with Bonferroni comparison; data are means (±SD).

4. Discussion

This study investigated the impact of social support on the incidence of cognitive impairment using a representative population-based sample of Portuguese older people during 4.6 mean years of follow-up. It was concluded that social support from friends decreases the hazard ratio of cognitive impairment.

With increasing age, older people have fewer social interactions, and most of the social interactions occur with family members. At the onset of this study, we expected that social support from family would have an impact on cognitive impairment. We also expected that married people would be less at risk of cognitive impairment than divorced, separated, widowers, or single individuals. Some studies report that being married when compared to being a widower has a protective effect against cognitive impairment [16,28]. However, the results from this study do not support those initial expectations as a statistically significant relationship between social support from family and cognitive impairment has not been found. In fact, the group composed of divorced, separated, widowed, and single participants had a lower hazard ratio for cognitive impairment than the one consisting of married participants. Murata et al. (2017) reports that support from family may be an obligation and may sometimes be misunderstood, whereas support from friends is voluntary and often involves activities of common interest mostly outside of the home, which arguably may provide increased physical and cognitive stimulation [13].

Some studies value the importance of social support in the cognitive function of older people [12]. Weng et al. (2020) posits that positive relationships and more social activities results in more brain activity and less depression [18]. Brown et al. (2009) studying a neighbourhood context claims that support from friends has more impact on cognitive function than support from family [29], whereas Noguchi et al. (2019) adds that friends are typically of the same age, share the same experiences, and have similar lifestyle and geographical proximity, which also acts on reducing loneliness [12]. All these lines of evidence support the main finding of this study, which suggests that social support from friends decreases the hazard ratio of cognitive impairment.

We did not find differences in either gender or marital status in the perception of social support from friends, but we did find differences regarding age and years of education. Older and less educated participants have a lower perception of social support. For older participants, this perception may be reflecting the decrease in social interactions observed as age increases [16]. Smith et al. (2018) reported that social isolation was more frequent in less educated participants [30] and postulated that this may be due to a reduced social network membership.

The lower perception of social support is associated with cognitive impairment even after adjusting for sex, age, and marital status. This agrees well with other studies [12,13,29], which also find that people with cognitive impairment have less participation in the community and fewer interactions and access to social resources [21].

The observed protective effect of social relations could be due to reverse causality, being the cause of less social interactions rather than the consequence of it. We tried to control for this effect by excluding participants who had cognitive impairment at the baseline.

In agreement with other studies, men are at lower risk of cognitive impairment [31,32], with Laws et al. citing hormonal differences as a cause due to a lack of oestrogen in women [33].

Ageing is consistently associated with an increased risk of cognitive impairment [34–36], as we also report.

The major strength of our study is the prospective study design and the exclusion of participants with cognitive impairment at baseline.

There are some limitations to the present study. The first is assessing cognitive function by using the MMSE scale without clinical assessment or any other tests. Despite, MMSE being the most cited small-sized scale used for dementia and cognitive impairment assessment and despite being considered a reliable and valid test for cognitive impairment [25,37], clinical assessment or validation by using other tests would have provided further confirmation. Similarly, the use of the MSPSS scale to assess social support, which is targeted to assess the perception of social support but not the social support actually received, is another limitation. Secondly, we could not distinguish the relatives who provided social support, for example, if they were the spouse, children, or other family members. The participants lost to follow-up were older and had fewer years of education than the participants included in our study and, therefore, had a higher risk of cognitive impairment. This could have resulted in an underestimation of the new cases of cognitive impairment. The inability to diagnose dementia meant that we could not exclude participants with dementia from the study and, therefore, may have overestimated some of the results.

5. Conclusions

In conclusion, this prospective study allows us to confirm the importance of social support from friends in reducing the risk of cognitive impairment. Participants aged 80–85 years old or with fewer years of school had a lower perception of social support. Recognising the impact of social support, especially social support received from friends, can be useful for health professionals to improve their care provision and better advise their users. It can also contribute to the definition of health promotion policies that favour social networks through the development of supporting community groups, neighbourhood help groups, or social support services for older people.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Restrictions apply to the availability of these data. Data were obtained from [38] and are available (https://ispup.up.pt) (accessed on 20 April 2021) with the permission of [38].

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7. DISCUSSION AND CONCLUSIONS

7.1. Main achievements

The number of studies in the world collecting epidemiological data on cognitive impairment are scarce. The studies we examined report that the global prevalence of cognitive impairment ranged from 5.1% to 41.0% (median= 19.00%; 25th percentile= 12.00%; 75th percentile= 24.90%).

With regard to the world region where data were collected, in Europe the prevalence of cognitive impairment ranges from 5.1% to 41.0% (median = 12.10%; 25th percentile = 9.94%; 75th percentile = 23.90%) (52-65, 73, 80, 84, 85, 124-130); in North America, it ranged from 7.1% to 28.3% (median = 20.10%; 25th percentile = 19.00%; 75th percentile = 24.70%) (34, 66-71, 88, 131-135); in South America, it ranged from 24.3% to 37.5% (median = 34.00%; 25th percentile = 29.15%; 75th percentile = 35.75%) (87, 136, 137). In Asia the prevalence ranges from 6.5% to 37.0% (median = 19.44%; 25th percentile = 13.25%; 75th percentile = 25.55%) (36, 38, 50, 81, 82, 86, 89, 90, 92, 138-163). In Africa, cognitive impairment prevalence ranged from 18.4% to 33.0% (median = 25.70%; 25th percentile = 18.40%; 75th percentile = 33.00%)(164, 165) and in Australia from 7.7% to 33.3% (median = 20.50%; 25th percentile = 7.70%; 75th percentile = 33.30%) (166, 167). Europe is the region with the lowest median prevalence worldwide.

At the global level the studies report the incidence of 22.0 to 215.0 per 1000 person-years (median= 56.50 per 1000 person-years; 25th percentile= 41.77; 75th percentile=76.50).

