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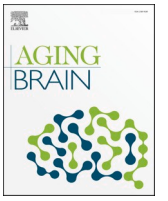

Rethinking the detection and diagnosis of Alzheimer's disease: Outcomes of a European Brain Council project

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ABSTRACT

Alzheimer's disease (AD), the most common form of dementia, is a progressive and debilitating neurodegenerative condition which robs people of their memory, their independence, their relationships and, ultimately, their lives. It affects close to 7 million people in the European Union (EU) alone.

The detection and diagnosis of AD relies on a system that remains focused on the late stage of the disease, despite a better understanding of the disease progression. Clinical practice and healthcare systems' readiness to detect, diagnose and treat the disease effectively are still lagging. The use of biomarkers (cerebrospinal fluid tests (CSF) and positron emission tomography scans (PET)), which are central to a diagnostic assessment for people with AD symptoms, as well as relevant diagnostic facilities are under-utilised. PET imaging is expensive and of limited availability, and CSF sampling may be considered invasive.

The European Brain Council's 'Rethinking Alzheimer's disease: Detection and diagnosis' White Paper has looked at the barriers to early diagnosis and how the healthcare systems infrastructure for detection and diagnosis of AD need to be transformed in order for people with AD to benefit from innovative solutions once they become approved for use.

Introduction

Today, we know that Alzheimer's disease (AD) is a continuum, consisting of an "at-risk phase" (pre-clinical stage – defined by AD biomarker positivity in asymptomatic individuals), a "Mild Cognitive Impairment (MCI) due to AD" or prodromal phase, and "dementia", which can be further classified in mild, moderate or severe (Fig. 1) [1–2]. AD contributes to 60–70% of dementia cases worldwide [3]. European estimates show 6.9 million people presenting with AD, 15 million with MCI, and 52 million with preclinical AD, together constituting 25% of all Europeans aged 50 and above [4].

Globally, AD represents a huge burden for the economy and nations' healthcare and social care systems [5–6]. The societal and economic cost of dementia in Europe is high and expected to increase in the years to come. AD falls inequitably on women, who are not only at greater risk of developing AD than men, but are also more likely to act as caregivers [7].

It is estimated that 75% of worldwide dementia cases today are undiagnosed [4]. Dementia, especially in its early stages, remains under-detected, under-diagnosed, under-disclosed, and under-managed [8]. The diagnosis of AD is a combination of both cognitive

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tests and pathophysiological tests. Historically, the diagnosis and treatment of AD focused on clinical symptoms. Today, the in-vivo biomarkers measured by CSF analysis or PET that are used at specialised and tertiary care to determine the core pathophysiological alterations that characterise AD across its preclinical and prodromal phases are under-utilised [9].

While blood-based biomarkers (BBBs) are in development and hold significant potential to support earlier detection of AD, they are still not available at scale. In the future, BBBs could have two triage roles. One would be a 'rule out' role, in primary care to determine patients' probability of having AD who should then be referred to secondary settings for more advanced biomarker-based investigations such as CSF or PET [10]. When BBBs can demonstrate an accuracy similar to already existing tools (CSF and PET), they could rather have a 'rule in' role where they would replace CSF and PET and refer people with AD to treatment.

Clinical practice and healthcare systems' readiness to detect, diagnose and treat the disease effectively are still inadequate.

Given the above, the European Brain Council (EBC) recently launched its Rethinking Alzheimer's disease White Paper: Detection and Diagnosis,[11] the key points of which are presented here.

Material and methods

Based on a sample of five EU countries (Czech Republic, Germany, Italy, the Netherlands and Sweden), EBC has examined the barriers to early detection and the challenges that need to be overcome to ensure health care systems are appropriately equipped to provide timely and accurate diagnosis to those who may benefit most from new diagnostic tools and therapies.

To develop this project, EBC focused on the identification of the barriers to early detection (at a pre-clinical stage, where it is believed that a therapeutic intervention could potentially halt or slow disease progression overall). EBC organised interviews with experts from different countries, including the project's selected 5 EU countries (Box 1), conducted an online survey and organised a webinar to gather expertise and propose policy recommendations.

To assess the impact of early detection and timely, accurate diagnosis of AD, the project has made a health-economic evaluation of the implementation of BBB tests in combination with cognitive tests to improve triaging at the primary care level, compared to a 'usual' care scenario where only cognitive tests are used. The model estimated both the short-term impact on the cost of the diagnostic process (net annual savings) and the long-term costs and benefits – expressed in quality-adjusted life years (QALYs) - over a predicted time horizon of care needs of 20 years, using the Swedish healthcare setting as an example. The analysis was performed with a societal perspective.

The model used a Markov framework with a 1-year cycle time. It simulated the journey of patients seeking evaluation for subjective memory complaints. The model had two interacting layers. The first layer captured a patient's journey through different evaluation stages (cognitive and/or blood-based biomarker testing by a primary care clinician and confirmatory specialist evaluation using biomarker CSF testing at secondary care) depending on the true health states (Cognitively normal, MCI due to AD, MCI due to other causes). Similar to previously published model-based analyses of AD, the second layer modelled the disease progression across 3 disease states (Mild-AD, Moderate-AD, Severe-AD) and the location of care (Community Care or long-term care facility).

