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Review Article

The MOPEAD project: Advancing patient engagement for the detection of "hidden" undiagnosed cases of Alzheimer's disease in the community

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Abstract In most, if not all health systems, dementia is underdiagnosed, and when diagnosis occurs, it is typically at a relatively late stage in the disease process despite mounting evidence showing that a timely diagnosis would result in numerous benefits for patients, families, and society. Moving toward

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earlier diagnoses in Alzheimer's disease (AD) requires a conscientious and collective effort to implement a global strategy addressing the multiple causes hindering patient engagement at different levels of society. This article describes the design of the Models of Patient Engagement for Alzheimer's Disease project, an ongoing EU-funded public-private multinational initiative that will compare four innovative patient engagement strategies across five European countries regarding their ability to identify individuals with prodromal AD and mild AD dementia, which are "hidden" in their communities and traditionally not found in the typical memory clinic setting. The strategies include an online AD citizen science platform, an open house initiative at the memory clinics, and patient engagement at primary care and diabetologist clinics.

Keywords: Alzheimer's disease; Early diagnosis; Diagnostic gap; Patient engagement; Population-based screening; Citizen science

1. Introduction

The prevalence of dementia is rapidly increasing in developed countries because of social and demographic changes. This trend is expected to worsen in the coming decades, with the number of cases possibly even tripling in the next 25 years [1]. The associated economic and social costs of this progression are posing a threat to public health. The 2015 World Alzheimer Report estimates that costs derived from dementia care have increased from 604 billion in 2010 to 818 billion US$ in 2015 [1,2]. The possibility of an upcoming dementia pandemic has gained increased recognition over the years with the World Health Organization and various national governments, making dementia management and prevention a global health priority and drawing plans that increase funding and define strategies to defeat Alzheimer's disease (AD) [3–5].

However, a crucial, and often overlooked, facet of this problem is that a significant proportion of people with cognitive decline remain undiagnosed or "hidden" in their communities. Our knowledge of the pathophysiological process leading to AD dementia has increased significantly in the last decades. Today, we are aware that the first pathological changes of AD begin many years before the onset of the clinical symptoms and that this is probably the best stage to modify the disease progression [6]. We also have sufficient evidence that early diagnosis leads to important benefits. Nevertheless, it is clear that in most, if not all health systems, dementia is underdiagnosed, and when diagnosis occurs, it is typically at a relatively late stage in the disease process [7]. Studies conducted over the last 10 years in high-income countries show that less than one-half of cases of dementia are routinely recognized and documented in primary care case note records [8,9]. These figures are even more disturbing when considering institutionalized people [10] or inhabitants of developing countries [11].

The causes of underdiagnosis are complex, involving various factors operating at different levels of society including the general public, medical professionals, and health care administration/organizations. Time constraints, lack of specific training, and appropriate diagnostic tools, added to the sense of having little to offer patients due to the few pharmacological treatments available and poor knowledge of possible social care interventions, can discourage general practitioners' (GPs') efforts to reach an early diagnosis [12,13]. Specific concerns regarding the potential harm of treatments and diagnostic tests, the logistical and time-consuming burden, or poor prognosis despite accurate diagnosis and treatment can cause unfavorable attitudes that delay seeking medical aid in patients and families alike. Stigma about dementia is also still common in the general population [14,15]. Finally, regardless of population or health care provider attitudes, the organization of health care systems sometimes makes it difficult for individuals with subtle forms of cognitive impairment to access specialized diagnostic centers [16]. The low diagnostic rate leads to multiple unfavorable consequences. An obvious one is that undiagnosed patients are not offered access to treatments and support services. A delay in diagnosis denies patients and caregivers the opportunity to plan and make timely health, financial, and social decisions during disease stages in which they retain greater cognitive and functional capacity. Finally, this delay constitutes a significant obstacle toward advancement in AD research as most clinical trials seeking to cure or prevent AD call for participants at early disease stages.

Despite the current controversy regarding the economic and health benefits of population-based screening for cognitive decline [17,18], interviews with patients, families, and society show that a timely diagnosis is desirable from both personal and social perspectives. Alzheimer Europe conducted in 2017 a survey involving 1409 carers from 5 different European countries. On average, 53% of the participating carers felt that the diagnosis would have been more beneficial earlier [19]. Although the effectiveness of current treatment strategies is limited, there is increasing evidence that early diagnosis and intervention leads to significant economic and social

benefits. Several health-economic studies carried out in different countries showed that identifying AD individuals at an early stage (prodromal AD and mild AD dementia) results in cost savings and health benefits compared with no treatment or treatment in the absence of early assessment [20,21]. Furthermore, the disappointing results of clinical trials carried out in individuals with dementia have given rise to the idea that interventions have occurred too late in the disease process and that earlier action will bring higher chances of success [22], reinforcing the crucial role of earlier diagnosis from a perspective of treatment, whether drug or nonpharmacological, development.

The clear need for a paradigm shift in AD diagnosis, moving toward earlier diagnoses, requires a conscientious and collective effort of increasing patient engagement (PE). This calls for a global strategy addressing the multiple causes hindering PE at different levels of society. Awareness of the value of early diagnosis needs to be raised among the general population, health care providers, and decision-makers alike. New strategies and models promoting PE are needed to identify "hidden" cases of prodromal AD and mild AD dementia in the community. For example, open house initiatives (OHIs) allow people from the general population to visit a memory clinic and undergo a cognitive check-up without a medical referral [23], and Internet-based tools [24] are also promising and innovative approaches in addition to the classic scheme of GP referrals.

Unfortunately, studies regarding the effectiveness and cost-efficiency of these innovative strategies that could guide their implementation are scarce. Furthermore, important differences exist between nations in terms of socioeconomic situation, organization of health systems, and ethnic and cultural backgrounds [16]. Even within countries, significant cultural and linguistic diversity may also affect how people define, perceive, and respond to illness [25,26]. These differences can affect key factors related to PE including but not limited to ease of access to memory clinics, cultural beliefs about disease and scientific research, and the rate of Internet use among the elderly. Identifying the most effective PE strategies necessitates a careful evaluation of each strategy in each environment as countries have different health care systems and social and cultural attitudes.

In the present article, we will describe the rationale and strategy of Models of Patient Engagement for Alzheimer's Disease (MOPEAD), an ongoing EU-funded public-private multinational initiative aiming to contribute to the paradigm shift of moving AD diagnosis to the earlier stages of the disease.

