Challenges to identifying risk versus protective factors in Alzheimer's disease

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Alzheimer's disease (AD), a neurodegenerative disorder characterized by a progressive loss of cognitive functioning and independence in daily living, remains an unsolved challenge in modern health organization[1,2].

In the landscape of AD research, the spotlight mainly gravitates around identification of risk factors (both genetic and environmental) and of biomarkers for early disease diagnosis. In contrast, little attention is devoted to 'protective factors', which indeed can balance the presence of risk-factors delaying the disease onset or smoothing its aggressiveness up to a level that the clinical symptoms will never appear during the life span[3].

The recent study by Fortea et al.[4] aimed to explore the impact of having two copies of the APOE4 gene on the risk of developing AD. Their analysis of data from multiple large studies revealed that from age 55 APOE4 homozygotes had significantly higher levels of AD pathological markers than those with two copies of the APOE3 gene. By age 65, most APOE4 homozygotes had abnormal amyloid levels and positive amyloid brain scans. Symptoms also began earlier in APOE4 homozygotes, around age 65. Despite these findings, in the later stages of dementia, brain scans showed no differences between APOE4 and APOE3 homozygotes. The study suggests that APOE4 homozygotes may have a unique genetic form of AD, requiring different approaches to prevention, clinical trial inclusion and treatment. Most of the conclusions are exclusively based on the idea of a *biologically defined* AD even in absence of symptoms. The ongoing debate between *biological* and *clinical/neuropsychological* diagnoses, however, underscores the need for a comprehensive approach to AD diagnosis. This approach should recognize individual *resilience factors*, including genetic profiles, and integrate both pathological and protective markers to accurately predict risk of disease onset and trajectory.

Within this frame, a pivotal role is played by Cognitive Reserve (CR), which refers to the brain's ability to withstand neuropathological damage through various compensatory mechanisms, such as neural/synaptic plasticity, efficient neural networks organization, and cognitive abilities training[5]. Indeed, individuals with high CR - despite harboring similar levels of neuropathological burden as those with low reserve - are either fully protected (no clinically evident disease) or exhibit delayed onset of symptoms and slower disease progression[6]. Recognizing the importance of CR shifts the focus from merely identifying risk factors to empowering individuals to boost their cognitive resources through innovative drugs and non-pharmacological approaches (i.e. transcranial stimulation), lifestyle modifications including cognitive training and social engagement, thus offering a promising avenue for intervention and prevention strategies[7].

Additionally. based on clinical experience and initiatives, undertaken within the Interceptor Project, launched and funded by the Italian Medicines Agency and the Italian Ministry of Health[8], we have the possibility to observe a large sample of Mild Cognitive Impairment (MCI) over three-year period. This population has a significantly higher risk of developing dementia over time compared to an age, gender, and education-matched population with normal cognition[9]. From these observations and previous studies, it is important to highlight that amyloid positivity in the absence of clinical symptoms does not support a diagnosis of AD. Furthermore, MCI individuals with APOE4/4 may exhibit amyloid positivity and memory deficits that do not progress, as seen in conditions such as limbic-predominant age-related TDP-43 encephalopathy (LATE) and primary age-related tauopathy (PART)[10].

The prevailing debate between proponents of a biological diagnosis and those advocating for a clinical/biological definition underscores the need to consider individual resilience factors that

contribute to maintaining cognitive function, even in the presence of brain pathology typical of AD, including a specific genetic profile.

We argue that the exclusive reliance on biological markers neglects the diverse array of protective factors that can shield individuals from developing symptomatic AD. Moreover, we share the concern regarding the potential stigma associated with a biological diagnosis in the absence of symptoms. Labeling individuals as AD when they are cognitively healthy (and with a non-marginal possibility to remain so for the rest of their life) solely based on biomarker/genetic profiles has profound implications for their social, professional, and emotional well-being. This highlights the importance of adopting a comprehensive approach, considering both risk markers and protective factors for the definition of a precise risk stratification at the individual level. By exploring factors such as CR and the measurable contribution to it from social engagement, physical activity, cognitive training, genetic profile, medical co-morbidities and many other factors, a more precise identification of those individuals who may maintain normal cognitive function despite the presence of an underlying AD-like pathology will be achieved. This approach may also be useful for the definition of interventional strategies targeting those individuals who might mostly benefit from pharmacological and non-pharmacological therapeutic interventions (i.e., cognitive training, neuromodulation).

Last but not least, we should be aware of the ethical and organizational dilemmas associated with the commercial interest in the promotion of diagnostic kits allowing a “biological diagnosis” in asymptomatic subjects, without a precise quantification of the risk of future progression. Everyone can try to imagine the impact of a wrong prediction of this type on personal, affective, familiar, social (including health insurances) and professional life.

A more careful consideration and transparent debate within the scientific community is needed to directly focus attention on the welfare of patients and their families in order to avoid deterministic inequalities and stigma.

Statements and Declarations

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Competing Interests
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CP: Conceptualization, Writing- Original draft preparation
CC: Conceptualization, Writing- Original draft preparation
SC: Writing- Reviewing and Editing
NC: Writing- Reviewing and Editing
MC: Writing- Reviewing and Editing
CM: Writing- Reviewing and Editing
DP: Writing- Reviewing and Editing
AR: Writing- Reviewing and Editing
PS: Writing- Reviewing and Editing
FT: Writing- Reviewing and Editing
NV: Writing- Reviewing and Editing
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