The first layer used sensitivity and specificity of the assessment tests to calculate the transition probabilities between assessment states and the second layer. The second layer was guided by disease progression, treatment discontinuation, and re-initiation rates. Each year, patients could die, progress or regress in terms of disease severity, discontinue or reinitiate treatment, transition from living in the community to living in a long-term care facility, or stay in the same health state. In the model, patients living in a long-term care facility could not return to living in community care. As treatment options for patients with AD diagnosis, the model considered Donepezil for Mild- and Moderate-AD and Memantine for Severe-AD. The model was informed using data from literature, and assumptions were made when data were not available.

The barriers to early detection and diagnosis

Across the EU and indeed globally, the journey to receiving a diagnosis of AD is still complex and plagued by a number of barriers with healthcare systems ill-equipped to detect AD. The diagnosis of dementia is all too often made late, when the symptoms are already far advanced [8]. In the EU, the overall mean length of time between problems being noticed and the diagnosis being made can be up to 2.1 years (1.6 years in Italy and the Czech Republic and 2.6 years in the Netherlands) [12].

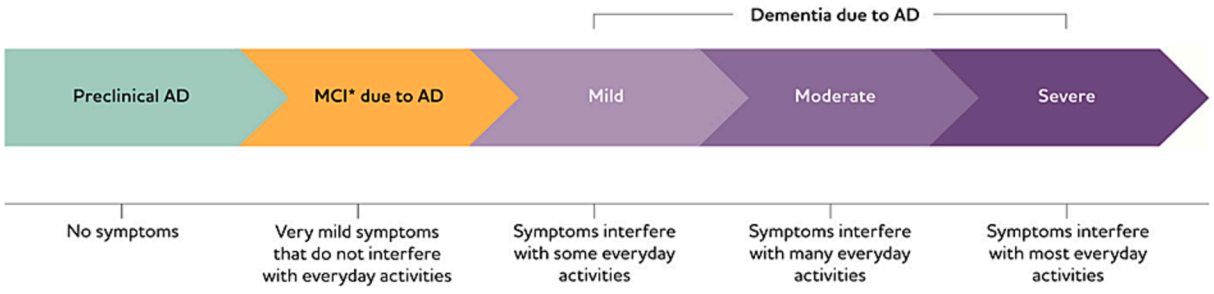

Fig. 1. Alzheimer's Disease Continuum (Alzheimer's disease facts and figures. Alzheimer's Dementia, 2020) [2].

Box 1
: list of experts, affiliations and countries.

Experts representation

Country	Affiliation	Job position	Name
Czech Republic	Masaryk University	Assistant Professor	Lenka Krajčovičová
Denmark	European Academy of Neurology	Co-chair, EAN Scientific Panel Dementia and Cognitive Disorders	Kristian Steen Frederiksen
Netherlands	Alzheimer Nederland	Scientific Director	Marco Blom
	Vrije Universiteit Amsterdam	Health Economist	Hana Marie Broulíková
	Alzheimer Center Amsterdam	Scientific Director	Wiesje van der Flier
	EQT Life Sciences	Head Dementia Fund	Philip Scheltens
	Amsterdam UMC	Professor in Neurochemistry, Chair of the Neurochemistry lab	Charlotte Teunissen
Germany	Central Institute for Mental Health	Head of the Department of Geriatric Psychiatry	Lutz Froelich
	German Alzheimer's Association	Managing Director	Saskia Weiß
Ireland	Irish Dementia Working Group	Vice Chair	Helen Rochford-Brennan
Italy	University of Geneva	Full Professor of Clinical Neuroscience	Giovanni B. Frisoni
	University of Perugia	Full Professor of Neurology	Lucilla Parnetti
Sweden	Lund University	Full Professor of Neurology, Lund University	Oskar Hansson
	Karolinska Insitutet	Professor of Health Economics	Linus Jönsson
Switzerland	Women's Brain Project	Scientific Director	Maria Teresa Ferretti

Stigma and misconceptions about AD

Stigma is a primary barrier to timely diagnosis and care [13]. While we now have normalised conversations about health issues such as diabetes or blood pressure, there is still huge stigma when it comes to talking about brain disorders, including dementia.

Awareness campaigns are instrumental in raising awareness and reducing stigma. Nevertheless, very few countries run such campaigns that provide information about the signs and symptoms of AD. When they do, these campaigns are not commensurate with needs [13].

