Chapter 8a(ii)

Non-pharmacological interventions

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Due to medical successes and advancements, there has been a decline in death rates at younger ages and consequently increase in longevity. Older adults are living healthier and more active lives and are contributing to society until an advanced age. However, aging populations pose medical and societal challenges due to degenerative conditions, comorbidities, and polypharmacy, frailty and dementia. Although the actual number of people with dementia is increasing (because of increased longevity), the age-specific incidence of dementia has fallen in several countries [1]. This is thought to be the result of improvements in education, nutrition, health care, and lifestyle.

Around 50 million people worldwide are living with dementia, and as the global population is aging, this number is estimated to increase to 152 million by 2050, accompanied by major societal and economic challenges [2]. The current global costs of dementia are more than US$ 1 trillion annually [2]. During the current ongoing COVID-19 pandemic, older adults have been particularly susceptible to the effects of COVID-19 with regards to the severity of symptoms, need for hospitalization and death [3,4]. Nevertheless, statistics from England (March 2021), where the COVID-19 vaccination rollout has been efficient, with high uptake levels among those aged 50+ years, showed that dementia and Alzheimer's disease (AD) were the leading cause of death (approximately 10.1% of registered deaths in March) [5]. This is in contrast to previous months when COVID-19 was the leading cause of death [5]. In the near future, these trends may be observed in other countries as vaccine

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programmes progress. Moreover, independent of age, dementia and Alzheimer's disease are risk factors for disease severity and death due to COVID-19 [6]. This further highlights the importance of dementia and AD in this age group during the pandemic circumstances.

Dementia and late-onset AD are multifactorial conditions, with various demographic, lifestyle, vascular, metabolic and environmental risk factors. Importantly, the literature has identified various risk factors that play a role throughout the life course. The most recent *Lancet Commission report on dementia prevention, intervention, and care* has suggested that the modification of 12 risk factors may prevent or delay 40% or more of dementias [7]. The identified risk factors were, early in life: low levels of education; in midlife: hypertension, traumatic brain injury, excessive alcohol consumption, hearing impairment, and obesity, while in late life: depression, smoking, social isolation, physical inactivity, diabetes and air pollution. This evidence highlights that different factors increase the risk for dementia during different life stages [7]. Other novel factors (e.g., sleep) were highlighted in the report, but more evidence is needed before they are added to the list of risk factors. Addressing these factors at a population level should be the objective of national public health strategies whilst the evaluation of these factors at an individual level should be the basis of a plan for non-pharmacological interventions for those at risk of dementia or with Mild Cognitive Impairment (MCI) or early/prodromal AD.

The World Health Organization (WHO) published the first guidelines for "*Risk reduction of cognitive decline and dementia*" in 2019 [8]. The Guidelines evaluate the quality of the evidence for individual interventions to decrease cognitive decline and the risk for dementia, and makes recommendations based on their value. The strongest recommendations are for physical exercise, smoking cessation, a balanced diet and management of diabetes mellitus. Conditional recommendations are made for cognitive interventions, Mediterranean diet and decreasing alcohol. Although there was a lack of evidence for the value of social activity in risk reduction, the guidelines recognized the contribution of social participation and support to overall health and well-being. Based on their review of the evidence, diet supplementation with vitamins and polyunsaturated fatty acids is not recommended. The WHO guidelines focused on individual risk and protective factors, while it did not consider multidomain interventions.

In the absence of disease modifying drugs, it is important to simultaneously address modifiable lifestyle, vascular and psychosocial risk factors for early dementia, and to integrate them into preventive lifestyle interventions. The main objectives/aims of non-pharmacological interventions for people with

MCI and early AD are to reduce the rate of progression of disease and maintain quality of life by:

- ► Mitigating risk factors and enhancing protective factors
- ► Maintaining cognitive abilities and cognitive reserve
- ► Optimizing physical and psychological health
- ► Complementing pharmacological interventions

Overview of risk and protective factors

An overview of risk and protective factors for cognitive decline and dementia and the optimal time for intervention is shown in Fig. 1 below.

