



Review

Should we screen for cognitive decline and dementia?[☆]

Laura Calzà^{a,b,*}, Daniela Beltrami^a, Gloria Gagliardi^a, Enrico Ghidoni^c, Norina Marcello^c, Rema Rossini-Favretti^d, Fabio Tamburini^d

^a Health Sciences and Technologies – Interdepartmental Center for Industrial Research (CIRI-SDV), University of Bologna, Italy

^b Pharmacy and Biotechnology (FaBiT), University of Bologna, Italy

^c UOC Neurologia, ASMN-IRRCS Reggio Emilia, Italy

^d Classical Philology and Italian Studies (FICLIT), University of Bologna, Italy

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ABSTRACT

Due to increased life expectancy, the prevalence of cognitive decline related to neurodegenerative diseases and to non-neurological conditions is increasing in western countries. As with other diseases, the burden might be reduced through personalized interventions delivered at early stages of the disease. Thus, there is an increasing demand, from both social and healthcare systems, for instruments and strategies to recognize cognitive decline, and possibly distinguish the precursor of serious neurodegeneration from “benign senile forgetfulness” or the temporary consequences of illness or trauma. However, this goal faces both technical and ethical issues. In this article we deal with the following: (i) re-definition of cognitive decline and its relationship with frailty definitions, starting from the recent work of international consensus groups for presymptomatic Alzheimer disease recognition; (ii) ethical problems concerning anonymous and personalized cognitive screening and the need for appropriate counselling; (iii) the need for more sensitive and specific tools to detect and distinguish pathological levels of cognitive decline and delineate the contribution of non-pathological decline to accumulated frailty impacts and (iv) the potential of the language domain and spontaneous speech analyses.

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[☆] After the first, Authors are listed in alphabetic order.

* Corresponding author at: CIRI-SDV, University of Bologna Via Tolara di Sopra 41/E, 40064 Ozzano Emilia, Italy.
E-mail address: laura.calza@unibo.it (L. Calzà).

1. Introduction

The impact of increased life expectancy on the EU population is a major challenge for social and health care systems. Thus, reduction of age-related frailty and functional and cognitive decline, for the prevention of adverse medical events in elder people is a key strategy to contain and even decrease the associated financial burden on social and healthcare systems. Population-based screenings would be an obvious strategy to identify frail individuals for personalized care and interventions, and their success would represent an evidence-based to support politicians' and health authorities' initiatives. Indeed, a number of information and communication technology (ICT)- based instrument and programmes are already active in EU countries [1]. However several issues, including clinical validation and ethical concerns, make this goal quite ambitious and challenging, in particular regarding the possibility to improve and refine the effectiveness of screening strategies within the cognitive domain.

The aim of this article is to highlight major questions threatening this goal, starting from the document "Prevention of functional decline and frailty", action plan number 3 (A3 group) "Prevention and early diagnosis of frailty and functional decline, both physical and cognitive, in older people" published at the 1st Conference of Partners of the EU initiative "European Innovation Partnership on Active and Healthy aging" (EIP-AHA), held on November 6th, 2012 in Brussels. Although references to documents and papers prepared in the context of the Alzheimer's Disease (AD) are predominant, the focus of this article is to discuss possible use of wider "population-based cognitive screening" inclusive of non-AD and non-neurological conditions. The following points will be discussed: conceptual framework; ethical problems moving towards cognitive screening; and the need more sensitive and specific screening tools, including novel approaches, with a particular focus on language analysis. This article (Sections 1, 2, 3 and 5) is based on position and consensus papers and documents included in the PubMed database identified through search for articles published in the last ten years, with combinations of the terms "cognitive decline", "cognitive frailty", "screening", "ethics or ethical issues". The text has been discussed and reviewed by the "cognitive decline" working group in the context of the EIP-AHA A3 group, and approved by all authors.

2. Conceptual framework. Frailty, cognitive frailty and cognitive decline: beyond in the context of neurological disorders

2.1. Frailty

Frailty has been described as a multidimensional syndrome characterized by decreased reserve and diminished resistance to stressors [2]. In the attempt to categorize the progression from healthy, independent life to gradual deterioration or wasting away of physical and mental faculties leading to disability, the EIP-AHA documents report definitions for pre-frailty, frailty, functional decline and cognitive decline (see http://ec.europa.eu/research/innovation-union/pdf/active-healthy-ageing/a3_action_plan.pdf).

In spite of the fact that the original concept for frailty definition was based on the physical status [3], the most recent revisions consider three domains contributing to frailty composition: physical, cognitive and psychosocial [4]. The inseparable cognitive dimension in the frailty syndrome has led to the introduction of the new concept of cognitive frailty. According to the definition from the International Academy on Nutrition and Ageing (I.A.N.A.) and the International Association of Gerontology and Geriatrics (I.A.G.G.) international consensus group, "cognitive frailty" is an

heterogeneous clinical manifestation characterized by the simultaneous presence of both physical frailty and non-dementia cognitive impairment, also including a psychological component [5].

