Editorial

What is missing: “Prevent and cure Alzheimer’s”

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Abstract

To control the global epidemic of dementia, multidisciplinary guidelines should be directed at the healthy general population. The PREVENTION strategy should be accompanied by a strong PROMOTION strategy for healthy and successful aging that prevents the development of mild cognitive impairment and dementia.

What we must promote are policies and methods that aim: first, to maintain good brain and mental health. Second, to control the 12 known modifiable risk factors (low educational level, high blood pressure, hearing loss, smoking, obesity, depression, a sedentary lifestyle, diabetes, social isolation, excessive alcohol consumption, brain trauma, and air pollution). Third, to promote the identification of apparently non-modifiable genetic risk factors in subjects with resistance and resilience to connect their families to primary and secondary prevention programs. Fourth, to identify families with longevity to search for genetic variants of resilience or resistance to neurodegenerative diseases. Fifth, to develop a model for the evaluation of genetic factors taking into account the presence or absence of susceptibility and protection causality variables to allow identifying the populations with the highest risk. Sixth, to develop low-cost peripheral biomarkers that are indicators of early diagnosis and the evolution of the disease. And lastly, we must promote longitudinal cognitive self-assessment based on programs available online that will be supervised and evaluated by a tele-education unit, tele-guidance and tele-medicine to identify the population at risk that could benefit from primary, secondary, and tertiary prevention programs and palliative or curative treatments. The sum of the age factor, the presence of modifiable risk factors, a genetic susceptibility score, a biomarker alteration score, and a score in longitudinal cognitive functioning will make possible to identify the populations at greatest risk on whom promotion policies, prevention and longitudinal monitoring should focus.

Inventing the cure for Alzheimer's is like imitating nature without reading it. But there is an easier method: **read it to imitate it**. This is a possible way to prevent and cure Alzheimer's and other neurodegenerative diseases.

Dementia, which currently affects 50 million people in the world, is predicted to increase to 150 million in 2050 and its economic burden will raise to over 3 trillion dollars annually. Most dementias are caused by Alzheimer's disease; they are progressive and incurable. These are also known as primary dementias, which means their cause is unknown. Only fewer than 15% of all dementia cases are reversible or secondary dementias with known and treatable causes (WHO, 2017).

The most effective strategy to address this significant global public health issue, which disproportionately impacts middle- and low-income countries, is **prevention**. Delaying the onset of Alzheimer's disease symptoms by 5 years could cut both the prevalence and the costs of the disease by half, according to the 5/50 plan (Brookmeyer R et al, 1998). Current public health policies aim to manage the 12 primary modifiable risk factors for dementia: low educational level, high blood pressure, hearing loss, smoking, obesity, depression, a sedentary lifestyle, diabetes, social isolation, excessive alcohol consumption, brain trauma, and air pollution (Livingston G et al, 2020). By controlling these factors, it's possible to prevent up to 40% of all dementia cases, as the remaining 60% are considered non-preventable, often due to genetic or other non-modifiable factors. However, the proposition here is that even this 60% of presumed non-modifiable dementias, typically attributed to genetic factors, could potentially be preventable. If we could delay the symptom onset of sporadic Alzheimer's disease, which usually starts after the age of 65, by more than two decades, we might nearly eradicate its prevalence and economic impact (almost 100%), essentially equating to curing the disease.

Nevertheless, to achieve this goal, we must emulate nature itself. This is the conclusion we reached through the study of two cases of resistance and resilience to autosomal dominant Alzheimer's, published in Nature Medicine in 2019 and 2023 (Arboleda-Velasquez J et al., 2019; Lopera F et al., 2023). In our view, we should interpret nature and apply its principles. Our research showed that nature reveals both the ailment and its remedy; we can discern from nature the problem as well as the solution. Nature conducted an extraordinary experiment with these two individuals: it bestowed upon them a gene that causes Alzheimer's and simultaneously, another genetic variant that shielded them from the disease's symptoms for over two decades. Therefore, a possible solution is to COPY nature by developing gene or pharmacological therapies that imitate the protective mechanism observed in these high-risk individuals.

But the most exciting aspect is that if nature has shown us that both the disease and its cure for Alzheimer's exist within it, it is reasonable to believe that the same applies to other neurodegenerative diseases. This idea opens up a broad spectrum of possibilities for the prevention and treatment of incurable diseases.

Palliative and eventually **curative** treatments for individuals with dementia should be considered only when preventive measures do not succeed, with a focus on at-risk populations. The higher-risk group

consists of patients with mild cognitive impairment (MCI). MCI represents an intermediate state between normal cognitive function and dementia, characterized by cognitive or behavioral disorders that affect daily life, yet without the loss of autonomy or independence seen in dementia.