At primary care level, the entry point to diagnosis, a barrier exists due to some primary care practitioners' misconceptions about AD. Globally, almost 62% of healthcare providers think that dementia is part of normal ageing [14]. Many general practitioners (GPs) do not receive enough training about AD and other dementias to facilitate diagnosis, identify early symptoms, and differentiate these symptoms from other disorders [13]. Consequently, they have difficulty recognising the early symptoms of dementia or tend to overlook their importance, lack confidence in their ability to detect dementia, particularly in its early stages. They also feel uninformed about available support services for the person living with AD and their care-givers [8]. Some GPs are reluctant to refer symptomatic people for formal diagnosis with a specialist out of concern that the lack of a disease modifying treatment (DMT) negates the value of diagnosis —so called "therapeutic nihilism" [15].

GPs currently deal with patients presenting with a number of diseases that need to be diagnosed early (cardiovascular diseases, diabetes…). Carrying out initial cognitive testing may be difficult to fit into the usual 10–15-minute GP visit. This results in primary care clinicians not developing or maintaining necessary skills and workflows for evaluation of memory complaints, resulting in a vicious cycle of underdiagnosis [15].

Structural barriers

Currently, when a GP or family physician assesses cognitive complaints of the patient using cognitive tests, the next step is usually to refer the person to a dementia specialist. It can be a neurologist, psychiatrist or geriatrician who will run confirmatory neurocognitive testing and determine the aetiology of the disease, ideally after ruling out possibly reversible causes like substance use, depression, and detecting possible structural causes such as a past stroke [15]. In people with confirmed cognitive decline, biomarker testing will increase the certainty/accuracy of the diagnosis of AD [15].

Despite being the entry point for most people living with AD, GPs lack access to the diagnostic tools required to make an initial diagnosis and competency to use them. They still use basic screening tools, which have high false (positive and negative) rates [12]. Those who already have access to basic screening tools may lack access to the more advanced diagnostics needed to move persons along the diagnostic pathway [13].

The diagnostic infrastructure varies among the 5 EU countries studied in the Paper. The ratio of GPs to the general population is inadequate, placing GPs under great stress [13]. In the EU, the specialists involved in diagnosing cognitive impairment and dementia vary in each country. For instance, in Sweden, geriatricians and psychiatrists are involved in diagnosis (rather than neurologists) [16]. In Germany and Sweden, approximately 60% of psychiatrists would be involved in formal diagnosis of MCI due to AD, whereas the remaining 40% primarily practice psychotherapy [9].

The availability of the dementia specialist workforce to see people with MCI in the diagnostic phase depends on the capacity of each specialist to conduct the evaluations [16]. Referral to a specialist who is crucial in making a formal diagnosis can take as long as three years due to a lack of available specialists. Several countries face chronic shortages of geriatricians, neurologists, psychiatrists, and other experts [13–16]. The shortage of specialists is expected to worsen with the increase of ageing populations [16]. Country-specific workforce projections by specialty are scarce in publicly available reports, and those available are limited to certain geographies, exhibiting different trends by specialties, and showing uncertainty in the projections [16].

The EU 2020 Annual Report on shortage and surplus occupations show high magnitude medical workforce shortages for nursing professionals, GPs, health care assistants and associate professional nurses, as well as medical specialised practitioners. Denmark, Estonia, Finland, Luxembourg, the Netherlands, Norway, Romania, Slovenia and Spain reported health professional shortages [17].

There are also differences between countries regarding the diagnostic infrastructure and the availability of biomarkers. The currently available diagnostic facilities and tools are often not used to their potential or insufficient. In 2020, PET scanners were generally the least available and used across the EU [18]. Relative to population size, all EU Member States (besides Denmark) present ratios of 0.5 units per 100,000 inhabitants or less (0.8 for Denmark) [19].

Provider payment methods and levels of co-payments have an impact on the number of medical consultations. In the countries where doctors are paid predominantly by fee-for-service (as in Germany), there are higher consultation rates than those countries where doctors are mainly paid by salaries or capitation (as in Sweden). In these latter countries, patient co-payments are high for a large proportion of the population, which may result in individuals not consulting a doctor or delaying seeing a doctor because of the cost of care [20].

The number and type of doctor consultations can vary among different socio-economic groups. Wealthier individuals are more likely to see a doctor than individuals in the lowest income quintile, for a comparable level of need. Income inequalities in accessing doctors are much more marked for specialists than for GPs [13].

Cross-roads in the earlier detection and diagnosis of AD

The re-conceptualisation of AD as a clinical and biological construct and the development of biomarker-guided targeted therapies

call for a next-generation global framework of clinical care pathways for individuals with AD. As PET imaging is expensive and of limited availability, and CSF sampling may be considered invasive, on-going research into DMTs and the rapidly advancing development of BBBs for AD promises improved early detection of AD, given the broad availability, scalability and cost-effectiveness of blood tests globally [9]. Under this framework, new clinical pathways – which may differ by country and clinical context – must enable early detection and timely, accurate, and effective diagnosis at the early stages of MCI due to AD and mild AD dementia (Fig. 2).

