

Dementia prevention: call to action

The first WHO Ministerial Conference on Global Action Against Dementia, hosted in March, 2015, showed that the focus on finding the causes and cures for dementia, including Alzheimer's disease, is intensifying. Since development of a cure for dementia by 2025 is unlikely, risk reduction is the most effective approach to delay onset and potentially reduce the number of new cases.¹ Such an approach needs to be set in the context of up-to-date prevalence studies showing how the incidence of dementia might be changing across time and societies. The Blackfriars Consensus² highlighted various risk factors, focusing on the options for vascular risk reduction, since this accounts for substantial attributable risk and has a robust evidence base.

That well designed clinical trials are essential to test prevention approaches is widely accepted, and the same idea applies to dementia. Intervention studies in dementia prevention are only just becoming possible. These studies have provided evidence of feasibility, but they now need to be expanded since studies have generally focused on a narrow range of risk factors (eg, omitting computer use³ and hearing correction), had only short-term follow-up using cognition as a proxy,⁴ had not been done for long enough to examine the incidence of dementia, did not include a follow-up after dementia onset to look at predictors of progression, and had insufficient statistical power and representation of the general population.

There is an urgent need for large, definitive, multicentre, international randomised controlled studies of lifestyle-based interventions to investigate how far risk factor reduction can decrease or delay incidence of dementia, to which existing cohorts could contribute. The Internet means that lifestyle-based interventions are now more feasible using touch-screen devices such as

smartphones and tablets. Increasing evidence shows that, at least for some people, goal setting, monitoring and action planning, using information about health and lifestyle, promoting cognitive activities and exercise, and managing hearing problems could be integrated into a feasible and appealing package. Proof-of-concept studies (eg, Healthy Ageing Through Internet Counselling in the Elderly [HATICE]) exist and are ongoing. Building on these findings, joint efforts between countries are now needed to estimate risks in relation to local cultures and socioeconomic circumstances, which affect lifestyles and diets, so that essential evidence on best practice in dementia prevention can be generated.

We need also to know the scope for lifestyle-based interventions—the relative effects of the various elements of each intervention; how these interventions could be best targeted either at the population and community level or at the family and individual level; how long lifestyle-based interventions need to be adopted before benefits are seen; and how much benefit might accumulate over time—and to link levels of risk reduction to potential benefits. The most cost-effective approaches are usually those that can be easily adopted and rolled out on a large scale rather than those delivered at individual levels. At present, recommendations are undermined by the absence of well designed, properly scaled clinical and population-based trials. Policy statements use best existing evidence, but such evidence is not based on trials. Therefore, a compelling need for robust research evidence exists.

We call on WHO and the World Dementia Council to support large-scale research investment into these urgently needed population-orientated trials and to work with national governments and research funding bodies to encourage collaboration towards a concerted objective.

We declare no competing interests.

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Pointing the FINGER at multimodal dementia prevention

The FINGER trial (June 6, p 2255)¹ results have been highly anticipated and are of great interest to people trying to advance dementia prevention. This study delivers positive news but also raises challenging issues for the specialty.

The FINGER trial combined four lifestyle-based strategies comprising about 360 intervention hours. On a composite cognitive measure, the intervention group improved by 0.23 SDs. Controls who continued standard care plus psychoeducation likewise improved by 0.19 SDs. The absolute difference was 0.04 SDs on a group basis, and 0.02 SDs when analysing individual change, amounting to a Cohen's $d=0.13$.

One of the first challenges to consider is that, although the control group was designed for a modest decline in the primary outcome,¹ this group



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For more on the WHO Ministerial Conference see <http://www.who.int/nmh/concept-note-conference-on-dementia-march2015.pdf>

For a full list of signatories see online appendix

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improved significantly. Without the expected natural history, showing the counterfactual is difficult. Self-selection bias is therefore a concern, especially when recruiting from a population-based sample and selecting for several risk factors. The so-called unwilling, who refuse to sign up for hundreds of hours of intervention, could benefit most from such preventive efforts.

Community-level cluster trials, such as changing the design of a town to enable more walking opportunities (to target physical inactivity), are ambitious, but have great relevance to public health. Another option is two-staged trials that begin with a low-intensity intervention for all participants and then randomly allocate decliners into higher-intensity action or an activity-matched control group. Matching is crucial because, after FINGER, we do not know whether 360 h of any additional activity is sufficient to produce such weak effects.

Additionally, results of the FINGER trial question the assumption of therapeutic additivity. Systematic reviews suggest that computerised cognitive training yields an estimated effect size of $d=0.23$,² antihypertensive therapy $d=0.29$,³ and aerobic exercise $d=0.33$.⁴ Effects in the FINGER trial were therefore about half those observed in stand-alone trials and generally outside their 95% CI.

Lifestyle interventions do not automatically add up when combined, and worse, can even subtract. The FINGER trial is not the first trial to show this trend. Our SMART trial⁵ targeted secondary prevention for mild cognitive impairment, and we reported that combined resistance exercise and cognitive training was less effective than exercise alone.⁵ Overdosing is a possible explanation with strong evidence from individual lifestyle interventions.² Clearly, applied research is needed on how to implement lifestyle modification effectively.

Finally, we should not forget that no evidence-based model exists to link marginal changes in cognitive trajectories to modification of dementia

incidence. Categorical change in risk for cognitive impairment and translation of cognitive gains to protection of daily function are closer to dementia incidence outcomes. These issues are technical obstacles for approval of a preventive drug,⁶ and, in our view, the same standards should apply to non-pharmacological interventions. We look forward to publication of results of effect on daily function.

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Findings from observational studies have shown several modifiable risk factors for subsequent cognitive impairment and dementia. Clinical trials are an imperative next step to test cause and effect; however, results from the mostly single intervention studies have been disappointing so far. The FINGER trial,¹ in which investigators combined lifestyle advice, management of cardiovascular disease risk, and cognitive training in a multimodal intervention for patients aged 60–77 years, is therefore

a welcome addition to the small evidence base.

At 2 years' follow-up, the authors assessed cognitive function across several domains, reporting a 25–150% improvement in the intervention group compared with the general health advice (usual care) control group. In view of the negative findings from previous lifestyle interventions and cognitive training trials to reduce or delay cognitive ageing,² because cardiovascular disease risk factors in middle age (rather than at old age) are associated with dementia risk,³ and because, by comparison, even the most successful prevention strategies for coronary heart disease, such as lipid-lowering and antihypertensive therapy, reduce disease risk only by 20–50%,^{4,5} the positive effects in the FINGER trial seem surprisingly large.

A learning effect can arise from growing familiarity with testing procedures. In the FINGER trial, the investigators administered an extensive programme of cognitive training for the intervention group, but not for the control group. Learning effect might therefore explain the large effect of the multifactorial intervention in this trial. We urge the results of the FINGER trial to be interpreted with caution because they are likely to be overestimates.

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