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Review Article

Dementia Appraisal: Overview of Good Clinical Practices, Barriers, and Gaps for Integrated Care

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Abstract

Introduction: The increasing prevalence of dementia and mild cognitive impairment is a priority for health systems and society in the coming years. The aim of this study was to provide an overview of good clinical practices, barriers, and gaps for integrated dementia care. **Methods:** An electronic search was conducted on PubMed database for the last five years for articles relevant to the scope of the study, conducted in humans, written in Portuguese or English, and open access. National and international guidelines and consensus documents recognized in Europe were also included.

Results: With increasing life expectancy and aging as major risk factors, the number of people living with dementia will become unsustainable for medical, social, and informal care. Ineffective care pathways lead to unnecessary medical interventions and suboptimal care. People with dementia should be involved in all stages of care and research. High-quality epidemiological data by disease severity and dementia subtype are needed. The development of novel technologies to improve clinical assessment of cognition and function that are sensitive and accurate in early stages of dementia and can be used in primary care is also an unmet need. A strategy to improve dementia care from diagnosis to end of life is lacking. Research into effective models of care and new treatment pathways with a more accurate selection of patients in early stages of the disease is crucial. **Conclusions:** There are currently several gaps in dementia care. Integrated care pathways, patient-centered approaches, and the establishment of a workforce based on a comprehensive and pragmatic framework are priorities that should be included in public health strategies.

Keywords: Alzheimer's disease; dementia; diagnosis; epidemiology; healthcare management; therapeutics

Introduction

Dementia is a neurodegenerative disease and the leading cause of disability and dependency among older adults worldwide. It was the seventh leading cause of death in adults globally in 2019 [1]. Dementia is a growing public health problem with a major impact on the quality of life of patients and their families, with global medical, social, and informal care costs estimated at $1.3 trillion annually and expected to exceed $2.8 trillion by 2030 [1]. As the condition remains underdiagnosed in low-income countries, these figures could rise substantially. With the significant increase in dementia cases, the number of Emergency Department (ED) visits, hospitalizations, and institutionalizations will rise, as will the associated costs.

Another unmet need is community/patient and caregiver education and literacy about dementia [2–4]. The lack of time in medical consultations, which prevents the physician from discussing with the caregiver how to manage some behavioral

disturbances or progressive loss of autonomy in the loved one often results in feelings of sadness and disability, as well as anxiety and depression for the caregiver. On the other hand, the increasing demand for "memory consultations" in some countries has led to long waiting lists, lack of standardization, and inequity in dementia care.

What can we expect by 2030? New treatments with monoclonal antibodies promise better outcomes, but their cost and specificity for certain patient populations may be barriers to their widespread use. Digital health with remote monitoring technologies can enable early intervention and promote patient-centered care. However, definition of the patient pathway, well-defined strategies across the continuum of care, and robust approaches to overcome issues of Internet access and low levels of technological literacy are urgently needed.

In Portugal, epidemiological and economic data on dementia are scarce and new methodological strategies are needed to improve access to accurate and early diagnosis for specific subgroups and knowledge of their specific characteristics. Due to the aging of the population and the interactive effects of modifiable risk factors, the health system and society will have to cope with an increasing number of people with dementia. The aim of this study was to use the 360º health analysis framework to provide an overview of good clinical practices, barriers, and gaps for integrated dementia care.

Materials and methods

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach, an electronic search was conducted on PubMed database including the last 5 years (from April 2018 to April 2023). Studies on any form of dementia were included using one of the following queries: dementia [MeSH Major Topic] or Alzheimer [MeSH Major Topic] or Lewy body disease [MeSH Major Topic] or frontotemporal dementia [MeSH Major Topic] or Parkinsonism [MeSH Major Topic]). Independent searches were conducted on the different topics to provide a comprehensive review using the following queries: prevalence [MeSh terms]; incidence [MeSh terms]; risk factors [MeSh terms]; diagnosis [MeSH major topic]; treatment [MeSH major topic]; clinical trials [MeSH Terms]; organization and administration [MeSH terms]. Search results were narrowed by selecting human studies, written in Portuguese or English, open access, and including the following article types: case reports, clinical studies, consensus conferences, guidelines, reviews, and systematic reviews. Relevant articles within the scope of the study were selected. Two independent reviewers assessed the articles selected for eligibility by reviewing the title, abstract, or both. Articles related to basic research, diseases other than dementia, and other topics outside the scope of dementia management were excluded (Table 1). A final assessment was performed after full-text reading for evaluation of the quality of studies and number of participants and for the authors' scientific assessment.

Inclusion criteria
Articles about epidemiology, risk factors, diagnosis, treatment, and dementia management
Exclusion criteria
Articles about basic research
Articles about diseases other than dementia
Articles on topics outside the scope of dementia care
Articles on topics too specific for the purpose of this study (e.g., disease genetics, pathophysiology, etc.)

Table 1: Criteria for inclusion and exclusion of articles in the review.

Results

A total of 2940 articles were initially retrieved from the PubMed search, of which 195 were included in the review after study criteria assessment (Figure 1). Eight additional articles were included due to their relevance to the scope of this review.

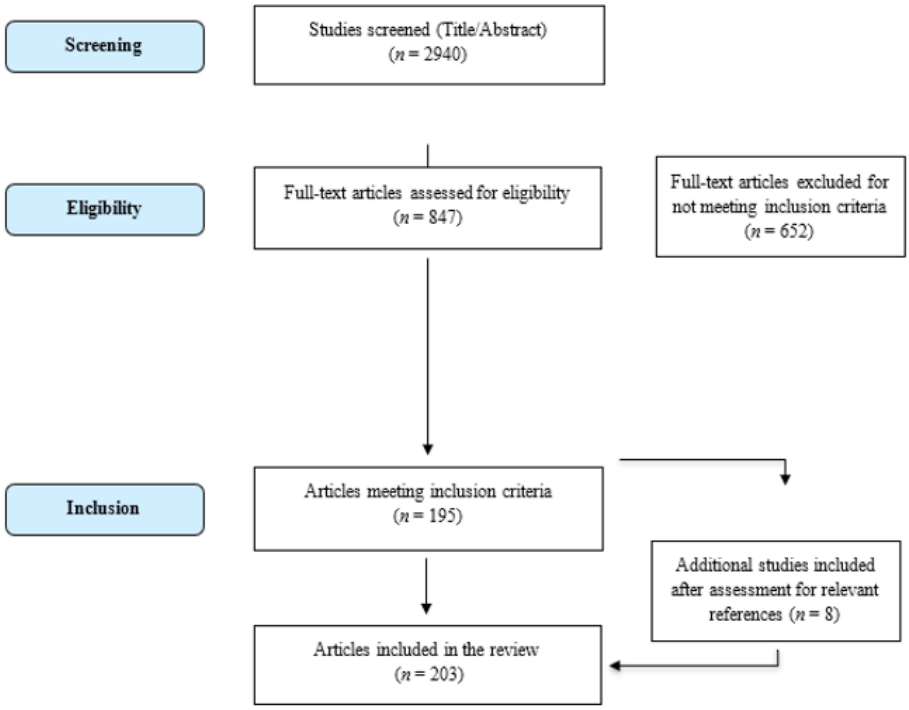


Figure 1: Flowchart of studies included in the review.

Dementia in numbers: Epidemiology & Economics

According to the World Health Organization (WHO), more than 55 million people worldwide are currently estimated to be living with dementia [5], and this number is expected to increase to approximately 153 million by 2050, particularly in low- and middle-income countries (LMIC), where more than 60% of people with dementia live [1,6,7]. The prevalence of the disease varies among ethnic groups within countries [1,6,7]. A recent systematic review and meta-analysis reported a higher incidence of dementia in black compared with white ethnic groups, and similar incidence in Asian and Latino compared with white ethnic groups [8]. The same study reported a higher prevalence of dementia in Malay and Indian compared with Chinese ethnic groups [8]. Despite these numbers, reliable data on the prevalence of the disease among different ethnic and racial groups, as well as among sexual minorities and in different parts of the world, particularly LMIC, are still lacking [1]. Data on young-onset dementia are also very limited [1].

The risk of having a diagnosis of clinical dementia increases with age, doubling approximately every 5 years up to age 85 [9]. Women are more likely to have the disease than men after the age of 80, while men are more likely to have the disease before the age of 70 [9].

