

PERSPECTIVE

CCCDTD5: Reducing the risk of later-life dementia. Evidence informing the Fifth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD-5)

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Abstract

The Fifth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD-5) was a year-long process to synthesize the best available evidence on several topics. Our group undertook evaluation of risk reduction, in eight domains: nutrition; physical activity; hearing; sleep; cognitive training and stimulation; social engagement and education; frailty; and medications. Here we describe the rationale for the undertaking and summarize the background evidence—this is also tabulated in the Appendix. We further comment specifically on the relationship between age and dementia, and offer some suggestions for how reducing the risk of dementia in the seventh decade and beyond might be considered if we are to improve prospects for prevention in the near term. We draw to attention that a well-specified model of success in dementia prevention need not equate to the elimination of cognitive impairment in late life.

KEYWORDS

Alzheimer's disease, dementia, exercise, hearing loss, multicomponent, nutrition, prevention

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Dementia prevention increasingly seems plausible.^{1,2} In many countries the age-adjusted incidence of dementia is falling, and although the meanings, mechanisms, and extent are contested, a lower incidence challenges the dogma of dementia as inevitable.^{3,4} Internationally two streams of dementia prevention efforts are recognized. One is multidomain “lifestyle” interventions, catalyzed by the Finnish GHeriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial’s demonstration that some individuals benefit (albeit with considerable effort)⁵. Its promise is being tested on a large scale⁶ including a plan to build on the pan-Canadian COMPrehensive ASSESSment of Neurodegeneration and Dementia (COMPASS-ND) study.⁷ Skepticism abounds, especially whether such lifestyle interventions can ever be effective in people possessing an apolipoprotein E (APOE) ε4 allele. Both sides of the argument can muster evidence in their favor.^{8–10}

The second prevention approach also comes with controversy: It is the effort to intervene on the mechanism(s) said to give rise to Alzheimer’s disease (AD). For now, this mostly consists in seeing the disease as one or a series of single-protein abnormalities. The anti-amyloid monoclonal antibody medication aducanumab showed initial promise,¹¹ and although it was judged likely to be futile to continue testing¹² most recently the drug been resurrected.¹³ This has not been without controversy.^{13,14} This and like efforts represent one approach, and one that is commanding substantial resources.

The reason to consider other approaches is that most dementia occurs in late life—in Canada most cases occur between the ages of 75 and 95.¹⁵ Most people with dementia by that age are frail to some degree.¹⁶ The degree of frailty is important both in the risk for late-life cognitive impairment¹⁷ and in whether people with the neuropathological features of AD (diffuse and neuritic plaques, and neurofibrillary tangles) are expressed as clinical dementia.¹⁸ In consequence, there remains merit in exploring ways to prevent dementia that focus on putatively proximal causes and to consider how overall health affects brain health. Furthermore, and especially in low and middle-income countries, whatever interventions are undertaken should be cost-effective enough, and priced so as to be widely available.³

Against this background, the Fifth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD-5) took a broad view of late-life dementia.¹⁹ We reflected on the fact not just that most dementia occurs in late life but that it is believed to have multiple causes. The community-based Rush studies suggest that although the risk of dementia attributed to AD is about 65%, this is the case only when combined with seven other neuropathological features.²⁰ AD exists on its own in only 9% of cases at autopsy.²¹ For the most part, we were able to build updates from a 2017 comprehensive overview of dementia prevention.¹ In each case of new methods and targets, however, we supplemented information there (when present) with updates, especially focusing on Canadian data. In consequence, we offer recommendations on nutrition, physical exercise, hearing loss, sleep, cognitive training and rehabilitation, social deprivation, frailty, and anticholinergic medications; vascular risk factors were the focus of a separate inquiry. These many interventions appear to have importance both

RESEARCH IN CONTEXT

- 1. Systematic Review:** Building on comprehensive reviews up to 2017, for each area of inquiry, the authors conducted additional reviews of more recent papers in PubMed to identify relevant studies, specifically related to mid-life and late-life strategies for reducing the risk of later life dementia. Articles were supplemented by authors through their familiarity with existing literature.
- 2. Interpretation:** Our findings led to recommendations in each of eight areas of reducing the risk of dementia (nutrition, physical activity, hearing, sleep, cognitive training, social vulnerability, frailty, and medication). Our recommendations were voted upon at the Fifth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD-5). Recommendations reaching 80% consensus have been included in the article.
- 3. Future directions:** Our group is one of eight CCCDTD-5 subgroups that evaluated topics for the conference. The recommendations are going through a knowledge translation process to aid in the diagnosis and treatment of people with dementia. The next conference (CCCDTD6) is planned for 2026.

across the life course and in primary, secondary, and sometimes tertiary AD prevention.

