

## Cognitive decline - an editorial meander

### *Of all the things I've lost - I miss my mind the most.*

This may be spoken in jest, but for many patients and for many practitioners the loss of a sharp mind is a fearful prospect and one that concerns them more as they age. What is important is to be aware of this potential worry in any consultation, and to explore whether it is an aggravating factor of the patient's symptoms, and even - possibly - a covert reason for the appointment.

### How common is cognitive decline?

Cerebral performance decreases with age and this is normal. It is called cognitive decline and goes hand in hand with physical ageing. With ageing comes a decrease in measurable brain volume. The natural changes require adjustments of expectations in many domains. From the medical point of view it needs to be assessed to diagnose if the person's decline is too rapid and if, and when a pathological point is reached.

### Factors associated with slowing cognitive decline include:

**Social:** Humans are social animals and when interactions with others are eroded or lost due to a reduction in the person's inter-human ties, then isolation can accelerate cognitive decline. The stimulus of human-to-human contact is vital in mental health and the lack thereof is retrogressive. If a patient declares (or their practitioner notes) cognitive concerns, their social status is the first line of questioning to pursue. Interventions to counter loneliness have proved helpful ([Hoang et al JAMA Netw Open 2022;5:e2236676](#)).

Studies have demonstrated that social support by family and friends is associated with the promotion of neuro-cognitive health ([Salinas et al JAMA Netw Open 2021;4:e2121122](#)). Researchers found that the **kind of** social support is an important factor with "supporting listening" being one of the most valuable in establishing cognitive resilience. (*Your editor, who has an interest on the art of listening, found this intriguing*).

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Some other phenomena have received attention, such as “social robots” with which the person can interact – at ever-increasing degrees of sophistication – and animal companions. A recent study investigated the association between pet ownership and cognitive decline among adults aged 50 and older involving 8,000 participants ([Li et al JAMA Netw Open 2023; 6:e2349241](#)). Key findings were as follows:

- Pet ownership was associated with slower rates of decline in composite verbal cognition, verbal memory, and verbal fluency.
- The association was observed among individuals living alone, but not among those living with others. Living alone was identified as a significant modifier in the association between pet ownership and cognitive decline.
- This may be associated with a protective effect against cognitive decline and is one of very few modifiable factors

**Health factors:** Deterioration or changes in physical health can impinge on mental health so enquiry into well-being needs exploring. The associations between cardiovascular status and brain function are close so checking of basic cardiac function is essential ([Lennon et al JAMA Netw Open 2023;6:e2333353](#)).

Any co-morbidities need to be known about and medications. Sensory functions need checking, for example hearing status ([Andries et al JAMA Oto Head Surg 2023 doi 10.1001/jamaoto.2022.5046](#)).

A woman’s menopausal symptoms and any hormone therapy needs recording. Higher rates of dementia in women are linked with longevity although there are suggestions linking menopausal hormone therapy with dementia risk ([Pourhadi et al BMJ 2023;381:e072770](#)).

**Physical activity:** The association between physical activity and brain health is close but complex. Whether it is mediated through better cardiovascular perfusion and oxygenation, better relaxation and sleep, or with “brain protective molecules” enhancing plasticity is unknown ([Mazo et al Brain Plasticity 2022;8:5-18](#)). The “lifelong maintenance of physical activity was most optimal” in warding off cognitive deterioration ([James et al J Neurol Neuros & Psy 2023 doi 10.1136/jnnp-2022-329955](#) & [Mitchell et al J Epid Com Health 2023;77:189-95](#) & [Cruz et al JAMA Neurol 2022;79:1059-63](#)).

The possibility that exercise plays a role in decreasing depression and thereby slowing cognitive decline in a dose-response fashion has been supported by research and should be energetically encouraged ([Pearce et al JAMA Psychiatry 2022;79:550-9](#) & [Iso-Markku et al JAMA Netw Open 2024;7:e2354285](#)).



To quote from a nation-wide guideline about activity in general, it was deduced that “Physical activity is remarkable medicine...27 major physical and mental health benefits with strong research support, all of which are compelling (e.g., lower all-cause mortality).” As a sedentary lifestyle becomes more seductive – activity becomes more relevant! ([Bustamante et al JAMA Pediatr 2023;177:111-3](#)).

