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Editorial

ICOPE Healthy Longevity Integrative Preventive Care, Alzheimer's Disease Prevention and Early Diagnosis

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Healthy Aging, for the W.H.O, is maintaining our functions to be able to continue to do what we value the most (1). The W.H.O Integrated Care for Older People (ICOPE) program selected six functions: vision, hearing, mobility, memory, vitality and psychological health to be maintained to enable Healthy Longevity (2). Our intrinsic capacity (IC) represents the sum of these 6 functions. We can measure IC, both in clinical practice and research (3); moreover, IC is now part of the International Classification of Diseases (ICD) (4). IC is a major predictive factor for disability, not only in epidemiological cohorts, but also in clinical practice (5).

W.H.O designed the ICOPE program to maintain our functions in an integrated way (1, 2). For instance, around 30% of older adults at the ICOPE screening step 1 report that, in the past 2 weeks, they have felt sad and depressed and have lost interest in activities they value (2–5). Such individuals will likely stay more at home, have poor appetite, loss of muscle and mobility, cognitive decline and become more at risk to be dependent. We cannot anymore only focus on memory and the brain, and forget the integration with other functions, to maintain brain health in an aging population. This is why we need to implement such integrative programs in our memory clinics. We believe that adopting a holistic approach to promoting Healthy Longevity through the function-centered ICOPE model is of critical importance in the field of Alzheimer's disease prevention. Indeed, beyond cognitive impairment, IC decline has been associated with neurocognitive disorders including Alzheimer's disease, especially considering its complexity and multifaceted nature (6). Previous evidence also reported tight interconnections between functional capacity domains, with disruption in one domain possibly affecting others, ultimately leading to reduced system resilience with detrimental effects on brain health (7). Although impaired mobility is not a characteristic symptom of Alzheimer's disease, its early manifestation during the preclinical phase of the disease, including sarcopenia, balance and gait disturbances, highlights the importance of a thorough assessment for early disease detection and prevention. Sensory impairments, such as olfaction, hearing and visual loss, have strongly been associated with Alzheimer's disease, even decades before the onset of any cognitive symptoms, underscoring the importance of systematic testing to support early intervention. Furthermore, other IC domains such as vitality with unintentional weight loss, reduced grip strength and psychological health including depression can either influence or be influenced by cognitive impairment. Thus, addressing early signs of deterioration within IC domains through the ICOPE model holds real potential for Alzheimer's disease prevention.

From a molecular perspective and beyond pathophysiological and clinical aspects, the latest findings in the field of Geroscience (8) also suggest that decline in IC is closely linked to aging biology pathways involved in Alzheimer's disease, highlighting the critical importance of promoting Healthy Longevity through the function-centered ICOPE model for dementia prevention. Indeed, key factors such as chronic inflammation, oxidative stress, mitochondrial dysfunction and cellular senescence, not only contribute to loss of function but are also prominent in Alzheimer's pathophysiology (9). An integrated system biology approach could thus unravel complex interactions across IC domains, revealing shared aging mechanisms underscoring dementia progression. Understanding the early interconnected molecular changes associated with IC decline, even before the onset of any cognitive symptoms, could pave the way for personalized and preventive medicine interventions to preserve cognitive health at the initial stages of risk trajectories.

Since implementing the ICOPE MONITOR digital program in our clinical practice in France, we have tracked 65,531 seniors to date (October 26, 2024) and conducted 109,807 step 1 assessments, including follow-up steps. Only 13.4% of these 65,531 subjects had no step 1 alert. Among these 65,531 community-dwelling subjects (mean age 74 years old, 63% women), 48.3% have memory complaint and/or cognitive decline, 18.7% poor appetite and/or weight loss, 40.1% vision alert, 46.4% hearing difficulties, 35.8% poor mental health and 28.5% mobility limitations. Interestingly, these functional declines are more pronounced in individuals with memory complaints or objective cognitive decline and in the oldest old, underscoring the importance for dementia prevention of focusing not only on memory

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monitoring and intervention but also on other functions, thus enhancing global IC. In a work in progress in the Multidomain Alzheimer Preventive Trial (MAPT), we have observed that individuals with healthy longevity and good IC scores were able to maintain their memory function (composite cognitive score) at 5 years, compared to those with abnormalities at the ICOPE screening step 1. Our research perspectives include investigating the associations between IC, the biology of aging and the onset of brain blood biomarkers including p-tau217. Recent findings from the UK Biobank (6) support ICOPE-based integrative approach to optimize cognitive health and prevent Alzheimer's disease and related dementias. In this study, over a median follow-up period of 13.5 years, a worse IC composite score was associated with a higher risk of dementia, Alzheimer's disease and vascular dementia, in a dose-response manner. Interestingly, the relationship was stronger in younger individuals, in line with previous findings suggesting potential greater benefits from risk factors modification in midlife and highlighting the importance of implementing healthy longevity integrative and preventive strategies as early as possible. Notably, IC showed a strong association with dementia risk among individuals with genetic predisposition. This highlights the importance, within a personalized medicine framework, to identify subjects most likely to benefit from ICOPE-based interventions designed to optimize IC for Alzheimer's disease and related dementia prevention.

We are currently conducting a large, long-term randomized controlled trial (RCT) in 1,000 older adults living in the community, with at least 2 positive alerts at ICOPE step 1. We aim to evaluate the effectiveness of the ICOPE integrative preventive care program in preventing decline in the six functional domains including cognition, compared with usual care delivered by the primary care physicians. Secondary objectives include assessment of cost-effectiveness as well as aging biology and brain health biomarkers.

Overall, we strongly advocate for adding integrative preventive care using the ICOPE framework, following the W.H.O recommendations, within our memory clinics and clinical practices. This approach could significantly enhance our ability to better prevent Alzheimer's disease as well as to maintain functions in older adults with dementia, and to potentially increase the impact of anti-amyloid drugs. One additional immediate consequence of ICOPE step 1 will also be to promote targeted and personalized multi-domain interventions, including aiming at preserving cognitive health. I.C.O.P.E soon associated with blood biomarkers will pave the road for early diagnosis in primary care.

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