Thus, several consensus documents mentioned in this paper introduced the strong recommendation to consider the cognitive status evaluation as part of the assessment of frailty, to both (i) recognize very early signs of cognitive decline associated with neurological diseases; and (ii) recognize cognitive symptoms occurring in systemic diseases and reversible conditions [see for example 6,7]. The phenotypic integration of cognitive and physical assessment is regarded as an obvious way to improve predictive efficacy of all diagnostic or screening approaches for frailty [7]. The normal process of age-related cognitive decline across the life-span is in fact characterized by increasing difficulties with new learning and memory, speed of information processing, language and other cognitive functions, associated or preceded by sensory deterioration [8]. Deterioration in cognitive function can occur as a consequence of a pathological process such as dementia, stroke or acquired brain injury, or as a symptom in chronic diseases (cardiovascular diseases, diabetes, chronic obstructive pulmonary disease) malnutrition, psychiatric conditions, inappropriate poly-therapy and dosages. A successful screening strategy for cognitive performance can help in the effort to distinguish normal cognitive ageing, from its deterioration due to contingent cognitive symptoms in systemic diseases, and from progressive deterioration due to neurological diseases.

2.2. Cognitive decline and deterioration

The paradigm for diagnostic criteria and screening tools for cognitive decline is predominantly AD. In this setting, over the past few decades several organization and working groups have elaborated consensus and position papers over the past few decades with increasing contributions stemming, largely, from progress in the knowledge of pathological mechanisms and biomarkers from biology. These papers are generally intended for "research purposes", although there is an obvious impact in clinical practice. Table 1 reports the main steps in the re-definition of diagnostic criteria for cognitive disorders.

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now Alzheimer Association) (NINCDS-ADRA), in considering AD as a clinico-pathological entity, first elaborated diagnostic criteria in 1984 [9], further updated in 2011 [10], based on 3 rules: (i) the diagnosis of AD is clinico-pathological: it cannot be certified clinically, and needs a post-mortem confirmation to be ascertained; (ii) the diagnosis of AD can only be 'probable'; and (iii) the diagnosis of AD can only be made when the disease is advanced and reaches the threshold of dementia.

The international Working Group on the New Criteria for the Diagnosis of Alzheimer Disease (IWG) elaborated new diagnostic criteria, considering AD as a clinico-biological entity, with the following rule: biomarkers can be considered as surrogate markers of the histopathological changes. According to this, and in contrast with other working groups, the clinical diagnosis can be established in vivo and no more reference to dementia is needed [11,12], and AD is a clinical entity that encompasses both predementia and dementia phases, and its diagnosis can be established in vivo based on a dual clinico-biological entity.

"Mild cognitive impairment" (MCI) was introduced as a nosographic entity at the end of the last century, to define "an intermediate state of cognitive function between the changes seen in ageing and those fulfilling the criteria for dementia and often Alzheimer's disease [13]. Amnesic MCI (aMCI) is distinguished by impairment in memory (plus or minus other domains). Evidence suggests this subtype is the most likely to convert to AD. However,

Table 1
Evolution of diagnostic criteria for AD, MCI and preclinical stages of dementia.

| Organization Chronology | NINCDS-ADRA 1984 | NIA/AA 1999 | IWG 2007–2010 | NIA/AA 2011 | IWG2 2014 |
|-------------------------|--|---|--|--|---|
| Concepts | <i>AD as clinical-pathological entity</i> (i) The diagnosis of AD is clinico-pathological: it cannot be certified clinically and needs a post-mortem confirmation to be ascertained; (ii) The diagnosis of AD can only be 'probable'; (iii) The diagnosis of AD can only be made when the disease is advanced and reaches the threshold of dementia (post-mortem) | <i>Mild Cognitive Impairment</i> An intermediate state of cognitive function between the changes seen in ageing and those fulfilling the criteria for dementia and often Alzheimer's disease | <i>AD as clinical-biological entity</i> –A core clinical phenotype: low free recall that is not normalized by cueing –The presence of biomarkers evidence consistent with AD (structural MRI; FDG/PiB PET; A β /tau/Ptau in the cerebrospinal fluid) | 3 stages: –AD dementia stage –MCI stage –Preclinical stage 2 types of MCI criteria: –For clinical setting –For research purposes that are based on the use of biomarkers | <i>AD as clinical-biological entity</i> –A core clinical phenotype: episodic memory impairment (gradual and progressive change in memory function over more than 6 months; amnesic syndrome of hippocampal type) –In vivo evidence for AD pathology: one of the followings (decreased Ab42 + increased tau or b-tau in CSF; increases amyloid PET; AD autosomal dominant mutation |
| Outcome | Stages: –Probable AD –AD dementia | Types: –Amnesic MCI –Non amnesic MCI | New entities: 2007: Prodromal AD 2011: asymptomatic at risk state for AD; presymptomatic AD | New entities: Preclinical/ presymptomatic AD (+MCI + AD) | New entities: Atypical AD |
| Refs. | [7,8] | Reviewed in [9] | [10,11] | [12] | [13] |