Identification of "at risk" individuals

Individuals who are at increased risk for dementia, and who can benefit from non-pharmacological interventions can be identified from their medical history, investigations in primary and/or secondary care and calculation of an individualized "dementia risk score" (Table 1).

A validated instrument to estimate an individual risk score is the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score [9]. The

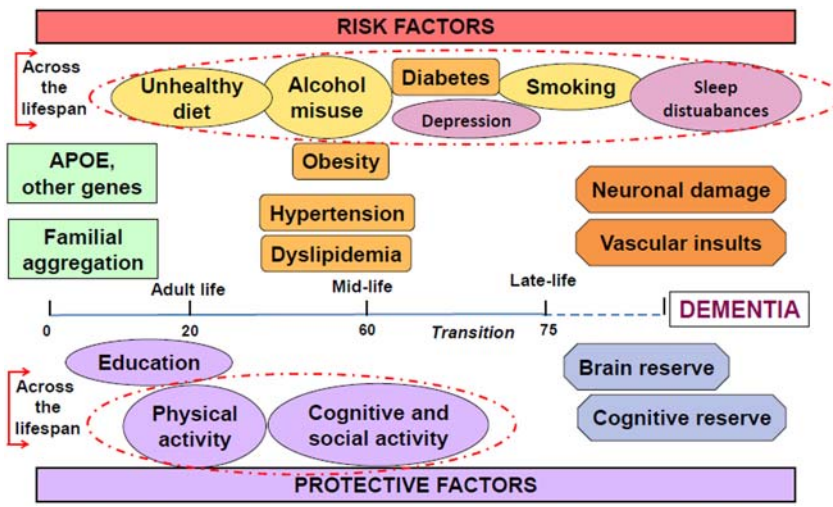

FIG. 1 Overview of risk and protective factors for dementia. *Credit: Evidence from recent epidemiological studies have linked several modifiable risk and protective factors to AD and dementia. Thus, besides genetic factors, exposure to various environmental and lifestyle risk factors during the whole life course influences the risk for disease and its timing. For multifactorial conditions, there is a need to target several risk factors simultaneously for optimal preventive effects.*

TABLE 1 Factors predictive of dementia.

Medical history	Investigations
Co-morbid conditions: diabetes, hypertension, history of depression, delirium, excess alcohol, frailty, smoking family history of dementia	ApoE4 status MCI subtype: Amnestic or multidomain 0.5 SD from expected ability for function or neuropsychological testing Neuroimaging/CSF: White matter hyperintensities, hippocampal and/or global cerebral atrophy and ventricular enlargement; abnormal brain $A\beta_{1\text{-}42,}$ Tau on PET or CSF

CAIDE score identifies demographic and modifiable vascular risk factors in midlife that are highly predictive of the likelihood of developing dementia 20 years later. The tool uses parameters that are readily available in primary care, and it has been externally validated in a multi-ethnic population [10]. The addition of other parameters associated with dementia risk (obesity, smoking, pulmonary function, and depression) did not improve predictability; however, the inclusion of diabetes improved the predictability score for Asian participants, but not for black or white participants [10] (Fig. 2).

In the future, assessments of "risk" are likely to include Polygenic Risk, biomarkers as well as demographic and lifestyle factors as those included in CAIDE. While risk scores including biomarkers may be feasible in research and specialized clinical settings, pragmatic risk scores (such as CAIDE) including widely available information (demographics, lifestyle and vascular risk factors) are important for wider implementation in primary care settings. Several other dementia risk scores have been developed [11], and they differ in whether they target midlife or late-life risk factors, the prediction duration, the proportions of modifiable or non-modifiable risk factors and whether they include biomarkers.