1 | METHODS

As outlined in the main paper,¹⁹ we were guided by the Appraisal of Guidelines, Research and Evaluation (AGREE) II collaboration for clinical practice guidelines. AGREE II revised a 2003 statement, and the goal was to improve the outcomes associated with the implementation of guidelines. Its six domains and 23 items oblige a clear scope and purpose, the involvement of a variety of stakeholders, a rigorous evidence review to be methodologically exacting, and with the results presented clearly, supported by tools that aid applicability in a fashion that makes clear editorial independence. The AGREE II Guidelines are notable for a statement on the strengths and limitations of the body of evidence. Some of the requirements, well suited to clinical trials of interventions that are masked to the recipients (eg, a placebo-controlled trial of a medication or a sham procedure for an invasive procedure) are less readily available in prevention studies: for example, people will have some clear insight into whether they have exercised to x% of exhaustion y times a week, or have changed their diets. Even so, the basics—especially consistency of results across studies, including the magnitude of effect, including that of benefit and

of harm, and the applicability to practice—remain rightly influential in understanding the desire for and likelihood of uptake. In like manner, we aimed to follow the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system.²³ Still we recognize that intelligent people of good will can disagree on which interpretation might be drawn. Here, for example, the approach to consensus building required a threshold for acceptance of recommendations of 80% endorsement. Likewise, recommendations obtaining <60% endorsement were dropped. In the consensus building, finalized at an in-person October 2019 consensus meeting, recommendations that had obtained between 60% and 80% endorsement, and thereby required revision, were presented and discussed, with re-voting to see if the 80% threshold was then met. That meeting was attended by two delegates per each of the eight working groups.

We began by reviewing the results of a 2017 international consensus conference.¹ Each team conducted a search in PubMed to identify reports related to the risk factor under study. Articles were supplemented by authors through expertise and familiarity with existing literature. Studies were included if they were meta-analyses, English or French language, included older adults, and investigated the relationship between the risk factor (or an intervention meant to alleviate it) and at least one cognitive outcome. In general, the risk and related interventions were defined broadly. For example, “physical activity” included aerobic exercise (including walking), resistance training, dance, and mind-body exercise. Where a more restrictive approach was undertaken, this is noted (eg, as detailed in the results, the frailty section did not include studies of risks for cognitive frailty, but did include interventions on that state). In cases where there were several recent meta-analyses available, the review that was most inclusive of recent studies was considered. Each team included a focus on Canadian guidelines. Where new data were available we updated those statements. To increase the chance of applicability to practice context (an AGREE II rating criterion) we also sought out Canadian data when available and relevant. Here we recapitulate the recommendations from the main paper¹⁹ and describe the items that did not meet the required 80% threshold. For each recommendation, we offer a short narrative summary. The key evidence is summarized in tables, presented in an Appendix.

2 | RESULTS

2.1 | Nutrition

Overall, against the background of ambient risk from a regular diet, some dietary factors appear to either increase the risk of cognitive decline or to protect against it. Risk is conferred by diets high in alcohol, saturated fats, and refined sugars (Appendix; Table 1).

