Are large simple trials for dementia prevention possible?

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NEW HORIZONS

Are large simple trials for dementia prevention possible?

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Abstract

New trials of dementia prevention are needed to test novel strategies and agents. Large, simple, cardiovascular trials have successfully discovered treatments with moderate but worthwhile effects to prevent heart attack and stroke. The design of these trials may hold lessons for the dementia prevention.

Here we outline suitable populations, interventions and outcomes for large simple trials in dementia prevention. We consider what features are needed to maximise efficiency. Populations could be selected by age, clinical or genetic risk factors or clinical presentation. Patients and their families prioritise functional and clinical outcomes over cognitive scores and levels of biomarkers. Loss of particular functions or dementia diagnoses therefore are most meaningful to participants and potential patients and can be measured in large trials.

The size of the population and duration of follow-up needed for dementia prevention trials will be a major challenge and will need collaboration between many clinical investigators, funders and patient organisations.

Keywords: dementia, trials, epidemiology, function, older people
Dementia is a major healthcare and social challenge, but there is no available treatment to delay its onset or progression. Despite poor progress to date, optimism remains that new agents or novel strategies of evaluation will be effective.

Here we analyse the possible populations, interventions, outcomes and designs relevant to randomised trials to test new interventions targeting dementia incidence. We concentrate on efficient and reliable designs that could reduce costs for academic trialists, and examine whether the design of large trials that have led to the successful preventative strategies in cardiovascular disease are relevant to dementia prevention.

Populations at high risk and populations for long-term follow-up

An ideal trial population for dementia prevention would be easily identified, highly motivated to participate, with a high risk of dementia within a short follow-up. Populations could be identified by age, clinical and polygenic scores for dementia, high-risk polymorphisms, frailty or mild cognitive impairment (MCI).

Although age is a strong risk factor for dementia, the incidence of dementia even in the oldest old is modest (85 per 1000 person years at age 85 years and above). [1] Any advantage of recruiting the very old might be mitigated by their competing risk of death. The annual mortality rate of 80–84 year-olds: is 6%, so there would be substantial loss-to-follow-up over a five-year trial. [2] However, healthy older people can be identified simply, in large numbers, and are highly motivated to prevent a dementia which many will have experienced through family or friends. [3]

Dementia risk prediction scores based on clinical variables could be implemented in electronic records to identify high-risk populations, but the best score is not obvious. Some are poorly validated [4,5] and it is unclear which score identifies the highest risk population. [6,7] Risk scores are acceptable to participants. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) used a threshold of a risk score to identify suitable participants, although most of those surveyed for eligibility (84%) already had a high score, so the benefit of using the risk score was small. [8,9]

Available polygenic scores only explain a modest proportion of the variance in dementia incidence at younger ages, [10] but might perform better at older ages. [11] Although measurement of polygenic scores adds complexity, the cost of a gene chip is modest. Potential participants who are APOE ε4 carriers and have elected not to be informed of the results of their genetic tests could be approached from existing registers, but the gain in the number of dementia cases in a recruited population who are APOE4 positive or have higher polygenic scores is likely to be modest compared with easier to approach populations such as those with a family history of dementia, or a higher clinical risk score (see Table 1).

Participants with some evidence of impairment on cognitive tests but normal activities of daily living, i.e. with MCI, are at higher risk of dementia compared with those with no cognitive impairment. However, the clinical course of MCI is not always predictable: patients may improve, remain stable or progress to dementia. [12] MCI prognosis depends very much on the setting. In specialist clinics, ~10% develop dementia annually, compared with ~5% in the community. Incidence further depends on age, APOE and cognitive status. [13,14] Because of differences in these characteristics, trials recruiting participants with MCI have had varying progression to dementia.

The approach to potential participants is important. Although post is cheap, response rates are poor compared with in-person approaches. For example, in a trial of computerised cognitive training, only 5% of those approached by post consented. [15] However in the FINGER study where participants who had previously taken part in health surveys, had a high response to a screening invitation (43–57%) of whom approximately half took part. [9]