In several high-income countries of North America and Europe, a decreasing trend in the incidence of all-cause dementia has been observed over the past 40 years, probably due to educational, socioeconomic, health care, and lifestyle changes [6,10,11]. In contrast, the prevalence of age-specific dementia is increasing in Japan, South Korea, Hong Kong, Taiwan, and LMIC. The absolute number of people with dementia worldwide is expected to increase substantially in the coming years [6].

Alzheimer's disease (AD) is the most common subtype of dementia (60–80%), followed by vascular dementia (VaD; 13%), Lewy body dementia (LBD; 5%), Parkinson's disease dementia (3.6%), and frontotemporal dementia (FTD) (3%) [1]. Although FTD is not common in all age groups, it is one of the most common subtypes below the age of 65, accounting for approximately 10% of all cases in this age group [12].

Despite remarkable advances in diagnostic biomarkers, most epidemiologic studies are based on old sets of clinical diagnostic criteria or algorithms based on brief cognitive screening tests, which may not be sensitive or specific for early stages of the disease and do not distinguish between different etiologies of dementia, thus underestimating its true prevalence and incidence [10].

The World Health Organization (WHO) estimated a global societal cost of dementia in 2019 of US$1.3 trillion, depending on the severity of the disease and income region. Worldwide, the estimated annual cost per person with dementia is approximately US$16,000 for mild dementia, US$27,000 for moderate dementia, and US$36,000 for severe dementia [13]. AD is associated with an estimated $236 billion in direct and long-term costs in the United States [1]. Unpaid caregiving costs are currently estimated at approximately $220 billion annually [1].

Dementia in Portugal

Epidemiologic studies on cognitive impairment in Portugal are scarce, as are data on the prevalence of different forms of dementia. Garcia et al. estimated the number of Portuguese people with dementia to be 92,470 and those with AD to be 48,706 in 1991, based on European prevalence rates [14]. Nunes et al. conducted the first Portuguese epidemiologic study of neurocognitive disorders in people aged 55-79 years living in a northern region of the country (9,015 inhabitants) and estimated a prevalence of dementia of 2.7% (1,146 participants) and similar proportions of AD and VaD subtypes. However, the sample was not nationally representative [15]. Santana et al. estimated the prevalence of dementia in 2013 to be 5.9% of people aged 60 years or older (160,287 people) by extrapolating the prevalence of dementia in Western Europe [16]. Gonçalves-Pereira and colleagues applied a 10/66 Dementia Research Group (DRG) population based research program in two geographical areas in southern Portugal (one urban and one rural site), excluding nursing home residents [14]. The prevalence of dementia was 9.23% using the 10/66 DRG algorithm and 3.65% using DSM-IV criteria, with AD being the most common dementia (41.9%). Apart from the fact that these results cannot be generalized to the whole country, the figures suggest that previous studies may have underestimated the true prevalence of dementia in Portugal. According to the most recent data, the number of people living with dementia in Portugal in 2019 was 200,994 [7].

The cost of dementia therapies in Portugal was estimated at around 37 million euros per year in 2013, with rivastigmine, donepezil, and memantine being the most prescribed therapies. However, more studies are needed on the direct and indirect costs of the disease [16].

Risk factors for dementia

Dementia is a multifactorial disease with non-modifiable risk factors, such as age and genetics, and several potentially modifiable risk factors that can potentially be targeted to reduce the prevalence of the disease (Table 2).

Risk Factor	
Non-modifiable	
Age	The risk of dementia increases with age.
Genetics	Genes play a role in the risk of dementia, but most dementias are sporadic. APP, PSEN1, PSEN2, MAPT, cr9orf72 are the most studies genes.
Gender	Women are disproportionately affected by the disease, with higher prevalence and proportion of related deaths and more (DALYs)
Modifiable	
Education	Lower educational attainment is one of the most common modifiable factors.
Hypertension	Midlife hypertension is associated with an increased risk of late-life dementia.
Obesity	Midlife obesity is associated with an increased risk of late-life dementia, independent of other risk factors.
Diabetes	Diabetes is associated with a high risk of dementia, which increases with the duration and severity of the disease.
Smoking	Tobacco smoking is associated with an increased risk of dementia.
Cardiovascular disease	Several cardiovascular diseases are associated with an increased risk of dementia, including heart failure, atherosclerosis, stroke, atrial cardiopathy, hypercholesterolemia, and chronic kidney disease.
Physical inactivity	Physical inactivity is associated with an increased risk of dementia.
Hearing loss	Hearing loss is an independent risk factor for dementia.
Depression	Depression is associated with an increased risk of dementia, but is also part of the prodrome and early stages of dementia.
Social isolation	Social isolation increases the risk of dementia.
Alcohol	The association between alcohol consumption and cognitive function depends on the frequency and amount of alcohol use. Heavy drinking is associated with dementia.
Traumatic brain injury	Traumatic brain injury is a risk factor for dementia.
Air pollution	Exposure to some pollutants, such as PM2.5, NO_2, and carbon monoxide, is associated with an increased risk of dementia.
Sleep disturbances	Sleep disorders are associated with an increased risk of dementia.

Drugs	Some anticholinergic drugs, such as antihistamines, sleep agents, and treatments for overactive bladder, may be associated with an increased risk of dementia, especially Alzheimer's disease.
Visual impairment	Visual impairment is associated with cognitive decline and dementia.

APP – amyloid precursor protein; PSEN1, PSEN2 – presently 1/2, MAPT – gene encoding the tau protein involved in auxopathies, DALY –disability-adjusted life years, PM2.5 – fine particulate matter, NO2 – nitrogen dioxide

Table 2: Potentially modifiable risk factors for dementia.

Non-modifiable risk factors

Age

Aging is a complex and irreversible process involving multiple organs and cell systems and is considered the strongest non-modifiable risk factor for the development of dementia [17–19]. The risk of dementia increases with age, with an estimated 19% of people aged 75-84 years and up to 50% of people over 85 years developing the disease [17].

Genetics

Although most cases of AD and related dementias are sporadic, genes play a role in risk for these diseases. About 70% of the risk of developing AD can be attributed to genetics, although only a few cases are hereditary [20,21]. The main genes associated with AD are amyloid precursor protein (APP) and presently 1/2 (PSEN1/2), which are responsible for familial and early-onset AD (<5% of cases). Apo lipoprotein E (APOE) variant ε4 is the major driver of sporadic AD, leading to late-onset AD (LOAD) in the general population [17,20,21]. Other risk factors for LOAD include single nucleotide polymorphisms in CLU, PICALM, CR1, BIN1, ABCA7, CD2AP, CD33, EPHA1, and MS4A cluster [20].

Less is known about the genes involved in non-AD dementias. A family history of FTD is one of the most important risk factors for the disease. Approximately 40% of cases have a family history of dementia, but less than 10% have a clear autosomal dominant inheritance pattern [12]. More than 10 genes have been associated with FTD, with the gene encoding the tau protein involved in taupathies (MAPT) and the gene encoding progranulin (PGRN) and intronic expansion of a hexanucleotide repeat in C9orf72 accounting for about 60% of familial FTD [22].

APOE, glucocerebrosidase, and alpha-synuclein have been associated with LBD [21]. Mutations in the NOTCH3 gene are associated with the development of autosomal dominant cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which can cause VaD.

Although genetic risk strongly influences the development of dementia, it is the combination of an individual's genetic makeup and exposure to environmental factors that determines the onset of the disease [10].

Gender

Studies have shown gender differences in the development of dementia. Women are disproportionately affected, with a higher prevalence of the disease at all ages, more disability-adjusted life years, and a higher proportion of related deaths [1]. Some studies show that women are at higher risk for AD, while men are at higher risk for VaD [18].

Several factors may explain these differences, including selective survival of men with healthier cardiovascular (CV) risk profiles, educational attainment, and biological mechanisms such as hormone exposure [9,19,23]. The literature suggests that estrogens have a clear role in modulating the risk of dementia, with evidence that hormone replacement therapy may have both beneficial and harmful effects. However, further studies are needed to confirm these findings [19,23].