In Europe the incidence of cognitive impairment ranges from 30.70 to 76.50 per 1000 person-years (median = 56.50 per 1000 person-years; 25th percentile = 51.45; 75th percentile = 76.5) (57, 59, 75, 76, 125). In North America, it ranged from 41.8 to 215.0 per 1000 person-years (median = 60.40 per 1000 person-years; 25th percentile= 47.19; 75th percentile= 65.42)(77-79, 132, 168) and in Singapore the incidence was reported as 22 per 1000 person-years (90).

In Portugal, the crude prevalence of cognitive impairment in a sample of older people between 65 to 85 years old was 15.5% (95% CI:12.7-18.7), being higher in women, increases with age and decreases with the number of schooling years. The standardized prevalence rate for the European population(169) was 16.50%. In the same cohort but with a population over 55 years old, the prevalence of cognitive impairment was 9.30%, and of 9.80% for the standard European population. The most common causes of mild cognitive impairment/dementia were vascular, followed by Alzheimer's disease.

After 6.2 mean years of follow-up time, we observed that the incidence was 26.97 per 1000 person-years (95% CI: 20.30–35.80), higher in women, in older participants and in those who do not have schooling. The standardized incidence rate using the standard European population(169) was 34.40 per 1000 person-years. Neither retirement age nor marital status has a significant effect on cognitive impairment prevalence or incidence. The prevalence of cognitive impairment in Portugal is within the estimated interval for the European population, and the incidence is lower than for the majority of the European countries.

Also, social support from friends reduces the risk of cognitive impairment for older people. The participants aged between 80 and 85 years, those with less than four years of schooling or those with cognitive impairment, perceive less social support from friends.

7.2. Discussion and future directions

We studied the epidemiology of cognitive impairment and its determinants to develop the quantitative framework of cognitive impairment and establish the risk groups on which health policy should focus.

From a global view, to report epidemiological data, we did a systematic review of the literature on the prevalence and incidence of cognitive impairment (Paper I). We included studies with three different constructs, Cognitive Impairment (CI), Mild Cognitive Impairment (MCI) and Cognitive Impairment No Dementia (CIND), as they generally refer to the same entity despite minor differences. We found a high degree of heterogeneity in methodologies and results in the included studies and therefore conducted the study considering the minimum age of inclusion in the sample, the sample size, the diagnostic strategy, and the globe's region.

The global prevalence of cognitive impairment varies between 5.1% to 41.0% (34, 36, 38, 50, 52-71, 73, 80-82, 84-90, 92, 124-167), and the global incidence varies between 22 and 215 per 1000 person-years studies (57, 59, 75, 76, 78, 79, 90, 125, 132, 168).

The studies vary in the participants' inclusion minimum age, which could contribute to differing reports, so we grouped the studies into account this variable. It allowed us to report that the incidence is higher in studies with samples recruited starting at 60 years old than in studies with participants over 70 years old, which may result from a bias in detecting cognitive impairment in older people or a bias in classifying as dementia in these people as well.

The various studies are congruent in the finding that cognitive impairment increases with age (70, 76, 127, 129).

We did not find any statistically significant differences between the variables sample size, diagnostic strategy and region of the globe. However, it shall be noticed that increased sample size has no impact on the epidemiological estimates of cognitive impairment. Evaluating the method used to diagnose cognitive impairment does not allow us to infer a pattern of results in prevalence and incidence studies, thus confirming the need for standardisation of the diagnostic method (83). However, in extensive population studies, we understand that it is simpler and cheaper to use standardised and validated diagnostic tests instead of clinical evaluations by neurology specialists to assess many participants. Therefore, we argue that developing and validating further standardised tests to diagnose cognitive impairment would be beneficial.

Analysing reports of different regions of the globe, we found that the median prevalence and incidence are lower in Europe than in the rest of the world, probably due to differences in social and economic structures (170). Further studies should clarify this issue.

By 2050, Portugal will be one of the European countries with a higher percentage of senior people and the highest old-age dependency ratio. To find helpful information for the definition of preventive health measures, we study the epidemiology of cognitive impairment in Portugal (Paper II). We evaluated the participants of the EPIPorto cohort aged 65 to 85 years. The prevalence of cognitive impairment was 15.5%. Higher than in previous studies in Portugal, which enrolled participants over 50 years or 55 years of age (58, 72, 73). These studies used MMSE as the screening test and completed this with a neurologist evaluation.

The prevalence is within the range estimated for the European population in studies using a diagnosis strategy similar to ours (54, 59).

The prevalence was higher in women, possibly due to hormonal causes (171); increases with age, the higher the age, the highest the risk of cognitive decline and dementia (54, 58, 74, 124, 172); and decreases with schooling years, due to higher cognitive reserve for participants with more years of education (54, 138, 172-174).

We did not find statistically significant differences in the impact of marital or work status.

After 6.2 years of follow-up, the cognitive impairment incidence was 26.97 per 1000 person-years, lower than estimates in Europe (55, 59, 76) and North America (77, 78, 175). However, this may be due to older samples, other diagnostic criteria used in these studies, or food intake and personal genetic characteristics. The incidence is higher in participants without schooling, which is in concordance with the impact of education years reported before (59, 136, 176).

We did not find statistically significant differences in the impact of marital or work status on cognitive impairment incidence, despite other studies referring that this is higher for non-married (177) and retired senior people (40, 178). Further studies on the retirement age impact should consider factors potentially influencing cognitive outcomes such as work and retirement characteristics.

With participants of the EPIPorto cohort, but only including data from the third follow-up, between 2013-2015, we assessed the aetiology and prevalence of cognitive impairment (Paper III). We selected participants aged more than 55 years. In this instance, we used MMSE and MOCA as screening tests, complete with clinical evaluations by a neurologist. We reviewed clinical records and brain imaging results, as well as performed the following laboratory tests: blood count, ionogram, thyroid function, vitamin B12, syphilis and HIV serologies. The prevalence of cognitive impairment was 9.3%, lower than the 15.5% found in the same cohort in the evaluation done between 1999 and 2004. Several factors could have contributed to the lower prevalence estimate. First, we have to consider that the two constructs are different. The first study uses the concept of cognitive impairment measured by a screening test to the population that has the value to identify the population's elements at a higher risk of developing a clinical problem. In the second study, the prevalence resulting from the application of screening tests is 9.3%. After evaluation by a neurologist, the prevalence of Mild Cognitive Impairment is 4.1%, referring to a clinical diagnosis established by a neurologist of a progressive neurological disease, which already excludes causes of

altered cognitive performance such as congenital cognitive impairment and anxiety/depression. Second, we analysed a younger sample in the more recent study, starting at 55 years of age. Third, from 1999-2015, the above 65 years old Portuguese population's demographic characteristics in the cohort also changed. The percentage of senior people increased from 15.9% to 20.5% (179), the number of senior people without education decreased by 36.7%, while those with higher education increased by 247.7% (180). Forth, as a further contributing factor, participants with cognitive impairment might be less prone to reassess, and cohort follow-up losses tend to be older and have fewer education years, both factors related to higher cognitive impairment and dementia.

