Cerebral Circulation - Cognition and Behavior 6 (2024) 100199

Contents lists available at ScienceDirect

Cerebral Circulation - Cognition and Behavior

journal homepage: www.sciencedirect.com/journal/cerebral-circulation-cognition-and-behavior

What have clinical trials taught us about brain health?

Keon-Joo Lee [a], Hee-Joon Bae [b,*]

[a] Department of Neurology, Korea University Guro Hospital, Seoul, South Korea
[b] Department of Neurology and Cerebrovascular Center, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea

ARTICLE INFO

Keywords:
Clinical trials
Brain health
Multidomain approach
Cerebral small vessel disease
Mendelian randomization

ABSTRACT

The Global Burden of Disease Study projects an almost tripling of dementia cases worldwide in the next 30 years making it important to recognize and understand modifiable risks and preventatives for cognitive impairment. Recent studies suggest that prevention or treatment of cardiovascular risks may be an important strategy to prevent or slow the progression of cognitive impairment. In 2017, the American Heart Association and American Stroke Association introduced metrics for "optimal brain health". These metrics defined brain health in terms of ideal health behaviors and factors.

Since then and leading up to 2017, a number of clinical trials have been conducted to investigate the potential of modification of cardiovascular risks on prevention of dementia or cognitive impairment and thus, enhancement of brain health. This discussion is a review of findings from clinical trials focusing on interventions, including antihypertensive agents, glycemic control and lipid-lowering therapies, multidomain approaches, and antithrombotic medications. Notably, the results highlight the promise of intensive blood pressure lowering strategies and multidomain approaches, as evidenced by the FINGER trial. The review also discusses the potential of treatment or prevention of cerebral small vessel disease (cSVD) and the application of Mendelian randomization as a strategy to preserve brain structure and function.

Introduction

The global increase in life expectancy is paralleled by a rising prevalence of dementia and cognitive impairment [1,2]. According to a projection from the Global Burden of Disease (GBD) Study, the number of dementia cases reached an estimated 57 million in 2019. This figure is anticipated to increase to over 152 million by 2050 [3]. Notably, even a minor delay in the onset of Alzheimer's disease (AD) has the potential to significantly decrease its prevalence, and consequently helps to mitigate its human and economic burdens [4].

Research has uncovered various cardiovascular factors as potential risks for cognitive impairment, positioning them as modifiable targets for prevention of cognitive impairment and dementia [5]. In 2017, a writing group from the American Heart Association and American Stroke Association published a set of metrics that define "optimal brain health" in adults [6]. These metrics are grounded in the American Heart Association's "Life's Simple 7″, which comprises four ideal health behaviors: non-smoking, meeting physical activity recommendations, adhering to a diet consistent with current guidelines, and sustaining a body mass index under 25 kg/m2. Additionally, they proposed three optimal health factors: untreated blood pressure below 120/80 mm Hg, untreated total cholesterol beneath 200 mg/dL, and a fasting blood glucose level under 100 mg/dL. Since then and leading up to 2017, clinical trials have been carried out to ascertain whether interventions for these health behaviors and risk factors could serve as strategies to enhance brain health.

In this review, we present a narrative overview from the authors' perspective, focusing on clinical trials that primarily address cardiovascular risks and brain health. Additionally, we delve into recent advances in enhancing the efficacy of clinical trials. This includes the innovative use of neuroimaging biomarkers for cerebral small vessel disease (cSVD). We also highlight other promising strategies that are emerging in the field.

* Corresponding author at: Department of Neurology and Cerebrovascular Center, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82 Gumi—ro 173 beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, South Korea.
E-mail address: braindoc@snu.ac.kr (H.-J. Bae).

https://doi.org/10.1016/j.cccb.2023.100199
Received 19 August 2023; Received in revised form 26 December 2023; Accepted 27 December 2023
Available online 28 December 2023

Summary of the clinical trials

Antihypertensive agents and intensive blood pressure control (Table 1)

Hypertension, particularly in mid-life, is a recognized risk factor for future cognitive impairment [7–9]. Data to support the relationship of midlife hypertension and subsequent cognitive impairment is largely derived from observational epidemiologic studies. On the other hand, most of the clinical trial participants in blood pressure lowering clinical trials are generally older persons in whom it has been difficult to show a benefit of blood pressure lowering or administrative of blood pressure lowering medications on cognitive outcomes or the occurrence of dementia.

For instance, the Systolic Hypertension in the Elderly Program (SHEP) trial evaluated over 4700 adults aged 60 and above [10]. They were treated with a combination of a diuretic and beta blocker or given a placebo. After five years, there was no discernible difference between the two intervention groups in terms of cognitive, emotional, and physical function. Similarly, the Medical Research Council's Treatment Trial of Hypertension randomized almost 4400 patients aged 65 to 74 years, with treatments involving a beta blocker, diuretics, or placebo [11]. After close to five years of follow-up, no association emerged between the antihypertensive treatment and changes in memory or attention. The Study on Cognition and Prognosis in the Elderly (SCOPE) trial assigned approximately 5000 older patients aged 70–89 years with elevated BP to either candesartan treatment or a placebo [12]. Nearly four years later, there was no statistically significant difference in the risk of dementia or the Mini-Mental State Exam scores between treatment groups.

Several other trials, including Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-Cog) [13], Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and the parallel Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) [14], and Heart Outcomes Prevention Evaluation-3 (HOPE-3) [15], similarly found no significant difference in dementia risk or cognitive decline between respective treatment and control groups, although there were disparate study methodologies. However, it should be noted that in the Systolic Hypertension in Europe (Syst-Eur) trial, nitrendipine and, if needed, the addition of enalapril and hydrochlorothiazide in adults aged 60 years and older reduced the risk of dementia after two years of treatment [16].