Abbreviations: FDG-PET-FluoroDeoxyGlucose Positron Emission Tomography, IWG-Working Group on the New Criteria for the Diagnosis of Alzheimer Disease, held by Bruno Dubois, MRI-Magnetic Resonance Imaging, NIA/AA-National Institute of Aging/Alzheimer's Association, NINCDS-ADRA-National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, PiB PET-Pittsburgh compound B Positron Emission Tomography.

current consensus also recognizes the non-amnesic MCI subtype (naMCI) where impairment manifests in one or more cognitive domains excluding memory [13].

In 2011, the National Institute on Ageing and the Alzheimer's Association (NIA/AA) developed recommendations to determine the factors which best predict the risk of progression from "normal" cognition to MCI [14]. In this continuum frame, the preclinical stage of AD preceding MCI was introduced. In this spectrum, the following groups of subjects are included: (i) presymptomatic autosomal dominant mutation carriers (APOE gene $\epsilon 4$ allele); (ii) asymptomatic biomarker-positive (low A β_{1-42} in the cerebrospinal fluid, or high PET amyloid binding) older individuals at risk for progression to MCI due to AD and AD dementia; (iii) biomarker-positive individuals who have demonstrated subtle decline from their own baseline that exceeds that expected in typical ageing, but do not yet meet criteria for MCI. This preclinical stage would include a number of informal definitions like "presymptomatic", "latent", "premanifest", and "preclinical". In the absence of biomarker information, the distinction between MCI and dementia is often made based on an assessment of the individuals functional ability, i.e. still intact activities and instrumental activities of daily living.

The 2011 NIA-AA core criteria for dementia includes: (i) difficulties in independent functioning; decline from a previous level of functioning; (ii) no delirium or major psychiatric disorders; cognitive impairment based on history and mental status examination; and (iii) cognitive impairment in at least two of the following domains: learning and memory; reasoning; visuo-spatial abilities; language; personality [14,15].

In 2014, the IWG proposed advances of the previous criteria based on a better biomarkers definition, also introducing "atypical AD", and defining criteria for non-AD dementia [16]. On the contrary, "dementia" has been eliminated from the Diagnostic and Statistical Manual of Mental Disorders V criteria (American Psychiatric Association, <http://www.dsm5.org/Pages/Default.aspx>) and replaced with "major or minor neurocognitive disorder", based on the fact that the previous dementia terminology required the presence of memory impairment for all of the dementias, whereas it has been recognized that memory impairment is not the first domain to be affected in all of the other diseases that cause a neurocognitive disorder.

The "take-home message" from this extensive work and consensus effort is the formal definition of preclinical and prodementia

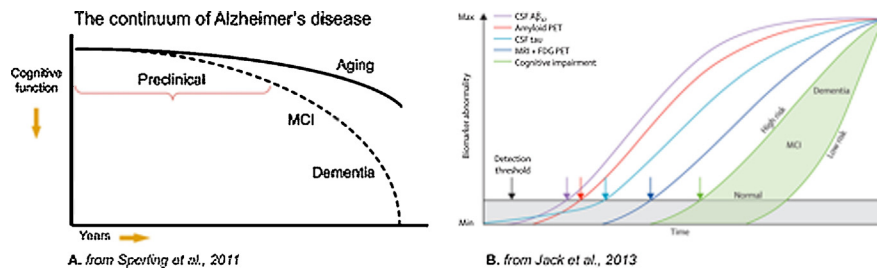


Fig. 1. The biological and clinical continuum of the Alzheimer's disease. A. Model for a clinical trajectory of Alzheimer's disease (from [14]). The preclinical stage precedes MCI, and includes presymptomatic and asymptomatic individuals expressing amyloid- and tau-related biomarkers. B. Model for biomarkers trajectory of Alzheimer's disease (from [17]). The green area identify the cognitive impairment range, from normal to dementia, in which the high- to low-risk individual profile shapes the time for the clinical onset.

stages of AD as entities preceding the MCI and dementia clinical stages. In Fig. 1A, the model of clinical trajectory of AD proposed by NIH-AA is illustrated [16], showing the long preclinical phase including presymptomatic (autosomal dominant mutation carriers) and asymptomatic (biomarker-positive older individuals) subjects before MCI. This "preclinical phase" is deeply investigated to find "biomarkers" to define what can be called the "AD-signature". The proposed model to link immunohistology to biomarkers is presented in Fig. 1B [17], where the concept of "high" and "low" risk individuals is introduced, based on the concept of "cognitive reserve" which varies significantly among individuals. The final target is to provide instruments for the early detection of the so-called "AD-signature". As a consequence, the challenge for the AD field is now to develop sensitive and specific biomarkers and diagnostic criteria to explore the "preclinical stage", thus facing key questions such as sensitivity and specificity of the screening instruments, costs, and ethical issues. Part of these key questions can furthermore be transferred to the matter of cognitive impairment in neurological conditions other than AD, and non-neurological conditions.