The prevalence obtained in this study is lower than the one reported for most European countries (126, 128), even compared to other Mediterranean countries (80, 125, 129). It could be explained by the evidence of higher consumption of omega-3 and omega-6 acids, particularly in fatty fish (181, 182) and the lower prevalence of carriers and homozygosity for the E4 allele of the APOE gene found in Portugal (183). In 47% of participants, the cause of cognitive impairment was static or reversible affection like Anxiety, depression, hypothyroidism and sleep apnea. In participants with MCI, the leading cause was Vascular Alzheimer Disease (52.8%). The Portuguese population health policy should focus on controlling blood pressure, increasing physical activity, and promoting a healthy diet, especially in high-risk groups.

Previous studies have shown that social support from society and family's may impact the cognition in older people, but further research on the impact on the incidence of cognitive impairment should be done (18, 184). We used a sample of participants in the EPIPorto cohort study aged 60 to 85 years that were followed between 2009 and 2015 to assess the impact of social support from family, friends or other significant ones on cognitive impairment (Paper IV). It allowed us to report that the increase in social support from friends decreases the risk of cognitive impairment. That, lower perception of social support from friends or a significant other is associated with cognitive impairment even after adjusting for sex, age and marital status, which is in concordance with other studies (17, 20, 185). One possible explanation is that friends are the same age and have shared experiences, lifestyles, and closeness, reducing loneliness, resulting in more social activity and greater intellectual activity (17, 108, 109, 185). So, it is recommendable to the development of health policies in order to promote and favour a social network for the older people

We did not find a statistically significant effect between social support from family and cognitive impairment, probably because family support may be an obligation and sometimes misunderstood, and support from friends is voluntary. Most of the time, doing activities of common interest, mainly outside the home, increases physical and cognitive stimulation (20).

7.3. Strengths and Limitations

This study has its strengths and, despite our efforts, some limitations. We tried to have a research strategy to reduce or control the effects of the limitations, but due to the studies characteristics, that was not possible in some cases. Following, we describe the strengths and limitations cross the studies methodologies.

The literature's systematic review strengths are the global view of epidemiological data on cognitive impairment and population-based studies. The limitations are publication bias, language bias, ignoring the aetiology of cognitive impairment and not pairwise review.

Regarding the studies of prevalence and incidence of cognitive impairment in EPIPorto, the main strengths are a population-based study, a long-term prospective study of follow-up, the use of the MMSE with cut-off points adjusted to the educational level of the participants and excluding participants with cognitive impairment at baseline. As study limitations, we may have overestimated the epidemiological reports because we did not exclude cases of dementia and the impact that mortality has as a competitive risk. On the other hand, the participants lost to follow-up were older, underestimating the results.

Based on the third cohort assessment (2013-2015), we conducted another prevalence study in the same court. The focus was on the aetiology of cognitive impairment, and so we used a different diagnostic methodology. We report a lower prevalence of cognitive impairment was lower, but we must take into account the different construct, that the sample has an inclusion age ten years lower than the 1999-2004 report and that in the period 1999-2015, the population percentage of older people increased and also increased the percentage older people with more years of schooling.

The study on the effect of social support has specific limitations due to the study perception of social support and not measure the social support received. Second, when

analysing the family's social support, the family member's bond who provides social support was not distinguished, whether the wife, son or another family member impacted the results.

8. CONCLUSIONS

In short, this study allows reviewing global epidemiological data on cognitive impairment, reporting that the global prevalence of cognitive impairment ranges from 5.1 to 41.0% and the incidence ranges from 22.0 to 215.0 per 1000 person-years. The median prevalence and incidence of cognitive impairment are lower in Europe than in other world regions.

The epidemiological studies of cognitive impairment in Portugal are scarce, and we conclude that the prevalence of cognitive impairment is 15.5%, within the estimated range for the European population. The incidence is 26.97 per 1000 person-years, lower than in most European countries, probably due to higher consumption of oily fish and the lowest prevalence of carriers and homozygous for the 4 allele of the APOE gene in Portugal.

We identified women, senior and older people with lower education as a risk group for cognitive impairment.

We suggest promoting a healthy diet and regular physical exercise to reduce the risk of cerebrovascular disease, one of the major causes of Mild Cognitive Impairment.

This prospective study confirms the importance of social support in reducing the risk of cognitive impairment and the need for a social support network, favouring contact with friends, to reduce this risk. Also, older participants or those with fewer years of schooling have a lower perception of social support. Thus, social policies are recommended to develop and increase social support networks and develop community support groups or social support services.

The results presented aim to contribute to a better definition of public health policies and for health professionals, mainly from primary health care, to promote and improve care and education to users and families.

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Appendices

On the following pages, we present the supplementary information published.

Appendices 1 – PAPER I - Cognitive Impairment Crude Prevalence

Table with all the information of the selected studies on the prevalence of cognitive impairment of the systematic review.

Appendices 2 – PAPER I – Cognitive Impairment Crude Incidence

Table with all the information of the selected studies on the incidence of cognitive impairment of the systematic review.

Appendices 3 – PAPER I – Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Table with the results of the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the systematic review.

Appendices 4 – PAPER I – PRISMA 2009 Checklist

Table with the results of the PRISMA Checklist of the systematic review.

Appendices 5 – PAPER II – Supplementary figure of the MMSE score.