2. The MOPEAD project: Aims and structure

MOPEAD responds to the topic "Evolving models of patient engagement and access for earlier identification of Alzheimer's disease" within the Innovative Medicines Initiative (IMI-2) research agenda. This project has received funding from the IMI-2 Joint Undertaking under the grant agreement number 115985. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and the European Federation of Pharmaceutical Industries and Associations. IMI is a European public-private partnership that supports health research and innovation, where there is an unmet medical or social need, with the goals of accelerating the medicines development process, generating new scientific insights, and developing resources for open use by the research community. MOPEAD is a multinational project carried out by a multidisciplinary consortium of 14 members, including academic institutions, pharmaceutical companies, technology companies, and relevant stakeholders such as patient associations, working across five work packages (see Table 1).

MOPEAD's overall goal is to identify the most effective PE strategies considering a set of contextual variables (i.e., nationality, socioeconomic status, gender, ethnicity) and describe the most effective and cost-efficient screening methodologies for identification of prodromal AD and mild AD dementia. To this end, MOPEAD will evaluate and compare four innovative PE strategies across five European countries (Germany, Slovenia, Spain, Sweden, and the Netherlands) regarding their ability to identify individuals at risk of or with mild AD dementia, which are "hidden" in their communities and traditionally not found in the typical memory clinic setting. The PE strategies include an online AD citizen science platform, an OHI at the memory clinics, and PE at primary care physician (PCP) and diabetologist clinics. Through a five-country and multicenter prescreening approach, MOPEAD will identify individuals with cognitive impairment and refer them to a reference memory clinic to undergo a complete diagnostic evaluation. A specialized team will use a combination of clinical, biomarker, and health-economic variables to build models describing the effectiveness and cost-efficiency for each prescreening strategy, tool, and country to determine the optimal prescreening procedures that could be implemented in each country. Finally, MOPEAD will help bridge the gap between clinicians and health decision-makers by distributing and advocating these PE models for broader application and replication with the goals of raising awareness regarding the benefits of early detection of cognitive decline for the general population, health professionals, and health policy makers.

The primary objective is to produce estimates of positive screening results, by comparing the results of the prescreening strategies with the posterior complete diagnostic evaluation, across all participating countries. Secondary objectives include determining the most effective screening method within each country and evaluating the cost-efficiency of each prescreening approach. The project consists in an initial recruitment

Table-1
MOPEAD consortium members

Partner	Country	Type of institution	Leader	Activities
Fundació ACE	Spain	Academic and clinical center	Mercè Boada	Management, clinical core, analysis, and dissemination
Eli Lilly and Company Ltd	UK	Pharmaceutical company	Laura Campo	Management, clinical core, analysis, and dissemination
ASDM Consulting	Belgium	SME	Annette Dumas	Dissemination
Astra Zeneca	USA	Pharmaceutical company	Craig Shering	Clinical core
European Institute of Women's Health	Ireland	NGO	Peggy Maguire	Dissemination
GMV Soluciones Globales Internet S.A.U.	Spain	IT company	Adrián Rodrigo	Clinical core and analysis
Karolinska Institutet	Sweden	Academic and clinical center	Bengt Winblad	Clinical core and analysis
Modus Research and Innovation Ltd	UK	Not-for-profit SME research organization	Neil Stewart	Management
Spomincica	Slovenia	Patient association	David Krivec	Dissemination
University of Cologne Medical Center	Germany	Academic and clinical center	Frank Jessen	Clinical core
University Medical Centre Ljubljana	Slovenia	Academic and clinical center	Milica Kramberger	Clinical core
Vall d'Hebron Research Institute	Spain	Academic and clinical center	Rafael Simó	Clinical core (Run 4)
VU Medical Center	The Netherlands	Academic and clinical center	Pieter Jelle Visser	Clinical core
Alzheimer Europe	Luxembourg	Patient organization	Jean Georges	Management and dissemination

Abbreviations: MOPEAD, Models of Patient Engagement for Alzheimer's Disease; SME, small and medium enterprise.

period, which includes the prescreening and screening (full diagnostic evaluation) visits, followed by a data analysis and result dissemination period. MOPEAD is a cross-sectional observational study by design. Treatment pattern and initiation or changes are solely at the discretion of the physician and the patient with no attempt to influence the prescribing patterns of any individual investigator. Participation in the study will in no way influence payment or reimbursement for any treatment received by patients during the study. The MOPEAD protocol and participant information sheets have been approved by the local ethical review boards of all the recruiting sites.

The MOPEAD project workflow contains four main components as presented in Fig. 1 and described below. The prescreening component, a set of four multicenter prescreening strategies will be implemented in each country with the goal of identifying people with prodromal AD or mild AD dementia as well as increasing engagement and awareness of AD within the community. The people whose results are positive in the prescreening stage will be referred for a full diagnostic evaluation at the memory clinic of reference in their country. The data analysis component will use a combination of clinical and health-economic metrics for economic modeling and cost-effectiveness analyses to determine the most effective screening procedures recommended to be implemented in each country. Finally, the project results and policy recommendations to encourage deployment of early diagnosis strategies and facilities will be disseminated by another specialized team.

3. MOPEAD clinical core

The core of MOPEAD's clinical activities is organized in a "funnel" structure (see Fig. 2). Four different PE models will be set up in each of the five participating countries. Each model is a prescreening strategy that takes place in a different setting and applies different tools adapted to the "real-world" circumstances of each setting. For example, short cognitive tests and easily calculated dementia risk scores will be used in the GP setting where time is a crucial limiting factor, whereas online versions of traditional neuropsychology tests are used in the Internet-based prescreening strategy. In addition, the prescreening models will include a set of common elements to facilitate their comparison.

The prescreening models implemented in MOPEAD will combine traditional tools and innovative paradigms for the detection of individuals with cognitive impairment. One innovative strategy is the use of dementia risk scores. Several longitudinal observational studies have found strong associations between some modifiable risk factors (hypertension, diabetes, smoking, hypercholesterolemia, atrial fibrillation, low education, depression) and the risk of developing AD dementia [27]. These findings are useful to identify individuals at high risk of developing dementia based on the accumulation of known risk factors and have led to the development of dementia risk scores [28]. The innovative approach in MOPEAD is to use these risk scores to identify individuals with cognitive impairment due to AD in a cross-sectional manner, instead of using them as longitudinal predictors of dementia. MOPEAD will also incorporate the subjective cognitive decline (SCD) [29] paradigm, which has been proposed as a marker of neurodegenerative pathology in people in whom a formal neuropsychological examination is not able to detect cognitive impairment. Its validity is supported by growing evidence that a diagnosis of SCD is associated with the presence of AD biomarkers as well as increased risk of developing mild cognitive impairment (MCI) and dementia [29,30].