3. Moving from cognitive assessment towards cognitive screening

3.1. The importance of early diagnosis

There are several main reasons for the need to identify a "pre-clinical phase of cognitive decline", from both a biological and medical point of view. (i) Detection of preclinical dementia is an imperative need for the discovery and the development of effective treatments in AD. For example, the Alzheimer's Association provided guidelines for the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting [18]. (ii) Detection of risk indicators related to non-neurological diseases when still reversible might significantly improve the quality of life and disease outcome, and prevent cognitive decline [6]. (iii) Identification of cognitive frailty and pre-frailty would help to implement strategies for secondary and tertiary prevention of adverse events, like hospitalization, to personalize the medical management of vulnerable people in critical settings, such as the perioperative setting (in relation to anaesthesia, pain, mobilization, etc.), and to support decisions for chronic therapies (e.g. psychiatric and analgesic drugs prescription). It would also support the management of non-medical contexts such as employment or welfare support, or care needs assessment. Indeed, the monitoring of cognitive status to identify early defects is recognized as a key clinical strategy to ameliorate the outcome in chronic diseases, such as diabetes, hypertension, kidney and liver diseases, also leading to an improvement of adherence to treatments, and preventing the risk for serious short- and long-term physical

complications. For example, the 2013 Diabetes Conference stated that physical and mental health care are both priorities to establish the efficacy and cost-effectiveness of paradigms of diabetes care [19]. Consensus also exists on the need for more studies in chronic kidney diseases to monitor every-day cognitive abilities and to provide longitudinal data describing change in multiple domains of cognitive functioning [20]. Cardiovascular diseases and cognitive decline share several risk factors. Hypertension is recognized as the most important modifiable vascular risk factor for development and progression of cognitive decline [21]. Hepatic encephalopathy is a paradigm for a metabolic condition affecting cognition [22].

Thus, the discussion moves towards (i) the identification and development of appropriate instruments for cognitive frailty; (ii) the existence or not of a "common signature" in early defects due to neurological (e.g. AD) and non-neurological conditions; (iii) the context in which to use cognitive screening instruments (specialist care, primary care, non-clinical settings); (iv) the purpose and modalities of cognitive screening (anonymous population screening or individual assessment).

3.2. Screening tools

"To screen" implies the use of exquisitely sensitive, extremely specific, and low cost tools, to be administered on large populations of healthy people and resulting in a very accurate positive or negative predictive value, in order to monitor the so-called "detectable pre-clinical phase (DPCP)" [23]. Screening is not a diagnostic procedure, and can be carried out anonymously or to identify "at risk" subjects (see 5).

Preclinical and clinical studies in AD have provided a large body of evidence concerning the research pillars to be investigated to develop instruments for early diagnosis of cognitive defect, e.g. imaging, biomarkers in biological fluids, and psycho/neurocognitive tests. Research on biomarkers is directed towards specific disease mechanisms (e.g. genetic factors, amyloid and tau associated biomarkers in the cerebrospinal fluid in AD), and not yet towards more general neurobiological mechanisms that are not necessarily associated with specific diseases but that could underlie a cognitive defect. Thus, results can so far only be applied to a selected population.

At the moment, neuropsychological tests are regarded as the most implementable screening instruments for the cognitive decline. Recent meta-analysis and consensus papers have indicated some brief screenings as the most sensitive cognitive tests to discriminate normal participants from people affected by MCI and dementia. These tools (e.g. Mini Mental State Examination – MMSE, Montreal Cognitive Assessment – MoCA, General Practitioners assessment of Cognition – GPCog, Clock Drawing Test–CDT, Verbal fluency, 3 Objects 3 Places–3OP,

etc.) measure those abilities that seem to be critical for an early diagnosis of cognitive decline (memory, executive functions, verbal and visuospatial abilities, attention and orientation) [18,24–28].

However, as recognized by the Alzheimer's Association Medicare Annual Wellness Visit Algorithm for Assessment of Cognition, the neuropsychological tests suffer from several biases, such as uneven quantity and quality in published research and appropriate validation in populations with different educational levels. Moreover, not enough studies are available which compare the use of the above mentioned brief cognitive screening tests in population-based screening vs. more targeted approaches. Finally, non-invasive personal monitoring techniques for new cognitive measures are listed among the recommended milestones of the US National plan to address AD [29].

The U.S. Preventive Services Task Force (USPSTF), in updating its recommendation on screening for cognitive impairment in older adults, concluded that the clinical importance of their benefit is unclear because the average effects of benefit observed in trials was small or had a large amount of imprecision [28]. However, part of the concern is related to the poor validation of existing screening tools, leading to the risk of over-diagnosis. This conclusion emphasizes the need of innovation for the development of more sensitive, specific and accurate tools.