Figure with the Box Plot of the Mini-Mental State Examination score of the population at baseline evaluation and participants with or without cognitive impairment at the follow-up evaluation.

Appendices 1 – PAPER I - Cognitive Impairment Crude Prevalence

Supplemental Table 1 – Cognitive Impairment Crude Prevalence

Region	Author, Year, Country	Prevalence % (95% CI)	Sample size	Age Cut-off	CI definition	Construct
Europe	Janelidze, 2018, Georgia[1]	27,7 (22.2-33.9)	238	>=65	MoCA >1.5 *SD* below mean value	MCI
Europe	Freak-Poli,2018, Holland[2]	9.33 (8.5-10.3)	4201	>=60	MMSE<26	MCI
Europe	Zaganas, 2018, Greece[3]	32.4(30.8-34.0)	3140	>=60	MMSE<24	MCI
Europe	Tsolaki, 2017, Greece[4]	15.3 (20-28.2)	443	>=61	Neuropsychological battery of tests	MCI
Europe	Veronese N, 2016, Italy [5]	32.7 (30.5-34.9)	2618	>=65	MMSE<24	CI
Europe	Wu YT, 2016, England[6]	33.7 (31.8-35.6)	2424	>=65	MMSE<=25	CI
Europe	Lara E, 2016, Spain[7]	9.6 (8.7-10,6)	3625	>50	1) Presence of cognitive concerns; 2) Objective evidence of impairment in one or more cognitive domains; 3) Preservation of independence in functional abilities; 4) No dementia.	MCI
Europe	Papachristou E, 2015, Great Britain[8]	41 (39.1-44.1)	1530	>76	TYM, a simple 10-task self-assessment cognitive screening instrument which has sound psychometric properties scores between 33 and 45 (if older than 80 years of age) or 46 (if younger than 80 years of age)	MCI
Europe	Brujin RF, 2014, Holland[9]	9.94 (9.0-10.9)	4198	>55	1) Presence of subjective cognitive complaints; 2) Presence of objective cognitive impairment; 3) Absence of dementia.	MCI

Europe	Juncos-Rabadán O, 2014, Spain[10]	31.4 (27.9-35.0)	689	>50	1) Evidence of concern about a change in cognition, in comparison with the previous level; 2) Evidence of poorer performance in one or more cognitive domains that is greater than expected for the patient's age and educational background; 3) Preservation of independence in functional abilities; 4) Non-fulfilment of diagnostic criteria for dementia.	MCI
Europe	Moretti F, 2013, Italy[11]	24.5 (23.5-25.4)	6921	>61	Score less than 1.5 SDs below the mean value scored by subjects of comparable age and education.	MCI
Europe	Rodríguez-Sánchez E, 2011, Spain[12]	14.9 (10.6-19.2)	327	>65	1) Mild cognitive or functional impairment reported by the participant or informant that did not meet criteria for dementia; 2) Performance on neuropsychological or functional measures that was both below expectations and ≥ 0.5 standard deviations below published norms on any test.	CI
Europe	Paul C, 2010, Portugal[13]	9.6 (7.7-11.0)	1268	>50	Portuguese version MMSE adapted to different education levels and illiterate people	CI
Europe	Nunes B, 2010, Portugal[14]	12.0% (9.3-15.4)	433	55-79	Mini-Mental State Exam and neurological evaluation	CIND
Europe	Dlugaj M, 2010, Germany[15]	12.1 (9.8-14.4)	4145	>50	1) Objective memory disorder; 2) Absence of other cognitive disorders or repercussions on daily life; 3) Normal general cognitive function; 4) Absence of	MCI

					dementia.	
Europe	Etgen T, 2010, Germany[16]	10.7 (9.8-11.7)	3903	>55	6-Item Cognitive Impairment Test - scores higher than 7 are consistent with cognitive impairment	CI
Europe	Luck T, 2010, Germany[17]	11.6 (10.3-13.0)	2331	>75	1) No dementia; 2) Evidence of cognitive decline: self and/or informant report; 3) Preserved basic activities of daily living.	MCI
Europe	Ravaglia G, 2008, Italy[18]	7.7 (6.1-9.7)	1016	>65	MCI was defined as age- and education-adjusted score 1.5 SDs or fewer below the reference threshold on any of the tests used for detailed neuropsychological testing.	MCI
Europe	Luck T, 2007, Germany[19]	15.4 (14.1-16.6)	3242	>75	1) No dementia; 2) Evidence of cognitive decline; 3) Preserved basic activities of daily living.	MCI
Europe	Zanetti M, 2006, Italy[20]	16.2 (12.8-20.2)	400	>65	MMSE <= 24, with age and education correction and the Clock Drawing Test.	MCI
Europe	De Ronchi D, 2005, Italy[21]	5.1 (4.6-5.6)	7930	>61	Scored 2 or more standard deviations lower than the corrected mean MMSE score.	CIND
Europe	Hanninen, 2002, Finland[22]	5.3 (3.9-7.1)	806	>=60	Score 1.5 SD below the cut-off	MCI
Europe	Saks K, 2001, Estonia[23]	23.1 (19.8-26.6)	811	>=65	MMSE <25	MCI

Europe	Frisoni GB, 2000, Sweden[24]	15 (13.1-16.9)	1435	75-95	1) One standard deviation below the mean of age- and education-defined strata; 2) One standard deviation below the age- and education- specific mean computed from a statistical mode.	MCI
Europe	Di Carlo A, 2000, Italy[25]	10.7 (9.7-11.8)	3425	65-84	1) MMSE<24; 2) Neurologist evaluation.	CIND
North America	Aliberti, 2018, USA[26]	19	7338	>=65	Aproach for HRS self-respondents.16,17 The method includes the following cognitive tests: (1) immediate and delayed recall of 10 com- mon nouns, (2) serial subtractions by 7, and (3) a backward count task from 20.	CIND
North America	Richard E, 2013, USA[27]	19.9 (18.2-21.6)	2160	>65	Neurologist evaluation.	MCI
North America	Ortiz GG, 2012, Mexico[28]	13.8 (11.9–16.0)	1142	>60	MMSE score <18	CI
North America	Mejia-Arango S, 2011, Mexico[29]	25.1 (23.1-26.3)	7166	>60	10th percentile of Cross-Cultural Cognitive Examination or IQCODE	CIND
North America	Cortés AR, 2011, Mexico[30]	24.7 (20.1-29.8)	324	>60	MMSE≤24	CI
North America	Gamaldo AA, 2011, USA[31]	22.4 (19.0-26.1)	554	>50	MMSE and SPQMSQ score 1.5 SD below the sample mean.	MCI
North America	Sachs GA, 2011, USA[32]	20.1 (19.0-21.5)	3957	>60	Short Portable Mental Status Questionnaire	CI