Delays in detection and diagnosis of AD can lead to irreversible worsening of the disease. The future detection and diagnostic pathway should focus on the pre-dementia stage, where people living with AD, as well as primary care practitioners, will be on the first line to detect AD in a timely manner. In the future, besides carrying out cognitive tests, the primary care practitioner would ideally be able to use BBBs with increased accuracy. They would constitute a first line for primary care practitioners to decide to refer or not to refer to a second line memory clinic or specialised centre for confirmation ('triage role'). Using BBBs at the GP level may also be

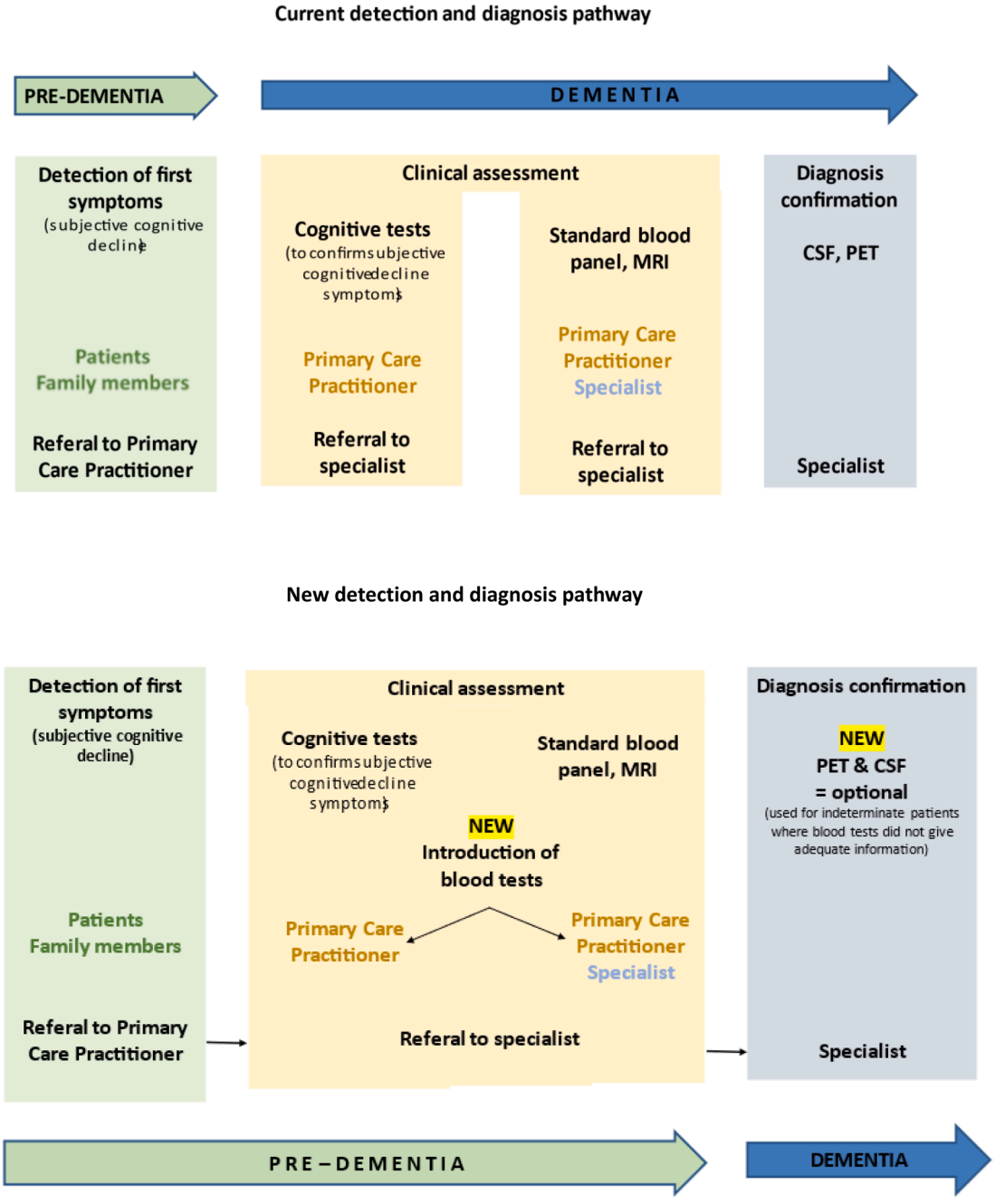

Fig. 2. Current and new detection and diagnosis pathways.

interesting to exclude AD and help GPs to concentrate on other causes for the condition. This will change the primary care practitioner's role and call for a healthcare system transformation where new opportunities for valuable prevention and risk reduction behaviours will become more salient, for which access to more accurate diagnostic tools will be pivotal (Fig. 2).

The introduction of BBB testing alongside medical history, physical exams, and a range of neurological and neuropsychological tests of mental function (both at GP and specialist level) will only achieve their transformative potential if health systems can overcome infrastructure and economic barriers [21].

The value of rethinking the AD detection and diagnosis pathway

The EBC White Paper studied the health-economic effects of the implementation of BBB tests in combination with cognitive tests, to improve triaging at the primary care level, compared to a 'usual' care scenario where only cognitive tests were used. Using the Swedish healthcare setting as an example, the short-term impact on the cost of the detection and diagnostic process, and the relative balance of benefits and costs over a predicted 20-year time horizon of care needs were studied (Fig. 3).