If willing, individuals classified as positive in the prescreening stage will be referred to their memory clinic

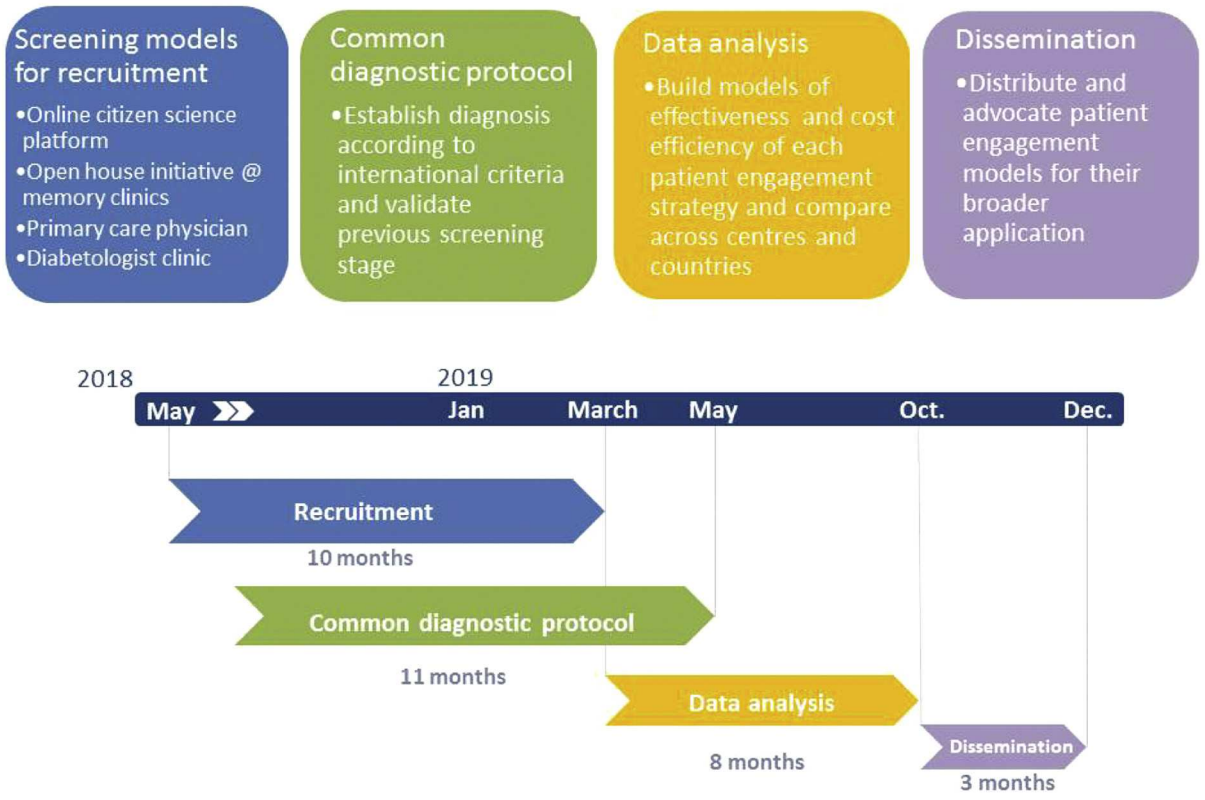

Fig. 1. MOPEAD chronogram and activities. Abbreviations: MOPEAD, Models of Patient Engagement for Alzheimer's Disease; WP, work package.

of reference to undergo a full standardized diagnostic evaluation screening for cognitive impairment. The project objective is to prescreen at least 100 individuals per PE strategy in each country, adding up to a total of 2000 screened participants (400 per country and 500 per engagement strategy). Thirty-three individuals from each PE strategy will be referred to the standardized diagnostic evaluation (132 per country and 165 per engagement strategy). Because the number of full diagnostic assessments in each country is fixed, the final number of

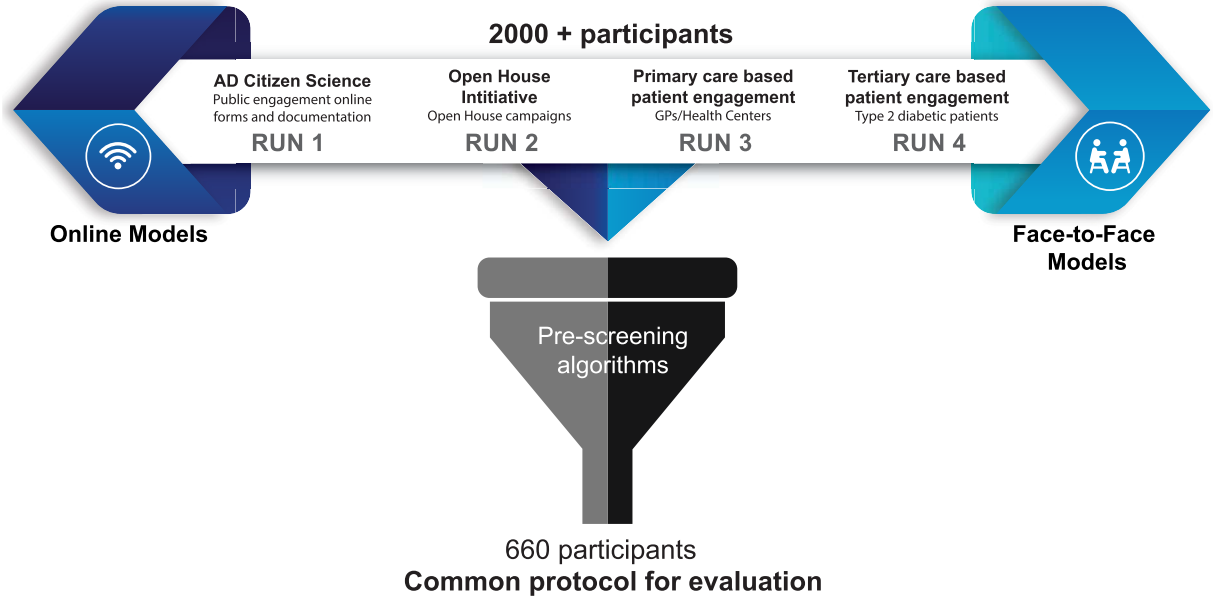

Fig. 2. MOPEAD's clinical activities: Four prescreening strategies (i.e. RUNS) and the standardized diagnostic evaluation. Abbreviation: MOPEAD, Models of Patient Engagement for Alzheimer's Disease.

individuals that undergo prescreening could increase over 100 and vary between the PE strategies to reach the prespecified referral number.