Choosing interventions to prevent dementia onset

It is clear that amyloid plaques are important markers of Alzheimer’s disease and that mutations in amyloid processing lead to early onset dementia. This is supported by pathway analyses of genome wide association studies (GWAS). [16] However, drugs targeting soluble and insoluble amyloid, amyloid pre-processing and vaccines against amyloid have yet to be shown definitively to be effective. This may be because of adverse effects, [17] low amyloid positivity in trial participants or that intervention needs to be given at the very earliest stages of amyloid accumulation. Moreover, amyloid burden correlates only modestly with cognitive
and behavioural deficits, [18] and removal of brain amyloid [assessed by positron emission tomography (PET) or cerebrospinal fluid (CSF) studies] has yet to correlate with clinically meaningful improvements in cognition. Targeting tau protein has shown promise in animal models, and clinical trials run by pharmaceutical companies are testing anti-tau agents in phase 2 and phase 3 trials. [19]

Inflammatory pathways are appealing because several agents target single or multiple inflammatory pathways. Although GWAS supports inflammatory mechanisms as a cause of dementia, [16] animal studies suggest that inflammation (i.e. microglial activation) has both beneficial and harmful effects in the brain that may vary over the course of disease, and therefore the optimal intervention period is uncertain. [20]

Lipids are of particular interest because the ε4 allele of APOE is a strong risk factor for Alzheimer’s disease. People with an ε4 allele have higher total cholesterol (~0.25–0.5 mmol/L) and triglycerides than those without, and therefore higher blood cholesterol is one potential mechanism for the effect of the ε4 allele. [21] In the brain, the role of APOE is less certain. GWAS studies also show the importance of cerebral lipid metabolism as a risk factor for Alzheimer’s disease. [16] However, new approaches to managing lipids are needed as blood cholesterol lowering agents have so far been neutral for dementia prevention. [22]

Currently, the most plausible, modifiable targets for dementia prevention are other cardiovascular risk factors, chiefly high blood pressure and diabetes. Biological mechanisms link the cerebral vasculature with Alzheimer’s disease and neurodegeneration. [20,23] Vascular damage leads to blood brain barrier breakdown, parenchymal accumulation of neurotoxic moieties, inflammation and synaptic dysfunction and accumulation of Aβ and tau through failure to clear proteins along perivascular spaces and through aberrant metabolism. [20] The earliest physiological change in human carriers of APOE ε4 is vascular dysfunction, and in apoE ε4 animal models early degeneration of vascular endothelial cells and pericytes. [20] Observational cohorts demonstrate associations between higher dementia risk with higher mid-life blood pressure, [24] poorer sleep, [25] less exercise [26] and diabetes, [27] but the association between polygenic scores of hypertension, LDL cholesterol and diabetes with Alzheimer’s dementia has been inconsistent. [28]

It is uncertain why blood pressure lowering or statins—which reduce the risk of stroke by about a fifth—do not lead to a consistently detectable reduction in dementia incidence. This may be because dementia prevention needs a longer duration of therapy or a greater intensity of intervention as in Systolic Blood Pressure Intervention Trial (SPRINT-MIND) [29] in comparison to the prevention of myocardial infarction and stroke. [30]

Although most potential treatments for dementia have a biological or epidemiological rationale, choosing a single candidate with the highest chance of success is difficult. One approach is to start with systematic reviews of experiments in model systems, genetic studies, or of early stage human trials. For example, an adaptive trial in progressive multiple sclerosis has used systematic reviews to identify candidate agents [31]. The selection process began with systematic review of the in vivo experimental data, which identified candidate agents. These candidates were further winnowed based on safety data, efficacy, risk of bias of the underlying literature, the number of patients contributing evidence, biological plausibility and central nervous system penetration. [32] Further selection of agents can be made with an adaptive trial design. Multi-arm adaptive trials use pre-specified rules to select between agents during the course of the trial (e.g. by measuring the effects of different agents on a responsive biomarker), so unsuccessful agents can be rejected, and successful ones taken forward to the later trial stages. However, for such a trial to be successful for dementia outcomes would need a responsive biomarker signal that would be expected to change more quickly than clinical variables (see below).

### What cognitive outcomes should be measured?

Variability during the serial measurement of cognition potentially obscures treatment effects. Contributing to this variability are sleep quality, anxiety and variation in circumstances of test administration e.g. different examiners and noisy or poorly-lit rooms. In addition, any single cognitive test is not likely to be sensitive to all cognitive domains. Therefore, small but clinically relevant treatment effects could go undetected.

