

## Editorial

# Towards 2022: What are prevention and risk reduction in Alzheimer's disease?

**Ricardo F. Allegri<sup>1</sup>**

How to cite this article:

Allegri, R. F. (2021). Editorial. Towards 2022: What are prevention and risk reduction in Alzheimer's disease? *Journal of Applied Cognitive Neuroscience*, 2(2), e00004009.  
<https://doi.org/10.17981/JACN.2.2.2021.00>

The increase in life expectancy has led in recent years to neurodegenerative pathologies, such as Alzheimer's disease, that were strange in the last century, now become so frequent that there is talk of a new epidemic. It is estimated that approximately 50 000 000 patients suffer dementia around the world (World Health Organization-[WHO, 2012](#)). Alzheimer's disease is the most common dementia, and brain pathology begin up to 25 years before the first clinical symptoms appear ([Bateman et al., 2012](#)). Thus, Alzheimer currently has five stages, the pre-symptomatic, the mild cognitive impairment, and the mild, moderate and severe dementia.

Since the original description in 1904 by Alois Alzheimer, the disease could only be definitively diagnosed by neuropathological, and the clinical diagnosis was only probable or possible (NINCDS ADRDA, [McKhan et al., 1984](#)). In recent years, more detailed knowledge of structural neuroimaging (hippocampal volume by MRI), metabolic (FDG-PET), molecular (amyloid PET), and cerebrospinal fluid studies (A $\beta$ 42, tau and f-tau) make it possible to diagnose Dementia due to Alzheimer's disease while the patient is alive ([McKhan et al., 2011](#)) and even at pre-symptomatic stage of the disease ([Sperling et al, 2011](#)).

<sup>1</sup> Instituto Neurológico Fleni, FAAN, Buenos Aires, Argentina.  
Contact mail: [rallegri@fleni.org.ar](mailto:rallegri@fleni.org.ar)  
ORCID: <http://orcid.org/0000-0001-7166-1234>

Early diagnosis of these patients is key given that if we manage to delay the onset or evolution of Alzheimer's disease by five years, the prevalence of Alzheimer's disease is reduced by 50% and if we delay it for 10 years it is reduced by 75% (Brookmeyer, Johnson, Ziegler-Graham & Arrighi, 2007). In the US, every six months of delay in the onset and progression of the disease corresponds to a projected savings of U\$4.7 trillion over 10 years and about U\$18 trillion over 50 years (Wimo & Prince, 2010; Brookmeyer et al., 2007; Prince, Bryce & Ferri, 2011; Getsios, Blume, Ishak, Maclaine & Hernández, 2012).

This situation has led in 2012 that WHO together with ADI-Alzheimer's Disease International published the report "Dementia: a public health priority" highlighting the importance of taking early actions in the management of these patients (WHO, 2012).

All this knowledge about the different clinical and preclinical stages of the disease as well as the economic and socio-sanitary cost have led in recent years to prioritize prevention both in the proper management of risk factors (Kivipelto et al., 2020) as in pharmacological prevention (Cummings, Lee, Zhong, Fonseca & Taghva, 2021).

Prevention is defined as actions aimed at eradicating, eliminating or minimizing the impact of disease and disability (Feinleib, 2001). The terms "prevention" and "risk reduction" have been frequently used interchangeably when speaking of clinical interventions to delay or prevent the onset of a disease, however prevention in a broad sense is not only reducing risks but also includes pharmacological treatments (Hodes et al., 2019).

Prevention can be divided into levels (WHO EMRO, 2015):

1. *Primary Prevention*: avoid or delay the onset of the disease (vaccination, elimination and control of environmental risks, health education, etc.).
2. *Secondary Prevention*: it is aimed at detecting the disease in early stages in which the establishment of adequate measures can prevent its progression or prevent its complications.
3. *Tertiary Prevention*: includes those measures aimed at treatment and rehabilitation to minimize the consequences and sequelae of the same.
4. *Quaternary prevention*: that has to do with preventing relapses.

In the case of Alzheimer's disease, which, as mentioned, begins neuropathological many years before the onset of clinical symptoms, the example of "risk reduction" is the international work FINGER (Kivipelto et al., 2020) acting on the control of the vascular factors (hypertension, diabetes, dyslipidaemia, obesity, and sedentary lifestyle), diet, physical and cognitive exercises, while the possibility of investigating drugs before clinical symptoms begin is what is known as secondary prevention (period in which the subject has the pathology but not the symptoms) and primary prevention before the pathology begins.