3.1. Online patient engagement: AD citizen science online platform

MOPEAD will use the citizen science approach, a new concept rapidly gaining relevance whereby the general public takes part in a collaborative project and agrees to have their data collected, analyzed, and used in scientific research [31]. The AD citizen science prescreening model will implement a low-cost patient recruitment tool using Web-based technologies for citizens who request cognitive assessment. In return for their collaboration, they will be offered reliable information, and the possibility to receive further health assessment.

This strategy begins with online marketing techniques. People surfing the Internet will be directed to the AD citizen science landing pages by means of various online marketing techniques. For example, typing in a particular search word or set of words (through the "AdWords" tool offered by Google) results in an advertisement appearing that redirects the user to a "landing page" where he/she finds information related to his/her search. At this point, the citizen also receives information about the MOPEAD study and is invited to undergo an online cognitive evaluation. Depending on the result of the tests (prescreening), the user is invited to a MOPEAD memory clinic to undergo a full diagnostic evaluation. Generating trust in the user will be a crucial factor for the success of the AD citizen science run, and therefore, the online marketing campaign will be adapted to each language and country and the "landing pages" will be housed under the Web pages of the medical centers participating in MOPEAD. Various quality control metrics will be continuously monitored to implement potential improvements such as changes to the words used in AdWords, changes to the design or content of the landing pages, and reinforcing the campaign for specific countries.

The Paired Associates Learning and Spatial Working Memory tests from the CANTAB platform developed by Cambridge Cognition Ltd. were selected as the online cognitive tests because they are short, language-independent, visual tasks with available data showing good sensitivity for detecting AD and high correlation with neuroimaging and cerebrospinal fluid AD biomarkers. The criteria for referral to the diagnostic evaluation at the memory clinic are scoring below the prefixed cutoff (adjusted by age and education) on the online cognitive tests, being between 65 and 85 years of age, and absence of previous diagnosis of cognitive impairment.

3.2. Memory clinic patient engagement: Open house initiative

Patients with subtle forms of cognitive impairment often have problems accessing specialized diagnostic centers because a prior GP referral is most often needed. To overcome this obstacle, MOPEAD will implement an OHI in each of the five participating countries by which individuals between 65 and 85 years of age from the general public who may be worried about their memory and do not have a previous diagnosis of cognitive impairment are invited to attend a memory clinic for free cognitive screening. The usefulness of this approach is supported by the previous experience of Fundació ACE, which has evaluated more than 2300 people as part of the OHI since it started in 2008, resulting in the diagnosis of 87, 736, and 1660 individuals with AD dementia, MCI, and SCD, respectively [23].

The OHI will be advertised according to a marketing campaign specifically designed to ensure homogeneity across the five participating countries to facilitate ex-post comparisons of cost-efficiency and economic modeling. Any individual from the community that meets the inclusion and exclusion criteria will be able to sign up, through a phone call, mail, or in person, for a free cognitive screening without the need of a GP referral. The prescreening protocol is based on well-validated instruments that are easy to administer and collect cognitive, demographic, and medical data in less than 45 minutes. The picture version of the Free and Cued Selective Reminding Test [32] was selected for memory screening as suggested by the International Working Group because of its high sensitivity for AD detection [33]. General cognition will be evaluated with the Mini-Mental State Examination (MMSE). Data on demographics, social and medical history, level of education, and current medications will be collected through a self-administered questionnaire. The Hospital Anxiety and Depression Scale [34] will provide validated measures of anxiety and depression. Finally, an assessment of SCD consisting of three qualitative questions will be included as previous studies have shown this approach is useful for predicting further progression to MCI and dementia [29,30]. The criteria for referral to the diagnostic evaluation at their memory clinic of reference are a MMSE score between 20 and 27, significant memory impairment according to the Free and Cued Selective Reminding Test total score, or subtle memory impairment according to the Free and Cued Selective Reminding Test total score plus 3 positive answers to the SCD questions.

3.3. Primary care–based patient engagement: Primary care physician clinics

Recent studies highlight the potential impact that primary prevention strategies involving modification of lifestyle and cardiovascular risk factors could have on the incidence and future prevalence of dementia. The primary care setting has a central role in such activities, as it focuses on large populations, where even small intervention effects may have a significant impact on disease and on people "at

high risk" due to the burden of multiple cardiovascular risk factors and disorders (hypertension, obesity, hyperlipidemia, diabetes, ischemic cardio-cerebrovascular disease, etc.) [35]. Furthermore, the vast majority of elderly subjects in many countries frequently visit the PCP, and the PCP is often the first to whom cognitive complaints are reported. However, dementia and cognitive impairment are frequently underdiagnosed in primary care settings in most health systems [7]. This low rate of dementia diagnosis depends on multiple factors, some of them related to PCPs, such as beliefs and attitude toward early diagnosis benefits (as current drug treatments have mild beneficial effects [36]) or inadequate training programs in cognitive disorders [12,13]. Other structural problems of the health system such as time constraints for the necessary workup or the absence of adequate postdiagnostic support services may discourage the PCP from making an early diagnosis [37].

Here, the prescreening protocol was designed to improve early detection of cognitive decline in the primary care setting. It will include three different easily administered tools: the MMSE; a new version of the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) dementia risk score; and the three-question SCD assessment. The CAIDE dementia risk score predicts the risk of developing late-life dementia based on the presence of multiple readily available clinical and social variables. It is based on a longitudinal observational study carried out in Finland and has been validated on an external multi-ethnic cohort in the United States [38]. MOPEAD will use a new version recently developed by researchers of the Karolinska Institute based on data from the same Finnish cohort. This new age-adjusted version of CAIDE is intended to be used in elderly individuals (instead of middle-aged individuals) and has demonstrated to predict dementia in the short term (unpublished data). The SCD assessment has also shown utility for identifying people with increased risk of developing cognitive impairment or dementia. In the AGECODE study carried out in Germany, cognitively healthy elderly adults who answered positively to the 3 SCD questions presented a 3-year hazard ratio of 3.5 for developing dementia [30].