Variability could be reduced by repeating cognitive tests—allegorical to other continuous variables such as blood pressure—but this could come with increased cost, more missing data and learning effects. Large international trials pose particular problems for trials aiming to measure cognition and function that may differ by world region and culture. Better training, especially in the differences in language and culture, might help, as well as the development of scales that take into account the differences expected between countries and groups of people. [33]

There is a tension between the complexity of cognitive tests and the resources available to perform them in most

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**Table 1.** Proportion of patients developing dementia at 10 years, estimated from the Rotterdam study [6]

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Age at recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>65</td>
</tr>
<tr>
<td>% Dementia by 10 years</td>
<td></td>
</tr>
<tr>
<td>No memory complaints</td>
<td>4 5 8</td>
</tr>
<tr>
<td>No memory complaints + APOE ε4 positive</td>
<td>6 10 15</td>
</tr>
<tr>
<td>No memory complaints + history of stroke</td>
<td>6 10 15</td>
</tr>
<tr>
<td>No memory complaints, but difficulties with IADL</td>
<td>5 8 12</td>
</tr>
<tr>
<td>Memory complaints, but no difficulties with IADL</td>
<td>5 7 11</td>
</tr>
</tbody>
</table>

IADL: instrumental activities of daily living (finance or medication).
settings. In highly resourced trials (such as the SPS3 [34]) extended cognitive batteries can be performed, increasing costs and limiting populations to those easily followed up. Although short tests do not cover all cognitive domains, they are simple to perform at large scale and demonstrate cognitive decline in patients who are in the later stages of disease. [35]

An alternative to cognitive testing is to measure the time taken to reach clinically meaningful milestones i.e. the diagnosis of dementia or MCI. Clinical outcomes and other functional thresholds have greater meaning to patients and clinicians than cognitive scores. In SPRINT-MIND, the use of an adjudicated clinical milestone (the development of dementia or two consecutive adjudicated MCI events) was critical to accrue enough events reliably to demonstrate an effect in an analysis of intensive BP lowering on dementia or MCI. [29] These adjudicated outcomes were resource intensive to measure and had greater face-validity.

The measurement of clinical outcomes implies the measurement of both function and cognition. The measurement of both means disease trajectories can continue to be measured later into the disease course, where the recruitment of a friend or family member would allow the report of function when cognition was difficult to measure and hence could reduce loss-to-follow-up.

**Trial design**

Large simple trials have been influential in other areas of medicine. Vascular researchers pioneered large-scale randomised trials [37] which led to widespread adoption of treatments that have contributed to decreasing the burdens of stroke, myocardial infarct, diabetes and other vascular diseases in high income, and to some extent in low- and middle-income countries. [38,39] The application of efficient, simple trial designs to target dementia mean trials can be larger, allowing more precise estimates of treatment, and greater generalisability of therapies at similar or lesser cost than trials of high complexity.

Thus far, the bulk of the clinical trial designs in dementia prevention has used labour-intensive examinations, application of expensive technology and relatively short follow-up based on cost and other design limitations. Large trials are probably necessary in dementia prevention, because:

**Effect sizes are likely to be moderate, because multiple pathologies lead to cognitive impairment in most individuals**

Protein folding disorders, vascular pathologies and inflammation are found together in many—up to two-thirds—patients with dementia. [40,41] If agents are efficacious for one of these multiple pathologies and all pathologies contribute to varying extent to the clinical phenotype (although Alzheimer's pathology is most commonly found), we can expect only moderate effects on overall dementia incidence or cognitive decline. Large numbers must be recruited to a trial with clinical outcomes to reliably assess for moderate benefits.

**Loss of clinically meaningful function, and dementia, are important outcomes but are less frequent than small changes in cognitive scores over short periods of time.**

For disabling diseases, preventing or delaying loss of clinically meaningful function provides a better test of efficacy than improving cognitive tests, imaging or other biomarkers. Outcomes that cross important functional boundaries are the most important to older people. [42] Although cognitive scores and biomarker outcomes provide evidence of efficacy in phase II trials or in adaptive designs, large-scale trials with functional outcomes due to cognitive or behavioural impairment are needed to convince patients, doctors, regulators and payers that treatments are worthwhile.