Recommendation 1a (BOX 1): Mediterranean diet. Of the dietary patterns that appear to offer some protection, the best evidence supports adherence to a Mediterranean diet to decrease the risk of cognitive decline^{24–26} (Appendix; Table 1, Recommendation 1a). A Mediterranean diet is characterized by high intake of vegetables, fruits

BOX 1—Nutrition and Cognitive Decline

- 1a. We recommend adherence to a Mediterranean diet to decrease the risk of cognitive decline. GRADE 1B (91%).
- 1b. We recommend a high level of consumption of mono- and polyunsaturated fatty acids (MUFAs and PUFAs) and allow consumption of saturated fatty acids (SFAs) to reduce the risk of cognitive decline. GRADE 1B (92%).
- 1c. We recommend increasing fruit and vegetable intake. GRADE 1B (88%).

and nuts, cereals, fish and monounsaturated fatty acids (MUFAs); relatively low intakes of meat and dairy products; and moderate consumption of alcohol.^{26–28}

Recommendations 1b and 1c (BOX 1): Diet constituents (fat and fruits and vegetables). This evidence also contributes to support of a diet rich in mono- and polyunsaturated fatty acids (MUFAs and PUFAs), fruit and vegetables, and vitamin D, and low in saturated fatty acids (SFAs).²⁷ Regarding milk or dairy products, growing evidence suggests a potential protective effect on cognitive function.^{29,30} Fish and fish oil are rich sources of omega-3 fatty acids (ie, MUFAs), specifically eicosapentaenoic acid (or EPA) and docosa-hexaenoic acid (or DHA).^{28,31,32} Alpha-linolenic acid (or ALA) is an omega-3 fatty acid present in seeds and oils, green leafy vegetables, and nuts and beans. Linoleic acid, an omega-6 fatty acid (ie, PUFA), is present in grains, meats, and the seeds of most plants. Saturated fatty acids are present in large quantities in meat, processed meat, milk, yogurt, cheese, butter are predominantly in the form of palmitic acid.

The literature up to now does not show enough to support for a ketogenic diet. Pre-clinical studies and research to date suggests only that it is a promising but unproved means of managing or preventing cognitive decline. In short, even if it clear that diet is an important modifiable factor to prevent or protect against cognitions, more studies are required to determine the recommended duration and amounts of nutrients.

2.2 | Physical activity

Recommendations 2–4 (Box 2). The data on physical exercise continue to evolve. As is not rare, going from observational studies to clinical trials is accompanied by a diminution in the size of treatment effects, but still suggest benefit. The controlled trials evidence is also remarkable for some heterogeneity in impact based on the type of exercise and its intensity.

We recommend physical activity interventions to improve cognitive outcomes among older adults, including those with MCI.^{33–38} Evidence supports that both aerobic and resistance exercise have the potential to improve cognitive outcomes, which supports the notion that a multimodal exercise program might lead to larger gain. However, comparative studies of multi-modal versus aerobic exercise

BOX 2—Physical activity interventions to improve cognitive outcomes among older adults

2. We recommend physical activity interventions of at least moderate intensity to improve cognitive outcomes among older adults. GRADE 1B (96%).

- a. We recommend aerobic exercise and/or resistance training of at least moderate intensity to improve cognitive outcomes among older adults. GRADE 1B (94%).
- b. There is promising evidence that dance interventions and mind-body exercise (for example, tai chi, qi gong) of moderate dose improve cognitive outcomes among older adults but results from larger, high-quality trials are needed. GRADE 2B (84%).

3. We recommend physical activity interventions to improve cognitive outcomes among people with mild cognitive impairment (MCI). GRADE 2B (94%).

- a. We recommend aerobic exercise to improve cognitive outcomes among people with MCI. Grade 2B (94%).
- b. There is promising evidence to support resistance training and mind-body exercise (eg, tai chi, qi gong) to improve cognitive outcomes among older adults with MCI but results from larger, high-quality trials are needed. Grade 2C (83%).

4. We recommend physical activity interventions to reduce the risk of dementia, including AD and vascular dementia. GRADE 2B. (96%).

or resistance training only are not yet available. There is also emerging evidence that other forms of exercise such as dance and mind-body exercise (eg, tai chi, qi gong) may improve cognitive outcomes among older adults, though the type of mind-body exercise may again moderate effects.^{34–36, 38}

While improving cognitive outcomes in both healthy adults and those with MCI might reasonably lead to an effective reduction of dementia, direct evidence from clinical trials that physical activity interventions reduce the risk of dementia is still lacking.³⁹ Despite this gap, the pattern of results across several earlier observational studies and randomized controlled trials (RCTs) among adults with and without MCI provides support to recommend physical activity interventions as a part of dementia prevention strategies⁴⁰ (Appendix; Table 2). In addition, physical activity is understood to improve cardiovascular and cerebrovascular health, which may contribute to dementia risk⁴¹ (Appendix; Table 2, Recommendation 4). The risk in recommending physical activity is low, where physical activity is likely to contribute to improved functional abilities even if individuals are diagnosed with dementia^{42,43} (Appendix; Table 2, Recommendation 3 a and b).