4. The need for novel methods: the language domain and perspective of automatic analysis of language production

In the attempt to overcome pitfalls of conventional neuropsychological tests, and in searching for a cognitive domain that is sensitive to very early alterations, the language seems to be a potential candidate. Language presents impaired and spared domains across the lifespan, although interfering cues, like education and sensory decline may impact on this [30]. This functional pattern challenges models based on a general age-related reductions in cognitive resources, predicting a general cognitive declines [31]. In particular, language production shows reliable age-related declines [32]. Older adults produce propositionally and syntactically simpler speech than younger adults in natural contexts, use more vague terms, have more frequent and emptier pauses, and are slower to access phonological information in experimental contexts. People presenting a progressive decline in mental ability often show insidious deficits in language processing even in the very early, presymptomatic stages of the disease [30,31]. Thus, the investigation of this cognitive domain seems to be promising in the context of detectable pre-clinical phase, with regards to both early diagnosis and a potential screening tool. A number of longitudinal retrospective studies have already demonstrated that linguistic features could act as a prodromal marker of cognitive dysfunction: for example, the Nun study [33], the Iris Murdoch study [34] or the Harold Wilson project [35].

Conventional neuropsychological tests of language are performed in a non-ecological setting, thus impacting on the naturalness of the participant's responses [36], and are assessed focusing on: comprehension of easy and short sentences; repetition and/or production of simple words and instructions; phonemic and semantic lexical access; semantic abstraction; simple verbal construction of a thought. Most aspects of pragmatics (use of language for different purposes, changing language according to the needs of a situation, following rules for conversations, etc.), prosody and contextual abilities of language are not considered in a quantitative prospective and do not influence the final score and diagnosis.

Verbal and nonverbal abilities may be assessed through the analysis of the spontaneous discourse, which allows study of language used in a real-world context, giving attention to the

intentions, the attentional state of the speaker and the communicative context in which it takes place. This type of analysis has been limited by its time-consuming nature. However, during the last few years, automated computational techniques at least partially overcome this limitation, providing this to be a crucial source of information that can reveal latent patterns and regularities. The development of new sophisticated techniques from Natural Language Processing (NLP) have been used to analyze written texts, clinically elicited utterances and spontaneous production [37]. These computational methods have been already successfully applied to the characterization of language change over the course of normal ageing and to the study of linguistic cues of cerebral functional disorders: not only in the case of language disruption associated with focal brain lesions, but also for MCI and sub-types, such as AD and Fronto-Temporal Lobar Degeneration [38,39].

In the frame of the OPLON project (OPportunities for active and healthy LONgevity) supported by the Italian Minister for Instruction, University and Research, as one of the strategic project for the national research agenda ("smart cities"), we are working to build methods to identify cognitive frailty at very early stage by processing language productions. This instrument will be developed to be used at General Practitioner level, for frequent, low-cost and non-intrusive cognitive decline screening and cognitive status monitoring, and abnormal results will be addressed to a specialist setting. The methodological key is the building of a device able to analyze and classify the spoken production of enrolled participants, identifying objective cues in patients' speeches relative to healthy controls. The system will conduct a quantitative analysis of spoken texts, computing acoustic/prosodic, lexical, morpho-syntactic and semantic characteristics [38,40,41].

Statistically relevant features will be the input for a machine learning system, which has been previously trained on annotated linguistic corpora. The functioning of a similar device can be basically outlined as follows: Recording of speech sample; Automatic transcription of speech sample; Automatic annotation (i.e. Part of Speech tagging, syntactic parsing, word sense and semantic role labelling. . .); Multidimensional features computation; Data classification through Machine Learning system(s). NLP techniques are usually developed and trained on well-formed, written text. Although pathologic language can present some difficulties for these algorithms, current automatic systems are sufficiently reliable for these tasks, being already able to distinguish between healthy control and patients with a fair degree of accuracy if properly set up [38].

Additionally, further members of the EIP-AHA A3 group are examining the utility of assessment of language based socio-emotional component of cognition, autobiographical memory specificity. Ability to recall autobiographical events in a manner that is specific as to time and place accompanied by description of detail, as opposed to over-general categories or extended time periods has been associated with ability to recall detail as opposed to general gist from text, and to underlying measures of working memory and executive function, especially measures of updating within executive function [42,43]. Ability to recall specific events has been repeatedly shown to decline in normal old age, worsening with increasing general cognitive impairment. However, its proposed use as a screening tool has some specific benefits as assessed in several independent studies, being associated to mood disorders, social and daily hassles or trauma, measures of independence function. Thus, given the simplicity of its measurement and analysis (a simple cue word technique is used, and in depth linguistic analysis is not necessary) and the perceived face validity to screening participants, its use as an indicator of "real-world" functional cognition is proposed in addition to the in depth automated linguistic analysis proposed above.