It has been hypothesized that more intensive blood pressure lowering compared to standard treatment may be advantageous in relation to cognitive outcomes, and several studies have addressed the question. The Intensive Versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional Decline In the Elderly (INFINITY) trial enrolled older participants (aged 75 years and older) who had systolic hypertension along with white matter hyperintensities (WMHs) on MRI scans [17]. The study randomized participants into two groups based on BP targets, intensive treatment ($\leq$130 mm Hg) vs. standard treatment ($\leq$145 mm Hg), and monitored changes in cognitive function. Results showed that intensive treatment reduced accrual of subcortical white matter disease, but there were no significant differences in gait speed and cognitive outcomes between treatment groups with the exception of sequential choice reaction time, It was significantly better in the intensive treatment group. The Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT MIND) trial compared intensive BP control (a target of 120 mm Hg) against the conventional target (140 mm Hg) among adults aged 50 years and older with hypertension and an elevated risk of cardiovascular disease [18]. Assessments included tests of overall cognitive function, memory, learning, and processing speed, along with in-depth screening for Mild Cognitive Impairment (MCI) and dementia. The blood pressure lowering portion of the trial formally ended earlier than planned due to differences in cardiovascular outcomes favoring the intensive group, however, the trial extended its follow-up to 5.1 years. The main cognitive results showed that the primary outcome, probable dementia, did not significantly differ between two groups, but a main secondary outcome, the combination of MCI and probable dementia, was significantly reduced in the intensive BP treatment group compared to the standard treatment group. Meta-analysis supports the contention that intensive blood pressure lowering is beneficial in relation to prevention of dementia and cognitive decline [19,20]. In fact, blood pressure lowering may be more important than class of blood pressure lowering medication used to achieve a target blood pressure [21,22]. The clinical trials discussed above are summarized in Table 1.

Glycemic control in patients with diabetes

Type 2 diabetes is associated with a 1.25- to 1.91-fold increased risk of cognitive impairment and dementia [23]. Furthermore, individuals with diabetes mellitus may have a diminished total brain volume and more prominent regional brain atrophy [24,25]. Despite these observations, it has been difficult to show a benefit of blood glucose control in such patients. A number of clinical trials have been designed to study whether intensive glucose control can mitigate cognitive impairment.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, an international randomized controlled trial spanning 20 countries, enrolled over 11,000 diabetic patients with either a history of vascular disease or vascular risk factors [26]. Participants were treated with either standard glucose control methods or an intensive regimen, which utilized gliclazide and additional necessary medications to attain a target HbA1c $\leq$6.5 %. After a median follow-up of 5 years, both groups demonstrated similar rates of cognitive decline and dementia incidence.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial was designed to ascertain if intensive management of hyperglycemia, blood pressure, or lipid levels could curtail cardiovascular events or mortality relative to conventional care [27]. The trial included 10,251 diabetic participants, either with existing cardiovascular disease or their associated risk factors. A sub-study of ACCORD, the MIND (Memory in Diabetes) trial, aimed to evaluate if these three interventions could mitigate cognitive decline and alternations in brain structure over a span of 40 months [28]. There were 2977 participants enrolled in the study. For the main cognitive outcome, a comparison of the Digit Symbol Substitution Test (DSST) at baseline and at 20 and 40 months. There were no statistically significant differences between intensive and standard treatments after 40 months though measures of total brain volume favored the intensive treatment group. An extended study, ACCORDION MIND, followed 1328 participants out to 80 months [29]. Intensive therapy did not provide any significant cognitive or brain MRI advantage at 80 months.

The ORIGIN trial (Outcome Reduction With an Initial Glargine Intervention) evaluated whether normalizing fasting glucose levels with insulin could reduce cardiovascular events in individuals aged 50 years and plder with dysglycemia and HbA1c <9 % who also displayed other cardiovascular risk factors [30]. While the results did not exhibit significant cognitive differences between those on insulin glargine versus standard care or between those on omega-3 fatty acid versus placebo, an interesting finding emerged: Participants with dysglycemia, but no definite evidence of diabetes had a decelerated cognitive trajectory of decline if they received insulin glargine compared to conventional treatments [31].

Another important strategy to consider is the impact of linagliptin, a dipeptidyl peptidase-4 inhibitor, on cognitive impairment. This was explored in two key studies. The CARMELINA-COG study, a substudy of the CARMELINA (CArdiovascular and Renal Microvascular outcomE study with LINAgliptin) trial, evaluated linagliptin versus placebo in patients with type 2 diabetes having HbA1c levels between 6.5 to 10.0 % and at high CV or renal risk [32]. Another pertinent study, the CAROLINA-COGNITION study, a subgroup analysis of the CAROLINA

Table 1
Effects of antihypertensive agents or intensive blood pressure lowering on cognitive outcomes: a summary of clinical trials.

Clinical trial	N	Age at inclusion (mean)	Follow-up, years	Intervention	Cognitive outcome	Result
SHEP [10]	4736	≥60 (72)	5.0	Chlorthalidone ± atenelol vs. placebo	Short-Comprehensive Assessment and Referral evaluation (Cognitive, emotional, and physical function and leisure activities)	No effect on cognitive function
MRC Treatment Trial of Hypertension [11]	2584	65–74 (70)	4.5	Atenolol vs. hydrochlorthiazide + amiloride vs. placebo	Rate of change in paired associate learning test and trail making test part A scores	No effect on cognitive function
SCOPE [12]	4964	70–89 (76)	3.7	Candesartan vs. placebo	Reduction of MMSE ≥4 or diagnosis of dementia	No effect on cognitive function or dementia
HYVET-Cog [13]	3336	≥80 (84)	2.2	Indapamide ± perindopril vs. placebo	Occurrence of dementia (*DSM-IV* criteria)	No effect on dementia
ONTARGET [14]	22,629	≥55 (66)	4.7	Ramipril vs telmisartan vs a combination of both drugs	Occurrence of cognitive impairment (clinically diagnosed or MMSE≤23 or drop of ≥3 points)	No effect on cognitive impairment
TRANSCEND [14]	5231	≥55 (67)	–	Telmisartan vs. placebo	Occurrence of cognitive impairment (clinically diagnosed or MMSE≤23 or drop of ≥3 points)	No effect on cognitive impairment
HOPE-3 [15]	2361	≥70 (74)	5.7	Candesartan + hydrochlorothiazide vs. placebo	Changes in Digit Symbol Substitution Test, the modified MoCA, and the Trail Making Test Part B scores	No effect on cognitive function
Syst-Eur [16]	2418	≥60 (70)	2.0	Nitrendipine ± enalapril ± hydrochlorothiazide vs. placebo	Incidence of Dementia (*DSM-III, Revised*, criteria) and MMSE	Active treatment reduced the incidence of dementia by 50 % (p = 0.05)
INFINITY [17]	199	≥75 (81)	3.0	intensive treatment (24- hour SBP ≤130 mmHg) vs. standard treatment (24-hour SBP ≤145 mmHg)	Changes in executive functioning and processing speed (Trail Making Test, Symbol Digit Modalities Test, Digit Span Memory Test, Hopkins Verbal Learning Test, Stroop Color and Word Test, and 2 subtests from the California Computerized Assessment Package, Simple Reaction Time and Sequential Reaction Time)	No effect on cognitive function except sequential choice reaction time was significantly better in the intensive treatment group
SPRINT MIND [18]	8561	≥50 (68)	5.1	intensive treatment (SBP treatment goal <120 mmHg) vs. standard treatment (SBP treatment goal <140 mmHg)	Occurrence of probable dementia, mild cognitive impairment and a composite outcome of mild cognitive impairment or probable dementia.	Intensive BP control significantly reduced the risk of mild cognitive impairment (HR, 0.81; 95 % CI, 0.69–0.95) and the combined rate of mild cognitive impairment or probable dementia (HR, 0.85; 95 % CI, 0.74–0.97).