**Diet:** There is considerable interest in a dietary approach to reducing the risk of rapid cognitive decline and dementia. The association between obesity and dementia risk has made it the “Top Modifiable Risk Factor in the US” ([Slomski JAMA 2022;328:10](#) & [Anand et al JAMA Netw Open 2022;5:e2146324](#)).

The evidence for this is substantial through brain mapping which measured and matched cortical thickness readings in Alzheimer’s Disease with obesity ([Morys et al J Alz Dis 2023;91:1059-71](#)). It seems it is not only the calorie count that is involved but the type of food ingested with higher intake of ultra-processed foods being implicated in a “faster rate of decline in both executive and global cognitive function” ([Goncalves et al JAMA Neurol 2022 doi 10.1001/jamaneurol.2022.4397](#) & [Li et al Neurol 2022;99:e1056-e1](#) & [Glans et al Neurol 2023,100:e28-e37](#)).

In keeping with the mental healthy diet concept, specific variations of the classical Mediterranean diet have been linked to evidence of less risk of cognitive decline through weight loss and better cardiovascular health ([Chen et al JAMA Psychiatry 2023 doi 10.1001/jamapsychiatry.2023.0800](#)).

Adherence to mostly plant-based diets with “green leafy vegetables” high on the agenda have provide empirical evidence of benefit, even to the extent of confirmation in autopsy reports ([Agarwal et al Neurol 2023 doi 10.1212/WNL.000000000207176](#)).

Other dietary components have also received attention – for example:

**Gluten** – there was no correlation found between gluten intake and cognitive function ([Wang et al JAMA Netw Open 2021;4:e2113020](#)).

**Flavanols** – some association was found with “Higher dietary intake of total flavanols and flavanol constituents were associated with a slower rate of decline in global cognition and multiple cognitive domains.” ([Holland et al Neurol 2022 doi 10.1212/WNL.000000000201541](#)).

**Plant proteins** – “Intake of protein, especially from plants, in middle age is associated with higher odds of healthy aging and positive mental and physical health status in older women” ([Swift Medscape 2024](#)).

**Alcohol** – A study from South Korea found that a moderate consumption of up to 30g of alcohol per day was found to be linked to a decreased risk of dementia



compared with abstinence or excessive intake ([Jeon et al JAMA Netw Open](#) 2023;6:e2254771).

**Drugs:** Some medications are associated with cognitive side effects – both positive and negative. Generally drugs controlling blood pressure are helpful, especially those that stimulate angiotensin receptors, as they can lower the risk of cognitive decline and by implication, deterioration to dementia ([Marcum et al JAMA Netw Open](#) 2023;6: e2249370).

There is a range of other drugs that *may* have positive effects but their actions are due to side effects or are too far-fetched to be offered as main-stream solutions, such as erectile agents which may slow deterioration ([Adesuyan et al Neurology](#) 2024 doi 10.1212/WNL.0000000000209131), serotonin reuptake inhibitors ([Langley et al Neuropsychopharm](#) 2023;48:664-70) which may blunt emotions and it is unknown whether psychedelics could be beneficial ([Bradberry et al JAMA Psychiatry](#) 2022 doi 10.1001/jamapsychiatry.2022.0665 & [Davis et al JAMA Psychiatry](#) 2021;78:481-9). It is not beyond the realms of possibility that GLP-1 agonists could reduce cognitive decline through their weight-loss and cardiovascular activities, so judgement is best reserved ([Gershberg Medscape](#) 2024).

### **Preventative measures**

The means for preventing abnormal cognitive decline are based on advice about a healthy lifestyle.

The outcomes from large trials are similar, namely a healthy diet, exercise, social contacts, cognitive activities, no smoking or excessive drinking.

Publications supplying the evidence supporting these factors are:

- Healthy lifestyles for dementia prevention - [Sabia et al BMJ](#) 2023;380:p117
- Association between healthy lifestyle and memory decline - [Jia et al BMJ](#) 2023;380:e072691
- Healthy Lifestyle and Cognition in Older Adults - [Dhana et al JAMA Neurol](#) 2024 doi 10/1001/jamaneurol.2023.5491.