The criteria for referral to the diagnostic evaluation at their memory clinic of reference are one of the following: an MMSE score between 20 and 27, a new CAIDE risk score suggesting high risk of dementia, or a new CAIDE risk score suggesting medium risk of dementia plus 3 positive answers to the SCD questions.

3.4. Tertiary care–based patient engagement: Diabetologist setting

Patients with type 2 diabetes (T2D) have an increased risk of cognitive impairment and double the risk of dementia (vascular and AD) compared with people without diabetes [39,40]. In fact, T2D and AD share common pathogenic mechanisms [41] and diabetes may accelerate AD development [42]. Furthermore, insulin resistance precedes T2D and independently increases the risk for AD [43]. Although the pathophysiological links between the 2 diseases are not completely known, several hypotheses have emerged. One theory focuses on microvascular abnormalities accompanying neurodegeneration, which have been described in both diseases leading to the proposal of microvascular damage as a risk marker for development of AD in patients with T2D [44]. This line of research has led to the creation of a diabetes-specific dementia risk score (DSDRS), which uses several clinical and demographic variables (age, gender, education, history of diabetic foot syndrome, acute metabolic events, depression, microvascular disease, cardiovascular disease, and cerebrovascular disease) to produce a 10-year dementia risk score. The authors reported 10-year dementia risks ranging from 5% for the patient with the lowest score, up to 73% for the highest score [45]. In this context, it is reasonable to hypothesize that the diabetologist office could be an appropriate setting to identify individuals with hidden cognitive impairment.

The protocol includes the MMSE, the three-question SCD assessment, the DSDRS, and data on microalbuminuria, retinopathy, and glycemia from the last 2 years extracted from the medical records, as well as a hypoglycemia questionnaire specifically developed for MOPEAD. The criteria for referral to the diagnostic evaluation at their memory clinic of reference are an MMSE score between 20 and 27, a DSDRS score indicating high risk of dementia, or a DSDRS indicating medium risk of dementia plus 3 positive answers to the SCD questions.

3.5. Complete diagnostic evaluation in the memory clinic

Individuals meeting the specified criteria of each PE model identified in the prescreening stage will be referred, if willing, to a reference memory clinic to undergo a complete diagnostic evaluation using a common protocol, which is described below (see Fig. 3). This evaluation has two main objectives. The first is to reach a diagnosis for the people who test positive in the prescreening runs, and the second is to provide clinical and biomarker variables that will be used to validate the four different prescreening models, i.e., to determine the rate of true/false positives. The critical features of this evaluation are that it achieves a standard-of-care clinical diagnosis according to international criteria and that it consists of a common homogeneous protocol across all sites and countries to ensure the resulting data are comparable.

The protocol will include (1) a physical and neurological examination with the following variables: height, weight, BMI, blood pressure, presence of motor disorders, oculomotor disturbances, and other neurological signs; (2) a neuropsychological assessment including the MMSE

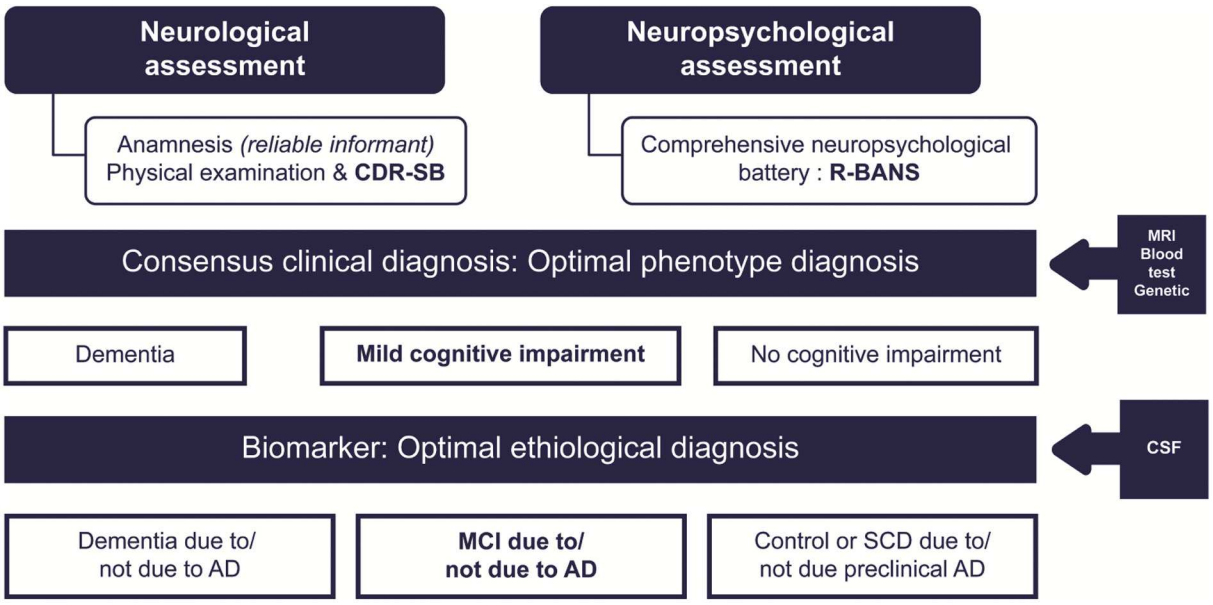

Fig. 3. Complete diagnostic evaluation protocol. CSF biomarker and genetic evaluation are optional. Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; CDR-SB, Clinical Dementia Rating Scale–sum of boxes; CSF, cerebrospinal fluid; DSDRS, diabetes-specific dementia risk score; FCSRT, Free and Cued Selective Reminding Test; HADS, Hospital Anxiety and Depression Scale; MCI, mild cognitive impairment; MOPEAD, Models of Patient Engagement for Alzheimer's Disease; MRI, magnetic resonance imaging; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SCD, subjective cognitive decline.

and the Repeatable Battery for the Assessment of Neuropsychological Status test battery that includes measures of immediate and delayed memory, visuospatial/constructional ability, attention, and language [46]; (3) assessment of functional status by means of the Clinical Dementia Rating Scale–sum of boxes score, which includes performance in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care [47]; (4) assessment of resource utilization by selected items of the Resource Utilization in Dementia questionnaire (RUD v 4.0) [48]; (5) affective symptom evaluation with the Hospital Anxiety and Depression Scale [34]; (6) standard blood workup including blood count, ionogram ($Na+$,$K+$,$Cl-$, $Ca++$), hepatic function (alanine aminotonsferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, bilirubin), glucose and glycated hemoglobin, renal function (creatinine, Modification of Diet in Renal Disease Equation), lipidic profile (total cholesterol, low-density lipoprotein, high-density lipoprotein), thyroid function (thyroid stimulating hormone, T4), coagulation (activated partial thromboplastin time, prothrombin time, international normalized ratio), and B12; (7) optional blood sample for the apolipoprotein E (APOE) genotype; (8) optional cerebral spinal fluid analysis centralized at the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital in Gothenburg (Sweden) including measurement of Aβ42, Aβ40, total tau, and phospho-tau levels; and (9) neuroimaging evaluation including 3DT1W, 3D-FLAIR, 2DT2, and 3D SWI MRI sequences. Additional advanced sequences such as resting-state functional magnetic resonance imaging, arterial spin labeling, and diffusion tensor imaging will be acquired at some clinical sites as a substudy.