SHEP, Systolic Hypertension in the Elderly Program; MRC, Medical Research Council; SCOPE, Study on Cognition and Prognosis in the Elderly; HYVET-Cog, Hypertension in the Very Elderly Trial cognitive function assessment; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease; HOPE-3, Heart Outcomes Prevention Evaluation-3; Syst-Eur, Systolic Hypertension in Europe; INFINITY, Intensive Versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional Decline In the Elderly; SPRINT MIND, Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension; SBP, systolic blood pressure; MMSE, Mini-Mental State Examination; DSM, Diagnostic and Statistical Manual of Mental Disorders; MoCA, Montreal Cognitive Assessment; HR, hazard ratio; CI, confidence interval.

(CARdiovascular Outcome study of LINAgliptin versus glimepiride in type 2 diabetes) trial, compared linagliptin versus glimepiride in individuals aged 40 to 85 years with HbA1c levels ranging from 6.5 to 8.5 % [33]. However, both studies concluded that linagliptin did not demonstrate a significant benefit in preventing cognitive decline.

In summary, trials focused on intensive glucose control in diabetes patients have shown neutral results in relation to cognitive outcomes. However, a sub-study from the ORIGIN trial suggests that persons with dysglycemia but without overt diabetes mellitus might benefit from insulin glargine, a hypothesis that may merit further exploration.

Lipid lowering therapies, including statins

Statins and other lipid-lowering therapies have garnered interest as potential prevention strategies for cognitive impairment and dementia [34]. However, evidence from randomized trials to date has not demonstrated significant benefits from these treatments.

The Heart Protection Study involved over 20,000 adults aged between 40 and 80 years, all of whom had cardiovascular disease and diabetes [35]. Participants were either administered simvastatin or a placebo. After a follow-up period of 5 years, cognitive decline-measured using the modified Telephone Interview for Cognitive Status Questionnaire showed no significant differences between the two groups.

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) enrolled 5804 adults aged 70 to 82 years, with either vascular disease or a high risk of developing it [36]. This study evaluated the effects of pravastatin treatment versus a placebo in preventing cardiovascular events. Cognitive assessments in a substudy focused on global cognition, executive function, and processing speed [37]. Three years into the study, there were no notable differences in cognitive decline between the pravastatin and placebo groups.

The Heart Outcomes Prevention Evaluation-3 (HOPE-3) study allocated participants without cardiovascular disease, but who had intermediate cardiovascular risk to either statin treatment or a placebo to assess the prevention of cardiovascular events [38]. The cognitive substudy of HOPE-3, conducted over 5.7 years, found no significant differences in psychomotor speed, attention, or global cognition (Montreal Cognitive Assessment [MoCA] test) when comparing the statin-treated group with the placebo group [15].

Multidomain approach

Although individual behavioral interventions targeting cognitive decline, such as diet or aerobic exercise, have demonstrated limited efficacy [39,40], multidomain strategies that combine diet, exercise, cognitive training, and social engagement have shown more promising results (Table 2).

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is such an example of the potential of multidomain interventions [41]. Over its two-year duration, the study offered participants nutritional guidance, exercise, cognitive training, social activities, and consistent management of metabolic and vascular risk factors. Participants were 60–77 years of age. With 1260 elderly individuals from the general population considered at risk for cognitive decline, the study concluded with positive findings on global cognition (Neuropsychological Test Battery), executive functioning, and processing speed. Participants were deemed to be of high enough risk based on the Cardiovascular Risk Factors, Aging, and Dementia (CADIE) Dementia Risk Score. Interestingly, even those carrying the ε4 allele of the APOE gene (associated with higher dementia risk) benefitted from the intervention [42]. The study has been extended and the study design is being utilized worldwide.

The Multidomain Alzheimer Preventive Trial (MAPT) enrolled 1680 non-demented, community-dwelling participants from memory clinics in France [43]. The trial aimed to gauge the effects of a multidomain intervention either alone or combined with omega-3 polyunsaturated fatty acid supplementation. While the primary results did not show significant cognitive improvements over three years, a post hoc analysis of both multidomain groups revealed a noticeable delay in cognitive decline, especially among participants with higher dementia risk.

The Dutch Prevention of Dementia by Intensive Vascular Care (preDIVA) trial was conducted over six years, employing a multidomain cardiovascular intervention for preventing dementia [44]. Over 3500 community-dwelling participants aged 70–78 years were included. Although there was no significant effect on dementia incidence or cognition, in a sub-analysis there was a reduced risk of non-Alzheimer's dementia within the intervention group, most pronounced among participants with untreated hypertension at the study's start who remained committed to the intervention. The lack of effect of the multidomain intervention was attributed to modest baseline cardiovascular risks and the high quality of usual care in the comparison group.

The Taiwan Integrated Geriatric Care (TIGER) trial targeted community-dwelling outpatients aged 65 years or older with a minimum of three chronic medical conditions [45]. This trial incorporated an integrated multidomain strategy. Over a year, participants underwent 16 sessions (2 h each) focusing on group exercises, cognitive training, nutrition, disease education, and individualized care from geriatric professionals. The primary outcome using the 36-item Short Form Health Survey (SF-36) scores, indicated improvement of physical and mental component scores for the intervention group when compared to the standard care group. In addition, when compared with usual care, the multidomain intervention significantly improved overall cognitive performance and the MoCA subtests of naming, concentration, language, abstract thinking, delayed recall, and orientation.

Overall, multidomain interventions which blend such strategies as diet, exercise, cognitive training, and social engagement have shown varying degrees of success in relation to cognitive and other outcomes. To broaden the reach of the FINGER multimodal strategy across diverse geographical, cultural, and economic contexts, the World-Wide FINGERS (WW-FINGERS) initiative was launched in 2017, spanning over 25 countries [46]. WW-FINGERS harmonizes multidomain interventions across these diverse cultures and geographies, facilitating data sharing and analyses. The overarching goal is to forge a robust evidence base that will inform and shape upcoming dementia prevention strategies.