Modifiable risk factors

The Lancet Commission on Dementia Prevention, Intervention and Care 2020 update identified 12 modifiable risk factors for dementia that account for approximately 40% of all dementia cases worldwide: low education, hypertension, hearing impairment, smoking, midlife obesity, depression, physical inactivity, diabetes, social isolation, excessive alcohol consumption, head injury, and air pollution [6].

Education

Low educational attainment, especially lack of secondary education, is one of the most prevalent modifiable factors for dementia. Higher levels of childhood and lifelong education reduce the risk of dementia [24–26], particularly in those with a high genetic predisposition [27]. However, there is no evidence that it is a protective factor against FTD [12]. Several population studies have shown that cognitive stimulation (in the form of leisure-time cognitive activities) in mid- and late-life is also associated with a lower risk of dementia [28–30].

Hypertension

The association between blood pressure and dementia is complex. Midlife hypertension (40-65 years) is associated with an increased risk of dementia in later life in several studies [20,31–33]. On the other hand, lowering blood pressure in later life appears to be associated with an increased risk of dementia. U-shaped associations have been observed in people aged 75 years and older, with a systolic blood pressure (SBP) of 160-170 mmHg being associated with the lowest risk of dementia [32,33]. However, further studies are needed to confirm these findings in LMIC and in racially, ethnically and socioeconomically diverse populations, as well as in older age groups [32].

A recent meta-analysis reported that the use of either calcium channel blockers or angiotensin II receptor blockers was

significantly associated with a lower risk of dementia compared with angiotensin-converting enzyme inhibitors and beta-blockers, but the same was not true for diuretics [34].

Obesity

Several studies have shown that midlife obesity (35-64 years) is associated with an increased risk of developing dementia in later life, independent of other vascular or socioeconomic risk factors [35]. There are no clinical trials with data on the effect of weight loss before the age of 65 on the prevention of dementia [36,37]. Body mass index (BMI) decreases in the years prior to a diagnosis of dementia [36–38]. Recent studies have shown an inverse correlation between late-life BMI and dementia risk [39], and this difference appears to be most pronounced in those with a genetic predisposition to higher BMI [40].

Diabetes

Both type 1 and type 2 diabetes are associated with a high risk of dementia, which increases with duration and severity of diabetes [41–43] and, independently, with glycated hemoglobin (HbA1c) variability over the years [44]. A Cochrane review showed no effect of intensive versus standard diabetes control on cognitive decline or dementia [45], and a Korean cohort study showed that a history of hypoglycemia in people with diabetes was associated with a higher risk of dementia [46]. The effect of antidiabetic therapy in providing increased protection against dementia is inconsistent in the literature [47].

Smoking

Compelling evidence indicates that tobacco smoking is associated with an increased risk of dementia [7,48–51]. There is limited and weak observational evidence linking passive smoking to an increased risk of cognitive impairment or dementia [52]. Some studies have suggested that smoking cessation reduces the risk of dementia even later in life [48,50,53,54] and that early cessation has benefits, highlighting the importance of smoking cessation in midlife [54].

Cardiovascular risk factors

Extensive clinical and epidemiological evidence has demonstrated a strong association between dementia and heart failure [55], atherosclerosis [56], and stroke [57–59] independently. Up to 64% of people aged 65 years or older with a history of stroke have cognitive impairment, and up to one-third develop dementia [59]. A recent systematic review and meta-analysis and a retrospective cohort study showed that atrial fibrillation (AF) is a risk factor for dementia in both young (<65 years) and old age, but the underlying mechanisms remain unclear [60,61]. Atrial cardiopathy (an abnormality in the structure or function of the left atrium) was also significantly associated with an increased risk of dementia, with only a small percentage of the effect mediated by AF or stroke [62]. There is also strong evidence that chronic kidney disease and albuminuria are risk factors for dementia [63–65].

The relationship between hypercholesterolemia and dementia risk remains unclear due to conflicting evidence. A 2016 Cochrane review reported that statins given to older people at risk of vascular disease did not prevent cognitive decline or dementia [6]. On the other hand, a 2018 meta-analysis of 25 cohort studies suggested that statin use may reduce the incidence of all types of dementia but not VaD [66]. Further studies are needed to clarify these issues. A recent cohort study showed that low levels of high-density lipoprotein cholesterol were significantly associated with incident AD up to several decades later, both in early adulthood (35-50 years) and in middle adulthood (51-60 years), as were high triglyceride levels in early adulthood (35-50 years) [67].

A UK study of 7,899 people aged 50 years who were followed for 25 years calculated a CV health score based on several CV risk factors (smoking, obesity, fasting glucose, blood cholesterol, blood pressure) and concluded that better scores were associated with a lower risk of dementia in people without CV disease [6]. These findings emphasize the importance of controlling CV risk factors in midlife.

Physical inactivity

Approximately one-third of the adult population in the United States, Europe, and the United Kingdom is physically inactive [68]. Physical inactivity is associated with an increased risk of dementia [6,50,69]. Exercise can reduce weight and diabetes risk, improve CV function, decrease glutamine, and increase hippocampal neurogenesis [6,50]. Epidemiologic studies show that physical activity is an independent protective factor against dementia [50,70–72].

Hearing impairment

Hearing impairment is very common in older adults, affecting up to two-thirds of people over the age of 70 [73], but is severely undertreated, with less than 20% of adults receiving any treatment for the condition (e.g., hearing aids) [73]. A growing body of evidence shows that hearing loss is an independent risk factor for dementia [74–76] and precedes the onset of dementia by 5 to 10 years [75]. A direct effect on brain volume and an indirect effect on social engagement, mental health, and physical activity may explain the increased risk of dementia [6,50,75,77], but more research is needed to investigate the potential causal mechanisms underlying this association.

Observational studies suggest that treatment of hearing loss (e.g., hearing aids) may reduce the burden of dementia by up to 8% [6]. However, evidence from several small clinical trials has been inconsistent. Some studies suggest that treatment of hearing loss may improve memory, but this has not been seen in people without dementia or in studies of people with AD [78].

Depression

Depression is associated with the incidence of dementia but is also part of the prodrome and early stages of dementia [6]. Several studies support that depression is associated with an increased risk of dementia, especially in the later stages of life [6,50,68,79]. However, few studies have distinguished between treated and untreated depression as a risk factor for dementia. Evidence on the role of antidepressants in reducing the risk of

dementia is lacking. Animal models have shown that selective serotonin reuptake inhibitors may reduce amyloid plaque burden and cognitive impairment [80], but robust evidence in humans is lacking and needed.

Social isolation

Social contact is thought to be a protective factor against dementia, with a number of studies suggesting that social isolation increases the risk of dementia. This association is complex and interrelated with other risk factors [6,50,81]. Several studies have shown that it is the quality and diversity of the social network, rather than its size, that predicts protection against cognitive decline and dementia [81]. Targeted interventions aimed at reducing social isolation and providing a social network for older people may act as a protective factor against dementia and other geriatric syndromes [6,50].

Alcohol consumption

Alcohol is strongly linked to cultural patterns. The relationship between alcohol consumption and cognitive function depends on the frequency and amount of alcohol consumed. Heavy drinking is associated with brain changes, cognitive impairment, and dementia [82]. However, there are not enough data to predict what amount of alcohol increases the risk of dementia.

An overview of systematic reviews on the epidemiology of alcohol consumption and risk of dementia or cognitive decline showed that the risk of dementia may decrease with light to moderate drinking (less than 21 units per week) [83]. The UK Whitehall study showed a higher risk of dementia among those who drank more than 14 units of alcohol per week and among long-term abstainers, with the risk increasing linearly with higher levels of consumption [84].

Head injury

Traumatic brain injury (TBI) is considered a risk factor for AD and other dementias, increasing proportionally with the severity and frequency of TBI [85–87]. Approximately 5% of all cases of dementia worldwide are thought to be due to TBI [88]. A systematic review and meta-analysis conducted in 2021 found a moderate association between TBI and the risk of dementia, but no association between TBI and the risk of AD [89]. It also reported a higher risk of dementia in Asian people, males, and people with a mean age below 65 years [89]. A cohort study conducted in 2021 supported TBI as a risk factor for dementia, but did not find an association between TBI and specific types of dementia [85]. Blood-brain barrier dysfunction, mitochondrial function, β-amyloid pathology, chronic neuroinflammation, tau deposition, vascular damage [90], and white matter degeneration may play a role in the development of dementia [89].