North America	Langa KM, 2008, USA[33]	12.2	7486	>70	35-point scale that includes: an immediate and delayed 10-noun free recall test to measure memory; a serial seven subtraction test to measure working memory; a counting backwards test to measure speed of mental processing; an object naming test to measure knowledge and language; and recall of the date, the president, and the vice-president to measure orientation. Prevalence adjusted with HRS survey.	CI
North America	Mejia-Arango S, 2007, Mexico[34]	7.1 (6.3-7.8)	4183	>65	10th percentile of Cross-Cultural Cognitive Examination.	CI
North America	Manly JJ, 2005, USA[35]	28.3 (25.9-30.8)	1315	>65	1) Memory complaint; 2) Score below a 1.5-SD cut-off using normative corrections for age, years of education, race/ethnicity, and sex; 3) Preserved activities of daily living; 4) No diagnosis of dementia.	MCI
North America	Purser JL, 2005, USA[36]	24.7 (23.2-26.2)	3673	>65	0 to 3 errors indicating intact cognition, and 4 or more errors indicating impaired cognition.	MCI
North America	Lopez OL, 2003, USA[37]	22 (20.6-23.4)	3602	>=75	Neurological, neuropsychological, neuroradiological and psychiatric testing.	MCI
North America	Lopez OL, 2003, USA[38]	19.0 (17.3-20.4)	3608	>75	1) Participants or their families reported cognitive problems; 2) There were no neurological, psychiatric, or systemic illnesses that could explain their presence of cognitive deficits.	MCI

South America	Pozo, 2018, Ecuador[39]	37,5 (29.6-45.9)	144	>=65	MMSE<24	CI
South America	Ono, 2018, Brasil[40]	24.3 (20.0-29.1)	1702	>=60	MMSE<19 for no education or <23 for some education	CI
South America	Winter Holz A, 2013, Brasil[41]	34.0 (31.7-36.5)	1514	>60	MMSE score <23	CI
Asia	Han, 2018, South Korea[42]	27 (25.9-28)	6818	>=60		MCI
Asia	Soleimani, 2018, Iran[43]	37 (32.1-41,9)	393	>=60	MMSE<24	MCI
Asia	Zhang Y, 2018, China[44]	23.3 (22.2-24.4)	5558	>=60		CIND
Asia	Liu, 2018, China[45]	34.1(30.4-38.0)	622	>=65	A cut-off score of 2 or greater on the AD8	MCI
Asia	Rao D, 2017, China[46]	14.2(12.7-15.7)	2111	>=65	(1) Cognitive concern or complaint by the subject or a person familiar with the subject, with a CDR score of 0.5; (2) objective impairment in one or more cognitive domain (memory, executive function, visuo-constructive skills, or verbal fluency), based on perfor- mance 1.5 standard deviation below that expected for the subject's age and education; (3) essentially normal functional activity, based on the results of the CDR and FAQ; and (4) absence of dementia, based on the Diagnostic and Statistical Manual of Mental Disorders	MCI
Asia	Pedraza, 2017, India[47]	34 (31.2-36.5)	1235	>=50	MOCA and neurologists evaluation	MCI

Asia	Ren, 2017, China[48]	29,9(25.9-34.3)	480	>80	MMSE + MOCA	MCI
Asia	Han, 2017, China[49]	13.7 (12,1-15,2)	2017	>=60	The thresholds for those who were illiterate, or attended at most primary school, middle school, or university were ≤ 17, 17–20, 21–22, and 23–24	MCI
Asia	Feng L, 2016, Singapore[50]	9.0 (7.8-10.8)	1575	>=55	MMSE<23	CI
Asia	Tang HD, 2016, China[51]	6.5 (5.7-7.4)	3471	>50	education modified MMSE score	MCI
Asia	Tzivian L, 2016, Philippines[52]	28.9 (26.9-30.9)	2050	>50	1) Presence of a subjective cognitive complaint (participants were asked if their cognitive performance had changed during the past 2 years. A complaint was considered present if the participant reported a decline in cognitive performance over time); 2) Presence of an objective cognitive impairment; 3) Not fulfil criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV); 4) Generally intact activities of daily living.	MCI
Asia	Vanoh D, 2016, Malaysia[53]	16 (14.1-17.7)	1993	>=60	MMSE<23	MCI
Asia	Nakamura, 2016, Japan[54]	8.4 (5.1-12.9)	239	>=65	Hasegawa's dementia scale (HDS-R) was used to assess cognitive function, and cognitive impairment was defined as a HDS-R score ≤20	MCI
Asia	Ma F, 2016, China[55]	11.3(8.1-14.4)	5214	>=65	Neuropsychological assessments and clinical examinations	MCI

Asia	Shimada H, 2016, Japan[56]	17.4 (16.2-18.7)	4290	>65	1) Objective cognitive impairment (indicated by an age- and education-adjusted score of at least 1.5 standard deviations below the reference threshold on tests commonly used for detailed neuropsychological assessment); 2) No evidence of functional dependency (e.g., no need for supervision or external assistance in performing ADL); 3) Exclusion by the clinical criteria for dementia.	MCI
Asia	Lyu J, 2016, South Korea[57]	28.5 (26.0-31.1)	1759	>65	Based on age, gender, and educational strata, the cut- off scores (2 standard deviation of the mean) from the K- MMSE normative data were used to determine cognitive im- pairment	CI
Asia	Giri M, 2016, China[58]	12.6 (10.0–15.8)	538	>60	Cognitive concern or complaint by the subject or a person familiar with the subject, with a CDR score of 0.5; (2) objective impairment in one or more cognitive domain (memory, executive function, visuo-constructive skills, or verbal fluency), based on performance 1.5 standard deviation below that expected for the subject's age and education; (3) essentially normal functional activity, based on the results of the CDR and FAQ; and (4) absence of dementia, based on the Diagnostic and Statistical Manual of Mental Disorders.	CI