The prevalence of MCI is highly variable but can reach up to 16% in adults older than 70 years (Petersen RC et al., 2010). Studies in Latin America are limited, yet a door-to-door study in Córdoba, Argentina, found a 13.6% prevalence of MCI in individuals over 50 (Mias C et al., 2007), and another in Medellín, Colombia, found a 9.7% prevalence of amnestic MCI (Henao-Arboleda E et al., 2008). Treatments for MCI are considered tertiary prevention, aiming to halt the progression to dementia. This population already exhibits symptoms impacting their quality of life. Thus, there should also be a focus on secondary prevention, which detects the disease early in high-risk individuals with silent neuropathological changes, to prevent progression to MCI and dementia. This approach should target a broader group of healthy individuals. Ideally, primary prevention would be prioritized, addressing disease causes to prevent its onset in at-risk but neuropathologically unaffected individuals.

In December 2020, the United Nations General Assembly declared the decade of 2021-2030 as the "Decade of Healthy Aging" to focus global attention on the over 1 billion people on the plant aged 60 and above. This demographic is more susceptible to developing dementia, as aging is the primary non-modifiable risk factor for the condition. In 2020, Latin America and the Caribbean saw more than 8% of their population aged 65 and older, a figure expected to double by 2050 and surpass 30% by the end of the century.

Following these recommendations, strategies that could be very effective in finding solutions for the prevention of Alzheimer's and potentially curing related diseases are proposed:

1. **Identify protected individuals in families with early-onset, autosomal dominant forms of Alzheimer's or neurodegenerative diseases:** These are individuals who, despite carrying a causal variant, do not develop the disease's symptoms or develop them much later than their family group's average onset age. The greater the deviation from the age of onset, the more significant the protective effect of the variant.

2. **Identify and study families with members affected by early and late-onset Alzheimer's disease:** These families, which may or may not exhibit an autosomal dominant inheritance pattern, have several members with early-onset Alzheimer's while others have late-onset Alzheimer's. It should be evaluated whether those with late-onset Alzheimer's carry any protective variants.

3. **Identify and study homozygotes for causal variants:** For several decades we believed that homozygosity for Alzheimer's causative genetic variants was incompatible with life. But with the discovery of homozygous cases of the E280A mutation in PS1 (Kosik et al, 2014) a new question arises: is the existence of homozygotes for pathogenic variants an indicator that homozygosity is compatible with life, or is it an indicator that those homozygotes carry protective variants that make them compatible with life? For this reason we must search for more cases of homozygotes in all populations with causative genetic variants and study the presence of protective genetic

variants in all of them.

4. **Identify and study cases of progeria:** Progeria is a disorder that is manifested by premature aging. It corresponds to the other side of the coin of successful aging. Therefore, the study of patients with progeria could help us understand the failure and success of aging. There could be cases of subjects with progeria with more successful aging in relation to the average life of their population group. The reason for this relative success could be due to the simultaneous presence of protective variants that counterbalance the genetic determinants of premature aging in progeria.

5. **Identify factors accelerating progeria, Alzheimer's and disorders related to autosomal dominant inheritance:** The heterogeneity in the age of onset of autosomal dominant Alzheimer's disease suggests that environmental and/or genetic factors that are protective and accelerative of the disease come together in the same affected population. Identifying and contrasting them could provide clues to more successful aging than expected within the context of pathological aging.

6. **Identify protected subjects carrying a high polygenic susceptibility score:** these are elderly individuals who carry a high number of susceptibility genes without developing or presenting symptoms of Alzheimer's disease or presenting very late-onset neurodegenerative disease.

7. **Work on the development of a polygenic resilience score for Alzheimer's disease and other neurodegenerative diseases:** Just as it has been possible to calculate a polygenic susceptibility score for Alzheimer's, it should be possible to calculate a polygenic resilience score for Alzheimer's and other neurodegenerative diseases.

8. **Identify moderately protected subjects:** these are subjects with causality genetic variants or high polygenic susceptibility score who develop a clinically benign form of the neurodegenerative disease, or who moderately escape the average age of onset of symptoms, according to their family group.

9. **Study and copy the lifestyle of populations with successful aging:** We believe that studying successful aging could be a good method to help find a preventive and curative solution for dementia. It has been described that the blue zones or special places in the world with high longevity, have a healthy lifestyle that controls most of the risk factors for dementia, achieving greater longevity than other places in the world when controlling modifiable factors.