This preliminary analysis showed that the use of BBB tests in combination with cognitive assessment in primary care can improve the efficiency of the evaluation process, increasing the number of correctly identified cases (i.e., patients with MCI due to AD) thereby reducing the number of 'unnecessary' (i.e., patients with no AD) referrals for more expensive (PET) or invasive (CSF) specialist evaluations. The improved triage is estimated to reduce specialist evaluations from 36% to 14% with an annual net cost saving of about EUR 4 million.[1,2] Furthermore, providing BBB tests in combination with cognitive assessment in primary care would also help to improve the detection of people with a possible early stage of AD, allowing them to receive a timely diagnosis and access to the care pathway. Even considering currently available symptomatic treatment options, the resulting benefits equate to an increase of Quality Adjusted Life Years (QALYs) of 0.033, and a reduction of health and social care costs of EUR 1,062 per people living with AD (Net Present Value) over a 20-year time horizon.

The analysis suggests that a combination of a cognitive screening test and BBB tests have the potential to improve the efficiency of AD diagnostic process and access to treatment. It also shows that early diagnosis and access to current symptomatic treatment options can improve individuals' outcomes and reduce costs.

With the introduction of upcoming DMTs, BBB tests (or equivalent diagnostic tools that can be implemented at primary care level) can become a more important solution for reducing obstacles to access, and have an even greater impact on costs and patient outcomes.

Overall, improvements in the efficiency of the AD detection process at primary care level can reduce the overall burden on the healthcare system and ensure timely access to treatment in a potentially cost-saving way.

Gender: Moving towards a more precise diagnosis

There is a gender and health equity dimension when talking about early diagnosis and early treatment of AD. Approximately two-thirds of people with AD are women, and the lifetime risk of dementia is higher in women [22]. AD diagnosis is often missed in women or occurs at an advanced pathological stage. Arguably or inferentially the incidence of MCI may also be higher in women than is appreciated. This is partly due to sex differences in neuropsychological tests, which rely heavily on verbal memory, and where women perform on average better than men, irrespective of AD pathology [22].

Considering sex (biological) and gender (socio-economic) differences is crucial in the development of detection and diagnosis solutions. In addition to biological differences, MCI is often overlooked in women as gender stereotypes tend to steer diagnosis towards depression rather than MCI due to AD. This highlights the importance of a timely diagnosis as well as of an early understanding and management of risk factors in women [22].

Both sex and gender can influence access to healthcare and accurate diagnosis of AD. They play a role not only with regards to prevalence and incidence of the disease, but also in terms of risk factors, biomarkers, symptoms onset and symptoms characteristic. The use of biomarkers has the potential to overcome gender biases and leverage sex differences for a more precise diagnosis. These differences are particularly relevant in the individual's diagnostic pathway and care journey, as among others, the prognostic and diagnostic value of biomarkers may be different between men and women. There is growing evidence that the levels of several currently used biomarkers differ between men and women. Adjusting the cut-offs based on sex-specific considerations can assist in detecting approximately 20% more women who missed out an MCI diagnosis [22].

In the future, when hopefully BBBs are used to detect at-risk individuals, it will be important to also consider sex-related aspects in the application of such biomarkers. To enable precision medicine, multidimensional data needs to be analysed and interpreted via predictive algorithms. In this context, sex and gender are crucial factors affecting the overall predictive power of clinical models. Indeed, it has been shown that including sex in predictive algorithms improves their efficiency [22].

There is still insufficient awareness of sex and gender influence on the diagnostic journey by the medical community and society overall. Considering sex- and gender-specific factors is a key step to improve access to and precision of diagnosis of AD, especially

[1] Details of the economic evaluation are available here: https://www.braincouncil.eu/wp-content/uploads/2023/03/RETHINKING-Alzheimers-Disease-Technical-Report-Final-2.pdf.

[2] This is estimate considering the current MCI incidence in the Swedish population above 55 years. With the introduction of upcoming DMT, it is expected that a larger number of people in that age range without MCI will seek assessment at primary care. In that case the projected net cost saving can go up to EUR 185 million.

during early stages. A paradigm shift towards precision neurology will optimise the diagnostic pathway and the individual's medical journey [22].

Scaling-up the readiness of health systems

The most urgent actions required are to foster an increased general awareness of the population about AD, improve professional education, and reduce stigma. This must be accompanied by a transformation of healthcare systems, where primary care professionals play a greater role. The infrastructure for detection and diagnosis must also be improved by matching healthcare workforce and services, by greater adoption and availability of biomarkers, their access to biomarkers and by an increase in the number of specialists. The potential benefits of moving towards a more coordinated care management approach involving all strands of disciplines relevant to AD must also be considered.