Non-pharmacological management strategies

Lifestyle interventions

Diet

It is generally acknowledged that nutrition can influence the risk for dementia and AD and the rate of progression [12]. Adoption of a Mediterranean diet (low meat and dairy; high fruit, vegetables, fish) reduces vascular risk factors, the risk for MCI and the risk for MCI conversion to AD dementia [7,13]. The mechanism is thought to be related to decreases in plasma glucose, serum

Factors		Points
Age years	< 47	0
	47-53	3
	>53	4
Education years	≥10	0
	7-9	2
	0-6	3
Sex	Women	0
	Men	1
Systolic BP mmHg	≤ 140	0
	> 140	2
BMI kg/m^2	≤ 30	0
	> 30	2
Total cholesterol mmol/l	≤ 6.5	0
	> 6.5	2
Physical activity	Active	0
	Inactive	1

FIG. 2 Risk factors included in the CAIDE dementia risk score.

insulin concentrations, insulin resistance, and markers of oxidative stress and inflammation [7].

The association between nutrition, diet and healthy brain aging has been the basis for the investigation of supplements to improve cognitive function in patients with MCI or AD dementia. Clinical trial evidence to date does not support the use of single-agent nutrients (Vitamins B, C, D or E, flavonoids, carotenoids, omega-3 fatty acids) to modify the course of cognitive decline in patients with MCI or early AD [14]. However, a broader nutritional approach combining multiple nutrition factors (such as the product Fortasyn Connect) has shown promise in early AD [15]. The constituents of Fortasyn Connect are a mixture of precursors and cofactors (long-chain omega-3 fatty acids, uridine, choline, B vitamins, vitamin C, vitamin E, and selenium) that were selected because of their profile of biological and neuroprotective properties relevant to early AD and the function of neuronal membranes and synapses [15]. Evidence from randomized controlled trials showed improvements in memory in mild AD, decrease in hippocampal atrophy and improvement in Clinical Dementia Rating-Sum of Boxes (CDR-SB) and AD Composite Score (ADCOMS) in prodromal AD [16,17]. This profile may support the use of Souvenaid in the management of patients with early AD, including MCI.

Exercise

A meta-analysis of 19 controlled studies with 23 interventions that included an exercise-only intervention compared with a non-diet, non-exercise control group and assessed cognitive function suggests that exercise, particularly aerobic exercise, delays the decline in cognitive function in people at risk for AD or have AD [18]. Exercise should be of moderate intensity, performed approximately 3 days per week for about 45 min per session.

Multi-domain interventions

Important evidence for the benefits of multidomain non-pharmacological interventions in "at risk" populations comes from the *Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability* (FINGER) study. This demonstrated the benefits of a 2-year, intensive multidomain intervention on global cognition, executive function and processing speed in older adults aged 60−77 years who were at increased risk of dementia [19]. The intervention comprised of dietary counseling, individualized physical exercise program, cognitive training, and management of metabolic and vascular risk factors.

Another two large multidomain lifestyle-based intervention studies have been conducted, the Multidomain Alzheimer Preventive Trial (MAPT) [20], and Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial [21] (See Ref. [22]) (Table 2).

There have been important lessons learned from these trials:

- Interventions need to be targeted to "at risk" individuals i.e., right population at the right time and individualized to their risk profiles.
- Importance of starting interventions early enough.
- The content of the interventions is critical; exercise must be of sufficient intensity, duration and frequency, and all intervention components need to be accompanied by motivational support and coaching.
- Especially among older adults, social interactions are important for maintaining motivation levels and providing additional cognitive stimulation.

Psychological symptoms

Depression, particularly late-onset, is associated with increased risk of dementia, and depressive symptoms are often found in the prodrome and early stages of dementia [23]. Other psychological symptoms also have a negative impact among individuals with MCI or early AD dementia. Apathy, which occurs frequently in association with depression in AD, has a negative impact on caregiver burden, activities of daily living and morbidity [24]. In people with MCI it is associated with increased risk of conversion to AD dementia

TABLE 2 Key features and results of multi-domain intervention studies.