10. **Search for genetic variants related to successful aging:** It is highly probable that genetic variants associated with successful aging exist and that these variants also confer protection against Alzheimer's and/or other neurodegenerative diseases. For this reason, we should look for:

    a) Long-lived families where an autosomal dominant pattern of successful aging can be demonstrated, suggesting the presence of a major gene related to longevity.

    b) Individuals with successful aging who carry genes that are known to cause Alzheimer's disease

or neurodegenerative diseases. For these individuals, demonstrating longevity is not required; successful aging is indicated by a significantly delayed onset of disease symptoms compared to their family group, as has been shown in subjects with resistance or resilience to Alzheimer's disease carrying protective genetic variants.

c) Individuals with successful aging who carry susceptibility genetic variants for Alzheimer's disease or other neurodegenerative diseases. For instance, long-lived individuals who are homozygous for the ApoE4 variant could have double protection and possess some protective variant that has enabled them to meet the challenge of successful aging and the high risk of dementia associated with the ApoE4 genetic risk factor.

d) Evaluate whether the genetic variants related to successful aging confer resistance or resilience to the onset of Alzheimer's disease symptoms or related disorders, which would show that these variants are not only longevity factors but also protective against neurodegenerative diseases.

11. **Study the mechanism of action of the identified candidate protective variants in cell and animal models:** This approach is an effective means to confirm that the candidate variant is protective and to understand how it exerts its protective effect.

12. **Copying Nature:** All the aforementioned strategies are methods of interpreting nature's signals in both the causal and susceptibility factors of Alzheimer's and related neurodegenerative diseases, as well as the resilience and resistance factors that should inform prevention and treatment. The ultimate step is to develop gene or drug therapies that replicate the protective variants' mechanisms of action, and to test these in cell models, animals, and eventually, in human populations at risk.

13. **Develop peripheral biomarkers:** Especially low-cost biomarkers that correlate with the risk of Alzheimer's or neurodegenerative diseases, to implement primary or secondary preventive measures at the appropriate time in individuals at highest risk.

14. **Longitudinal follow-up through self-assessment and telemedicine methods:** After identifying the at-risk populations and the degree of risk in the healthy population, longitudinal follow-up is necessary to determine the best interventions required at the most opportune time during the extended development of the disease. It's critical to recognize that the preclinical, asymptomatic stage of Alzheimer's and other neurodegenerative diseases can last between two and three decades.

15. **The protective genetic variants that should be identified in all these populations of interest are:** the E2 variant of the APOE gene (Corder EH et al, 1994; Vélez JI, Lopera F, et al., 2016; Eric Reiman et al., 2020), the A673T variant in the APP gene (Jonsson et al., 2012), the Christchurch R136S variant in ApoE3 (Arboleda-Velasquez JF et al., 2019), the R251G variant in ApoE4, and the V236E variant in ApoE3 (Liu CC et al, 2021; Le Guen Yan et al., 2022), and the Reelin-COLBOS variant H3447R (Lopera F et al., 2023). Candidate protective genetic variants are still under investigation,

and all protective variants discovered or confirmed will need to be validated in the near future.

All of the above strategies are critical in designing pharmacological and non-pharmacological clinical trials for Alzheimer's and other neurodegenerative diseases since there are multiple factors that can modify the action of experimental molecules, influencing the level of drug efficacy under study.

In conclusion, the primary action to control the global dementia epidemic should be directed towards the healthy population. Therefore, the PREVENTION strategy should be coupled with a robust PROMOTION strategy for healthy and successful aging that prevents the development of deterioration, MCI, and dementia.

What we must promote are policies and methods that aim to:

- Maintain good brain and mental health.
- Control the 12 modifiable risk factors.
- Promote the identification of apparently non-modifiable genetic risk factors in individuals with resistance and resilience to connect their families to primary and secondary prevention programs.
- Identify families with longevity to search for variants of resilience or resistance to neurodegenerative diseases.
- Develop a model for evaluating genetic susceptibility, taking into account the presence or absence of susceptibility and protective causality variables that allow identifying populations at highest risk.
- Develop low-cost peripheral biomarkers that are indicators of early diagnosis and disease progression.
- Promote longitudinal cognitive self-assessment in programs available on the internet that will be supervised and evaluated by Tele-Education, Tele-Guidance, and Tele-Medicine units to identify the at-risk population that could benefit from primary, secondary, and tertiary prevention programs, and palliative or curative treatments.

The combination of the age factor, the presence of modifiable risk factors, a genetic susceptibility score, a biomarker alteration score, and a score in longitudinal cognitive functioning will enable the identification of the populations at greatest risk, upon whom promotion policies, prevention, and longitudinal monitoring should be concentrated.

Most of these recommendations are part of the strategy for the next 10 years of our Alzheimer's Resistance project. But if other researchers adopt these strategies, together we can hasten the advent of preventative and curative solutions not only for Alzheimer's but for all neurodegenerative diseases.

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Disclosures

Lopera F is a co-inventor on a patent application filed by Mass General Brigham for the development of drugs based on ApoE Christchurch.