Future directions should include larger trials, in which physical exercise is part of a multimodal intervention. For physical activity, some should focus on behavior change and adherence, to drive maintenance

BOX 3—Hearing loss and dementia

- 5a. Persons with cognitive complaints, MCI, or dementia (and their care partner, if there is one) should be questioned about symptoms of hearing loss to improve cognitive outcomes and risk reduction. It is recommended that persons be asked whether they have any difficulty hearing in their everyday life (rather than asking if they have hearing loss). GRADE 1B (93%).
- 5b. If symptoms of hearing loss are reported, then hearing loss should be confirmed by audiometry conducted by an audiologist meeting relevant provincial regulations. If confirmed, audiologic rehabilitation may be recommended. This rehabilitation may include behavioral counseling and techniques, and may include the recommended use of a hearing aid or other device. GRADE 1A (98%).
6. We recommend following the World Health Organization 2019 guidelines for risk reduction of cognitive decline and dementia including: (1) audiological examination and/or otoscopic examination; (2) the review of medications for potential ototoxicity; and (3) referral to otolaryngology for persons with chronic otitis media or who fail otoscopy. GRADE 1A (93%).

after the active intervention period. Some may benefit from passive monitoring of the quality of the exercise (eg, via apps). In addition, the evidence is still inconclusive regarding effects to brain structure; this requires more high quality, large trials with imaging.⁴⁴ Exercise is likely appropriate “pre-hab” even in cases where people require interventions that might increase the risk of delirium (eg, surgery, chemotherapy).^{42,45–48} There is a need to individualize exercise recommendations, including tailoring for adherence and behavior change, both when recommending exercise and when designing long-term interventions. Potential differences between women/men require further evaluation.⁴⁹

2.3 | Hearing

Recommendations 5a/5b (BOX 3). Elicit symptoms of hearing loss and investigate (confirmed by audiometry) if present are both reasonable, and as discussed below, increasingly relevant.¹

Recommendation 6 (BOX 3) extends this to medication review, and referral under specified conditions (chronic otitis media, and failing otoscopy) that are not rare when symptoms are present.

New since the CCCDTD-4,⁵⁰ but present in the 2017 recommendations,¹ is advice about hearing loss. The latter suggested that to maximize hearing function, screening followed by maneuvers such as removing ear wax or using hearing aids be done.^{51–53} Based

BOX 4—Sleep and the prevention of dementia

- 7a. A careful sleep history, including assessment of sleep time, and symptoms of sleep apnea, should be included in the assessment of any patient at risk for dementia. Patients in whom sleep apnea is suspected should be referred for polysomnography and/or sleep specialist consultation for consideration of treatment. GRADE 1C (96%).
- 7b. Adults with sleep apnea should be treated with continuous positive airway pressure (CPAP), which may improve cognition and decrease the risk of dementia. GRADE 1C (96%).
- 7c. Avoiding severe (<5 hours) sleep deprivation, and targeting 7-8 hours of sleep per night, may improve cognition and decrease the risk of dementia. GRADE 1C (94%).
- 7d. Although associated with incident cognitive decline and dementia, there is insufficient evidence to recommend treatment of insomnia, long sleep time, daytime napping, sleep fragmentation, circadian irregularity, or abnormal circadian phase with a goal of improving cognition and decreasing the risk of dementia. GRADE 3C (90%).

on how common hearing loss is⁵⁴ and the three high-quality studies available at the time,⁵⁵⁻⁵⁷ hearing loss was calculated as having the highest weighted population attributable fraction. This was based on the high pooled risk ratio (RR) of hearing loss for dementia (pooled RR 1.94). Recent meta-analyses of cross-sectional and longitudinal studies^{58,59} have shown that hearing loss is associated both with poorer cognition in healthy older adults and with an average 30% increased risk of MCI or dementia.⁵⁹⁻⁶¹ Even so, the data summarized in the Appendix notes the lack evidence from RCTs that correcting hearing loss can prevent cognitive decline. Brief, validated tablet or iPad-based hearing screening tests are likely to become available for in-clinic screening.