When any form of cognitive impairment is diagnosed, the professionals at the memory clinic take over patient care and future treatment comprising state-of-the-art treatment plans, which may include assessment of eligibility for clinical trials. Participants whose results are negative will be offered lifestyle recommendations for cognitive well-being and clinical follow-up.

4. Data collection, management, and analysis

To achieve MOPEAD's goals, it is necessary to collect, store, and analyze information from individuals taking part in the study. The data analysis team is responsible for defining the data digitalization process from their source of input and has constructed a platform to collect, perform quality control, standardize, and encrypt the collected data for its subsequent exploration. This team will undertake analyses to determine the most effective PE strategy for identifying undiagnosed cases of AD (see Table 2).

These strategies are adapted to each specific country and context, and therefore, subanalyses for each country will be done in addition to the global sample analysis. Cost-effectiveness of the four models will be compared in terms of the number of patients recruited per month, economic cost of identifying an individual with AD dementia/MCI, and economic cost of identifying a subject with cerebrospinal fluid biomarkers compatible with AD

Table 2
Overview of data collected and outcome measures in MOPEAD

Prescreening runs	Data collected in prescreening	Data collected in complete diagnostic evaluation	Metrics evaluating run efficacy
1. AD citizen science online platform	- Run implementation costs - Demographic data - CANTAB test scores - Online SCD questions	- Demographic data - Anamnesis data - Physical examination data - CDR-SB score	- Number of prescreened participants by time - Cost of implementation - % of patients with AD
2. Open house initiative	- Run implementation costs - Demographic data - Medical history data - MMSE - FCSRT - SCD questions - HADS	- RBANS score - RUD-Lite selected Items - General laboratory measures - APOE genotype - CSF measures - MRI measures	- % of patients with MCI - % of patients with amnestic MCI - % patients with SCD - % of APOE E4+ participants - Degree of brain atrophy by MRI - Degree of cerebrovascular disease by MRI
3. Primary care–based patient engagement	- Run implementation costs - Demographic data - Medical history data - MMSE - CAIDE dementia risk score (adapted version)		- % of patients with CSF AD profile - Cost of a diagnosis of AD dementia - Cost of a diagnosis of MCI - Cost of finding an individual with AD profile in CSF
4. Tertiary care–based patient engagement (diabetologist setting)	- Run implementation costs - Demographic data - Medical history data - Hypoglycemia questionnaire - MMSE - DSDRS		

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; CDR-SB, Clinical Dementia Rating Scale–sum of boxes; CSF, cerebrospinal fluid; DSDRS, diabetes-specific dementia risk score; FCSRT, Free and Cued Selective Reminding Test; HADS, Hospital Anxiety and Depression Scale; MCI, mild cognitive impairment; MOPEAD, Models of Patient Engagement for Alzheimer's Disease; MRI, magnetic resonance imaging; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SCD, subjective cognitive decline.

regardless of their clinical phenotype, among other variables of interest. Resource use and cost data will be collected at both a subject and PE model level, and these unit costs will be used to estimate and compare the costs of each PE model. Finally, the data analysis component includes economic modeling activities aimed at calculating the health-economic impact of early AD diagnosis across and within each participating nation.

5. Dissemination program

MOPEAD's innovative approach requires a concise and proactive communication and dissemination strategy (see Fig. 4). This strategy is three-fold: The project will be presented and promoted among the general public. The overarching awareness-raising messages are that the diagnosis of AD is still occurring too late in clinical practice and that a cultural and paradigm shift toward making a timely diagnosis of AD at the initial symptomatic stages of the illness can provide patients with optimal opportunity for intervention, including involvement in clinical trials. The communication strategy also provides guidance and tools to the consortium members in charge of patient recruitment in the regional sites to help them reach the "hidden" and consequently undiagnosed cases of AD in the population. Finally, the project findings will generate easy-to-understand communication messages and policy recommendations that will drive behavior change in the population and pave the way for policy action that will foster interventions needed to better diagnose AD and stimulate faster recruitment of patients into research studies and clinical trials.

A series of communication tools (static and animated infographics) have been produced under the motto "Mind your memory, mind yourself." These tools aim to raise awareness about AD and its risk factors, the value of a timely diagnosis, and the differences of normal aging and dementia and to engage the public to take part in the project. They include "Calls to Action" for people to take care of their brain and their health. All this material has been translated in the language of the countries where the recruitment is taking place (Catalan, Dutch, German, Spanish, Slovene, Swedish). Besides raising awareness about AD, their aim is to prepare the ground for acceptance from the general population, health care professionals and providers, academics, interested stakeholders, and policy makers that innovative approaches are needed to design and implement the best early AD detection and prevention strategies.

The infographics and leaflet are available on the project website (https://www.mopead.eu/). The website also hosts all other communication activities carried out during the project: newsletters, articles published by the partners in selected professional and lay media, and press releases. Social media is extensively used to