### **Controversy - do multivitamins help?**

A controversy is brewing about the place of multivitamins to boost memory in older citizens. There have been many claims for multivitamin-mineral (MVM) supplements to enhance health but no studies have provided evidence that could substantiate the manufacturers' optimism. In the United States about a third of adults swallow health tablets but their national body that "judges" efficacy (the U.S. Preventative Services Task Force) does not feel there is sufficient evidence to promote or avoid



multivitamin supplements for the prevention of cardiovascular disease or cancer – or for that matter dementia.

The COSMOS studies involved cocoa and MVM supplements and looked at CVS and cancer effects. Their published results were negative but a sub-study called the COSMOS-Mind showed improved global cognition, episodic memory, and executive function ([Vyas et al Am J Clin Nutr 2024](#) doi 10.1016/j.ajcnut.2023.12.011). However, the difference in global cognitive function between MVM and placebo was small but the researchers are highly regarded academics and feel their findings warrant support and – hopefully – verification ([Manson Medscape 2023](#) & [Manson Medscape 2024](#)). Alternative views are expressed about the scale of the differences observed and the “outlier” status of the newest outcomes, so follow-up and corroborating data are eagerly awaited ([Labos Medscape 2023](#) & [Brooks Medscape 2024](#)).

However this controversy plays out, cognitive decline remains inevitable, as does its progression in some people, to dementia.

## Alzheimer's Disease

“Currently, more than 50 million people around the world live with dementia and this number will triple by 2050.” ([Ghahremani et al Alz & Dem 2023](#) doi 10.1002/dad2.12404).

“Alzheimer disease is an irreversible, progressive brain disease. It is characterized by the development of amyloid plaques and neurofibrillary tangles; the loss of connections between nerve cells, or neurons, in the brain; and the death of these nerve cells.” ([Garg et al Medscape 2019](#)).

It is genetically linked and the APOE gene is an attributable risk factor but recently the link between amyloid- $\beta$  presence and the development of clinical disability has become clearer. An important biomarker which measures astrocyte activity in blood has proved to be an “upstream event” that can forecast tau pathology ([Bellaver et al Nat Med 2023](#) doi 10.1038/s41591-023-02380-x). It should reach clinical application soon and will indicate the success of otherwise of interventions.

This year another biomarker has been tested and found to be reliable for clinical diagnostics. It is a tau immunoassay and should be commercially available shortly ([Ashton et al JAMA Neurol 2024](#) doi 10.1001/jamaneurol.2023.5319).

There are however issues with these products in that some are available “direct to consumer” which leaves interpretation and forecasting to the public with variable

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expectations and planning as well as insurance queries ([Arias et al JAMA Neurol 2023 doi 10.1001/jamaneurol.2023.4811](#)).

At present, there is a dearth of effective medications for dementia that can stop or reverse the progression of the disease but two contender medications are under scrutiny, both monoclonal antibodies ([Sims et al JAMA 2023 doi 10.1001/jama.2023.13239](#)). Drugs in this category are expensive with prices in excess of US\$20,000 per annum so relief is not in the offing for all.

*Editorial comment: It is estimated that 1 in 5 persons over the age of 65 years has clinically significant cognitive impairment. Two thirds of Alzheimer's Disease patients are female.*

*The chances of your seeing patients with early or established mental health issues are high - and rising. I hope this meander has been of interest and use.*

Two extracts from this year's *Menopause* publications are:

### **Does hormone therapy exacerbate other venous thromboembolism risk factors?**

By [Porterfield et al Menopause 2024;31:123-9](#). The conclusion was that "Hormone therapy exposure did not appear to adversely influence other risk factors, and exposure generally played a minor role in VTE risk. Contraceptives, however, were a strong risk factor."

### **The efficacy of purified pollen extract for reducing vasomotor symptoms in women: a systematic review and meta-analysis.**

By [Acquarulo et al Menopause 2024;31:154-9](#). The authors are cautious about their findings saying that pollen extract for improving vasomotor symptoms in uncontrolled studies "may have been due to the placebo effect" and practitioners recommending its use should be equally reserved.

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