Enhancing the role of GPs

Ideally, GPs can play a greater role in the detection of BBBs and diagnosis of AD in the future. GPs would need to be better educated about AD and trained to be less apprehensive about a shift in care (Fig. 2). The WHO has identified a set of actions to strengthen the

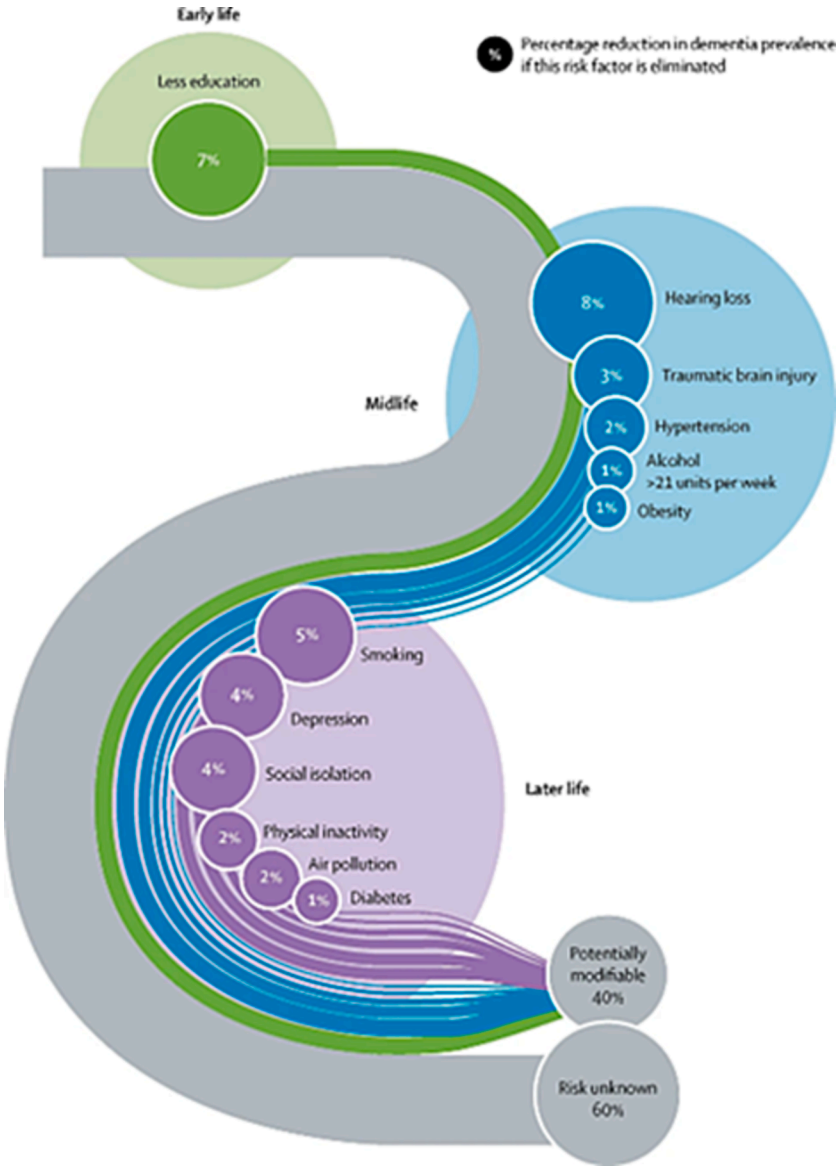

Fig. 3. Population attributable fraction of potentially modifiable risk factors for dementia [25] Adjusting the healthcare workforce and services.

health and care workforce. They include: aligning education with population needs and health service requirements, strengthening continuing professional development to equip the workforce with new knowledge and competencies, increasing public investment in workforce education, development and protection, and optimising the use of funds through innovative workforce policies [23].

Looking at how to increasingly involve primary care practitioners in the early detection of AD without overwhelming them, it is worthwhile to build on the current practices. Today, GPs deal with patients presenting with risk factors for AD (cardiovascular diseases, diabetes, etc.) that are routinely monitored. The same could be done with AD, with GPs managing co-morbidities and leading individuals to engage in dementia-associated risk factors prevention.

Early detection and diagnosis of AD can have repercussions on disease prevention giving the primary care practitioner a key role in raising awareness about the risk factors associated with AD. Evidence has identified 12 potentially modifiable risk factors for dementia: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution. Together these 12 modifiable risk factors account for around 40% of cases of worldwide dementias, which could theoretically be prevented or delayed. Evidence has also shown that it is never too early and never too late in the life course for dementia prevention [24]. This calls for a healthcare system transformation where new opportunities for valuable prevention and risk reduction behaviours will become more salient.

National healthcare systems are faced with a number of challenges that need to be adjusted to embrace innovation and improve individuals' quality of life. Proper health workforce planning and education is utmost required to ensure professionals are up-to-date with scientific developments, and a sufficient number of GPs and specialists are able to triage individuals who may need to be directed to confirmatory testing.