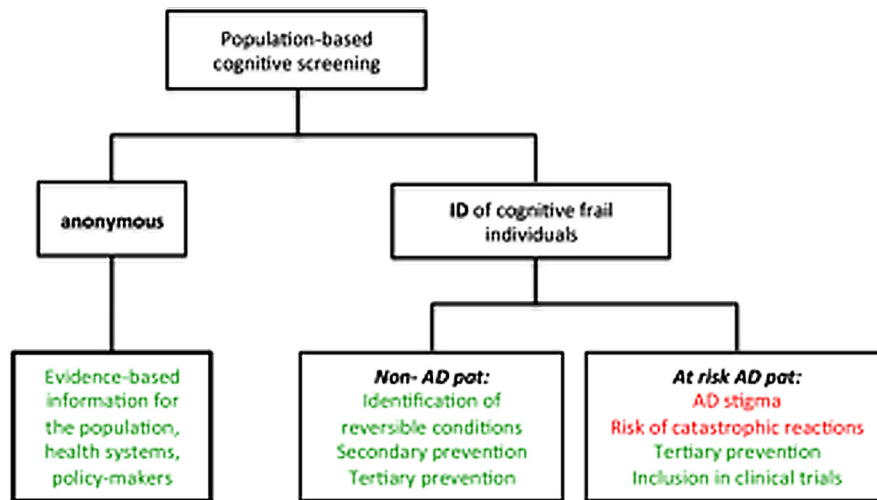


Fig. 2. Flowchart of some “pro” (green) and “contra” (red) considerations for population-based cognitive screening programmes, used in anonymous context (left arm) and aimed to identify cognitive frail subjects (right arm).

5. Ethical concerns

In almost all consensus and position papers referred to in this article, diagnostic criteria for cognitive decline are discussed according to their use in research or clinical settings. In fact, if early diagnosis of cognitive decline in selected, at risk, or symptomatic population is an accepted principle, as it is for all areas of evidence-based medicine, the current question about the possibility of disclosing cognitive frailty (or its potential) in the context of asymptomatic patients, and the uses to which screening is put is still open. Moreover, discussion about screening must be itemized into anonymous screening (i.e. for epidemiological, economic, social sciences purposes, etc.) vs the identification of individuals that meet specific risk criteria (i.e. for medical purposes).

The stringent ethical question that arises from the hypothesis of population/community-based screening programmes of cognitive frailty is: should people who are asymptomatic be told that they are more likely than others to develop a cognitive impairment [44]? The identification of “cognitively frail persons” in the context of a population-based screening programme might lead to two opposite scenarios: (i) to identify cognitive decline due to non-neurological disorders, that might be potentially reversible if early and correctly diagnosed; (ii) to identify participants in an asymptomatic phase of a neurodegenerative cognitive disorder. While the benefit in the first case is evident, the questions in the second scenario are related to the risk of disclosing an AD diagnosis in asymptomatic or minimally symptomatic persons with full insight, with no specific treatment options currently available *plus* the risk of catastrophic reactions related to an “AD-stigma” [45].

Fig. 2 suggests a summary flowchart of some “pro” and “contra” considerations for population-based cognitive screening programmes, to be considered in parallel with the development and validation of appropriate tools.

A recent position paper, considering the shift from pathological diagnosis to the assessment of risk factors (e.g. “at-risk individuals”), and based on interdisciplinary considerations [46], listed the following items and main determinants for this discussion: public policy goals; ethical issues of research participation; individual and social consequences; exploring diversity and promoting public dialogue.

Given the above debates and evidence, we suggest that the question should be less “AD-centred” and re-directed as follow: what is the potential benefit of population-based cognitive screening programmes vs the hazard of AD overdiagnosis? Potential

benefits include secondary prevention based on: (i) the recognition and correction of fully reversible cognitive declines due to non-neurological disorders and diseases, malnutrition, inappropriate poly-therapies, etc.; (ii) more appropriate management in hospitalization, prescribing, surgery and anaesthesia; (iii) appropriate steps to prevent injury (preventing falls, burns from leaving heaters or cookers on, dropping hot liquids etc.) in home-care; (iv) better adherence and management of other medical conditions, given that social isolation and depression are some of the biggest contributors to deterioration; (v) to enable policy makers to take decisions based on scientific evidences regarding medical and social economy in an ageing-population, to predict and plan care needs and housing decisions. Again, although the risk of AD overdiagnosis is probably still high at the moment, “strategies to overcome this limitation might be on the horizon” [17], thanks to the research in non-invasive biomarkers.

On-going research for non-invasive screening tools should consider not only pathology-based biomarkers (e.g. amyloid-related), but also novel markers exploring alterations in the cognitive reserve and synaptic function, able to detect early cognitive decline in a wide range of non-neurological and neurological conditions. To do this, research needs population-based studies and longitudinal design, able to bring in the same arena cognitive tools, blood tests, biomarkers including imaging, to finally validate the most appropriate screening tools in stratified populations.