Air pollution

High levels of nitrogen dioxide (NO2) and fine particulate matter (PM2.5) from traffic and residential wood burning are associated with dementia. In a systematic review of exposure to air pollutants and incident dementia, exposure to PM2.5, NO2, and carbon monoxide were all associated with an increased risk of dementia [6].

Sleep disorders

Growing evidence suggests that sleep disturbances such as insomnia, sleep-disordered breathing (such as obstructive sleep apnea), disrupted circadian rhythms, sleep-related movement disorders, and excessive daytime sleepiness are associated with a 50-80% increased risk of dementia [77,91]. A U-shaped association has been reported between sleep duration and risk of mild cognitive impairment or dementia, with an increased risk of dementia observed with less than 5 hours and more than 10 hours of sleep [6].

Diet

Several foods (green vegetables, berries, fish, and olive oil), nutrients (B vitamins, vitamin E, and omega-3 fatty acids), and phytochemicals (flavonoids) have been associated with a reduced risk of dementia [92]. No study has reported a beneficial effect of supplementation for the prevention of dementia [6]. More recently, studies have focused on the effect of whole diets rather than individual nutrients, concluding that diets such as the Mediterranean diet (high intake of vegetables, fruits, nuts, cereals, and olive oil and low intake of saturated fat and meat) may reduce the risk of dementia [77,93–95].

Drugs

Recent studies suggest that anticholinergics (including antihistamines, sleep agents, and treatments for overactive bladder) may be associated with a risk of developing dementia, particularly AD. These drugs are commonly used in the geriatric population and should be prescribed with special caution [50].

Visual impairment

Visual impairment is a major global health problem. A recent systematic review concluded that visual impairment is associated with cognitive decline and dementia, but the underlying mechanism is unclear [96]. Another recent study showed that cataract extraction significantly reduced the risk of developing dementia [97].

Others

The possible involvement of infectious agents in AD and other dementias has long been suggested [98,99]. The neurocognitive consequences of untreated human immunodeficiency virus (HIV) infection are well documented, and antiretroviral therapy has dramatically reduced the incidence of HIV-associated dementia. However, a U.S. cohort study concluded that despite antiretroviral therapy, people with HIV are at increased risk of dementia as they age and are diagnosed with dementia on average 10 years earlier than demographically similar people without HIV. Further research on risk factors for dementia in people treated for HIV is an unmet need [100].

Several observational studies have shown an increased risk of AD after COVID-19 infection. Inflammation and immune response are likely to play a relevant role in this association [98,99]. A recent systematic review and meta-analysis of 292,157

individuals found an association between influenza vaccination and a significantly lower risk of dementia [101], and a claims-based cohort study of 935,887 influenza vaccinated-unvaccinated matched pairs corroborated these findings, estimating an approximately 40% reduction in the development of AD in patients who received the influenza vaccine compared with those who did not [102]. A large UK cohort has provided some insight into the beneficial role of treatment and prevention of vitamin D deficiency on brain health and dementia risk, but randomized controlled trials are needed to confirm these findings [103]. Several studies have shown an increased risk of dementia in people with Down syndrome, especially at younger ages, which may be explained by the overexpression of genes involved in amyloid precursor protein processing and Alzheimer's neuropathic changes caused by trisomy 21 [58].

Emerging perspectives suggest an involvement of the gut microbiota in neurocognitive decline via a microbiota-gut-brain axis [104]. The specific mechanisms involved in this association remain largely unknown. Inflammatory bowel diseases such as ulcerative colitis (UC) and Crohn's disease (CD) have been potentially linked to changes in the composition of the microbiota and may be associated with an increased risk of dementia, but the evidence is conflicting [104]. A Danish and a German study recently reported a small increase in the risk of all-cause dementia in both UC and CD, with the Danish study also suggesting an association with FTD in CD patients [104,105].

Approaches for risk reduction

Dementia is a multifactorial disease with several potentially modifiable risk factors. Public health and individually tailored interventions targeting these risk factors have the potential to reduce the prevalence of the disease (Figure 2) [6,7,50,106]. Recent evidence suggests that high-risk populations may benefit most from these interventions compared with low-risk populations [6,50,106].

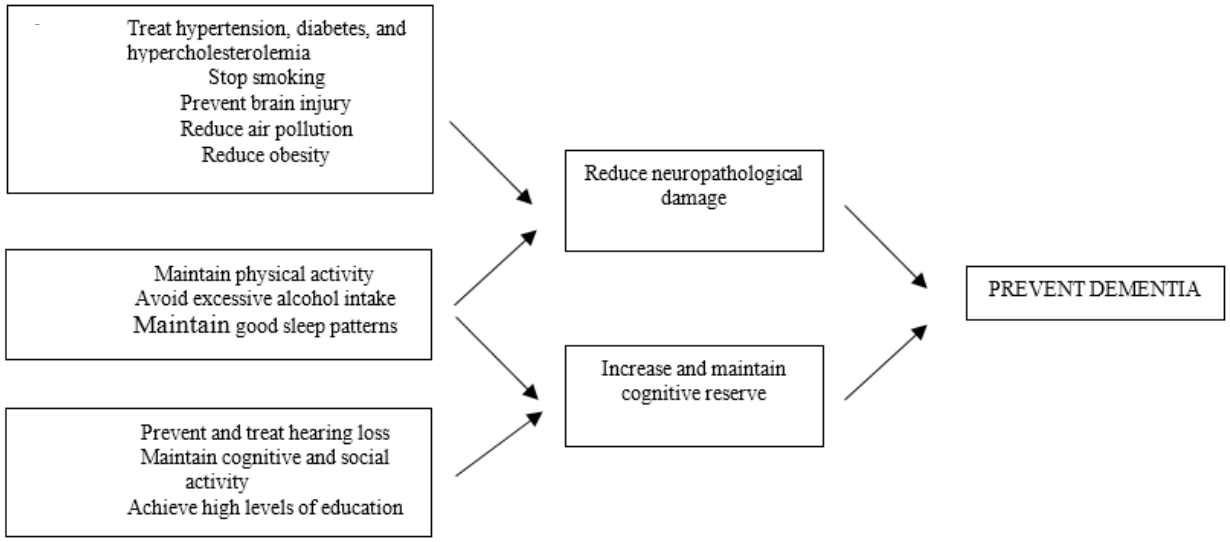


Figure 2: Potentially modifiable risk factors for the prevention of dementia.

Most interventions are lifestyle-related. According to the American Heart Association's Cardiovascular Health (CVH) guidelines, maintaining ideal levels of physical activity, fasting plasma glucose, and total cholesterol and stop smoking substantially reduce the risk of dementia in later life [106]. However, more research is required to explore the relationship between a favorable CVH score and cognitive outcomes in cognitively asymptomatic older populations. Other interventions include maintaining a healthy diet and sleep pattern, reducing alcohol consumption, using hearing protection, preventing brain injury, and remaining cognitively and socially active. Public health measures to reduce air pollution and promote children's education may also be helpful [6].

Despite the growing knowledge of modifiable risk factors for dementia, there is little evidence on the representativeness and methodology of interventions. There is a need to include marginalized populations, to consider exposure across the lifespan rather than only in midlife, and to ensure consensus on outcome measures that could be included in other chronic disease studies [1].

Dementia prediction models

Several dementia prediction models have been developed, but only a few have been externally validated. These include the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) score (long-term risk of dementia in middle-aged adults), the Australian

National University Alzheimer's Disease Risk Index (ANU-ADRI; individual exposure to risk factors known to be associated with an increased risk of AD in later life), the Brief Dementia Screening Indicator (BDSI; risk of dementia in older adults), and the Dementia Risk Score (risk of dementia in older adults) [107]. Of the 12 modifiable risk factors described above, only air pollution and hearing loss are not included in these models [21,107]. Three other models have recently undergone external validation: Mehta's RxDx-Dementia Risk Index (risk of dementia in patients with type 2 diabetes mellitus and hypertension), Nori's Alzheimer's Disease and Related Dementias (risk of AD and dementias in patients aged 45 years and older), and Walters Dementia Risk Score (5-year risk of first recorded dementia diagnosis in patients aged 60-79 years) [108].

Last year, the first dementia risk score calculated in a middle-aged Southern European population followed for 20 years was presented, allowing early identification of individuals who could be targeted for dementia prevention based on intensive risk factor control [109].