2.4 | Sleep

Recommendation 7a BOX 4 (sleep apnea). A body of large observational studies in diverse populations of older adults supports an association between sleep apnea, incident cognitive decline and dementia, and biomarkers of AD pathology⁶²⁻⁶⁵ (Appendix; Table 4, Recommendation 7a).

Recommendation 7b BOX 4 (CPAP). Randomized trials in younger adults have established the impact of CPAP on sleepiness and cognition; observational studies in older adults support an association between CPAP use and slower cognitive decline; and experimental studies in older adults support an impact of CPAP on biomarkers of

AD pathology; however, large RCTs assessing the impact of CPAP on cognitive decline and incident dementia in older adults are lacking. Notwithstanding this lack of RCT evidence, the benefits of CPAP in sleep apnea on other symptoms such as sleepiness are well-established, and the side effects are minimal, hence the strong recommendation.^{66,67}

Recommendation 7c. BOX 4 (Avoiding severe sleep deprivation, targeting 7-8 hours of sleep per night). A body of large observational studies in diverse populations of older adults support an association between short sleep duration, incident cognitive decline and dementia, and biomarkers of AD pathology. Moreover, experimental studies in cognitively normal adults support an impact of sleep deprivation on biomarkers of AD pathology; however, large RCTs assessing the impact of sleep extension on cognitive decline and incident dementia in older adults are lacking. Notwithstanding this lack of RCT evidence, the side effects of obtaining adequate sleep are minimal, hence the strong recommendation^{62,68-70} (Appendix; Table 4, Recommendation 7c).

Recommendation 7d. BOX 4 (insufficient evidence to recommend treating insomnia to prevent cognitive decline).

Although there is abundant evidence supporting an association between sleep fragmentation⁷¹⁻⁷⁶ (Appendix; Table 4, Recommendation 7d), insomnia^{64,77-79,80,81} (Appendix; Table 4, Recommendation 7d), excessive daytime sleepiness and long sleep^{68,77,79,82-85} (Appendix; Table 4, Recommendation 7d), need and incident cognitive decline and dementia, and some evidence supporting an association between circadian irregularity⁸⁶ (Appendix; Table 4, Recommendation 7d), delayed circadian phase^{79,87} (Appendix; Table 4, Recommendation 7d), and incident cognitive decline and dementia, the causal direction of these associations remains unclear, and even small treatment trials showing an impact on cognition and/or biomarkers of AD pathology are lacking. Therefore, at this point, there is insufficient evidence to recommend treatment of insomnia, circadian irregularity, circadian phase, or sleep fragmentation, with a goal of improving cognition and decreasing the risk of dementia.

2.5 | Cognitive training and stimulation

Recommendation 8a BOX 5 (individual and group training for those at risk). Several good quality RCTs have reported the impact of cognitive training on cognitive and non-cognitive tasks⁸⁸⁻⁹⁰ (Appendix; Table 5, 8 a and b). These studies used varying types of interventions (eg, home-based computer training, face-to-face group-based training) and tested effects in several ways, mostly by performance on cognitive measures, including ones on which people had not been trained. Inasmuch as people are aware of having taken part in cognitive training, concealment of allocation for the subject is inherently a challenge. Against that background, and relative to a control condition, there is moderate-quality evidence for small to moderate effects on global cognition in healthy older adults, MCI, and dementia. The evidence is stronger for effects on cognitive tasks that are close to the training content than on transfer tasks.^{88,89} There is evidence for retention of training effects from 3 to 12 months. A few moderate quality RCTs have provided

BOX 5—Cognitive training and late-life cognitive decline and dementia

- 8a. We recommend that when accessible, empirically supported individual computer-based and group cognitive training be proposed to people at risk, and those with a diagnosis of MCI or mild dementia. We recommend additional studies to optimize effective delivery of training, and evaluation of their cost-effectiveness. No specific program can be endorsed at this time. GRADE 1B (83%).
- 8b. We recommend that individuals be advised to increase or maintain their engagement in cognitively stimulating activities such as cognitively stimulating pastimes, volunteering, and life-long learning. No particular activities can be suggested at this time but data suggest that engaging in a variety of cognitively stimulating activities is preferable. GRADE 1C (96%).

evidence of a positive effect of cognitive training on long-term cognition and cognitive decline. No strong studies have provided evidence of a positive effect on clinical outcomes such as dementia.^{88,90} Cost-effectiveness data are not available.