**Relative to other outcomes, longer duration of follow-up may be needed between intervention and outcome measurement**

Current science suggests a long latency between the optimum period for intervention and the occurrence of dementia. The problems of trials with a very long interval between intervention and follow-up have not been resolved. A very long period of intervention or the long-term follow-up of patients in a trial with conventional methods probably would be associated with substantial loss to follow-up (as seen in long-duration cohort studies) unless linkage could be performed to reliable electronic health records, or a particular group could be targeted who agree to take part in low-intensity follow-up (e.g. web-form for cognitive tests, implemented in UK Biobank) and dilution of treatment effects, unless multiple methods to encourage long-term intervention adherence could be developed. However, long trial interventions are possible; the Heart Outcomes Prevention Evaluation-3 trial [43] trial of LDL and blood pressure lowering had 6 years of intervention followed by 3 years of follow-up, the UK Prospective Diabetes Study [44] of intensive glucose lowering lasted 10 years, and trials of tamoxifen in oestrogen receptor positive breast cancer compared treatment durations of 10 with 5 years. [45] “One-off” therapies with lasting effects (e.g. gastric banding) might lead to differences between randomised groups that last for many years.

If it is not the case that prevention requires a very long period between intervention and symptoms, differences in dementia incidence may be seen over a modest period (4–5 years) if higher risk populations are recruited. For example, SPRINT-MIND suggested a difference in dementia incidence over 5 years with an annual dementia or MCI rate of about 2 per 100 participant years.

**For a preventative strategy to be adopted widely for a common disease, it must be simple to deliver**

If, for example, PET targeted intravenous amyloid reduction strategies prove to be effective to reduce the rate of
studies of other agents. Many agents tested in cardiovascular (or their combination in a validated algorithm) in large effects to be found testing cognitive or functional measures adverse or beneficial effects. shorter trials with biomarker endpoints may miss off target make studies possible at lower cost. However, smaller and measurement of aspects of cerebral small vessel disease may neurofilament light chain [47] or computed tomography in small trials. [46] Simpler biomarkers in blood (e.g. randomisation designs that could be used as endpoints blood biomarkers might be discovered with Mendelian at older ages, is not clearly causal. New, causally related biomarkersthat are known to be causally related to cognitive and functional impairment. However, the most widely used biomarkers of pathologies of cognitive impairment are difficult to deliver at large scale as their assessment is expensive (e.g. markers of cerebral small vessel disease with MRI, measurement of amyloid or tau by PET or in CSF) and their association with clinical outcomes, particularly at older ages, is not clearly causal. New, causally related blood biomarkers might be discovered with Mendelian randomisation designs that could be used as endpoints in small trials. [46] Simpler biomarkers in blood (e.g. neurofilament light chain [47]) or computed tomography measurement of aspects of cerebral small vessel disease may make studies possible at lower cost. However, smaller and shorter trials with biomarker endpoints may miss off target adverse or beneficial effects. The third is to acknowledge that there may be important effects to be found testing cognitive or functional measures (or their combination in a validated algorithm) in large studies of other agents. Many agents tested in cardiovascular or other fields have potential effects dementia pathological pathways and beginning and end of study cognitive test allows one to test these hypotheses at modest cost. In comparison to these designs, large simple trials with clinically important outcomes offer the advantage of generalisability and validity of observed treatment effects. If such trials are to be delivered in dementia prevention, then it is important to identify easily recruitable populations at higher risk, important deliverable interventions and clinically meaningful outcomes which can be measured easily.

Alternatives to large simple trial designs

The first is to perform trials in smaller populations at particularly high risk of inherited dementia, e.g. those with a strong family history of dementia, those with extremes of polygenic risk scores for all cause dementia or Alzheimer’s disease or those with one or more high risk genetic variants (e.g. APOE ε4 polymorphisms). The challenges faced by such trials are the ethical and practical identification of potential participants and the possibility that trial results do not generalise to the prevention of sporadic dementia in old age (although there is a suggestion that similar pathways are important in both young-onset familial disease and late onset Alzheimer’s dementia) [16]. The benefit is a tractable design in a modest number of participants and short-duration length of follow-up that identifies a pathway that may be exploited in larger studies.

The second is to power trials based on changes in clinically relevant outcome were possible, it would be a major challenge. Populations at high risk could be identified with clinical variables, although only the oldest patients with comorbidity (stroke or frailty) would have an estimated 10-year risk of dementia of over 10% (Table 1). Participants with these comorbidities would have similar risks to those carrying APOE ε4. A long duration trial of a treatment with a moderate but worthwhile effect (e.g. a reduction in relative hazards of 15%) in one of these populations would need to recruit at least 8342 participants (Table 2), and possibly more depending on the risk of competing events. The most suitable targets are those targeting vascular risk factors. Although trials examining complex vascular risk interventions are underway, whether any one of the components of these complex interventions has an effect on dementia is uncertain and would need to be clarified to ensure the optimum dementia prevention package.

