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Editorial

Prevention of Cognitive Decline: A Goal in Sight?

Carol Brayne[a,*] and Edo Richard[b,c]
[a]*Department of Public Health and Primary Care, Cambridge Institute of Public Health, University of Cambridge, UK*
[b]*Department of Neurology, Donders Institute for Brain, Cognition & Behaviour, Radboud University Medical Centre, Nijmegen, the Netherlands*
[c]*Department of Neurology, Amsterdam University Medical Centre, University of Amsterdam, Amsterdam, the Netherlands*

There is accumulating evidence that up to 30% of all late-life dementia is attributable to potentially modifiable risk factors [1]. This has led to an increasing attention for interventions targeting the mostly vascular risk factors. The promise of potential prevention has led to a series of randomized controlled trials (RCTs) using single- or multidomain interventions to slow down or prevent cognitive decline and dementia. As opposed to the considerable number of industry-sponsored RCTs using molecular targets, interventions targeting multiple vascular and lifestyle-related risk factors generally aim to develop widely implementable interventions for a broad population at increased risk of dementia.

The existing data suggest modest impact from interventions for individuals, but so limited are the good news stories in dementia research that such findings have been seized on with enthusiasm. The FINGER trial from Finland, targeting multiple dementia risk factors in persons with no cognitive impairment, shows a small *excess improvement* in cognition over the considerable improvement seen in the control group after 24 months [2]. This glimpse of hope has been taken up with funding for FINGER style studies across the globe, with local adaptation. Other large trials, including preDIVA and MAPT, did not show a significant effect on their respective primary endpoints all-cause dementia after 72 months and cognitive decline after 36 months [3, 4]. Both studies have pointed toward areas of improvement and potential subgroups in whom this type of interventions may be more effective.

In this edition there are three papers on new investigator-initiated prevention trials. These include two protocols on multi-domain interventions and one providing much needed evidence about adherence to a single-domain intervention on physical activity. It should be noted that none of these provide results from a phase III RCT. This raises the question whether the previous phase III trials, which were generally neutral, were simply performed too soon with insufficient development of combinations of effective interventions, and the current studies prepare the ground for large scale phase III trials with a higher chance of success. For the two study protocols and the results of the phase II trial reported here, we focus on their approaches to the question they seek to address. Different target populations, intervention

*Correspondence to: Prof. Carol Brayne, Department of Public Health and Primary Care, Cambridge Institute of Public Health, University of Cambridge, Cambridge, UK. E-mail: cb105@medschl.cam.ac.uk.

types, and outcome measures used, betray the struggle of the field to find the optimal strategy to reach the common goal: prevention (or postponement) of cognitive decline and dementia. A crucial question is what the future value of these studies will be for wider populations in real-world settings.

A remarkable difference between the three presented studies is the choice of the target population. All select persons at increased risk of dementia, based on the presence of individual risk factors. But while the SMARRT trial targets persons between 70 and 89, the AIBL and MYB studies target much younger populations of over 60 and 55–77, respectively [5–7]. This illustrates the previously discussed trade-off between the optimal window of intervention versus the optimal window for effectiveness assessment [8].

Studies on dementia prevention use a wide range of outcomes, ranging from a biomarker such as hippocampal volume on MRI, to all-cause dementia. All three studies in this issue use cognitive decline as an effectiveness outcome measure. MYB is powered to detect a 0.1 standard deviation difference on a cognitive test battery, which raises the question whether such an effect should be considered proof of concept, or proven efficacy. All-cause dementia is generally the preferred outcome, since its clinical relevance is beyond doubt. But this outcome may not always be feasible because of the length of follow up and funding required. Although often used, cognition as an outcome poses problems of interpretation and meaning in its relevance to lived lives. The treatment effect in the FINGER trial is a good example: a statistically significant difference on a standardized composite cognitive score between the intervention and control group was found, but the effect size was small, and both intervention and control groups improved. This renders the meaning for long-term cognitive functioning uncertain. This is a challenging question for agencies such as the FDA and EMA; does a small effect on an intermediate outcome like cognitive decline justify large-scale, and expensive in terms of opportunity cost given limited resources, implementation? And how large should such an effect be, and how sustainable should it be before we accept it as proof of effectiveness? Although the SMARRT pilot trial will use change in cognitive functioning for the sample size calculation for the full-scale trial, it will potentially be able to power for all-cause dementia due to the target age range of 70–89, depending on the expected effect size and planned study duration of the full trial.