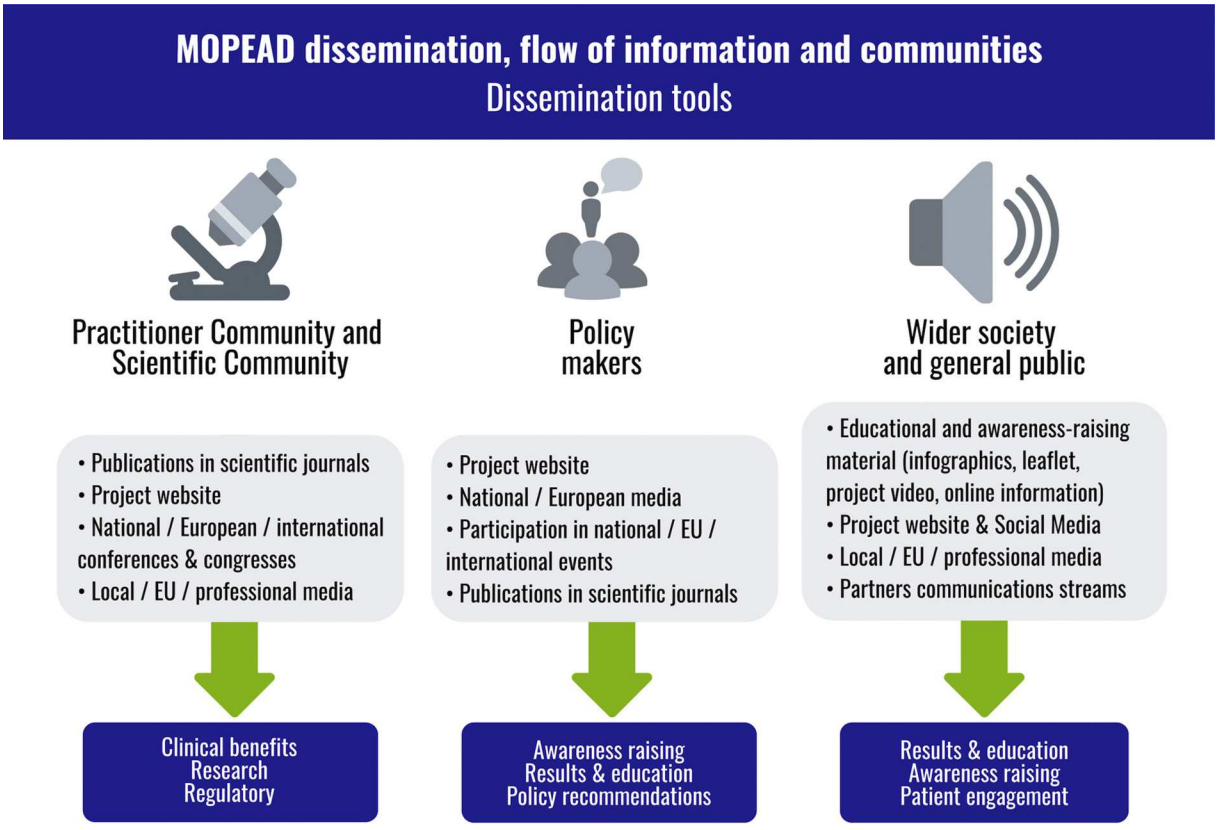

Fig. 4. MOPEAD dissemination strategy. Abbreviation: MOPEAD, Models of Patient Engagement for Alzheimer's Disease.

promote the project: Twitter (@MopeadEU), Facebook, LinkedIn (https://www.linkedin.com/groups/13555791), and YouTube. All partners are also invited to use their own social media streams to spread the project and prepare the ground for future action more widely.

Other outreach activities are planned by the project partners who present the project at international and national events and conferences, in-house publications, or other public engagements. The project will conclude with the presentation of its results, policy recommendations, and calls for actions at a conference that will be organized at the European level with participation of European and national stakeholders.

6. Conclusion

The widespread underdiagnosis and delay in diagnosis of cognitive impairment and AD present in most, if not all, of the world's health care systems is a crucial yet often overlooked factor that seriously impacts the lives of people with AD and their families. From a scientific perspective, this underdiagnosis delays recruitment to observational studies and clinical trials and thus hinders our understanding of AD pathophysiology and the development of disease-modifying treatments. MOPEAD was created to overcome this phenomenon by implementing and evaluating a set of four innovative PE strategies designed to attract groups of the population, which traditionally are not found in the memory clinic setting. The project reinforces the role of PCPs and other health professionals in the diagnosis of AD and also raises global awareness about the benefits of a timely diagnosis. Besides identifying the most effective strategies for detecting cases of prodromal and mild AD dementia "hidden" in the community, MOPEAD will undertake cost-efficiency analyses and provide economic models describing the potential impact of the evaluated PE strategies. The project's innovative design, multidisciplinary team, and multinational scope are clear examples of the benefits of public-private partnerships such as those financed by IMI. MOPEAD will provide much needed data and guidance for the implementation of innovative and sustainable health care infrastructure elements supporting early AD diagnosis across Europe and the world.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using PubMed. In most health systems, dementia is underdiagnosed or diagnosed at a relatively late stage in the disease process. There is mounting evidence showing that a timely diagnosis would result in numerous benefits for patients, families, and society. These relevant citations are appropriately cited.
2. Interpretation: Models of Patient Engagement for Alzheimer's Disease will compare four innovative patient engagement models across five European countries in their ability to identify people with prodromal and mild Alzheimer's disease dementia, which are "hidden" in their communities and traditionally not found in the typical memory clinic setting.
3. Future directions: The article describes the rationale and strategy of Models of Patient Engagement for Alzheimer's Disease, an ongoing EU-funded public-private multinational initiative aiming to contribute to the paradigm shift of moving Alzheimer's disease diagnosis to the earlier stages of the disease. Upcoming results will include effectiveness and cost-efficiency analyses comparing four innovative patient engagement models: an online Alzheimer's disease citizen science platform, an open house initiative at the memory clinics, and patient engagement at primary care and diabetologist clinics.