Recommendation 8b BOX 5 (maintaining engagement in cognitively stimulating activities). As detailed in the Appendix, there is strong evidence for an association between engagement in early life cognitively stimulating activities (education) and late-life cognitive decline and dementia^{1,88,91} (Appendix; Table 5, Recommendation 8 a and b). Several good quality studies have reported an association between engagement in whole-life cognitively stimulating activities (profession, leisure activities) and late-life cognitive decline and dementia⁹¹ (Appendix; Table 5, Recommendation 8 a and b). A few studies showed an association between engagement in late-life cognitively stimulating activities and less cognitive decline and dementia.⁹² In terms of the type of activities, some studies have assessed association between music and bilingualism. Evidence is mixed and weak. The variety and intensity of activities may be important. Only a few studies have investigated experimentally the effect of leisure activities (ie, volunteering and cognitively stimulating leisure) and reported short-term positive effect cognition and results are positive. No strong RCTs have provided evidence of positive effect of second language learning or music learning on cognition. A few moderate quality RCTs have provided evidence of a positive effect of cognitive training on long-term cognition, cognitive decline. No strong studies have provided evidence a positive effect on clinical outcomes such as dementia.

2.6 | Social engagement and education

Recommendation 9a BOX 6 (Social context and attention to social circumstances across the life course).

BOX 6—Social vulnerability, frailty, and education

- 9a. We recommend attention to social circumstances and supports across the life course, including poverty-reduction strategies and opportunities for social engagement. GRADE 1B (90%).
- 9b. We recommend support for educational attainment, particularly in early life (1B) but also for ongoing educational experiences in mid and later life. GRADE 1C (98%).

Social circumstances are complex and challenging to measure, let alone modify. Terminology in a voluminous literature varies, in part reflecting interest and approaches (eg, social support, engagement, participation, networks, isolation, and individual level socioeconomic status). This complexity has motivated capturing social vulnerability more holistically⁹³⁻⁹⁷ (Appendix; Table 6, Recommendations 9 a and b). Social factors also likely have an important impact over long time courses, so that most evidence comes from observational studies, where reverse causation can be a challenge (eg, difficulties in regulating social relationships and adhering to social norms as features of frontal impairment, not as causes of it.^{94,95} Lifelong personality differences may exist such that some people enjoy social engagement, and thus are drawn to rich social environments, whereas others find it stressful and find comfort in a solitary existence. There may also be important gender differences in the associations between social factors and dementia risk, for example, relationships with friends may be more important for women versus family and spousal relationships for men.⁹⁶ Even so, many observational studies have demonstrated associations between low social engagement, less frequent social contact, and more loneliness,⁹⁷ with risk of incident dementia in late life, although studies of social network size and satisfaction with one's social network have been less consistent^{96,98,99} (Appendix; Table 6, Recommendations 9 a and b).

Intervention studies are limited, although it is interesting to note that social interaction has (explicitly or implicitly) been part of multimodal intervention studies and may be a component of other interventions that appear to be unidimensional (eg, group exercise classes or cognitive training^{1,33-37} (Appendix; Table 6, Recommendations 9 a and b).

Recommendation 9a BOX 6 (Special importance of educational attainment in early life). Low educational attainment as a dementia risk has been consistently well established in observational studies (Appendix; Table 6, Recommendations 9 a and b). Education has also been proposed as a key contributor to cognitive reserve.¹⁰⁰ The contribution of bilingualism to cognitive reserve has also been studied, although associations have been less clear in prospective studies, and observational studies are prone to confounding by education and cultural differences.¹⁰¹ The timing of educational experience is relevant to consider, and it is unclear how the (clearly demonstrated) benefits of

BOX 7—Recommendation on interventions to manage frailty

10. We recommend that interventions to manage frailty be used to reduce the overall burden of dementia in older adults. GRADE 1B (81%).

early life schooling may be enhanced by participation in later life formal and informal learning experiences. Of pragmatic note, interventions to support social circumstances, educational opportunities, and general health across the life course are safe and come with other health and social benefits.