Antithrombotics and vasodilators

Antithrombotic medications play a pivotal role in the prevention of

Table 2
Effects of multidomain interventions on cognitive outcomes: a summary of clinical trials.

Clinical trial	N	Age at inclusion (mean)	Follow-up, years	Intervention	Cognitive outcome	Result
FINGER [41]	2654	60–77 (69)	2.0	Multidomain intervention (diet, physical exercise, cognitive training, and intensive vascular risk factor monitoring) vs. usual care	Changes in Neuropsychological test battery (NTB)	Multidomain intervention group had larger changes in estimated NTB Z-score at 2-year (0.20 vs. 0.16, p = 0·03)
MAPT [43]	1680	≥70 (75)	3.0	Multidomain intervention (cognitive training, diet, nutrition advice, and 3 preventive consultations) ±omega 3 polyunsaturated fatty acids vs. usual care	Changes in composite *Z* score combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding Test, ten MMSE orientation items, the Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale—Revised, and the Category Naming Test)	No effect on cognitive function
preDIVA [44]	3526	70–78 (75)	6.7	Multidomain intervention (tailored lifestyle advice and drug treatment if indicated for smoking habits, diet, physical activity, weight, hypertension, dyslipidemia, and type 2 diabetes mellitus) vs. usual care	Occurrence of dementia (*DSM-IV* criteria)	No effect on dementia
TIGER [45]	398	≥65 (73)	1.0	Multidomain intervention (physical exercise, cognitive training, nutrition and disease education, and individualized treatment by geriatric specialists) vs. usual care	Cognitive impairment defined as MoCA<26 and changes in MoCA	Multidomain intervention group significantly less likely to be cognitively impaired, and showed overall improvement in all MoCA domains (p = 0.0003 for naming and p<0.0001 for concentration, language, abstract thinking, delayed recall, and orientation) except the visuospatial domain

FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; MAPT, Multidomain Alzheimer Preventive Trial; preDIVA, Dutch Prevention of Dementia by Intensive Vascular Care; TIGER, Taiwan Integrated Geriatric Care; NTB, Neuropsychological test battery; MMSE, Mini-Mental State Examination; DSM, Diagnostic and Statistical Manual of Mental Disorders; MoCA, Montreal Cognitive Assessment.

cardiovascular and cerebrovascular events [47,48]. While longitudinal studies have suggested that aspirin is tied to slower cognitive decline in high-risk patients with AD or coronary heart disease [49,50], there has not been much clinical experimental evidence until recently that directly connects antithrombotic medications to enhanced brain health.

The ASPREE (Aspirin in Reducing Events in the Elderly) study included over 19,000 community-dwelling individuals aged 70 years and older (underrepresented US populations were aged 65 years and older) who lacked cardiovascular disease, physical disability, or previously diagnosed dementia [51]. In the study, participants were either administered a daily dose of 100 mg of aspirin or a placebo. After a median follow-up duration of 4.7 years, there were no substantial differences in dementia risk or occurrence of probable AD, MCI, or cognitive changes between the two groups.

Considering the established links between reduced cerebral blood flow, cerebral small vessel disease (cSVD), and cognitive impairment [52,53], vasodilators which enhance cerebral blood flow or medications that stabilize the blood vessel wall, emerge as possible therapeutic agents. The Lacunar Intervention Trial-2 (LACI-2) evaluated the impact of isosorbide mononitrate (ISMN) and cilostazol in patients diagnosed with clinical lacunar ischemic stroke [54]. ISMN acts a nitric oxide (NO) donor, amplifying the NO-cyclic guanosine monophosphate phosphodiesterase PDE5-inhibitor pathway, and cilostazol functions as a PDE3 inhibitor [55]. Both agents possess a vasodilatory property and have the potential to optimize endothelial function [55,56]. In this phase 2 trial, a total of 400 participants underwent treatments based on a 2×2 factorial design, involving either ISMN, cilostazol, or a combination of both. The results of the trial indicated that while cilostazol did not notably diminish cognitive impairment, ISMN did. Moreover, when combined, ISMN and cilostazol positively influenced the composite endpoint (composite of vascular events, dependence, cognition), reduced cognitive impairment, and enhanced the quality of life. These encouraging findings pave the way for a more extensive phase 3 trial for further validation of the findings.

Methods for improving trial efficiencies

Enhancing the efficiency of clinical trials is vital given the significant economic and time resources they require. Despite these challenges, the success rates for FDA approval, particularly in cardiovascular trials, remain modest [57]. To improve efficiency, strategies such as optimizing participant enrollment and incorporating advanced endpoints are being explored. For instance, extending treatment protocols in enrolled participants allows assessment of both short-term and long-term cognitive impacts [58]. Moreover, adopting endpoints sensitive to the CVD effects on brain structure and function can corroborate the biological plausibility of treatment effects [58,59]. This section discusses the use of image parameters as outcome measures, providing precise and early indications for streamlined trials and faster decision-making. Additionally, the utility of Mendelian randomization in clinical trial target prioritization is explored, potentially reducing inefficiencies and focusing trial efforts more effectively.

Incorporating neuroimaging parameters as outcome measures in clinical trials

cSVD is perceived as an endophenotype that predicts future cognitive impairment [6]. Representing approximately 25 % of ischemic strokes and the bulk of intracerebral hemorrhages in individuals aged above 65 years, cSVD plays a significant role [60]. Its impact extends to the majority of cases with vascular cognitive impairment and is closely linked to an array of related disorders, including those affecting mobility and gait, neurobehavioral symptoms, and mood [60]. Neuroimaging of cSVD markers include WMH, lacunar strokes, cerebral microbleeds, enlarged perivascular spaces, cortical superficial siderosis, brain atrophy, recent small subcortical infarcts, and cortical microinfarcts [61].

In 2013, the Standards for Reporting Vascular Changes on Neuroimaging 1 (STRIVE-1) was introduced to standardize the definitions of cSVD features observable on neuroimaging [62]. With aims to promote uniform terminology usage and enhance our understanding of cSVD, it also offered insights into the development of preventive and therapeutic strategies. The updated version, STRIVE-2 provides information on advancements in the field of cSVD [61].