Asia	Liu M, 2015, China[59]	15.9 (14.4-17.5)	2102	>60	MMSE - < 17 for illiteracy participants; <20 for participants with 1–6 education years; <24 for participants with more than 6 education years.	MCI
Asia	Sun Y, 2014, Taiwan[60]	18.8 (17.9–19.6)	10432	>=65	Score <=24 in literate elders and <=13 in illiterate elders in Taiwanese Mental State Examination (TMSE)	MCI
Asia	Xu S, 2014, China[61]	21.3 (19.7-22.9)	2601	>60	MOCA + neurologistis evaluation	MCI
Asia	Su X, 2014, China[62]	18.5 (15.8-21.8)	815	>60	1) Intact ADL; 2) Memory complaints (either self-reported or family members, caregivers); 3) MMSE; 4) Essentially intact ADL and IADL; 5) No clear dementia; 6) No abnormal memory impairment for age.	MCI
Asia	Zhang Y, 2014, China[63]	23.3 (22.2-24.4)	5550	>60	1) Mild cognitive or functional impairment that did not meet the criteria for dementia; 2) Performance on neuropsychological or functional measures below expectations and ≥ 0.5 standard deviations below published norms on any test.	CIND
Asia	Jia J, 2014, China[64]	20.8 (20.0–21.6),	10276	>65	1) Scored at least 1.5 standard deviations below the norm in memory, executive function, language, or visuoconstructive skill; 2) Global CDR score of 0.5 or less; 3) Preserved ability to perform daily activities and social functions; 4) Absence of dementia.	MCI
Asia	Leggett A, 2013, Vietnam[65]	12.9 (10.0-16.2)	489	>55	MMSE<24 (education adjusted)	CI

Asia	Shimada H, 2013, Japan[66]	18.8 (17.7-19.8)	5104	>65	MMSE	MCI
Asia	Zhu YP, 2013, China[67]	20.7 (18.5-23.1)	1211	>60	MMSE and MOCA	MCI
Asia	Rashid AK, 2012, Malaysia[68]	11.0 (8.2-14.4)	418	>60	Elderly Cognitive Assessment Questionnaire (ECAQ) - A score of 7 or more is indicative of normal memory and score of 4 and below indicates probable dementia.	CI
Asia	Lee LK, 2012, Malaysia[69]	21.1 (16.8-25.8)	333	>60	MMSE and geriatrician, gerontologist and clinical psychologist evaluations	MCI
Asia	Wada-Isoe K, 2012, Japan[70]	23.4 (20.7–26.2)	900	>65	1) Cognitive complaints; 2) Evidence of decline in cognitive function; 3) No impairment of functional activities of daily living; 4) No dementia.	MCI
Asia	Zhuang JP, 2012, China[71]	8.4 (8.3-8.5)	3176	>=55	MMSE score ≤ 17 for illiterates; ≤ 20 for primary school graduates (≥6 years of education); ≤ 24 for junior school graduates or above (≥9 years of education).	CI
Asia	Kim KW, 2011, South Korea[72]	24.1 (21.0–27.2)	8199	>65	MMSE and CERAD-K Neuropsychological Assesment Battery	MCI
Asia	Lu J, 2011, China[73]	20.4 (19.3-21.5)	8411	>65	MOCA	CI
Asia	Yen CH, 2010, Taiwan[74]	9.9 (8.5-11.5)	1626	>60	Nine item Short Portable Mental Status Questionnaire - 4 errors or more in 9 possible	CI
Asia	Choo IH, 2009, South Korea[75]	31.9 (28.0–35.8)	643	>65	1) A global CDR (clinical dementia rating-index of 0.5; 2) Exclusion of dementia	CIND

Asia	Taboonpong, 2008, Thailand[76]	15.0 (11.7-18.8)	420	>60	Chula Mental Test (CMT)<14 in 0-19 - abnormal cognition	CI
Africa	Ogunniyi A, 2016, Nigeria[77]	18.4 (14.9–21.8)	613	>65	IDEA cognitive screen. It tested 10-word learning (repeated three times), orientation, verbal fluency, abstract reasoning, delayed recall and praxis. For cut-off score of ≤7	CI
Africa	Inzelberg R, 2015, Israel[78]	33 (29.7-35.9)	906	>=65	Neurological and cognitive examinations	MCI
Australia	Anderson TM, 2007, Australia[79]	7.7 (6.5-9.0)	1792	>65	MMSE≤23	CI
Australia	Low LF, 2004, Australia[80]	33.3 (25.6-42.4)	131	70-79	1.5 SDs below age-corrected (and education where available) norms on at least one test in the neuropsychological battery and MMSE <24	CIND

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Appendices 2 – PAPER I – Cognitive Impairment Crude Incidence