2.7 | Frailty

Frailty defined either as a specific phenotype¹⁰² or as a state¹⁰³ has been linked to cognitive decline in both community-based observational studies and in relation to biomarkers and neuropathology.^{17,104,105} It also mediates the relationship between neuropathology and cognitive impairment, such that people with a low degree of frailty and a low degree of neuropathology are least likely to express dementia, whereas those with high degrees of each frailty and neuropathology are most likely to express dementia.¹⁸ Given their shared risk factors—including a strong relationship to ageing—there is overlap between interventions, such as exercise¹⁰⁶ (Appendix; Table 7, Recommendation 10). The term “cognitive frailty” has been proposed to capture the co-occurrence of MCI and the physical frailty phenotype; its status as an entity is controversial and is not basis for the current recommendation.¹⁰⁷

2.8 | Medications

Three large, well-designed pharmacoepidemiologic studies^{108,109} (Appendix; Table 8, Recommendations 11 a and b), and several reports with supporting evidence,^{110,111} have identified a significant relationship between cumulative use of anticholinergic medications and developing dementia. These data are supported by other pharmacoepidemiologic studies of lower quality. They showed that higher cumulative exposure to anticholinergic drug use may increase risk.

This is the case even though rates of incident dementia are likely to be influenced by the measure used to identify anticholinergic drug use. Even so, the most commonly used measures (Beers Criteria, Anticholinergic Burden Scale) consistently identify some specific classes of anticholinergic drugs as increasing dementia risk: Antidepressants with anticholinergic activity (eg, tricyclic antidepressants); anticholinergic agents used in the treatment of Parkinson disease (eg, benzotropine and trihexyphenidyl); anticholinergic agents used in the treatment of urinary incontinence (eg, oxybutynin, tolterodine, solifenacin). Note too that these risks are particularly increased in two populations with a

BOX 8—Recommendations on minimizing anticholinergic medications

- 11a. Exposure to medications known to exhibit highly anticholinergic properties should be minimized in older persons. Alternative medications should be used for specific indications where medications with anticholinergic properties are indicated (eg, depression, neuropathic pain, urge type urinary incontinence). GRADE 1B (100%).
- 11b. Multidimensional health assessment for older adults, including of medication use, with the aim of identifying reversible or modifiable health conditions and rationalizing medication use. GRADE 1B (92%).

higher intrinsic risk for which developing dementia have been identified (Parkinson disease, and diabetes mellitus)

Recommendation 11b BOX 8 (Reducing anticholinergic drug burden). Some preliminary evidence from controlled trials suggests that reducing anticholinergic drug burden can result in modest improvements in cognition^{112–115} but how best to achieve this at scale is not yet clear.

3 | CONCLUSIONS

The prevention group has made specific recommendations to suggest that people at risk of dementia be encouraged to adhere to a balanced diet, modeled on the Mediterranean diet where feasible, to engage in at least moderate energetic physical activity, to improve disordered sleep, to encourage cognitive training and intellectually stimulating activities, to pay attention to social circumstances and supports across the life course, to ameliorate the degree of frailty, and to minimize anticholinergic medications. The remit of the group, although broad and considering eight factors, was nevertheless constrained to items other than vascular risk factors, or pre-clinical treatment of abnormalities in amyloid and tau, or vascular risk factors; these were the foci of other groups. Even so, other areas merit further consideration. From a clinical perspective, perhaps the most salient is delirium.¹¹⁶ Although delirium is commonly super-imposed on dementia,¹¹⁷ on its own it has long been known to indicate (or put people at) high risk for developing dementia.¹¹⁸ Despite this, delirium for decades has gone unrecognized,^{119,120} even while remaining burdensome.¹²¹ It is telling that such preventive maneuvers that have had any success are characteristically multifactorial¹²² and address factors such as sleep,¹²³ physical exercise, nutrition and hydration, social engagement by family,¹²⁴ and a geriatric assessment,¹²⁴ of which mobilization and medications reviews are main stays.¹²⁵