The benefits of using imaging outcomes in trials include the possibility of smaller sample sizes and biological relevance [61,63]. Observational research has shown the possible application of such data to improvement of statistical power, especially when tracking longitudinal alternations in WMH volume and diffusion metrics [64]. Still, challenges persist. There are issues of missing data, slow patient recruitment, heightened trial costs, and concerns about generalizability of results. Notably, cSVD features, unless fully endorsed as valid surrogate endpoints, should not overshadow clinical outcomes. STRIVE-2 experts advocate for trial randomization that takes into account baseline cSVD severity [61]. Properly stratifying cSVD features, in tandem with other vital demographic and prognostic factors, is paramount, especially when changes in cSVD are being assessed as a trial outcome. Initiatives like HARNESS and FINESSE have been introduced to provide structured frameworks for cSVD imaging in clinical trials [63,65].

A case in point is a post-hoc analysis of the SPRINT-MIND trial that studied imaging parameters, notably WMH volume and brain atrophy [18]. By using MR scans including T1, T2, and fluid-attenuated inversion recovery (FLAIR) imaging, and comparing baseline and follow-up scans over roughly a 4-year interval, it was reported that the group on intensive BP lowering compared with standard therapy had slightly less progression of WMH lesions but a slightly greater decrease in brain volume including in the hippocampal region. The INFINITY trial further demonstrated these findings, revealing a less pronounced increase in WMH volume in the intensive BP control group [17]. Such results prompted the European Stroke Organization to recommend antihypertensive medications for those with covert cSVD and elevated BP ($\geq$ 140/90 mmHg) to prevent the progression of cSVD lesions and the consequent clinical symptoms that may ensue [66].

We highlight the emergence of novel imaging markers for cSVD, such as diffusion tensor imaging, functional studies, and blood-brain barrier imaging. These advanced imaging techniques offer significant insights into cSVD pathophysiology and could be key in assessing clinical trial efficacy [61,63]. However, a balance must be struck between the sophistication of these methods and their practicality [61]. While offering enhanced precision, their use might limit the generalizability of trial results in wider clinical settings.

The role of Mendelian randomization in the context of clinical trials: prioritizing intervention targets

Undertaking randomized clinical trials involves substantial investments, both financially and in terms of resource allocation [67]. When evaluating outcomes related to brain health, a detailed approach is necessary, encompassing comprehensive neuropsychological evaluations, cutting-edge neuroimaging, and prolonged observation. Given the historically modest success of clinical trials in elucidating effective intervention targets, one must consider efficient use of resources. Mendelian randomization—a powerful tool based on genetic epidemiology—offers such an opportunity. This observational epidemiologic method utilizes genetic variants as instrumental variables, mitigating the effects of unobserved confounding and strengthening the causal links between intervention and outcomes [68,69]. The surge in large-scale genome-wide association studies, particularly those centered on vascular risk factors, health-related behaviors, and outcomes such as stroke, dementia, cognitive functions, and cSVD markers, lays a robust groundwork for Mendelian randomization.

Consider the example of smoking, a major component of AHA Life's 7 [6]. It would not be ethical to study cigarette smoking in the setting of a

clinical trial. However, it could be studied by Mendelian randomization which provides insights into its cause and effects. Evidence from this approach indicates a notable causal link between active smoking and the onset of cognitive impairment, quantified by an odds ratio of 1.62 (95 % confidence interval: 1.29, 2.01) relative to no smoking [70]. Moreover, a Mendelian randomization study to investigate the relationship between lipid biomarkers and cSVD reveals a direct correlation between decreased high-density lipoprotein (HDL) cholesterol and increased risks associated with small vessel stroke and WMH volume [71]. In additional analysis, when genetic instruments tied to known lipid-altering drugs were employed, cholesteryl-ester transfer protein (CETP) inhibitors—agents that raise HDL cholesterol levels—emerge as a promising therapeutic target to counteract these risks. As another example, a recent Mendelian randomization analysis demonstrated that using genetic instrument for various classes of glucose-lowering agents, sulfonylureas may help prevent Alzheimer's dementia [72]. Modern research trends emphasize the importance of Mendelian randomization. One such advocacy comes from the Framework for Clinical Trials in Cerebral Small Vessel Disease (FINESSE), which champions the integration of Mendelian randomization for target prioritization in trials regarding cSVD [63].

However, while Mendelian randomization provides robust evidence for causal relationships, it is not without limitations. These include the potential for genetic pleiotropy, the complexity of determining the timing of effects, and the need for larger sample sizes compared to traditional observational studies to ensure sufficient statistical power [69,73].

Conclusion: lessons from clinical trials on brain health

As noted in this special issue of **Cerebral Circulation, Cognition, and Behavior**, the definition of brain health may be broad or more restrictive [74]. In this discussion the focus of the impact of clinical trials on brain health is largely from the perspective of cognitive impairment and dementia. It has been challenging to show a beneficial signal from clinical trials using cardiovascular medications when single interventions such as blood pressure lowering agents, those for glycemic control, or statin agents are concerned. However, several clinical trials stand out. For example, the SPRINT-MIND trial offers solid evidence that rigorous BP management may reduce the risk of cognitive decline and dementia, though the results emanate from a secondary outcome analysis. In addition, the LACI-2 phase 2 trial emphasizes the potential of cilostazol and ISMN in counteracting the risk of cognitive deterioration and other important outcomes in patients with symptomatic lacunar infarction. The FINGER trial's multidomain strategy also stands out as a promising approach for preservation of cognitive functions. Whereas the aforementioned strategies provide lessons for practitioners of clinical medicine, the findings require further study and validation.

Finally, advancements in brain imaging have underscored the significance of markers for cSVD. Such markers may not only be leveraged to boost statical power in trials but also deepen our understanding of underlying disease mechanisms. Moreover, the advent of the Mendelian randomization approach offers an opportunity to transform clinical trials by pinpointing intervention targets via this methodology, helping to optimize resource allocation, and more easily focus research protocols.

Disclosure

Hee-Joon Bae reports grants from Astrazeneca, Bayer Korea, Bristol Myers Squibb Korea, Dong-A ST, Jeil Pharmaceutical Co., Ltd., Samjin Pharm, Takeda Pharmaceuticals Korea Co., Ltd., and Yuhan Corporation, and personal fees from Amgen Korea, Bayer, Daiichi Sankyo, JW Pharmaceutical, Hanmi Pharmaceutical Co., Ltd., Otsuka Korea, SK chemicals, and Viatris Korea, outside the submitted work.