There are currently 126 investigational drugs in Alzheimer's disease at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) in 2021, the largest number being disease modifiers that act on onset or progression. There is a growing number of agents targeting non-Alzheimer's dementias (43%) and the total number of trial participants is more than 38,000 (Cummings et al., 2021).

In phase 2, there are 74 agents, 64 are disease modifiers, 11 anti-amyloid, 9 anti-tau, 12 anti-inflammatories, 12 neuroprotectives, 4 on bioenergetics metabolism, 3 vascular, and 4 proteostasis (Cummings et al., 2021).

In phase 3, there are 28 agents, 17 are disease modifiers, 5 are biological therapies, and 12 are small molecules. 5 anti-amyloid, one anti-tau, 2 anti-inflammatories, 3 neuroprotectives, 2 on bioenergetics metabolism, 1 vascular. There are 3 anti-amyloid studies in preclinical (secondary prevention) and 4 in prodromal. The anti-tau is for mild to moderate dementia (Cummings et al., 2021).

Several secondary prevention studies are supported by the US National Institute on Aging: 1. Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), phase II/III study gantenerumab and solanezumab in patients with an Alzheimer's disease mutation (Bateman et al., 2012) 2. The Alzheimer's Prevention Initiative APOE4 Trial, testing an anti-amyloid in APOE 4 homozygous normal volunteers (Reiman and Tariot) 3. Alzheimer's Disease Cooperative Study Anti-Amyloid Treatment in Asymptomatic AD Trial (A4). Secondary prevention with solanezumab in normal subjects with a positive amyloid biomarker in the brain.

Finally as we see today in research, in the coming years, primary and secondary prevention will be the basis of clinical treatment for Alzheimer's disease, based in risk reduction and drug prevention.

#### REFERENCIAS

- Bateman, R. J.; Xiong, C.; Benzinger, T.; Fagan, A. M.; Goate, A.; Fox, N. C.; Marcus, D. S.; Cairns, N. J.; Xie, X., Blazey, T. M.; Holtzman, D. M.; Santacruz, A.; Buckles, V.; Oliver, A.; Moulder, K.; Aisen, P. S.; Ghetti, B.; Klunk, W. E.; McDade, E.; Martins, R. N.; Masters, C. L.; Mayeux, R.; Ringman, J. M.; Rossor, M. N.; Schofield, P. R.; Sperling, R. A.; Salloway, S. & Morris, J. C. (2012). Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's disease. *The New England Journal of Medicine*, 367(9), 795–804.  
<https://doi.org/10.1056/NEJMoa1202753>
- Brookmeyer, R.; Johnson, E.; Ziegler-Graham, K. & Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. *Alzheimer's & Dementia*, 3(3), 186–191.  
<https://doi.org/10.1016/j.jalz.2007.04.381>
- Cummings, J.; Lee, G.; Zhong, K.; Fonseca, J. & Taghva, K. (2021). Alzheimer's disease drug development pipeline: 2021. *Alzheimer's Dement*, 7(1), 1–24.  
<https://doi.org/10.1002/trc2.12179>
- Feinleib, M. (2001). A Dictionary of Epidemiology, Fourth Edition - Edited by John M. Last, Robert A. Spasoff, and Susan S. Harris. *American Journal of Epidemiology*, 154(1), 93–94.  
<https://doi.org/10.1093/aje/154.1.93-a>
- Getsios, D.; Blume, S.; Ishak, K. J.; Maclaine, G. & Hernández, L. (2012). An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom. *Alzheimer & Dementia*, 8(1), 22–30.  
<https://doi.org/10.1016/j.jalz.2010.07.001>