To match the enhanced role of GPs', the ageing of the medical workforce also needs to be addressed. Some countries have seen a rapid ageing of their medical workforce over the past two decades. Italy is the most striking example with the share of doctors aged 55 and over increasing from about 20% in 2000 to 56% in 2019 [25]. The highest proportion of younger physicians (under 35 years) can be seen in the Netherlands (31.4 %) [26]. At the same time, changes in retirement patterns of doctors can be seen with many possibly continuing to practise beyond age 65, full time or part time, if the working conditions are adequate and if pension systems do not provide a disincentive for them to do so [26].

At national level, high concentration of doctors and specialised services can be seen in the regions of the capitals. This is particularly the case in the Czech Republic and Germany [27]. Generally, there is a perceived shortage of specialists, which is expected to worsen with the ageing populations. For instance, in Germany, the number of neurologists is predicted to remain relatively stable through 2030, with fluctuation of $\pm$ 3% between 2014 and 2030 [4]. Without a growth in the number of neurologists, the healthcare service will be inadequately prepared to adapt to the need to diagnose an increased number of people presenting MCI. The COVID-19 pandemic's toll on countries' healthcare workforce is continuing at a time of acute economic crisis. Personnel shortages, insufficient recruitment and retention, migration of qualified workers, unattractive working conditions, and poor access to continuing professional development opportunities are blighting the healthcare systems [24].

Further, there is inadequate data and limited analytical capacity, poor governance and management, lack of strategic planning, and insufficient investment in developing the workforce [20]. Very few countries report on healthcare workforces by urban/rural, hospital/primary healthcare and public/private distribution. Publicly available workforce projections are limited to certain geographies, exhibiting different trends by specialties, and showing uncertainty in the projections [20].

Improving healthcare system infrastructure

Some studies have warned that the existing healthcare systems are currently ill prepared: based on the hypothesis that a DMT becomes available, the current infrastructure to handle the potential caseload of MCI detection would lead to long waiting times for initial dementia specialist visits, followed by considerable waits for confirmatory biomarker testing. Delays like these could result in more than 1 million people progressing further along the AD spectrum while waiting for evaluation and treatment between 2020 and 2025 [4]. This missed opportunity to improve the person's quality of life can increase both the direct and indirect costs that are incurred at an advanced stage, and must be avoided. Ensuring scientific discovery into meaningful impacts requires health systems to strategically prepare for innovation and integration of new interventions [27].

Assessment tools typically used in clinical practice currently focus on measuring cognitive and functional decline over time, and are therefore less effective in the initial stages of the disease, when cognitive symptoms are subtle and functional impairment not yet evident [28]. The introduction of BBB testing (both at GP and specialist level) will only achieve their transformative potential if health systems can overcome infrastructure and economic barriers [21].

Current memory clinics do not have the programs and protocols in place to deal with the increasing number of individuals with normal cognitive performance who ask for an evaluation of their dementia risk, preventive interventions, or interventions to ameliorate their cognitive performance. This new health demand requires a shift in attention from people with cognitive impairment to worried (but cognitively unimpaired) individuals. The answer to this challenge could be the development of new services offering a precision medicine approach, 'Brain Health Services', devoted to responding to demands from cognitively unimpaired individuals concerned about their risk of dementia. The Brain Health Services model would help address dementia risk profiling, dementia risk communication, dementia risk reduction, and cognitive enhancement [29].

Moving towards a more coordinated care management approach

A more coordinated care management approach that provides intensive dementia specific services in primary care seems to offer

the most promising results [9]. An example of an innovation in this field is the creation of interdisciplinary memory clinics within primary care settings. The emerging evidence points to the potential benefits of these programs in building capacity within primary care, while improving the efficacy of the use of specialist expertise. More research is needed to evaluate cost-effectiveness, feasibility and long-term sustainability of these innovations, and to test their replicability in primary care practices [9].

Besides GPs, other professionals will have a role in identifying individuals with MCI or presenting with physical abnormalities that may point to increased risk for AD, namely, community nurses, diabetologists, cardiologists, ophthalmologists, gynaecologists. In the Czech Republic, for instance, pharmacies are increasingly engaged in the diagnostic process. People are used to going to pharmacies and often feel more comfortable and less stressed than in a doctor's practice. Pharmacists are effectively used to communicate with the ageing population. Additionally, in the Czech Republic, ČALS (the Czech National Alzheimer's Association) provides free testing and advertises this service through annual media and radio campaigns. Many people who believe that their GP's test was inaccurate, or that their GP did not investigate further, often seek out this free testing service.

Deploying registries

Patient registries and databases are key elements to develop clinical research, to improve AD care and healthcare planning. The AD data landscape remains fragmented in most countries. There is a large gap in data consolidation, with countries struggling to establish or develop systems to collect data across the care pathway (diagnosis, treatment, management). Regional variations, lack of coordination between levels of government, and absence of accurate standards make it challenging to gather a clear disease snapshot in each country. To address this gap, several countries are undertaking efforts to help streamline data collection related to AD and other dementias. This is the case in Sweden with the SveDem being used to collect and provide access to national dementia data while aiming to improve data robustness and breadth [13].