CRediT authorship contribution statement

Keon-Joo Lee: Conceptualization, Investigation, Writing – original draft. **Hee-Joon Bae:** Conceptualization, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

References

[1] K.M. Langa, E.B. Larson, E.M. Crimmins, et al., A comparison of the prevalence of dementia in the United States in 2000 and 2012, JAMA Intern. Med. 177 (1) (2017) 51–58, https://doi.org/10.1001/jamainternmed.2016.6807.
[2] C.L. Satizabal, A.S. Beiser, V. Chouraki, G. Chêne, C. Dufouil, S. Seshadri, Incidence of dementia over three decades in the Framingham Heart Study, N. Engl. J. Med. 374 (6) (2016) 523–532, https://doi.org/10.1056/nejmoa1504327.
[3] E. Nichols, J.D. Steinmetz, S.E. Vollset, et al., Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019, Lancet Public Heal. 7 (2) (2022) e105–e125, https://doi.org/10.1016/S2468-2667(21)00249-8.
[4] F. Lewis, S.K. Schaffer, J. Sussex, P. O'Neill, L Cockcroft, The trajectory of dementia in the UK – making a difference, Rep. Alzheimer Res. UK OHE Consult. (2014) (June).
[5] S. Norton, F.E. Matthews, D.E. Barnes, K. Yaffe, C. Brayne, Potential for primary prevention of Alzheimer's disease: an analysis of population-based data, Lancet Neurol. 13 (8) (2014) 788–794, https://doi.org/10.1016/S1474-4422(14)70136-X.
[6] P.B. Gorelick, K.L. Furie, C. Iadecola, et al., Defining optimal brain health in adults: a presidential advisory from the American Heart Association/American Stroke Association, Stroke 48 (10) (2017) e284–e303, https://doi.org/10.1161/STR.0000000000000148.
[7] L.J. Launer, G.W. Ross, H. Petrovitch, et al., Midlife blood pressure and dementia: the Honolulu-Asia aging study, Neurobiol. Aging 21 (1) (2000) 49–55, https://doi.org/10.1016/S0197-4580(00)00096-8.
[8] R. Malik, M.K. Georgakis, J. Neitzel, et al., Midlife vascular risk factors and risk of incident dementia: longitudinal cohort and Mendelian randomization analyses in the UK Biobank, Alzheimer Dement 17 (9) (2021) 1422–1431, https://doi.org/10.1002/alz.12320.
[9] R.F. Gottesman, A.L.C. Schneider, M. Albert, et al., Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study, JAMA Neurol. 71 (10) (2014) 1218–1227, https://doi.org/10.1001/jamaneurol.2014.1646.
[10] W.B. Applegate, S. Pressel, J. Wittes, et al., Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program, Arch. Intern. Med. 154 (19) (1994) 2154–2160. http://www.ncbi.nlm.nih.gov/pubmed/7944835.
[11] M.J. Prince, A.S. Bird, R.A. Blizard, A.H. Mann, Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults, BMJ 312 (7034) (1996) 801–805, https://doi.org/10.1136/bmj.312.7034.801.
[12] H. Lithell, L. Hansson, I. Skoog, et al., The study on cognition and prognosis in the elderly (SCOPE): principal results of a randomized double-blind intervention trial, J. Hypertens. 21 (5) (2003) 875–886, https://doi.org/10.1097/00004872-200305000-00011.
[13] R. Peters, N. Beckett, F. Forette, et al., Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial, Lancet Neurol. 7 (8) (2008) 683–689, https://doi.org/10.1016/S1474-4422(08)70143-1.
[14] C. Anderson, K. Teo, P. Gao, et al., Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies, Lancet Neurol. 10 (1) (2011) 43–53, https://doi.org/10.1016/S1474-4422(10)70250-7.
[15] J. Bosch, M. O'donnell, B. Swaminathan, et al., Effects of blood pressure and lipid lowering on cognition: results from the HOPE-3 study, Neurology 92 (13) (2019) E1435–E1446, https://doi.org/10.1212/WNL.0000000000007174.
[16] F. Forette, M.L. Seux, J.A. Staessen, et al., Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial, Lancet 352 (9137) (1998) 1347–1351, https://doi.org/10.1016/s0140-6736(98)03086-4.
[17] W.B. White, D.B. Wakefield, N. Moscufo, et al., Effects of intensive versus standard ambulatory blood pressure control on cerebrovascular outcomes in older people (INFINITY), Circulation 140 (20) (2019) 1626–1635, https://doi.org/10.1161/CIRCULATIONAHA.119.041603.
[18] J.D. Williamson, N.M. Pajewski, A.P. Auchus, et al., Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial, JAMA - J. Am. Med. Assoc. 321 (6) (2019) 553–561, https://doi.org/10.1001/jama.2018.21442.
[19] R. Peters, J. Warwick, K.J. Anstey, C.S. Anderson, Blood pressure and dementia: what the SPRINT-MIND trial adds and what we still need to know, Neurology 92 (21) (2019) 1017–1018, https://doi.org/10.1212/WNL.0000000000007543.

