BRAIN
ORIGINAL ARTICLE



# Alzheimer and cardiovascular genetic scores and cognition: the FINGER randomized controlled trial

Gazi Saadmaan,[1] Maria Carolina Dalmasso,[2,3] Maleeha Maria,[4] Jenni Lehtisalo,[1,5] Mikko Hiltunen,[6] Minna U. Kaikkonen,[4] Esko Levälahti,[5] Francesca Mangialasche,[7,8] Markus Perola,[5] Alfredo Ramirez,[3,9,10,11,12] Ruth Stephen,[1,7] Tiia Ngandu,[5,7,13] Miia Kivipelto[7,8,13,14,15,†] and Alina Solomon[1,7,14,†]

[†]These authors contributed equally to this work.

Alzheimer's disease and coronary artery disease are common late-life chronic conditions and share multiple risk factors, including the apolipoprotein E (*APOE*) ϵ4 allele. A meta-analysis of two multidomain lifestyle intervention trials found greater cognitive benefits in *APOE4* carriers compared with non-carriers. This study investigated the impact of genetic risk scores for Alzheimer's disease and coronary artery disease (AD-GRS, CAD-GRS) on cognition in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) randomized controlled trial.

FINGER included 1259 at-risk individuals without dementia from the general population, aged 60–77 years. Participants were randomized 1:1 to a 2-year multidomain lifestyle intervention or regular health advice. The primary outcome was change in cognition based on a modified Neuropsychological Test Battery (14 tests). Previous comprehensive AD-GRS and CAD-GRS were calculated using genome-wide association study data (1177 participants, with 585 in the control and 592 in the intervention groups, exploratory analysis).

The intervention-control difference in annual overall cognition change (95% confidence interval) for participants with AD-GRS above/below the median (i.e. higher/lower risk) was 0.032 (0.002–0.063) versus 0.017 (−0.011 to 0.045), and for CAD-GRS above/below the median was 0.031 (0.002 to 0.059) versus 0.016 (−0.012 to 0.044). AD-GRS or CAD-GRS were not significantly related to the intervention effect overall ($P > 0.46$), but for AD-GRS there were differences between females and males ($P = 0.024$). The intervention-control difference in annual overall score change was 0.045 (0.004 to 0.087) for higher-risk females, 0.003 (−0.040 to 0.047) for lower-risk females, 0.019 (−0.026 to 0.064) for higher-risk males, and 0.027 (−0.009 to 0.064) for lower-risk males.

People with genetic susceptibility for Alzheimer's disease/dementia or coronary artery disease can benefit from multidomain lifestyle interventions. Although the findings for the AD-GRS and CAD-GRS risk groups were similar to *APOE4* carrier status, with additional gender differences for AD-GRS, these exploratory findings need to be verified across several multidomain lifestyle trials to ensure adequate statistical power and inclusion of genetically diverse populations.

1 Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio 70210, Finland
2 Neurosciences and Complex Systems Unit (EnyS), CONICET, Hospital El Cruce, National University A. Jauretche (UNAJ), Florencio Varela B1888AAE, Argentina
3 Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, University of Cologne, Medical Faculty, Cologne 50923, Germany
4 A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio 70210, Finland
5 Department of Public Health, Finnish Institute for Health and Welfare, Helsinki 00300, Finland

Received February 05, 2025. Revised June 09, 2025. Accepted June 29, 2025. Advance access publication August 6, 2025

6 Institute of Biomedicine, University of Eastern Finland, Kuopio 70210, Finland
7 Division of Clinical Geriatrics, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm 171 76, Sweden
8 Medical Unit Aging, Theme Inflammation and Aging, Karolinska University Hospital, Stockholm 171 76, Sweden
9 Department of Old Age Psychiatry and Cognitive Disorders, University Hospital Bonn, University of Bonn, Bonn 53127, Germany
10 German Center for Neurodegenerative Diseases (DZNE Bonn), Bonn 53127, Germany
11 Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health Sciences Center, San Antonio, TX 78229, USA
12 Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Disease (CECAD), University of Cologne, Cologne 50923, Germany
13 Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio 70210, Finland
14 Ageing Epidemiology Research Unit, School of Public Health, Imperial College London, London W6 8RP, UK
15 Research and Development Unit, Stockholm Sjukhem, Stockholm 112 19, Sweden

Correspondence to: Gazi Saadmaan
Institute of Clinical Medicine/Neurology
University of Eastern Finland, Yliopistonranta 1C
P.O. Box 1627, Kuopio 70211, Finland
E-mail: gazi.hossain@uef.fi