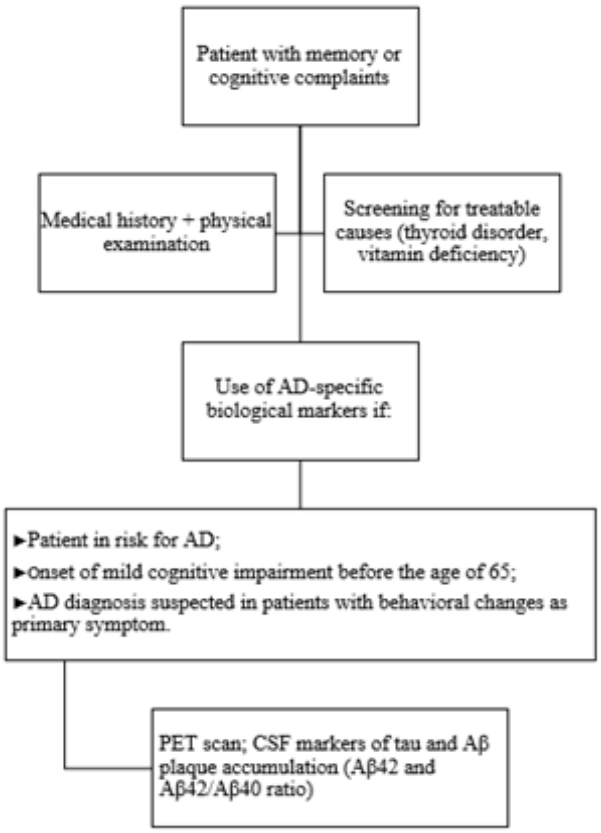
Dementia diagnosis

AD is the most common cause of dementia, followed by VaD. Less common causes include LBD, FTD and Parkinson's disease dementia. The differential diagnosis of dementia can be challenging due to overlapping symptoms [110].

The first AD guidelines were published in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association task force [111]. It was not until 2011 that the most recent guidelines were published, with the main difference from the 1984 guidelines being the recognition of different stages of AD and the inclusion of AD biomarkers. In 2016, the Aβ-amyloid tau neurodegeneration (ATN) classification was proposed to categorize multidomain biomarker findings [112].

Molecular imaging has provided insight into Alzheimer's neuropathology [113]. It is now acknowledged that neuropathological changes occurring approximately 30 years before clinical onset consist of deposition of Aβ plaques, neurofibrillary tangles composed of misfolded hyperphosphorylated tau (a naturally unfolded protein that assumes an abnormal configuration in the tauopathy brain), neuronal loss, and neuroinflammation with glial activation.

The clinical diagnosis of dementia begins with an assessment of symptoms and medical history, physical examination, and screening for treatable causes (such as thyroid disease or vitamin deficiencies). Because neuropathological changes can aid in the diagnosis, the analysis of biomarkers (physiologic, chemical, or anatomic parameters that effectively reflect certain pathophysiologic processes) can then be performed. Patients' clinical assessment is summarized in (Figure 3) [112].



AD, Alzheimer's disease; CSF, cerebrospinal fluid; PET, positron emission tomography

Figure 3: Clinical assessment of patients with suspected dementia

In AD, biomarkers are assessed either by neuroimaging techniques (non-invasive) [110,113] or by mass spectrometry or immunoassay quantification of cerebrospinal fluid (CSF) markers of neuropathologic changes. The CSF markers Aβ42, Aβ42/β40 ratio, and p-tau are typically reserved for patients with early-onset, progressive, or unexplained mild cognitive decline or with comorbidities that make AD diagnosis unclear [112].

Non-invasive techniques may focus on either the detection of amyloid deposition or neurodegeneration. A Cochrane systematic review from 2020 showed that magnetic resonance imaging (MRI) was not sufficient for early diagnosis of AD [114]. Fluorodeoxyglucose positron emission tomography (FDG-PET) subsequently emerged as a more specific biomarker for early diagnosis of AD, but has the disadvantage that by the time the technique detects hypometabolism, neuronal loss may be too advanced [110,112].

Early biomarkers that theoretically detect the first stages of

the disease, such as tau PET, Aβ PET, or structural MRI (sMRI), sometimes fail to distinguish between atypical phenotypes of AD and other dementias [110].

New processing methods for existing techniques (voxel-based morphometry, deformation-based morphometry [DBM], tensor-based morphometry [TBM], pattern-based morphometry [PBM], data-driven methods) have been developed to improve diagnostic accuracy. Other methods, such as functional MRI (fMRI) and optical coherence tomography (OCT), and other biomarkers, such as synaptic vesicle glycoprotein 2A (SV2A) and receptor for advanced glycation end products (RAGE), are currently being tested [110].

Analytical medicine also plays an important role in the diagnosis of dementia. Novel biomarkers, such as blood-based tests for Aβ, tau, or neurofilaments, are being used in selected populations. However, biomarker concentrations are lower in blood than in CSF, which poses a challenge to their use in clinical practice [112].

The clinical heterogeneity of FTD is also reflected radiologically, making it necessary to combine clinical manifestations with imaging findings [115].

An optimal biomarker is currently lacking. Therefore, improvements in existing methods and a combination of different diagnostic modalities are possible ways to improve early detection of AD and other dementias [110,116]. The combination of neuroimaging and artificial intelligence, through machine learning and deep learning, is also likely to become relevant in the near future [116].

Dementia treatment

Despite extensive and ongoing research in the field, no effective treatment for neurodegenerative diseases has been established. The established approach should always comprise a multidisciplinary assessment, include symptomatic non-pharmacologic and pharmacologic strategies, and focus on improving the patient's quality of life and reducing the burden on caregivers (Table 3 and Figure 4) [117].

Nonpharmacologic interventions	
Music therapy	Receptive/passive music therapy (listening to music); active music therapy (singing, improvising, playing instruments, clapping, dancing); singing a song associated with a memory to promote well-being, socialization, familiarity, and reduce anxiety. Rhythmic auditory cues to improve gait.
Art therapy	Creative activities (crayon or watercolor, coloring familiar objects, or drawing pictures based on memories or favorite seasons).
Aromatherapy	Administration of scented oils (e.g., lavender, lemon balm, orange, or cedar extracts) via diffusion, patches, or skin cream to induce calm and positive effects.
Animal-assisted therapy	Interaction with animals (most commonly with dogs) or feeding, grooming, and dressing the animals, or a more structured therapeutic program; to promote well-being, socialization, emotional support, and sensory stimulation.
Horticultural therapy	Indoor or outdoor gardening, adapted gardening tools; activities include picking seeds, filling containers, planting roots or seeds, touching, watering, organizing containers, cleaning floors, harvesting, cutting and washing; making potpourri, making a flower basket.
Light treatment	Exposure to certain levels of light (outdoor sunlight, light boxes, light visors worn on the head, ceiling lights, or dawn-dusk simulation) to improve circadian rhythms and behavior.
Massage	Tactile or therapeutic touch applied to the back, shoulders, neck, hands, or feet by a qualified massage therapist or trained staff or family members to induce a calm and positive effect.
Cognitive rehabilitation	Cognitive training, cognitive stimulation, cognitive rehabilitation, occupational therapy to adapt to cognitive limitations through compensatory strategies; to support activity engagement; reasoning exercises; compensatory mnemonic techniques such as visual imagery, face-name association, calendars, notes; puzzles, word games.
ADL training	Practicing restorative and compensatory techniques for daily self-care and household activities.
Physical exercise	Practicing moderate-intensity physical activity 3-4 times per week for 30-45 minutes; aerobic exercise (e.g., walking, cycling); resistance training (e.g., arm exercises such as biceps curls, forward shoulder raises, lateral raises using handheld dumbbells, and leg exercises such as sit-to-stand weighted exercises); dance; mind-body exercises (tai chi, yoga, qigong, pilates); virtual reality (stationary cycling or walking systems); fitness-based home video game consoles (e.g., Microsoft Kinect TM, Nintendo Wii Sports TM).