- Hodes, J. F.; Oakley, C. L.; O’Keefe, J. H.; Lu, P.; Galvin, J. E.; Saif, N.; Bellara, S.; Rahman, A.; Kaufman, Y.; Hristov, H.; Rajji, T. K.; Fosnacht, A. M.; Patel, S.; Merrill, D. A.; Kaiser, S.; Meléndez-Cabrero, J.; Melendez, J. A.; Krikorian, R. & Isaacson, R. S. (2019). Alzheimer’s “Prevention ”vs.“ Risk Reduction: Transcending Semantics for Clinical Practice. *Frontiers in Neurology*, 9(1), 1–8.  
<https://doi.org/10.3389/fneur.2018.01179>
- Kivipelto, M.; Mangialasche, F.; Snyder, H. M.; Allegri, R. F.; Andrieu, S.; Arai, H.; Baker, L.; Belleville, S.; Brodaty, H.; Brucki, S. M.; Calandri, I.; Caramelli, P.; Chen, C.; Chertkow, H.; Chew, E.; Choi, S. H.; Chowdhary, N.; Crivelli, L.; De La Torre, R.; Du, Y.;Dua, T.; Espeland, M.; Feldman, H. H.; Hartmanis, M.; Hartmann, T.; Heffernan, M.; Henry, C. J.; Hong, C. H.; Håkansson, K.; Iwatsubo, T.; Jeong, J. H.; Jimenez-Maggiora, G.; Koo, E. H.; Launer, L. J.; Lehtisalo, J.; Lopera, F.; Martínez-Lage, P.; Martins, R.; Middleton, L.; Molinuevo, J. L.; Montero-Odasso, M.; Moon, S. Y.; Morales-Pérez, K.; Nitrini, R.; Nygaard, H. B.; Park, Y. K.; Peltonen, M.; Qiu, C.; Quiroz, Y. T.; Raman, R.; Rao, N.; Ravindranath, V.; Rosenberg, A.; Sakurai, T.; Salinas, R. M.; Scheltens, P.; Sevlever, G.; Soininen, H.; Sosa, A. L.; Suemoto, C. K.; Tainta-Cuezva, M.; Velilla, L.; Wang, Y.; Whitmer, R.; Xu, X.; Bain, L. J.; Solomon, A.; Ngandu, T. & Carrillo, M. C. (2020). World-Wide FINGERS Network: A Global Approach to Risk Reduction and Prevention of Dementia. *Alzheimers & Dement*, 16(1), 1078–1094.  
<https://doi.org/10.1002/alz.12123>
- McKhann, G.; Drachman, D.; Folstein, M.; Katzman, R.; Price, D. & Stadlan, E. M. (1984). 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*, 34(7), 939–944.  
<https://doi.org/10.1212/wnl.34.7.939>
- McKhann, G. M.; Knopman, D. S.; Chertkow, H.; Hyman, B. T.; Jack, C. R. Jr, Kawas, C. H, Klunk, W. E; Koroshetz, W. J.; Manly, J. J.; Mayeux, R.; Mohs, R. C.; Morris, J. C.; Rossor, M. N.; Scheltens, P.; Carrillo, M. C.; Thies, B.; Weintraub, S. & Phelps, C. H. (2011). 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*, 7(3), 263–269.  
<https://doi.org/10.1016/j.jalz.2011.03.005>
- Prince, M.; Bryce, R. & Ferri, C. (2011). *World Alzheimer Report 2011. The benefits of early diagnosis and intervention*. London: ADI. Available:  
<https://www.alzint.org/resource/world-alzheimer-report-2011/>
- Sperling, R. A.; Aisen, P. S.; Beckett, L. A.; Bennett, D. A.; Craft, S.; Fagan, A. M.; Iwatsubo, T.; Jack Jr, C. R.; Kaye, J.; Montine, T. J.; Park, D. C.; Reiman, E. M.; Rowe, C. C.; Siemers, E.; Stern, Y.; Yaffe, K.; Carrillo, M. C.; Thies, B.; Morrison-Bogorad, M.; Wagster, M. V. & Phelps, C. H. (2011). Towards defining the pre-clinical 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*, 7, 280–292.  
<https://doi.org/10.1016/j.jalz.2011.03.003>

- WHO EMRO. (feb. 1, 2015). *Health Promotion and Disease Prevention Through Population-Based Interventions, Including Action to Address Social Determinants and Health Inequity*. Geneva: Regional Director/WHO. Available: <http://www.emro.who.int/about-who/public-health-functions/health-promotion-disease-prevention.html>
- WHO. (2012). *Dementia: A Public Health Priority*. London: WHO/ADI. Available: <https://apps.who.int/iris/handle/10665/75263>
- Wimo, A. & Prince, M. (2010). *World Alzheimer Report 2010*. London: ADI. Available from [https://www.alz.org/documents/national/world\\_alzheimer\\_report\\_2010.pdf](https://www.alz.org/documents/national/world_alzheimer_report_2010.pdf)