[20] R. Peters, S. Yasar, C.S. Anderson, et al., Investigation of antihypertensive class, dementia, and cognitive decline: a meta-analysis, Neurology 94 (3) (2020) e267–e281, https://doi.org/10.1212/WNL.0000000000008732.
[21] S. Mahinrad, F. Sorond, P.B. Gorelick, The role of vascular risk factors in cognitive impairment and dementia and prospects for prevention, Clin. Geriatr. Med. 39 (1) (2023) 123–134, https://doi.org/10.1016/j.cger.2022.07.007.
[22] P.B. Gorelick, Prevention of cognitive impairment: scientific guidance and windows of opportunity, J. Neurochem. 144 (5) (2018) 609–616, https://doi.org/10.1111/jnc.14113.
[23] M. Xue, W. Xu, Y.-N. Ou, et al., Diabetes mellitus and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 144 prospective studies, Ageing Res. Rev. 55 (2019), 100944, https://doi.org/10.1016/j.arr.2019.100944.
[24] W. Li, S.L. Risacher, E. Huang, A.J. Saykin, Alzheimer's Disease Neuroimaging Initiative. Type 2 diabetes mellitus is associated with brain atrophy and hypometabolism in the ADNI cohort, Neurology 87 (6) (2016) 595–600, https://doi.org/10.1212/WNL.0000000000002950.
[25] T. Zhang, M. Shaw, N. Cherbuin, Association between type 2 diabetes mellitus and brain atrophy: a meta-analysis, Diabet. Metab. J. 46 (5) (2022) 781–802, https://doi.org/10.4093/dmj.2021.0189.
[26] ADVANCE Collaborative Group, A. Patel, S. MacMahon, et al., Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes, N. Engl. J. Med. 358 (24) (2008) 2560–2572, https://doi.org/10.1056/NEJMoa0802987.
[27] J. Calles-Escandón, L.C. Lovato, D.G. Simons-Morton, et al., Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, Diabet. Care. 33 (4) (2010) 721–727, https://doi.org/10.2337/dc09-1471.
[28] L.J. Launer, M.E. Miller, J.D. Williamson, et al., Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy, Lancet Neurol. 10 (11) (2011) 969–977, https://doi.org/10.1016/S1474-4422(11)70188-0.
[29] A.M. Murray, F.-C. Hsu, J.D. Williamson, et al., ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial, Diabetologia 60 (1) (2017) 69–80, https://doi.org/10.1007/s00125-016-4118-x.
[30] ORIGIN Trial Investigators, H.C. Gerstein, J. Bosch, et al., Basal insulin and cardiovascular and other outcomes in dysglycemia, N. Engl. J. Med. 367 (4) (2012) 319–328, https://doi.org/10.1056/NEJMoa1203858.
[31] T. Cukierman-Yaffe, J. Bosch, R. Diaz, et al., Effects of basal insulin glargine and omega-3 fatty acid on cognitive decline and probable cognitive impairment in people with dysglycaemia: a substudy of the ORIGIN trial, Lancet. Diabet. Endocrinol. 2 (7) (2014) 562–572, https://doi.org/10.1016/S2213-8587(14)70062-2.
[32] G.J. Biessels, C. Verhagen, J. Janssen, et al., Effect of linagliptin on cognitive performance in patients with type 2 diabetes and cardiorenal comorbidities: the CARMELINA randomized trial, Diabet. Care 42 (10) (2019) 1930–1938, https://doi.org/10.2337/dc19-0783.
[33] G.J. Biessels, C. Verhagen, J. Janssen, et al., Effects of linagliptin vs glimepiride on cognitive performance in type 2 diabetes: results of the randomised double-blind, active-controlled CAROLINA-COGNITION study, Diabetologia 64 (6) (2021) 1235–1245, https://doi.org/10.1007/s00125-021-05393-8.
[34] K.J. Anstey, D.M. Lipnicki, L.-F. Low, Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis, Am. J. Geriatr. Psychiatry 16 (5) (2008) 343–354, https://doi.org/10.1097/JGP.0b013e31816b72d4.
[35] Heart Protection Study Collaborative Group, MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial, Lancet 360 (9326) (2002) 7–22, https://doi.org/10.1016/S0140-6736(02)09327-3.
[36] J. Shepherd, G.J. Blauw, M.B. Murphy, et al., Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial, Lancet 360 (9346) (2002) 1623–1630, https://doi.org/10.1016/s0140-6736(02)11600-x.
[37] S. Trompet, P. van Vliet, A.J.M. de Craen, et al., Pravastatin and cognitive function in the elderly. Results of the PROSPER study, J. Neurol. 257 (1) (2010) 85–90, https://doi.org/10.1007/s00415-009-5271-7.
[38] S. Yusuf, J. Bosch, G. Dagenais, et al., Cholesterol lowering in intermediate-risk persons without cardiovascular disease, N. Engl. J. Med. 374 (21) (2016) 2021–2031, https://doi.org/10.1056/nejmoa1600176.
[39] L.F. Ciria, R. Román-Caballero, M.A. Vadillo, et al., An umbrella review of randomized control trials on the effects of physical exercise on cognition, Nat. Hum. Behav. (2023), https://doi.org/10.1038/s41562-023-01554-4. February.
[40] L.L. Barnes, K. Dhana, X. Liu, et al., Trial of the MIND diet for prevention of cognitive decline in older persons, N. Engl. J. Med. (2023) 1–10, https://doi.org/10.1056/NEJMoa2302368.
[41] T. Ngandu, J. Lehtisalo, A. Solomon, et al., A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial, Lancet 385 (9984) (2015) 2255–2263, https://doi.org/10.1016/S0140-6736(15)60461-5.
[42] A. Solomon, H. Turunen, T. Ngandu, et al., Effect of the apolipoprotein E genotype on cognitive change during a multidomain lifestyle intervention: a subgroup analysis of a randomized clinical trial, JAMA Neurol. 75 (4) (2018) 462–470, https://doi.org/10.1001/jamaneurol.2017.4365.
[43] S. Andrieu, S. Guyonnet, N. Coley, et al., Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial, Lancet Neurol. 16 (5) (2017) 377–389, https://doi.org/10.1016/S1474-4422(17)30040-6.
[44] E.P.M. van Charante, E. Richard, L.S. Eurelings, et al., Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial, Lancet 388 (10046) (2016) 797–805, https://doi.org/10.1016/S0140-6736(16)30950-3.
[45] W.J. Lee, L.N. Peng, C.H. Lin, et al., Effects of incorporating multidomain interventions into integrated primary care on quality of life: a randomised controlled trial, Lancet Heal. Longev. 2 (11) (2021) e712–e723, https://doi.org/10.1016/S2666-7568(21)00248-8.
[46] M. Kivipelto, F. Mangialasche, H.M. Snyder, et al., World-Wide FINGERS Network: a global approach to risk reduction and prevention of dementia, Alzheimer. Dement. 16 (7) (2020) 1078–1094, https://doi.org/10.1002/alz.12123.
[47] D.O. Kleindorfer, A. Towfighi, S. Chaturvedi, et al., 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association, Stroke 52 (7) (2021) e364–e467, https://doi.org/10.1161/STR.0000000000000375.
[48] S.S. Virani, L.K. Newby, S.V. Arnold, et al., 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology joint committee on clinical practice guidelines, Circulation (2023), https://doi.org/10.1161/CIR.0000000000001168.
[49] J. Weng, G. Zhao, L. Weng, J. Guan, Alzheimer's disease neuroimaging initiative. Aspirin using was associated with slower cognitive decline in patients with Alzheimer's disease, PLoS One 16 (6) (2021), e0252969, https://doi.org/10.1371/journal.pone.0252969.
[50] T.N.M. Nguyen, L.-J. Chen, K. Trares, et al., Long-term low-dose acetylsalicylic use shows protective potential for the development of both vascular dementia and Alzheimer's disease in patients with coronary heart disease but not in other individuals from the general population: results from two larg, Alzheimer. Res. Ther. 14 (1) (2022) 75, https://doi.org/10.1186/s13195-022-01017-4.
[51] J. Ryan, E. Storey, A.M. Murray, et al., Randomized placebo-controlled trial of the effects of aspirin on dementia and cognitive decline, Neurology 95 (3) (2020) E320–E331, https://doi.org/10.1212/WNL.0000000000009277.
[52] B. Gyanwali, C.S. Tan, J. Petr, et al., Arterial spin-labeling parameters and their associations with risk factors, cerebral small-vessel disease, and etiologic subtypes of cognitive impairment and dementia, AJNR Am. J. Neuroradiol. 43 (10) (2022) 1418–1423, https://doi.org/10.3174/ajnr.A7630.
[53] A.E. Leeuwis, M.R. Benedictus, J.P.A. Kuijer, et al., Lower cerebral blood flow is associated with impairment in multiple cognitive domains in Alzheimer's disease, Alzheimer. Dement. 13 (5) (2017) 531–540, https://doi.org/10.1016/j.jalz.2016.08.013.
[54] J.M. Wardlaw, L.J. Woodhouse, I.I. Mhlanga, et al., Isosorbide mononitrate and cilostazol treatment in patients with symptomatic cerebral small vessel disease, JAMA Neurol. 2 (2023), https://doi.org/10.1001/jamaneurol.2023.1526.
[55] P.M. Bath, J.M. Wardlaw, Pharmacological treatment and prevention of cerebral small vessel disease: a review of potential interventions, Int. J. Stroke 10 (4) (2015) 469–478, https://doi.org/10.1111/ijs.12466.
[56] J. Wardlaw, P.M.W. Bath, F. Doubal, et al., Protocol: the Lacunar Intervention Trial 2 (LACI-2). A trial of two repurposed licenced drugs to prevent progression of cerebral small vessel disease, Eur. stroke J. 5 (3) (2020) 297–308, https://doi.org/10.1177/2396987320920110.
[57] A. Mullard, Parsing clinical success rates, Nat. Rev. Drug Discov. 15 (7) (2016) 447, https://doi.org/10.1038/nrd.2016.136.
[58] F.M. Elahi, S. Alladi, S.E. Black, et al., Clinical trials in vascular cognitive impairment following SPRINT-MIND: an international perspective, Cell Report. Med. 4 (6) (2023) 1–14, https://doi.org/10.1016/j.xcrm.2023.101089.
[59] C. Moran, S. Than, M. Callisaya, R. Beare, V. Srikanth, New horizons - cognitive dysfunction associated with type 2 diabetes, J. Clin. Endocrinol. Metab. 107 (4) (2022) 929–942, https://doi.org/10.1210/clinem/dgab797.
[60] J.M. Wardlaw, C. Smith, M. Dichgans, Small vessel disease: mechanisms and clinical implications, Lancet Neurol. 18 (7) (2019) 684–696, https://doi.org/10.1016/S1474-4422(19)30079-1.
[61] M. Duering, G.J. Biessels, A. Brodtmann, et al., Neuroimaging standards for research into small vessel disease—advances since 2013, Lancet Neurol. 22 (7) (2023) 602–618, https://doi.org/10.1016/S1474-4422(23)00131-X.
[62] J.M. Wardlaw, E.E. Smith, G.J. Biessels, et al., Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration, Lancet Neurol. 12 (8) (2013) 822–838, https://doi.org/10.1016/S1474-4422(13)70124-8.
[63] H.S. Markus, W.M. Van Der Flier, E.E. Smith, et al., Framework for clinical trials in cerebral small vessel disease (FINESSE): a review, JAMA Neurol. 79 (11) (2022) 1187–1198, https://doi.org/10.1001/jamaneurol.2022.2262.
[64] P. Benjamin, E. Zeestraten, C. Lambert, et al., Progression of MRI markers in cerebral small vessel disease: sample size considerations for clinical trials, J. Cereb. Blood Flow Metab. 36 (1) (2016) 228–240, https://doi.org/10.1038/jcbfm.2015.113.
[65] E.E. Smith, G.J. Biessels, F. De Guio, et al., Harmonizing brain magnetic resonance imaging methods for vascular contributions to neurodegeneration, Alzheimer. Dement. 11 (2019) 191–204, https://doi.org/10.1016/j.dadm.2019.01.002.
[66] J.M. Wardlaw, S. Debette, H. Jokinen, et al., ESO Guideline on covert cerebral small vessel disease, Eur. Stroke J. 6 (2) (2021), https://doi.org/10.1177/23969873211012132. CXI-CLXII.
[67] T.J. Hwang, D. Carpenter, J.C. Lauffenburger, B. Wang, J.M. Franklin, A. S. Kesselheim, Failure of investigational drugs in late-stage clinical development