Smarts homes	Labeling drawers and closet doors, visible workstations, providing ADL equipment, eliminating distractions; electronic medication dispensers, electronic orientation clocks, robotic device trackers and motion detectors, door alarms, memory aids, picture button phones, and stove reminder systems.
Pharmacologic interventions	
Anti-dementia agent	Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) N-methyl-D-aspartate receptor antagonists (memantine)
Symptomatic treatment/ Adjuvant drugs	Antidepressants, mood stabilizers, antipsychotics, benzodiazepines (important to avoid polypharmacy)
Other interventions	
Management of comorbidities (management of risk factors for vascular comorbidities)	
Caregiver and community support	
Nutrition and hygiene management	
Palliative and end-of-life care	

Table 3: Nonpharmacologic and pharmacologic strategies for patients with dementia.

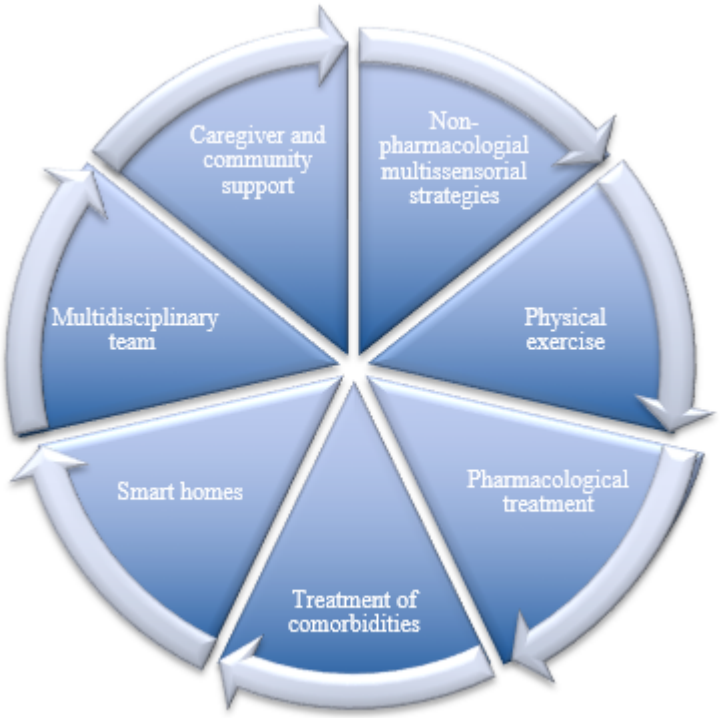


Figure 4: Comprehensive management of dementia.

Non-pharmacological strategies

Several non-pharmacological strategies, such as art programs and sensory activities, have gained attention as potential alternatives to pharmacological treatments, providing opportunities for social interaction, engagement, and connection, and reducing neuropsychiatric symptoms.

A music-based therapeutic intervention includes receptive/passive music therapy, which is based on listening to music (live or recorded), and active music therapy, which involves singing, improvising, or playing with sound-producing objects or musical instruments and may include movements such as hand clapping and dancing [118,119]. A minimum of five sessions of music-based intervention improves anxiety and depressive symptoms and general behavioral problems. It can also improve quality of life, with little or no effect

on cognition [120,121]. Singing can be used to facilitate language reconstruction in people with aphasia. Active music intervention has been shown to improve cognition, behavior, and functional status to a greater extent than receptive music intervention and usual care [122]. Rhythmic auditory cues have also been shown to improve gait, gait freezing, balance, and motor behavior in Parkinson's disease [123,124].

Art therapy involves creative activities and art-making processes (crayon or watercolor painting, coloring familiar objects, or drawing pictures based on memories or favorite seasons) that target cognitive, motor, emotional, and interpersonal skills. There is not enough evidence from randomized controlled trials to draw reliable conclusions about its effectiveness [125,126].

Aromatherapy has been used to treat behavioral and psychological symptoms of dementia, with the goal of reducing disruptive behavior and promoting sleep and well-being. The most used aromatherapy fragrance is lavender, but studies have also used lemon balm, orange, and cedar extracts. It is often delivered through electric diffusers and vaporizers or by skin massage. Although existing studies have several limitations and their conclusions are unclear, aromatherapy appears to be beneficial for people with dementia [127].

Animal-assisted therapy (AAT) is designed to improve physical, social, emotional, or cognitive functioning through social interaction. Animals used in AAT for dementia are most commonly dogs (corgis, retrievers, labradors). A robot and a stuffed animal may also be used. Interventions have included simple interaction with the animal, or more elaborate activities, such as feeding, grooming, and dressing the animals, or a structured therapeutic program to promote motor and social activities. Studies have shown that AAT can modestly reduce depressive symptoms, decrease feelings of loneliness, and improve quality of life [128–130]. AAT may promote more spontaneous communication and greater interaction [129]. Conversely, no clear benefits have been shown on social functioning, behavior, activities of daily living, self-care, or balance [128–130].

Other potential activities include horticultural therapy, massage, and light therapy, but the evidence supporting them is limited [131,132].

Cognitive rehabilitation

Cognitive exercises, including cognitive training, cognitive stimulation, and cognitive rehabilitation, can be effective in improving cognitive performance and executive function in daily living [133–135].

Occupational therapy can improve functional capacity and guide patients in adapting to their cognitive limitations through compensatory strategies. Patients and caregivers can be coached in problem solving, cueing, and simplifying activities, using compensatory strategies, and modifying the environment to support engagement in activities [134,135]. A systematic review provided evidence that people with moderate dementia who received multicomponent occupational therapy at home were better able to perform activities of daily living (ADL) and instrumental ADL, had fewer behavioral and psychological symptoms, and had better quality of life. The effect on depression or anxiety is not clear [134].

Cognitive stimulation, which refers to a range of activities such as puzzles, word games, and indoor gardening, and cognitive rehabilitation through thinking exercises have resulted in less functional deterioration in self-reported AD [135,136].

In a 5-week study, 35 patients with mild AD participated in a memory-based occupational therapy program consisting of five activity categories (physical, horticultural, musical, artistic, and instrumental ADL), while the control group participated in regular day care center activities [133]. The occupational therapy group showed improved cognitive function, reduced depression, and improved quality of life.

A randomized controlled trial (RCT) of 140 subjects with mild cognitive impairment (MCI) applied a cognitive training intervention program that included activities such as seven-piece board recovery training, picture reading memory, reading aloud and reciting sentences (memory), color reaction training and Schulte Grid training (attention), and calculation training, and an improvement in total Montreal Cognitive Assessment (MoCA) score was observed in the intervention group after 6 months of training, indicating that cognitive training is effective and may help reduce cognitive function decline in patients with MCI [137].

Physical exercise

Several exercise interventions have been used in people with dementia, including aerobic exercise (e.g., walking, cycling), resistance training (e.g., arm exercises such as biceps curl, forward shoulder raise, lateral raise using handheld dumbbells, and leg exercises such as sit-to-stand weighted), dance, and mind-body exercises. Physical activity has the potential to improve cognitive outcomes, and moderate- to high-intensity exercise or a multimodal exercise program may lead to significant gains [138–141].

Despite some conflicting results [139], both aerobic and resistance exercise have the potential to improve cognitive function (improving executive function, mental flexibility, and spatial memory performance), physical function, and independent functioning [135,138,140,141]. Exercise improves motor functions such as gait speed, agility, and balance, which are core components of basic ADL (e.g., toileting), and reduces the risk of falls [135,138,142].

The amount and intensity of exercise appear to be more important than the type of activity itself [135,140,141,143]. Moderate intensity exercise 3-4 times per week for 30-45 minutes for more than 12 weeks has been shown to have a positive effect on global cognition [142].

Physical activity improves overall psychological well-being across a range of neuropsychiatric symptoms, reduces symptoms of depression, anxiety and loneliness, and improves mood and life satisfaction [140,141].

Mind-body exercises (tai chi, yoga, health qigong, pilates) that promote skeletal muscle stretching and relaxation, as well as physical coordination and movement control, have been shown to have positive effects on motor function, depressive symptoms, and quality of life in people with Parkinson's disease, and may be beneficial for the well-being of people with MCI or dementia [138,144,145].

Simultaneous or interactive physical and cognitive training (namely stationary cycling with virtual reality tours or walkway systems) improves physical performance, gait, processing speed, executive function, and global cognition and clinical status. Benefits for working and episodic memory are less clear. The use of fitness-based home video game consoles (e.g., Microsoft Kinect TM, Nintendo Wii Sports TM) that provide rehabilitation games may be potentially useful e-health tools [135,146].