Supplemental Table 2 – Cognitive Impairment Crude Incidence

World Region	Author, Year, Country	Incidence per 1000 person-year	Follow -up (years)	Sample size (baseline)	Age Cut-off	CI definition	Construct
Europe	Veronese N, 2016, Italy[1]	51.5	4.4	2618	>=65	MMSE<24	
Europe	Luck T, 2010, Germany[2]	56.5 (50.7–62.7)	3	2331	>75	1) No dementia; 2) Evidence of cognitive decline: self and/or informant report; 3) Preserved basic activities of daily living.	MCI
Europe	Etgen T, 2010, Germany[3]	30.7	2	3903	>55	6-Item Cognitive Impairment Test - scores higher than 7.	CI
Europe	Luck T, 2010, Germany[4]	76.5 (64.7-90.4)	8	1692	>75	1) Absence of dementia; 2) Preserved ADLs or only minimal impairment in complex instrumental functions: assessed using the SIDAM-ADL scale; 3) Evidence of cognitive decline.	MCI
Europe	Ravaglia G, 2008, Italy[5]	76.8 (66.8-88.4)	4	1016	>65	Age- and education-adjusted score 1.5 SDs or fewer below the reference threshold on any of the tests used for detailed neuropsychological testing.	MCI
North America	Alhurani, 2016, USA[7]	47.19	4.4	1895	>=70	ClinClinical dementia rating scale Functional activities questionnaire + neurological evaluation; Clinical dementia Rating Scale; Functional activities Questionnaire, neurological evaluation	MCI
North America	Potvin O, 2011, Canada[8]	65.42	1	2785	>65	MMSE score below the 15th percentile according to norms for age, education, and sex	CIND
North America	Plassman BL, 2011, USA[9]	60.4 (45.6-75.3)	8	456	>72	1) Memory complaint; 2) Below a 1.5-SD cut-off using normative corrections for age, years of education, race/ethnicity, and sex; 3) Preserved activities of daily living; 4) No diagnosis of dementia.	CIND
North America	Mejia-Arango S, 2011, Mexico[10]	215 (205-224)	2	7166	>60	10 th percentile by sex and educational level (CCCE) or IQCODE	CIND

North America	Boyle PA, 2010, USA[11]	41.77	12	761	>54	Word List Memory, Word List Recall, and Word List Recognition; semantic memory was assessed via three tests: a 15-item version of the Boston Naming Test, Verbal Fluency, and a 15-item reading test; working memory was assessed via three tests: Digit Span Forward, Digit Span Backward and Digit Ordering; perceptual speed was assessed via four tests: Symbol Digit Modalities Test, Number Comparison, and two indices from a modified version of the Stroop Neuropsychological Screening Test; and visuospatial abilities were assessed via two tests: a 15-item version of Judgment of Line Orientation and a 16-item version of Standard Progressive Matrices. One additional test, Complex Ideational Material	MCI
Asia	Feng L, 2016, Singapore[12]	22	3	1575	>=55	MMSE<23	CI

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Appendices 3 – PAPER I – Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Supplemental Table 3 – Quality Assessment Tool for Observational Cohort and Cross- Sectional Studies

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Janelidze, 2018, Georgia	Freak-Poli,2018, Holland	Zaganas, 2018, Greece	Tsolaki, 2017, Greece	Veronese N, 2016, Italy	Wu YT, 2016, England
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?		y	y	n	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	y	y	y	n	y	y
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	n	n	n	n	n	y
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	y	y	y	y	y
13. Was loss to follow-up after baseline 20% or less?	o	y	y	o	y	y
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	n	y	y	y	y
TOTAL	11	12	13	10	13	14
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	H	H	M	H	H

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Lara E, 2016, Spain	Papachristou E, 2015, Great Britain	Brujin RF, 2014, Holland	Juncos-Rabadán O, 2014, Spain	Moretti F, 2013, Italy	Rodríguez-Sánchez E, 2011, Spain
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	y	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	y	y	y	n	n	n
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	n	n	y	n	n	n
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	y	y	y	y	y
13. Was loss to follow-up after baseline 20% or less?	y	o	y	o	o	o
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	y	y	y	y	y
TOTAL	13	12	14	11	11	11
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	H	H	H	H	H

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Paul C, 2010, Portugal	Nunes B, 2010, Portugal	Dlugaj M, 2010, Germany	Etgen T, 2010, Germany	Luck T, 2010, Germany	Ravaglia G, 2008, Italy
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	y	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	n	y	n	n	n	y
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	n	n	y	y	y	y
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	y	y	y	y	y
13. Was loss to follow-up after baseline 20% or less?	o	o	y	y	y	y
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	y	y	y	y	y
TOTAL	11	12	13	13	13	14
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	H	H	H	H	H

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Luck T, 2007, Germany	Zanetti M, 2006, Italy	De Ronchi D, 2005, Italy	Hanninen, 2002, Finland	Saks K, 2001, Estonia	Frisoni GB, 2000, Sweden
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	n	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	y	n	n	n	n	n
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	y	y	y	y	y	y
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	y	y	y	y	y
13. Was loss to follow-up after baseline 20% or less?	y	o	y	o	y	o
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	y	y	y	y	y
TOTAL	14	11	13	12	13	12
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	H	H	H	H	H

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Di Carlo A, 2000, Italy	Aliberti, 2018, USA	Richard E, 2013, USA	Ortiz GG, 2012, Mexico	Mejia-Arango S, 2011, Mexico	Cortés AR, 2011, Mexico
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	y	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	n	y	n	n	n	n
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	y	y	y	n	n	n
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	y	y	y	y	y
13. Was loss to follow-up after baseline 20% or less?	o	y	n	o	o	o
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	y	y	y	y	n
TOTAL	12	14	12	11	11	10
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	H	H	H	H	M

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Gamaldo AA, 2011, USA	Sachs GA, 2011, USA	Langa KM, 2008, USA	Mejia-Arango S, 2007, Mexico	Manly JJ, 2005, USA	Purser JL, 2005, USA
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	y	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	n	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	n	n	n	n	n	n
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	n	n	n	n	n	y
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	n	y	y	y	y
13. Was loss to follow-up after baseline 20% or less?	o	y	o	o	o	y
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	n	y	y	y	n	y
TOTAL	10	10	11	11	10	13
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	M	M	H	H	M	H

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Lopez OL, 2003, USA	Lopez OL, 2003, USA2	Pozo, 2018, Ecuador	Ono, 2018, Brasil	Winter Holz A, 2013, Brasil	Han, 2018, South Korea
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	y	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	n	n	y	n	n	y
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	y	n	n	y	n	y
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	y	y	y	y	y
13. Was loss to follow-up after baseline 20% or less?	y	o	o	o	o	y
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	y	y	y	y	y
TOTAL	13	11	12	12	11	14
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	H	H	H	H	H

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Soleimani, 2018, Iran	Zhang Y, 2018, China	Liu, 2018, China	Rao D, 2017, China	Pedraza, 2017, India	Ren, 2017, China
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	y	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	n	n	y	n	n	n
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	n	n	n	y	y	y
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	y	y	y	y	y
13. Was loss to follow-up after baseline 20% or less?	o	o	o	o	o	o
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	y	y	y	y	y
TOTAL	11	11	12	12	12	12
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	H	H	H	H	H