Four additional points require consideration. First, the emphasis on lifestyle factors overall, including physical inactivity, poor diet,

hypertension, and smoking have been linked to many late-life illnesses, also including many types of cancer, coronary heart disease, stroke and diabetes mellitus, in addition to dementia.¹²⁶ Related to this, observational studies suggest that multimodal interventions will be needed in late-life dementia.^{1,3} Compared to those with no individual risk factors or unhealthy behaviors, in multivariable models no single risk trumps everything else; rather effects are roughly additive.¹²⁷ In consequence, it is likely that understanding late-life dementia as a disease of aging, and addressing it as a likely outcome of interventions that reduce disease and impaired function, and further that increase the number of people in good health in late life can enhance opportunities for prevention. This has consequences for how we conduct clinical trials now, which often exclude people most at risk.¹²⁸ Likewise, a large number of interventions for which older adults are the prime target commonly have begun to evaluate their impact on cognition.¹²⁹ Understood in this light, prospects for dementia prevention might seem as closer to our grasp. This is not just a matter that many of the recommendations address issues that will have positive health effects, even if they do not necessarily reduce dementia risk; treating the whole package of disordered health in old age should be understood as important to the public health mandate. Furthermore, although different disciplines approach health in aging differently, many of the factors addressed are bound up in each other. For example, addressing hearing loss in older adults can improve communication and reduce social isolation and depression, which in turn can increase the likelihood that someone will engage in physical activity, thereby enriching social activities.

Finally a key point in understanding the impact of a preventive maneuver is to understand what success might look like. A model of success that obliges a diagnosis of “no cognitive impairment” as the outcome is highly likely to disappoint. This may be especially true, for competing reasons, for diagnoses that rely on a biomarker-defined disease, instead of clinically defined understanding of the degree of cognitive, functional, and behavioral impairment. Given the well-known poor correlation between the degree of neuropathology and the degree of cognitive impairment—and that this relationship is moderated by the overall health of the individual¹⁴⁸—imagining that success should entail change biomarker levels may be impose on the biomarkers a burden that they cannot bear. What is important to people living with dementia, and to their caretakers, may not readily conform to a model of disease reversal: Individually meaningful success can be achieved short of cure.^{130–132} Similarly, patient and caregiver reports of how late-life cognitive impairment impacts on their preferences and life satisfaction may also offer insights into just what successful prevention might consist.

CONFLICTS OF INTEREST

Kenneth Rockwood: In addition to academic and hospital appointments, Kenneth Rockwood is President and Chief Science Officer of DGI Clinical, which in the last 5 years has contracts with pharma and device manufacturers (Baxter, Baxalta, Biogen, Shire, Hollister, Nutricia, Roche, Otsuka) on individualized outcome measurement. In 2017 he attended an advisory board meeting with Lundbeck on dementia,

and in 2020 chaired a Scientific Workshop & Technical Review Panel on frailty for the Singapore National Research Foundation. Otherwise any personal fees are for invited guest lectures, rounds, and academic symposia, received directly from event organizers, for presentations on frailty.

Laura Middleton: Has received honoraria for public lectures and academic rounds and symposia regarding physical activity and lifestyle in relation to dementia risk and well-being of people living with dementia.

Mylène Aubertin-Leheudre: In addition to academic appointments, is scientific advisor for the Fonds de recherche en Santé du Québec and member of SARA-INT data and safety monitoring board (Biophytis) since 2019.

Melissa K. Andrew: reports grant funding from GSK, Pfizer, and Sanofi and payments from Sanofi and Pfizer for research on frailty in relation to vaccine preventable illnesses.

Susan K Bowles has received funding from the Canadian Frailty Network to evaluate interventions to decrease the Drug Burden Index.

Andrew Lim has attended an advisory board meeting for Eisai Ltd. concerning insomnia.

Sylvie Belleville receives consultancy fees from Sojceci and is head of the scientific committee for Lucilab.

None of the other co-authors have conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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