A RCT of 87 patients with MCI and AD compared cognitive and physical activity treatments for 6 months. In the cognitive treatment group, participants were trained to practice restorative and compensatory mnemonic techniques such as visual imagery, face-name association, calendar, notes, and prompts, and in the physical activity group, patients performed endurance exercises (cycling on a cycle ergometer, walking on a treadmill, arm cranking on a special ergometer) [147]. Both treatments were successful in slowing the usual decline in cognitive symptoms (as measured by the Mini-Mental State Examination [MMSE]), with positive effects on memory and attention. Benefits persisted at three-month follow-up.

Another RCT of 87 patients with moderate dementia compared ADL training (participants were encouraged to perform as many of their daily self-care and household activities as possible independently), exercise training (alternating strength and aerobic sessions), and combined therapy, and showed that six months of ADL training benefited executive function, physical endurance (walking longer distances), and depression [148]. Exercise training only benefited grip strength. Combined training showed additional benefits on functional mobility, depressive symptoms and agitation, and physical endurance.

Smart homes

The physical environment affects the way people with dementia perform ADL [149]. Simple modifications such as labeling drawers and closet doors, providing visible workstations, providing ADL equipment, removing distractions, cueing, and simplifying processes can help them live more independently. Electronic medication dispensers, electronic orientation clocks, robotic device trackers and motion detectors, door alarms, memory aids, picture dial phones, and stove reminders have the potential to assist patients and their caregivers and can have a positive impact on maintaining relationships, freedom, autonomy, safety, and quality of life. Incorporating assistive technology into dementia care is an ongoing process that should follow and evolve with the different stages of dementia, supporting the independence and care of people living with this disabling condition and helping them live quality lives [150].

Pharmacological strategies

Cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and N-methyl-D-aspartate receptor antagonists (memantine) are the only drugs approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of AD. Both have shown modest efficacy in reducing cognitive and functional decline and improving behavioral symptoms [117]. Cholinesterase inhibitors are recommended as first-line treatment for mild to moderate AD, and memantine for moderate to advanced AD [151]. Cholinesterase inhibitors and memantine are sometimes used in combination to improve efficacy. Rivastigmine is also approved for Parkinson's disease dementia [152]. None of these drugs is effective in FTD [152]. The risk-benefit ratio of cholinesterase inhibitors is still controversial, and tolerability may be poor (side effects possibly including nausea, vomiting, diarrhea, abdominal pain, anorexia, headache, insomnia, muscle spasms, bradycardia, and syncope). Memantine may cause dizziness, headache, constipation, somnolence, hypertension, and agitation [117,153,154].

Polypharmacy

Most patients with dementia have multiple comorbid chronic conditions and are therefore potentially at risk for polypharmacy. Inappropriate polypharmacy has been associated with frailty, increased incidence of falls, and reduced quality of life [117,155]. In particular, increased prescribing of symptomatic treatments for behavioral symptoms (e.g., benzodiazepines, z-drugs, antidepressants, and antipsychotics) is associated with a greater incidence of drug-drug interactions, adverse effects, and increased risk of falls and fractures due to sedation, orthostatic hypotension, and motor disturbances [155]. In addition, certain common medications such as anticholinergics (trihexyphenidyl, biperiden, butylscopolamine, atropine, amitriptyline, clomipramine, antimuscarinics for overactive bladder) have opposite mechanisms of action to cholinesterase inhibitors and may worsen cognition [117,155,156]. Psychotropic medications, including many tricyclic antidepressants (e.g., amitriptyline and imipramine) and other antidepressants (nortriptyline and paroxetine), many first-generation antihistamines, and several antipsychotics (chlorpromazine, perphenazine, olanzapine) should be avoided [117,156].

Novel investigational approaches

Novel therapeutic approaches for dementia are under investigation, which can be divided into seven categories: anti-amyloid therapy, APOE-based therapy, anti-tau therapy, anti-alpha-synuclein therapy, and anti-neuroinflammatory therapy, neuroprotective agents including N-methyl-D-aspartate receptor modulators, brain stimulation, repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS) [157–159].

In AD, the identification of multiple pathological hallmarks present before the onset of clinical symptoms has allowed to target different mechanisms of the disease (based on amyloid, tau, ApoE,

neurotrophins and their receptors, and inflammatory mediators) and to address AD prevention [160]. Research has mainly focused on reducing the amyloid burden through the development of various anti-amyloid biological drugs [161].

An important hallmark in the establishment of the amyloid hypothesis as the main research hypothesis over the last two decades was the identification of mutations in genes associated with early-onset familial forms of AD (accounting for 5-10% of all cases). These genes encode APP, which forms the A**β** peptide, and presenilin (PS) 1 and 2, which participate in the cleavage of A**β** from its immediate precursor. The hypothesis is that extracellular deposition of A**β** activates a cascade of events that includes recruitment and hyperphosphorylation of tau protein, synapse loss, and ultimately neuronal death. Therefore, reducing A**β** and amyloid plaque levels would improve AD symptoms and slow or even halt its progression. Huge investments have been made in the development of amyloid depleting agents, mostly monoclonal antibodies directed against the A**β** peptide in its various stages of aggregation, and a large number of clinical trials have progressed to phase III. Unfortunately, most have not succeeded [157,161,162]. Despite controversy, in 2021 the FDA approved aducanumab (Aβ immunotherapy) for the treatment of prodromal or mild AD patients after it was shown to reduce brain Aβ burden [157]. Recently, an antibody specifically directed against a protofibrillar form of A**β** (lecanemab) showed a moderate ability to slow cognitive decline [163]. However, several doubts have been raised, such as not being given at the optimal time in the course of the disease, not effectively targeting the desired target, or the role of amyloid in improving cognitive decline.

With the growing knowledge of the contribution of neuroinflammation to late-onset AD, there has been increased interest in clinical trials using anti-inflammatory agents in combination with anti-amyloid therapies [164].

Many lessons have been learned from the negative results of previous clinical trials, in particular the irreproducibility of animal models, the need to improve drug penetration into the central nervous system, the need to establish maximally tolerated doses, or the need for more accurate selection of eligible patients [165].

Phosphorilated tau by misfolded hyperphosphorilated tau include the use of induced pluripotent stem cells derived from people with AD (which may provide the conditions for preclinical drug efficacy and safety testing) and optimizing sample representativeness by accompanying clinical diagnosis with biomarkers (amyloid imaging or CSF/blood measures of amyloid and tau or phosphorilated tau). Earlier identification of the biological basis that could predict a favorable clinical response [165] is also an unmet need that should be addressed in the future.

Dementia care and support

Dementia and COVID-19

The lockdown contributed to a worsening of neuropsychiatric symptoms in people with dementia [166]. COVID-19 infection contributed to the decline in cognitive function through direct (vascular damage and neuroinflammation) and indirect (by enhancing other risk factors such as social isolation or mental disorders) mechanisms. The higher the baseline risk for dementia, the greater the long-term impact [167].

The pandemic posed new challenges for health care. Expert recommendations published immediately after the outbreak to address these challenges emphasized the use of electronic media for people at risk or living with dementia [168,169]. Psychoeducational interventions for informal caregivers through digital platforms were also recommended [170,171]. Since then, the paradigm has changed and many dementia care centers routinely adopted technological tools to improve social integration and provide clinical, psychosocial, and rehabilitative treatments [170]. From the patients' perspective, the few available studies show their interest in using telemedicine during this period [172,173].

It is noteworthy that prior to the COVID-19 pandemic, cost was considered a major barrier to the use of digital media in health care [174]. In this regard, COVID-19 was a turning point in reducing barriers to its use.

Challenges in access to care

Dementia requires multidisciplinary care from diagnosis to long-term care to enable people to live at home and be part of their community for as long as possible [175].

However, health and social care systems around the world often do not meet the needs of people with dementia, and the first step in the management of the condition − access to a dementia clinic or specialist − is not guaranteed. This is particularly critical in marginalized populations or those of low socioeconomic status. Some of these communities have a high prevalence and incidence of dementia influenced by potentially modifiable risk factors [176]. Timely diagnosis is difficult due to several factors: poor health literacy, cultural misconceptions about dementia, fear, financial costs, and lack of confidence in primary care teams to diagnose dementia [177]. Implementing the best practice model of care with the inclusion of socially marginalized groups may have the potential to optimize timely detection and improve patient management.