and publication of trial results, JAMA Intern. Med. 176 (12) (2016) 1826–1833, https://doi.org/10.1001/jamainternmed.2016.6008.
[68] D.A. Lawlor, R.M. Harbord, J.A.C. Sterne, N. Timpson, G Davey Smith, Mendelian randomization: using genes as instruments for making causal inferences in epidemiology, Stat. Med. 27 (8) (2008) 1133–1163, https://doi.org/10.1002/sim.3034.
[69] N.M. Davies, M.V. Holmes, G Davey Smith, Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians, BMJ 362 (2018) k601, https://doi.org/10.1136/bmj.k601.
[70] K.M. Bakulski, M. Fu, J.D. Faul, Y. Jin, E.B. Ware, Mendelian randomization of smoking behavior on cognitive status among older Americans, Alzheimer. Dement. 16 (S10) (2020) 41221, https://doi.org/10.1002/alz.041221.
[71] M.K. Georgakis, R. Malik, C.D. Anderson, K.G. Parhofer, J.C. Hopewell, M. Dichgans, Genetic determinants of blood lipids and cerebral small vessel disease: role of high-density lipoprotein cholesterol, Brain 143 (2) (2020) 597–610, https://doi.org/10.1093/brain/awz413.
[72] B. Tang, Y. Wang, X. Jiang, et al., Genetic Variation in Targets of Antidiabetic Drugs and Alzheimer Disease Risk: a Mendelian Randomization Study, Neurology 99 (7) (2022) E650–E659, https://doi.org/10.1212/WNL.0000000000200771.
[73] S. Burgess, G. Davey Smith, N.M. Davies, et al., Guidelines for performing Mendelian randomization investigations: update for summer 2023, Wellcome Open Res. 4 (2023) 186, https://doi.org/10.12688/wellcomeopenres.15555.3.
[74] P.B. Gorelick, F.A. Sorond, What is brain health? Cereb. Circ. Cogn. Behav. (2023) https://doi.org/10.1016/j.cccb.2023.100190.