Timely clinical and accurate pathological diagnosis offers individuals the opportunity to participate in clinical trials and help both them and their families plan for the future. Registries are also vital to assess the feasibility of clinical trials, to facilitate the planning of appropriate clinical trials, and to help support the enrolment of people living with ADs. Eighty percent of clinical studies are delayed because too few people sign-up to participate [30]. Trials matching services exist: several Alzheimer associations have developed initiatives where volunteers register their interest in participating in trials and are matched with studies that are recruiting participants [31].

Setting-up a pan-national AD registry would allow for a standardised set of statistics that would be an instrument for each country to regularly report on an epidemiological surveillance of AD.

Implementing national dementia plans

Most of the existing national dementia plans have a segment devoted to diagnosis, but few include a specific target for diagnosis rates or collect information about the number of newly diagnosed people with dementia [22]. National dementia plans, when they exist, still do not adequately address the early detection and timely diagnosis of AD and tend to place more focus on support after a diagnosis is made.

To match the current innovation context, future dementia plans that will be developed at national level will need to include provisions for the early detection and diagnosis of AD. To make this possible, awareness-raising efforts about the value of innovation in this respect actively supported by those directly concerned (people living with AD, their families and healthcare professionals), will be important.

Dementia strategies must also be flexible and include a mechanism allowing the additions of new provisions or taking stock of new evidence. In the Czech Republic, there is a regular monitoring of the implementation of the plan with a ministerial stakeholder platform. This is pivotal to ensure that scientific discovery brings meaningful impacts to people living with AD and the adaptation of the health systems to strategically prepare for innovation and integration of new interventions. Securing full funding for the implementation of national plans remains a challenge in many countries. Countries must move beyond developing plans to secure funding for implementation [13].

Reaching a consensus on real-world application of innovation

More research needs to be done on the real-world application of innovation. While an accessible, early, accurate diagnosis provides value in its own right, achieving consensus on the widespread and real-world application of BBBs is a pressing issue in light of emerging DMTs.

Opportunities for action and collaboration call for the emerging detection and diagnosis modalities to be sufficiently robust; a compelling framework for reimbursement and rational, equitable access, accounting for both the value of accurate diagnosis today and when expected DMTs are more readily available; and through the identification and sharing of real-world lessons and best practices to accelerate use in clinical practice [21].

The International Working Group on the clinical diagnosis of AD has proposed recommendations for how biomarkers should and should not be used for diagnosing AD in a clinical setting. They have, in particular, made recommendations for the use in clinical practice of blood biomarkers for amyloid β and tau pathology [32]. Their recommendations match the project's workshops experts' views that blood biomarkers require further standardisation and validation before they can be broadly regarded as secure evidence of AD pathology [33].

Promoting the importance of communication

Within the lay community, AD is among the most feared diseases, given its outcomes. Disclosing biomarker results and the related risk profile to people living with ADs should be seen as different from the disclosure of disease diagnosis. There is a big difference in the use and understanding of the term: for physicians, AD equates with neuropathological changes associated with varying degrees of disease manifestation, whereas for people living with ADs, AD equates with dementia, dependency, and death. In the future, being said to be at-risk for progression, instead of in the preclinical stage of AD, might help in discussions with people living with AD regarding the risk–benefit balance of a putative treatment and its side-effects [21]. The European Academy of Neurology and the European Alzheimer's Disease Consortium have issued a position statement on diagnostic disclosure, biomarker counselling, and management of people with MCI [33]. Alzheimer Europe has published a Position Paper on the disclosure of diagnosis [34]. A European consensus for the diagnosis of MCI and mild dementia is in its preparatory phase [35].

Conclusions

It is more than ever urgent to recognise the magnitude and socio-medical implications of AD. There is a strong need to support the creation of a new environment that will recognise the benefits of early detection of AD; improve local, regional and national access to already available and essential biomarker-based confirmatory diagnostic tests; develop guidelines for the standardised adoption and, implement of advanced diagnostic tools in clinical practice.

The Paper's set of recommendations calls on policymakers to drive national, EU and international policies that can improve the lives of people living with AD, and ensure health systems are better prepared to support early detection and diagnosis now, and when future innovative detection and diagnostic tools and therapies become available.

Cooperation and knowledge-sharing are key. By addressing the plurality of skills needed to detect and diagnose AD, and by learning from evidence-based data to improve healthcare systems, the Innovative Health Initiative, a public/private partnership involving several sectors of industry, has the potential to support Member States' healthcare systems and their readiness to embrace innovation. EU financial and regulatory instruments (Horizon Europe, Cohesion Funds and EU Recovery Plan, Pharmaceutical legislation, European Health Data Space) can help improve early detection and diagnosis of AD. Let's also build on the learnings from the achievements reached during the COVID-19 pandemic and from the EU Beating Cancer Plan.

And, last but not least, let's put the patients at the centre and hear their voice. Having received an early diagnosis has enabled some of them to become an advocate for those living with AD, to ensure their voice is heard and that they are involved. They have the experience. It is important that law makers understand and act upon their needs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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