Study (country)	Multidomain intervention	Participants	Outcome	Primary outcome results
FINGER (Finland)	**Intervention components**: Diet, physical activity, vascular risk management, cognitive training **Control group**: Regular health advice. **Duration:** 2 years. **Additional follow-up**: 7 and 10 years	**N** = 1260 participants **Age:** 60–77 years **Randomization:** Individual **Characteristics:** Elevated dementia risk based on CAIDE score ≥6 points, and average cognitive function or slightly below average. Participants were recruited from previous population-based national surveys.	Cognition measured using NTB (a composite measure of 14 standard cognitive tasks)	FINGER Intervention had beneficial effect on NTB: Difference in NTB change was 0.022 ($P = .030$) per year between the intervention and control groups
MAPT (France)	**Intervention components:** Multidomain Intervention (including diet, physical activity, cognitive training, preventive consultation) + omega-3 PUFAs versus multidomain versus omega-3 PUFAs **Control group:** Omega-3 PUFAs placebo capsule **Duration**: 3 years	**N** = 1680 participants **Age:** ≥70 years **Randomization:** Individual **Characteristics:** With memory complaints, IADL limitation or slow gait speed. Recruited using multiple strategies including advertisements and patient databases.	Cognition measured using a composite Z score that combines four cognitive tests	No significant difference between the three intervention groups and placebo. Between-group difference = 0.093 ($P = .142$) for multidomain + PUFA, 0.079 ($P = .179$) for multidomain and 0.011 ($P = .812$) for PUFA compared with placebo
PreDIVA (The Netherlands)	**Intervention components:** Advice on multidomain cardiovascular factors **Control group:** Usual care **Duration:** 6 years	**N** = 3526 participants. **Age:** 70–78 years. **Randomization:** Cluster randomization of 116 general practice clinics **Characteristics:** Recruited from general practice clinics.	Incidence of dementia	No effect intervention effect on dementia: HR 0.92 ($P = .54$)

[24]. Such evidence highlights the importance of evidence-based interventions for depression, such as cognitive behavioral therapy (CBT) [25].

Depression and anxiety are common in people with MCI and early AD dementia, and psychological therapies (CBT, interpersonal therapy, counseling, or multimodal interventions including a specific psychological therapy) were effective in reducing depressive and anxiety symptoms [23,26]. Mild/moderate depression may improve without specific treatment. However, there is benefit in identifying and addressing predisposing situational factors such as:

- Loneliness.
- Under-stimulation from lack of activity.
- Being cared for by a depressed carer.
- Improve communication - treat sensory impairment (auditory, visual).

For those people who do not respond to these interventions, behavioral activation can be considered [7,27].

Sleep

Sleep has an important role in the maintenance, disease prevention, repair, and restoration of physical and cognitive functions. More recently it has been recognized that sleep disturbances (circadian rhythm disturbance, altered duration, insomnia, poor quality, sleep apnea) are associated with an increased risk for all-cause dementia [28]. Both sleep disturbance and dementia are common in the elderly. Evidence from a review and meta-analysis found that participants who reported sleep disturbances had a higher risk of incident all-cause dementia, AD, and vascular dementia [28]. Insomnia was associated with incident AD, while sleep disordered breathing was also a risk factor of all-cause dementia, AD, and vascular dementia [28]. Sleep disturbances may be improved through lifestyle changes (sleepy hygiene), exercise and CBT for insomnia (CBTi) [29].

It is important to identify conditions that are associated with sleep disturbances and sleep disorders, as they are significant risk factors for cognitive decline and dementia [7,30], and may benefit from various targeted interventions.

Factors associated with sleep disturbances are:

- Circadian rhythm disturbance.
- Obstructive Sleep Apnea.
- Pain, physical health conditions, anxiety, lack of activity.
- Lifestyle factors contributing to poor sleep hygiene such as excessive alcohol. consumption, late heavy meals, and excessive/late caffeine consumption.