The decision to proceed to implementation of an intervention with a small effect may depend on the type of intervention. Low-risk interventions, such as lifestyle interventions, can be taken to the implementation phase (including assessment of cost, capacity, and resource implications) after showing a relatively small effect, even on an intermediate outcome such as a cognitive test. Such studies should also incorporate evaluation of long-term effectiveness related to clinical outcomes and risk of adverse events. If effectiveness for clinical outcomes remains uncertain, such implementation should be reviewed. This is rarely the case currently when 'good ideas' are rushed into policy without such care and attention. In contrast to such low-risk approaches, intensive diagnostic processes and high risk or expensive interventions, such as immunotherapy, must be tested not only for efficacy but also effectiveness and harm for clinically relevant outcomes with clear benefit beyond doubt before investment in robust implementation with populations of relevance.

Adherence to prevention programs is notoriously difficult to sustain. Results from the AIBL study are encouraging, showing that motivated people in the setting of an RCT resulting from a cohort study can sustainably adhere to a physical activity intervention. The finding is in line with previous reports on adherence from the multidomain FINGER trial, which used a similar approach by recruiting from a pool of participants in longitudinal observational studies. However, such populations of volunteers are highly atypical of those at increased risk of future dementia. Any findings must therefore be confirmed in a less structured real-world setting. The recruitment in SMARRT is closer to a real-world setting, recruiting from an integrated health care system in the US, although these are not fully population representative. Before implementation in a true real-world setting, an acceptable level of sustained adherence in relevant populations should be made tested and deliverable.

The three studies use different modes of delivery of the intervention. The intervention in SMARRT is rather intensive, aiming for at least a monthly face to face meeting with a healthcare worker. This may not be implementable in large parts of the world due to both logistical and financial reasons. The MYB, on the other hand, will use an approach which is completely online. This offers many advantages, and will be much easier and cheaper to implement. However, previous studies have shown that blended approaches, i.e., combining an online intervention with human support, are probably more effective

[9]. In this light, the results of the HATICE trial, probing a multi-domain interactive coach-supported internet intervention to improve the cardiovascular risk profile, are eagerly awaited [10]. The planned PRODEMOS RCT will take this one step further and will use a smartphone-based approach to reduce the risk of dementia, aiming to make dementia prevention available across the globe including settings with generally less access to preventive health care [11]. An important consideration to probe an online strategy, particularly using a smartphone, is that there may be little room for improvement left in high income countries, whereas in many low- and middle income countries (LMIC), economic growth and increasing prosperity are accompanied by an increase in unhealthy lifestyles. Smartphone possession is steeply on the rise in LMIC, making preventive approaches within reach for millions of people who previously hardly had access to health care.

Finally, the recently published SPRINT-MIND has been interpreted as showing encouraging results suggesting that intensive blood pressure lowering may prevent cognitive decline and dementia [12]. Although the study failed to show a statistically significant effect on all-cause dementia, it has been argued it was underpowered because of early termination due to substantial beneficial effect on incident cardiovascular disease. Dementia risk reduction studies will need to be carefully integrated with initiatives that cardiovascular disease taking into account this and other learning such as population evidence on the 'side effects' that might be usual in real world populations, but appear to be much lower in the SPRINT study creating concern about the implementation of guidance into frailer populations.

With so many prevention studies completed and ongoing, it is time to take stock. The International Research Network on Dementia Prevention (IRNDP) is a promising initiative in an emerging area bringing the global research community together, including LMICs in which risk is probably rising. The European Dementia Prevention Initiative (EDPI; http://www.edpi.org) has shown that collaboration can be instrumental, with three large international dementia prevention studies coming forth from such collaboration (HATICE, MIND-AD, and PRODEMOS). IRNDP may be a global platform for discussions on future trial design, such as the question whether we should take a step back and consider interventions targeting the population, rather than the individual. The AIBL proof of concept for sustainable adherence, the carefully designed pilot study necessary for a proper sample size calculation in SMARRT, and the ambitious MYB study may all inspire future dementia prevention study designs.

DISCLOSURE STATEMENT

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-0448r1).

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