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Han, 2017, China	Feng L, 2016, Singapore	Tang HD, 2016, China	Tzivian L, 2016, Philippines	Vanoh D, 2016, Malaysia	Nakamura, 2016, Japan
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	y	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	n	n	n	n	n	n
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	n	y	n	y	n	n
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	y	y	y	y	y
13. Was loss to follow-up after baseline 20% or less?	o	o	o	y	o	o
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	y	y	y	y	y
TOTAL	11	12	11	13	11	11
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	H	H	H	H	H

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Ma F, 2016, China	Shimada H, 2016, Japan	Lyu J, 2016, South Korea	Giri M, 2016, China	Liu M, 2015, China	Sun Y, 2014, Taiwan
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	y	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	n	n	n	n	n	y
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	n	y	y	n	n	y
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	y	y	y	y	y
13. Was loss to follow-up after baseline 20% or less?	o	o	y	o	o	o
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	y	y	y	y	y
TOTAL	11	12	13	11	11	13
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	H	H	H	H	H

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Xu S, 2014, China	Su X, 2014, China	Zhang Y, 2014, China	Jia J, 2014, China	Leggett A, 2013, Vietnam	Shimada H, 2013, Japan
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	y	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	n	y	n	y	n	n
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	y	n	n	y	n	n
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	y	y	n	y	y
13. Was loss to follow-up after baseline 20% or less?	o	o	o	o	o	o
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	y	y	y	y	y
TOTAL	12	12	11	12	11	11
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	H	H	H	H	H

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Zhu YP, 2013, China	Rashid AK, 2012, Malaysia	Lee LK, 2012, Malaysia	Wada-Isoe K, 2012, Japan	Zhuang JP, 2012, China	Kim KW, 2011, South Korea
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	y	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	n	n	y	y	n	n
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	y	n	y	y	n	n
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	n	y	n	n	y	y
13. Was loss to follow-up after baseline 20% or less?	o	o	o	o	o	o
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	y	y	y	y	y
TOTAL	11	11	12	12	11	11
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	H	H	H	H	H

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Lu J, 2011, China	Yen CH, 2010, Taiwan	Choo IH, 2009, South Korea	Taboonpong, 2008, Thailand	Ogunniyi A, 2016, Nigeria	Inzelberg R, 2015, Israel
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	y	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	n	n	y	n	n	n
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	n	n	y	n	y	n
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	n	n	y	y	n
13. Was loss to follow-up after baseline 20% or less?	o	o	o	o	o	o
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	y	y	y	y	y
TOTAL	11	10	12	11	12	10
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	M	H	H	H	M

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	Anderson TM, 2007, Australia	Low LF, 2004, Australia	Alhurani, 2016, USA	Plassman BL, 2011, USA	Potvin O, 2011, Canada	Boyle PA, 2010, USA	, 2011, Mexico
1. Was the research question or objective in this paper clearly stated?	y	y	y	y	y	y	y
2. Was the study population clearly specified and defined?	y	y	y	y	y	y	y
3. Was the participation rate of eligible persons at least 50%?	y	y	y	y	y	y	y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	y	y	y	y	y	y	y
5. Was a sample size justification, power description, or variance and effect estimates provided?	n	n	n	n	n	n	n
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	y	y	y	y	y	y	y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	y	y	y	y	y	y	y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	y	y	y	y	y	y	y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y	y
10. Was the exposure(s) assessed more than once over time?	n	n	y	y	n	n	n
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	y	y	y	y	y	y	y
12. Were the outcome assessors blinded to the exposure status of participants?	y	n	y	y	y	y	y
13. Was loss to follow-up after baseline 20% or less?	o	o	o	o	o	o	o
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	y	y	y	y	y	y	y
TOTAL	11	10	12	12	11	11	11
>80% yes= High, 60-80% yes- Medium, and <60% yes= Low	H	M	H	H	H	H	H

Appendices 4 – PAPER I – PRISMA 2009 Checklist

PRISMA 2009 Checklist

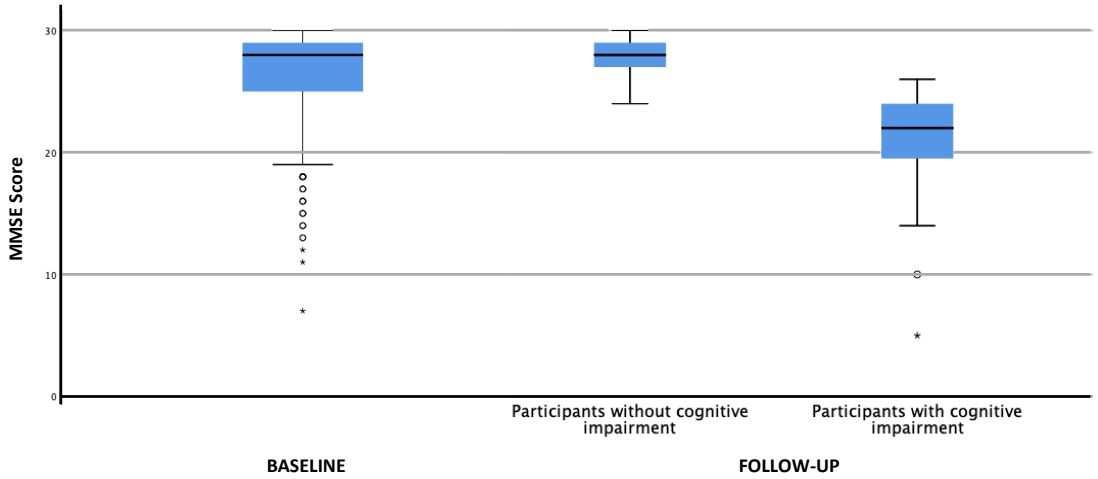
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4,5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	No
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	No
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2 Figure 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	No
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	No
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	No
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendices 5 – PAPER II - Supplementary figure of the MMSE score.

Figure S1. Box Plot of the Mini-Mental State Examination score of the population at baseline evaluation and participants with or without cognitive impairment at the follow-up evaluation.



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