Interventions that may benefit sleep are:

- Exercise.
- Low-intensity physical/mental activities can improve self-reported sleep quality.
- Bright light—helpful in circadian rhythm disorders although more data are required about timing, mode of delivery, wavelength of light.
- CBT—helpful in reducing anxiety, and CBTi which is specifically tailored for insomnia.
- Educating carers and patients about the value of improving and maintaining good sleeping patterns.

Hearing impairment

The recent Lancet Commission on Dementia highlighted hearing impairment is an established risk factor for dementia [7]; midlife hearing impairment is associated with greater volume loss of the temporal lobe and associated structures (the hippocampus and entorhinal cortex) [7,31]. The use of hearing aids appears to mitigate the excess risk of this impairment.

People at risk of impairment from excessive noise exposure should use protection, and those with a known impairment should be encouraged to use hearing aids. All older adults should have regular checks for early identification of hearing loss, including easily remedied causes such as ear wax.

Cognitive training/stimulation

There is mixed evidence for the value of cognitive interventions or cognitive treatments in early AD/MCI due to issues of quality, heterogeneity and lack of long-term data [7]. The only randomized control trial of behavioral activation compared with supportive therapy in people with amnestic MCI found a benefit on memory decline after 2 years [32]. A review on interventions aiming to prevent cognitive decline reported that for cognitive training the strength of the evidence was moderate; cognitive training improves performance in the cognitive domains that were targeted by interventions (e.g., memory, processing speed, reasoning), but these benefits did not transfer to other non-targeted cognitive domains [33]. Moreover, the benefits did not extend beyond 2 years, nor was it beneficial among individuals who already have Alzheimer's type dementia [33].

The evidence for the benefit of non-pharmacological management strategies for people with MCI and early AD is strongest for:

- Lifestyle—includes diet, alcohol use, nutrition, physical exercise, smoking.
- Depression.
- Sleep.

Role of health and care professionals

Health and care professionals have an important role in educating people about the importance of good control of long-term conditions, and appreciation of the importance of compliance with management recommendations and medications.

The following guidelines/suggestions promote healthy lifestyle:

Lifestyle factors (non-pharmacological) [34]:

- **Alcohol:** intake should be limited to 14 units per week spread over two to 3 days. For people who misuse alcohol, interventions should be offered to achieve abstinence or moderate drinking as appropriate and prevent relapse, in community-based settings. All interventions should be the subject of routine outcome monitoring and should inform decisions about ongoing psychological and pharmacological treatments [35].
- **Smoking:** The most effective way to quit smoking is with expert behavioral support from local stop smoking services combined with stop smoking aids [36].
- **Healthy diet and weight management**: Diet should include five portions of different fruit and vegetables per day, oily fish twice per week; sugar and salt should be kept to a minimum. Weight management strategies should combine healthy diet, physical activity and motivational support.
- **Physical activity:** Activity should consist of aerobic, resistance and flexibility elements, including 75 min of vigorous exercise [37].
- **Social Engagement:** Keeping in contact with friends/family, joining a community group or doing some volunteering can promote social engagement.
- **Mental Stimulation:** This includes doing puzzles, learning a new language, reading, playing card or board games, using electronic games available from the App store, or other activities that offer mental stimulation.

Conclusions

Dementia and late-onset AD are heterogenous and multifactorial conditions, with various metabolic, lifestyle, mental health and environmental risk factors. Importantly, most of the risk factors, as those listed in the Lancet Commission, are modifiable factors. With no disease modifying treatments for AD, early modification and targeting of these risk factors is crucial, both at the individual and societal level, in order to prevent or delay the onset of these conditions.