Patients diagnosed with dementia in primary care tend to be older and have poorer cognition, more behavioral symptoms, and more limitations in ADL [178]. This may be because most live alone, have easier access to primary care than to specialty care, and do not have co-resident relatives to mediate access to specialty care [179].

For caregivers, who provide most of the care for people with dementia, barriers to resource use need to be overcome, particularly in low-income settings [177,180]. People with AD or related dementias living in poor communities have fewer specific support resources and receive more hours of monthly care from a family member or other unpaid caregiver than people living in more favorable settings. Most caregivers need more and better information about care and self-care resources in their communities [181]. The inability to leave the person with dementia unsupervised

limits their access to community resources. On the other hand, the stigma associated with memory problems in some communities makes people reluctant to seek care [182]. The attitudes of informal caregivers may depend on their cultural background. Asian Americans are discouraged from seeking help by a strong sense of shame [183]. Latinos tend to misperceive significant memory loss and disorientation as normal features of aging [184]. Other studies describe barriers related to socioeconomic status, language problems, or waiting lists for services [184].

Some beauty salons and barbershops in American cities such as Chicago have been successful in screening for chronic conditions such as hypertension or cancer, particularly in African-American communities, raising the possibility that these types of businesses could support people with dementia and their caregivers as part of a dementia-friendly community strategy [185].

Lack of knowledge and stigmatizing beliefs are identified as the main barriers to seeking help. More active involvement of people with dementia and informal caregivers in the use of services, development of support services, and everyday decision-making related to dementia could overcome these barriers [184].

Quality of care

Management of dementia in the Emergency Department

Dementia often goes unrecognized in the ED because medical communication is difficult in this setting, and therefore the interaction between the healthcare professional and the patient with dementia is often ineffective [186]. This problem is associated with a return to the ED within one month [187]. Evidence shows that patients with dementia are 35-49% more likely to resort to the ED than patients without cognitive impairment [188] and are more than twice as likely to return to the ED within 30 days of a previous visit as older adults without dementia [189]. Ethnic minority, multimorbidity, neuropsychiatric symptoms, and rural residence are directly associated with ED use [190]. Inconsistent information from different health professionals, lack of time, and indifference have been identified as barriers. Staff education, smartphone and tablet resources, care partner training, or asynchronous telephone follow-up could achieve person-centered care [191].

Other ED care practices that could potentially improve outcomes for patients with dementia include comprehensive geriatric and pain assessment, delirium identification, sensory overload reduction, dementia companion, and home-hospital programs [192]. Coordination of medical and community services can prevent unnecessary ED visits. As more people with dementia are seen in primary care settings, caregivers and patients should be informed about community-based resources and support. Outpatient education programs for caregivers and primary care physicians could reduce ED visits and hospitalizations [193].

Hospitalization

The likelihood of hospitalization and length of stay increase with the severity of dementia, with the most common causes of hospitalization being urinary tract disorders, pneumonia, hip fracture, and syncope [194].

Nearly 50% of patients with dementia are not recognized as such when they are admitted to hospital, increasing the risk of developing delirium [195]. Clinical leaders need to address team involvement to integrate dementia care with other care programs and promote communication skills to support patients with dementia throughout their hospital stay. Although palliative care is typically focused on patients with advanced disease, evidence suggests that earlier initiation reduces caregiver burden and improves acute care utilization [196].

Long-term care

Long-term care includes nursing homes, assisted living, residential care, hospice, and home health care [197]. Training new staff in person-centered dementia care, developing systems for collecting and sharing the patient's life history, choices, and preferences, and fostering relationships among people with dementia, staff, and families are some of the recommendations for quality dementia care.

Digital health as a turning point in the continuum of care

Digital health has the potential to revolutionize the diagnosis, treatment, and management of dementia [198]. Digital health technologies, such as mobile health applications, wearable devices, and telemedicine, can provide innovative solutions to the challenges of dementia.

One of the key benefits of digital health technologies for people with dementia is the ability to remotely monitor their health and daily activities. This can enable home monitoring and early intervention, potentially reducing ED visits and hospital admissions, improving person-centered care, and promoting independence [1]. In addition, in the "pre-dementia" stages, sleep disturbances and autonomic dysfunction may be identified by wearable devices as early changes in patients at risk for dementia [199].

The identification and safety of people with dementia who become lost can also be supported by personal identification systems such as iris information, automated facial recognition programs [200], or genomic analysis. However, the biometric data that can be used to personally identify people with dementia must have adequate privacy protections in place for their collection, management, and use.

Telemedicine allows healthcare providers to conduct virtual visits and provide medical and emotional support without the need for in-person visits. Patients, caregivers, and healthcare professionals are generally satisfied with telemedicine, especially in rural areas where long distances to care centers can jeopardize continuity of care. However, not everyone benefits equally from telemedicine. The most vulnerable populations with hearing and vision impairment and advanced stages of dementia, or immigrants who are not fluent or comfortable in the local language, are typically excluded [201]. According to the population that participated in a telemedicine intervention, the main benefits are the provision

of care at home and the avoidance of costly and time-consuming face-to-face consultations, the distressing experience for patients with neuropsychiatric symptoms, and exposure to infections in overcrowded waiting rooms [198].

Telemedicine has also been used to assess dementia, demonstrating the feasibility of remote administration of standard scales and tests to patients and caregivers. Videoconferencing using Zoom, WhatsApp, or FaceTime has been associated with a positive impact on quality of life for older community-dwelling people with dementia and their caregivers compared with telephone conversations alone [202].

Digital health technologies can also provide cognitive stimulation and support for people with dementia. Some mobile health apps offer brain training games or reminiscence therapy, which have the potential to improve memory, attention, and cognitive function.

Nevertheless, WHO emphasizes that digital interventions should complement rather than replace existing services [203].

Conclusion

The increasing number of people with dementia in recent years and the perception of this growing trend have raised awareness of the heterogeneous characteristics of the dementia population. New risk factors are being identified to prevent dementia before its onset. New treatment pathways are being explored following the lack of success of anti-amyloid trials. Meanwhile, non-pharmacological approaches represent potentially useful treatment alternatives. The COVID-19 pandemic has stimulated telemedicine and the development of new treatments.

Epidemiological studies (both cross-sectional and longitudinal) that are representative of the ethnic/racial diversity of the disease and its subtypes are needed and should be regularly updated. The sharing of data from different sources, taking into account data protection measures (through prescription platforms) and different levels of care (from primary care to hospital and long-term care), would help in the development of a dementia registry in Portugal.

Research into prevention, diagnosis, and effective interventions is highly necessary to improve the quality of care, but no research can move forward without funding. In this sense, industry, academia, and public and private organizations should work together to develop research in under-researched areas of dementia, including access to care for marginalized populations and studies in dementias other than Alzheimer's disease.

Abbreviations: AAT - animal-assisted therapy. Aβ – amyloid beta. AD - Alzheimer's disease. ADL - activities of daily living. AF - atrial fibrillation. APOE - apolipoprotein E. APP - amyloid precursor protein. CD - Crohn's disease. CSF - cerebrospinal fluid. CV – cardiovascular. CVH - cardiovascular health. DALYs – Disability Adjusted Life Years. DRG - Dementia Research Group. ED - Emergency Department. FDA - Food and Drug Administration. FDG-PET - fluorodeoxyglucose positron emission tomography. FTD - frontotemporal dementia. HIV - human immunodeficiency virus. LBD - Lewy body disease. LMIC - low- and middle-income countries. LOAD - late-onset Alzheimer's disease. MCI - mild cognitive impairment. MRI - magnetic resonance imaging. NO2 - nitrogen dioxide. PM2,5 - fine ambient particulate matter. PSEN 1/2 – Presenilin 1/2. PT - physical activity. RCT - randomized controlled trial. rTMS- repetitive transcranial magnetic stimulation. SBP - systolic blood pressure. sMRI - structural magnetic resonance imaging. tDCS - transcranial direct current stimulation. TBI - traumatic brain injury. UC - ulcerative colitis. UK - United Kingdom. VaD - vascular dementia. WHO - World Health Organization

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