References

[1] Alzheimer's Disease International. World Alzheimer Report 2015. 2015. London, UK: Alzheimer's Dis. Int.; 87.
[2] Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina AM, Winblad B, et al. The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2017;13:1–7.
[3] World Health Organization. Dementia: a public health priority. 2012; Dementia; 112.
[4] National Dementia Strategies - Policy in Practice - Alzheimer Europe.
[5] National Plan to Address Alzheimer's Disease 2016 ASPE; 2016. Update.
[6] Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol 2016;15:455–532.
[7] Alzheimerś Disese International. World Alzheimer Report 2011:The benefits of early diagnosis and intervention.
[8] Connolly A, Gaehl E, Martin H, Morris J, Purandare N. Underdiagnosis of dementia in primary care: Variations in the observed prevalence and comparisons to the expected prevalence. Aging Ment Health 2011;15:978–84.
[9] Wilkins CH, Wilkins KL, Meisel M, Depke M, Williams J, Edwards DF. Dementia undiagnosed in poor older adults with functional impairment. J Am Geriatr Soc 2007;55:1771–6.
[10] Cherubini A, Ruggiero C, Dell'Aquila G, Eusebi P, Gasperini B, Zengarini E, et al. Underrecognition and undertreatment of dementia in Italian nursing homes. J Am Med Dir Assoc 2012;13:759.e7–13.
[11] Dias A, Patel V. Closing the treatment gap for dementia in India. Indian J Psychiatry 2009;51:S93–7.
[12] Vernooij-Dassen MJFJ, Moniz-Cook ED, Woods RT, Lepeleire J De, Leuschner A, Zanetti O, et al. Factors affecting timely recognition and diagnosis of dementia across Europe: from awareness to stigma. Int J Geriatr Psychiatry 2005;20:377–86.
[13] Moore V, Cahill S. Diagnosis and disclosure of dementia – A comparative qualitative study of Irish and Swedish general practitioners. Aging Ment Health 2013;17:77–84.
[14] Phillipson L, Magee C, Jones S, Reis S, Skaldzien E. Dementia attitudes and help-seeking intentions: an investigation of responses to two scenarios of an experience of the early signs of dementia. Aging Ment Health 2015;19:968–77.
[15] Perry-Young L, Owen G, Kelly S, Owens C. How people come to recognise a problem and seek medical help for a person showing early signs of dementia: A systematic review and meta-ethnography. Dementia 2018;17:34–60.
[16] Bond J, Stave C, Sganga A, O'Connell B, Stanley RL. Inequalities in dementia care across Europe: key findings of the Facing Dementia Survey. Int J Clin Pract Suppl 2005:8–14.
[17] Moyer VA. U.S. Preventive Services Task Force. Screening for Cognitive Impairment in Older Adults: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2014; 160:791.
[18] Wimo A. The end of the beginning of the Alzheimer's disease nightmare: A devil's advocate's view. J Alzheimer's Dis 2018; 64:S41–6.
[19] Alzheimer Europe. European Carerś Report; 2018.
[20] Getsios D, Blume S, Ishak KJ, Maclaine G, Hernández L. An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2012;8:22–30.
[21] Geldmacher DS, Kirson NY, Birnbaum HG, Eapen S, Kantor E, Cummings AK, et al. Implications of early treatment among Medicaid patients with Alzheimer's disease. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2014;10:214–24.
[22] Sperling RA, Jack CRJ, Aisen PS. Testing the right target and right drug at the right stage. Sci Transl Med 2011;3:111cm33.
[23] Rodriguez-Gomez O, Abdelnour C, Jessen F, Valero S, Boada M. Influence of Sampling and Recruitment Methods in Studies of Subjective Cognitive Decline. J Alzheimers Dis 2015;48:S99–107.
[24] Coathup V, Finlay T, Teare HJA, Kaye J, South M, Watt FE, et al. Making the most of the waiting room: Electronic patient engagement, a mixed methods study. Digit Heal 2018;4:2055207617751304.
[25] Mukadam N, Cooper C, Livingston G. A systematic review of ethnicity and pathways to care in dementia. Int J Geriatr Psychiatry 2011;26:12–20.
[26] Morhardt D, Pereyra M, Iris M. Seeking a diagnosis for memory problems: the experiences of caregivers and families in 5 limited English proficiency communities. Alzheimer Dis Assoc Disord 2010;24:S42–8.
[27] Rodríguez-Gómez O, Palacio-Lacambra ME, Palasí A, Ruiz-Laza A, Boada-Rovira M. Prevention of Alzheimer's Disease: A Global Challenge for Next Generation Neuroscientists. J Alzheimer's Dis 2014;42:S515–23.
[28] Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol 2006;5:735–41.
[29] Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chételat G, et al. Group SCDI (SCD-IW). A conceptual framework

for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2014;10:844–52.
[30] Jessen F, Wiese B, Bachmann C, Eifflaender-Gorfer S, Haller F, Kölsch H, et al. German Study on Aging, Cognition and Dementia in Primary Care Patients Study Group. Prediction of dementia by subjective memory impairment effects of severity and temporal association with cognitive impairment dementia and subjective memory impairment. Arch Gen Psychiatry 2010;67:414.
[31] Follett R, Strezov V. An Analysis of Citizen Science Based Research: Usage and Publication Patterns. PLoS One 2015; 10:e0143687.
[32] Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. Neurology 1988;38:900–3.
[33] Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria. Lancet Neurol 2007; 6:734–46.
[34] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
[35] Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011; 10:819–28.
[36] Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev 2018;6:CD001190.
[37] Bond J, Graham N, Padovani A, Mackell J, Knox S, Atkinson J. Screening for cognitive impairment, Alzheimer's disease and other dementias: opinions of European caregivers, payors, physicians and the general public. J Nutr Health Aging 2010;14:558–62.
[38] Exalto LG, Quesenberry CP, Barnes D, Kivipelto M, Biessels GJ, Whitmer RA. Midlife risk score for the prediction of dementia four decades later. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2014;10:562–70.
[39] Kopf D, Frölich L. Risk of Incident Alzheimer's Disease in Diabetic Patients: a systematic review of prospective trials. J Alzheimer's Dis 2009;16:677–85.
[40] Spauwen PJJ, Stehouwer CDA. Cognitive decline in type 2 diabetes. Lancet Diabetes Endocrinol 2014;2:188–9.
[41] Simó R, Ciudin A, Simó-Servat O, Hernández C. Cognitive impairment and dementia: a new emerging complication of type 2 diabetes—The diabetologist's perspective. Acta Diabetol 2017;54:417–24.
[42] Ciudin A, Espinosa A, Simó-Servat O, Ruiz A, Alegret M, Hernández C, et al. Type 2 diabetes is an independent risk factor for dementia conversion in patients with mild cognitive impairment. J Diabetes Complications 2017;31:1272–4.
[43] Ferreira LSS, Fernandes CS, Vieira MNN, De Felice FG. Insulin Resistance in Alzheimer's Disease. Front Neurosci 2018;12:830.
[44] Simó R, Hernández CEuropean Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Neurodegeneration in the diabetic eye: new insights and therapeutic perspectives. Trends Endocrinol Metab 2014;25:23–33.
[45] Exalto LG, Biessels GJ, Karter AJ, Huang ES, Katon WJ, Minkoff JR, et al. Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. Lancet Diabetes Endocrinol 2013; 1:183–90.
[46] Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol 1998; 20:310–9.
[47] Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982; 140:566–72.
[48] Wimo A, Gustavsson A, Jönsson L, Winblad B, Hsu M-A, Gannon B. Application of Resource Utilization in Dementia (RUD) instrument in a global setting. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2013;9:429–435.e17.