Evidence from the former generation of unimodal short-term and small clinical trials, which focused on individual lifestyle factors (e.g., diet, exercise, cognitive training) generally had moderate quality of evidence [8], although more recent trials are addressing limitations that were found in previous trials (inadequate sample size/trial duration). The WHO Guidelines focused on such individual factors, and provided strong recommendations for physical exercise,

smoking cessation, a healthy balanced diet and diabetes management [8]. The assessment of individuals at increased risk for dementia can be carried out through the use of dementia risk scores, which quantify the risk and can be used as an educational and motivational tool. While some risk factors focus on midlife risk factors for long-term prediction of dementia (e.g., 20 years when using the CAIDE dementia risk score), others are developed for late-life risk factors, and for short-term prediction [3−10] years, such as the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) (predicts dementia up to 6 years). Risk scores also differ in the extent to which they target modifiable factors. For example, the Lifestyle for Brain Health (LIBRA) risk score only focuses on modifiable factors, whereas others include genetics, age and other non-modifiable factors [38]. More recently, dementia risk scores have been proposed as surrogate outcomes that may reflect the intervention response [39].

Recent multidomain lifestyle interventions (FINGER, PreVDIVA, MAPT) have demonstrated the importance of selecting individuals who are at increased dementia risk for participation in the trial. For example, the FINGER trial used the CAIDE dementia risk score selected participants at higher risk for dementia, while PreDIVA showed in subgroup analyses that participants with untreated baseline hypertension showed most benefit. Similarly, in the MAPT trial in France, the intervention was effective among those with an increased risk for dementia at baseline (CAIDE score $\geq$6) or have elevated beta-amyloid in the brain [20]. In the PreDIVA trial in the Netherlands, lower dementia incidence was found among participants with untreated hypertension at baseline, and who were then prescribed treatments for their hypertension [21]. Collectively, these trials highlight the importance of selecting individuals at increased risk for dementia.

These trials have also demonstrated the value in simultaneously targeting multiple risk factors in order to prevent or postpone multifactorial conditions such as dementia and AD. By targeting lifestyle factors such as diet and exercise, and managing vascular and metabolic risk factors, such interventions also have the potential to reduce other health outcomes. For example, in the FINGER trial, those in the intervention group developed fewer chronic diseases during the 2-year trial, compared to the control group [40]. The trial also showed benefits for health-related quality of life [41] and daily functioning [42]. The Healthy aging through internet counseling in the elderly (HATICE) trial, which also simultaneously targeted multiple lifestyle factors improved cardiovascular risk factors including systolic blood pressure, body mass index and low density lipoprotein (LDL) cholesterol.

Most if not all of the risk factors summarized in this chapter tend to be chronic, and interventions are most optimal when they commence early, prior to negative physiological, neurological and health outcomes occur. For effective results, interventions also need to be of sufficient duration and

intensity. As shown with the aforementioned multidomain lifestyle interventions, whereas lifestyle advice may be insufficient, coaching and more frequent visits with health professionals and research nurses may increase the level of engagement and adherence to the interventions. Internet counseling - as that used in the HATICE trial - is also providing a promising tool that allows older adults to receive lifestyle interventions at the population level, while reducing costs and burdens on participants. Various mobile applications have been developed for specific lifestyle factors, and some are based on RCT evidence, such as the digital CBT App for insomnia *Sleepio* (also used by the National Health Service (NHS), England) [43,44], and the *Sleep Healthy Using the Internet (SHUTi)* [45]. It will be important for future evidence-based eHealth tools to integrate multiple lifestyle factors, similar to the multidomain trials.

While the multidomain trials to date have been conducted in high-income countries in Europe, it is important to test these interventions in middle- and low-income countries, while adapting the interventions to local settings. This is the goal of the World-Wide FINGERS network [46], which was launched in 2017. The aim of this network is to adapt the FINGER intervention model to numerous countries and world regions, and offer a platform that allows for data sharing, joint analyses, and collaborative opportunities.

In conclusion, evidence has been accumulating regarding several risk and protective factors for dementia, and targeting these factors can contribute to substantial dementia risk reduction. Evidence from lifestyle interventions suggest that they may offer a promising approach to reducing the risk for cognitive impairment and dementia, and important lessons have been learned on how to optimize the trial methodologies. Finally, ongoing and future work will support with wider-scale implementation of dementia risk reduction initiatives for various populations and settings.

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