Contributors

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|-----------------------|---|
| Laura Calzà | Literature review, manuscript preparation and coordination with the EIP-AHA A3 “cognitive decline” consensus group. |
| Daniela Beltrami | Literature review and manuscript preparation. |
| Gloria Gagliardi | Literature review and manuscript preparation. |
| Enrico Ghidoni | Literature review and manuscript preparation. |
| Norina Marcello | Literature review and manuscript preparation. |
| Rema Rossini-Favretti | Literature review and manuscript preparation. |
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Co-authors from the Cognitive Decline subgroup of the A3 Action Group in European Innovation Partnership for Active and Healthy Ageing (EIPAH):

- João Apóstolo, Portugal Centre for Evidence Based Practice, Health Sciences Research Unit: Nursing (UICISA: E), Nursing School of Coimbra, Portugal.
- Nadine Correia Santos, Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal, and ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal.
- Maria da Graça Pinto, Faculty of Arts and Humanities of University of Porto, Portugal.
- Joanne Feeney, School of Medicine, Dentistry and Biomedical Science, Queen's University, Belfast, Northern Ireland.
- Carol Holland, Aston Research Centre for Healthy Ageing, Aston University, Birmingham, B4 7ET, UK.
- Raúl Lopez-Anton, Department of Psychology and Sociology. University of Zaragoza, Zaragoza, Spain; Instituto de Investigación Sanitaria de Aragón (ISS-Aragón), Zaragoza, Spain.
- João O. Malva, Faculty of Medicine, University of Coimbra, Portugal–Ageing@Coimbra Reference Site.
- Maura Marcucci, Geriatric Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico & Dept. of Clinical Sciences and Community Health, University of Milan, Milan, Italy.
- Matthew DL O'Connell, The Irish Longitudinal Study on Ageing, Trinity College, Dublin, Ireland.
- Dina Popovic, Barcelona Bipolar Disorders Programme, Hospital Clinic, IDIBAPS, CIBERSAM, University of Barcelona, Barcelona, Spain.
- Mónica Sousa–University of Aveiro.
- Isabel Varela-Nieto, Institute for Biomedical Research, CSIC-UAM and IdiPAZ-CIBERER, Madrid 28029, Spain.
- Eduard Vieta, Barcelona Bipolar Disorders Programme, Hospital Clinic, IDIBAPS, CIBERSAM, University of Barcelona, Barcelona, Spain.

References

- [1] http://ec.europa.eu/research/innovation-union/pdf/active-healthy-ageing/gp_a3.pdf, (accessed date 26.05.15).
- [2] Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, et al. FOD-CC group (Appendix 1), searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. *J Gerontol A Biol Sci Med Sci* 2013;68:62–7.
- [3] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–56.
- [4] Malmstrom TK, Morley JE. The frail brain. *J Am Med Dir Assoc* 2013;14:453–5.
- [5] Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ousset PJ, Gillette-Guyonnet S, et al. IANA/IAGG. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging* 2013;17:726–34.
- [6] Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chételat G, et al. Subjective Cognitive Decline Initiative (SCD-I) Working Group. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement* 2014;10:844–52.
- [7] Ruan Q, Yu Z, Chen M, Bao Z, Li J, He W. Cognitive frailty, a novel target for the prevention of elderly dependency. *Ageing Res Rev* 2015;20C:1–10.
- [8] Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB. Alzheimer's Disease Neuroimaging Initiative. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. *Prog Neurobiol* 2014;117:20–40.
- [9] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–44.
- [10] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263–9.
- [11] 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.
- [12] Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* 2010;9:1118–27.
- [13] Petersen RC. Clinical practice. Mild cognitive impairment. *N Engl J Med* 2011;364:2227–34.
- [14] Jack Jr CR, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, et al. Introduction to the recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:257–62.
- [15] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:280–92.
- [16] Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol* 2014;13:614–29.
- [17] Jack Jr CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol* 2013;12:207–16.
- [18] Cordell CB, Borson S, Boustani M, Chodosh J, Reuben D, Verghese J, et al. Medicare Detection of Cognitive Impairment Workgroup Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. *Alzheimers Dement* 2013;9:141–50.
- [19] Ducat L, Rubenstein A, Philipson LH, Anderson BJ. A review of the mental health issues of diabetes conference. *Diabetes Care* 2015;38:333–8.
- [20] Anand S, Johansen KL, Kurella Tamura M. Aging and chronic kidney disease: the impact on physical function and cognition. *J Gerontol A Biol Sci Med Sci* 2014;69:315–22.
- [21] Qiu C, Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. *Nat Rev Cardiol* 2015, <http://dx.doi.org/10.1038/nrcardio.2014.223>.
- [22] Rivera Ramos JF, Rodríguez Leal C. Review of the final report of the 1998 Working Party on definition, nomenclature and diagnosis of hepatic encephalopathy. *Ann Hepatol* 2011;10(Suppl. 2):S36–9.
- [23] http://sphweb.bumc.bu.edu/otlt/MPH-Modules/EP/EP713_Screening/EP713_Screening_print.html, (accessed date 26.05.15).
- [24] Chen P, Ratcliff G, Belle SH, Cauley JA, DeKoshy ST, Ganguli M. Patterns of cognitive decline in presymptomatic Alzheimer disease. A prospective community study. *Arch Gen Psychiatry* 2001;58:853–8.
- [25] Bäckman L, Jones S, Berger AK, Laukka EJ, Small BJ. Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. *Neuropsychology* 2005;19:520–31.
- [26] Grober E, Hall CH, Lipton RB, Zonderman AB, Resnick SM, Kawas C. Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. *J Int Neuropsychol Soc* 2008;14:266–78.
- [27] Ismail Z, Rajji TK, Shulman KI. Brief cognitive screening instruments: an update. *Int J Geriatr Psychiatry* 2010;25:111–20.
- [28] Lin JS, O'Connor E, Rossom RC, Perdue LA, Eckstrom E. Screening for cognitive impairment in older adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2013;159:601–12.
- [29] Fargo KN, Aisen P, Albert M, Au R, Corrada MM, DeKosky S. (Alzheimer's Association National Plan Milestone Workgroup) 2014 Report on the Milestones for the US National Plan to Address Alzheimer's Disease. *Alzheimers Dement* 2014;10:S430–52.