A trial involving such a large number of participants would need international co-operation, multiple academic funders and strong engagement with communities of patients and clinicians. Some consortiums have begun, but to ensure healthy ageing for all across the world, we will need to form new collaborations between many regions, collaborators and patient organisations.

### Table 2. Sample sizes for different treatment effects in a two-arm trial, assuming a 5% drop-out rate over the course of a 10-year trial with α = 0.05 and β = 0.8

<table>
<thead>
<tr>
<th>% with outcome</th>
<th>Hazard ratio between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>5</td>
<td>13,275</td>
</tr>
<tr>
<td>10</td>
<td>6,638</td>
</tr>
<tr>
<td>15</td>
<td>4,425</td>
</tr>
<tr>
<td>Number of outcomes needed</td>
<td>631</td>
</tr>
</tbody>
</table>

Conclusion

If a large, simple dementia prevention trial with a clinically relevant outcome were possible, it would be a major challenge. Populations at high risk could be identified with clinical variables, although only the oldest patients with comorbidity (stroke or frailty) would have an estimated 10-year risk of dementia of over 10% (Table 1). Participants with these comorbidities would have similar risks to those carrying APOE ε4. A long duration trial of a treatment with a moderate but worthwhile effect (e.g. a reduction in relative hazards of 15%) in one of these populations would need to recruit at least 8342 participants (Table 2), and possibly more depending on the risk of competing events. The most suitable targets are those targeting vascular risk factors. Although trials examining complex vascular risk interventions are underway, whether any one of the components of these complex interventions has an effect on dementia is uncertain and would need to be clarified to ensure the optimum dementia prevention package.

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### Declaration of Conflicts of Interest

W.W. is supported by a Scottish Senior Clinical Fellowship [CSO SCAF/17/01] and received grants from the Alzheimer’s Society [UK], Chief Scientist’s Office, UK MRC, and the UK Stroke Association. S.A. is supported by a Tier 1 Canada Research Chair in Ethnicity and Cardiovascular Disease and the Michael G. DeGroote Heart and Stroke Foundation Chair in Population Health and has received speaking honoraria and consulting fees from Bayer, outside the submitted work. S.B. participates in research at McMaster University that is supported by grants from Sanofi, Bristol-Myers Squibb and the Rome Foundation, outside the submitted work. J.B. has received fees for participating in an Advisory Board and as an Adjudication Committee Member from Bayer, outside the submitted work. M.C. has received a travel grant
from Boehringer Ingelheim and Bayer for conference attendance. H.G. holds the McMaster-Sanoﬁ Population Health Institute Chair in Diabetes Research and Care and has received research grant support from AstraZeneca, Eli Lilly, Merck, Novo Nordisk and Sanoﬁ; honoraria for speaking from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanoﬁ; and consulting fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Janssen, and Sanoﬁ, Cirius and Kowa outside the submitted work. P.G. employer receives payment for work as a major cardiovascular event adjudicator and data safety and monitoring board member for a number of pharmaceutical companies. He has received personal fees for serving on the Bayer ARRIVE study steering committee, outside the submitted work. M.S. reports personal fees from BMS and personal fees from Daichi Sankyo, outside the submitted work. E.S. reports consulting fees from Portola and Alnylam, outside the submitted work. J.W. reported that his institution received funding from Biogen (unrelated to this study) and research support from the National Institutes of Health. T.C.Y. reports honoraria for speaking from Eli Lilly, Sanoﬁ Aventis, MSD, Medtronic not related to the submitted work. R.H. reports grants and personal fees from Bayer AG, outside the submitted work. S.Y. is supported by the Heart & Stroke Foundation/Marion W. Burke Chair in Cardiovascular Disease and has received research grants, honoraria and travel expenses for lectures from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, AstraZeneca and Sanoﬁ, outside the submitted work. G.P. is a Tier 2 Canada Research Chair in Genetic and Molecular Epidemiology and holds a CISCO Professorship in Integrated Health Biosystems. He has received consulting fees from Sanoﬁ, Illumina and Amgen and support for research through his institution from Sanoﬁ and Bayer, outside the submitted work. J.W. receives funding from the National Institutes of Health and Biogen.

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