- [30] Burke DM, Shafto MA. In: Craik FIM, Salthouse TA, editors. *The handbook of aging and cognition*. 2 New York: Psychology Press; 2008. p. 373–443.
- [31] Shafto MA, Tyler LK. Language in the aging brain: the network dynamics of cognitive decline and preservation. *Science* 2014;346:583–7.
- [32] Antonenko D, Flöel A. Healthy aging by staying selectively connected: a mini-review. *Gerontology* 2014;60:3–9.
- [33] Kemper S, Greiner LH, Marquis JG, Prenovost K, Mitzner TL. Language decline across the life span: findings from the nun study. *Psychol Aging* 2001;16:227–39.
- [34] Garrard P, Maloney LM, Hodges JR, Patterson K. The effects of very early Alzheimer's disease on the characteristics of writing by a renowned author. *Brain* 2005;128:250–60.
- [35] Garrard P. Cognitive archaeology: uses, methods, and results. *J Neuroling* 2009;22:250–65.
- [36] Bucks RS, Singh S, Cuerden JM, Wilcock GK. Analysis of spontaneous, conversational speech in dementia of Alzheimer type: evaluation of an objective technique for analysing lexical performance. *Aphasiology* 2000;14:71–91.
- [37] Elvevåg B, Garrard P. Language, computer and cognitive neuroscience. *Cortex* 2014;55:1–4.
- [38] Roark B, Mitchell M, Hosom J-P, Hollingshead K, Kaye JA. Spoken language derived measures for detecting Mild Cognitive Impairment. *IEEE/ACM Trans Audio Speech Lang Process* 2011;19:2081–90.
- [39] Fraser KC, Meltzer JA, Graham NL, Leonard C, Hirst G, et al. Automated classification of Primary Progressive Aphasia subtypes from narrative speech transcripts. *Cortex* 2014;55:43–60.
- [40] Alegria R, Gallo C, Bolso M, dos Santos B, Prisco CR, Bottino C, et al. Comparative study of the uses of grammatical categories: adjectives, adverbs, pronouns, interjections, conjunctions, and prepositions in patients with Alzheimer's disease. *Alzheimers Dement* 2013;9:P882.
- [41] López-de Ipiña K, Alonso J-B, Travieso CM, Solé-Casals J, Egiraun H, Faundez-Zanuy M, et al. On the selection of non-invasive methods based on speech analysis oriented to automatic Alzheimer disease diagnosis. *Sensors* 2013;13:6730–45.
- [42] Holland CA, Ridout N, Walford E, Geraghty J. Executive function and emotional focus in autobiographical memory specificity in older adults. *Memory* 2012;20:779–93.
- [43] Holland CA, Rabbitt PM. Autobiographical and text recall in the elderly: an investigation of a processing resource deficit. *Q J Exp Psychol* 1990;42:441–70.
- [44] Hughes JC. Conceptual issues in 'cognitive impairment'. *Curr Opin Psychiatry* 2015;28:188–93.
- [45] Gauthier S, Leuzy A, Racine E, Rosa-Neto P. Diagnosis and management of Alzheimer's disease: past, present and future ethical issues. *Prog Neurobiol* 2013;110:102–13.
- [46] Schickel S, Schweda M, Ballenger JF, Fox PJ, Halpern J, Kramer JH. Before it is too late: professional responsibilities in late-onset Alzheimer's research and pre-symptomatic prediction. *Front Hum Neurosci* 2014;8:921–7.