**Keywords:** genetic risk scores; Alzheimer's disease; cognition; randomized controlled trial; multidomain intervention



## Introduction

Alzheimer's disease, the most common cause of dementia, and coronary artery disease, the most common type of cardiovascular disease, are the main disabling chronic conditions at older ages. Dementias and cardiovascular diseases have a multifactorial aetiology, partly attributed to genetic predisposition, but also significantly influenced by a wide range of shared environmental, lifestyle and behavioural factors.[1] Precision prevention strategies addressing modifiable risk factors and their interplay with genetic factors are important for reducing the burden of multimorbidity that is increasingly common in older populations. Multidomain lifestyle interventions with or without pharmacological components targeting several risk factors and disease mechanisms simultaneously are an established feature of cardiovascular prevention research.[2] However, multidomain lifestyle interventions have only recently started to be adapted for dementia risk reduction. This has been tested successfully in randomized controlled trials (RCTs) such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), which reported significant beneficial intervention effects on the primary cognitive outcome (change in overall cognitive score) after 2 years.[3-5] It also showed multiple additional health benefits, including lower risk of cardio/cerebrovascular events up to 8-year follow-up, reduced frailty and reduced utilization of healthcare services and indication for cost-effectiveness.[6-8]

The interplay between genetic risk (e.g. in the form of polygenic scores) and lifestyle factors has been studied extensively for cardiovascular disease prevention[9] but only to a limited degree in the context of dementia prevention. Two RCTs have so far reported the impact of the apolipoprotein ϵ4 (*APOE4*) allele (the strongest genetic risk factor for Alzheimer's disease and a risk factor for coronary artery disease) on the cognitive benefits of multidomain lifestyle interventions. FINGER[3] and the Multidomain Alzheimer Preventive Trial (MAPT)[10] included a total of 2940 community-dwelling older participants at-risk for dementia, randomized to different 2-year or 3-year multidomain lifestyle interventions or control (regular health advice). Although neither trial alone was sufficiently powered to detect *APOE4* effects, a meta-analysis combining the trials indicated potentially more cognitive benefits in *APOE4* carriers compared with non-carriers.[11] This is important for dementia risk reduction strategies because the *APOE4*-related genetic susceptibility for Alzheimer's disease did not counteract the benefits of healthy lifestyle changes.

While the *APOE4* allele is widely recognized as the main genetic risk factor for sporadic Alzheimer's disease, genome-wide association studies (GWAS) have identified additional genetic loci associated with Alzheimer's disease.[12,13] It was recently estimated that the entire Alzheimer's disease genetic risk may be explained by up to 100 causal common variants.[14] Several polygenic risk scores have been developed by combining multiple risk alleles to provide a quantifiable measure of overall Alzheimer's disease genetic risk.[12] The most comprehensive Alzheimer's disease genetic risk score (AD-GRS) to date incorporates 83 genome-wide significant variants, not including *APOE*.[13] The AD-GRS has a relatively small but significant impact on Alzheimer's disease/dementia risk in addition to the impact of age, independently of *APOE* genotype.[13] It is also related to amyloid pathology and predicts faster progression of tau pathology and cognitive decline in people with Alzheimer's disease.[15] However, polygenic scores such as the AD-GRS have never been tested in multidomain lifestyle-based dementia prevention trials.

This study aims to investigate whether the AD-GRS can modify the previously reported cognitive benefits of the FINGER multidomain lifestyle intervention (exploratory analysis of a 2-year RCT). Given that several risk factors for dementia addressed by the FINGER intervention are also risk factors for cardiovascular diseases/coronary artery disease, we also investigated a previously validated comprehensive CAD-GRS (coronary artery disease-genetic risk score; 6 630 150 variants).[16] We hypothesized that older adults at-risk for dementia but without substantial impairment can benefit from multidomain lifestyle intervention even in the presence of genetic susceptibility for Alzheimer's disease or coronary artery disease. In addition, we investigate potential gender differences, based on previous reports of different impacts of genetic risk in females versus males for both Alzheimer's disease and coronary artery disease.[17,18]

# Materials and methods

## Study design

Details of the FINGER trial protocol,[3] study population characteristics[19] and primary outcomes[5] have been published. FINGER was a randomized controlled, parallel-group trial conducted at six sites across Finland. The trial received ethical approval from the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa.[3]

## Participants

Participants were enrolled from previous population-based observational studies. Inclusion criteria were age 60–77 years, an elevated Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) risk score, and cognitive abilities within the average range or slightly below, without any diagnosed or suspected dementia (Supplementary Table 1 and Supplementary material). Written informed consent was obtained from all participants, and all data were de-identified. Gender data were collected as recorded in the Finnish population registry.

## Randomization and masking

Participants were randomly assigned (1:1 ratio) into two groups: an intensive multidomain lifestyle intervention group or a regular health advice group (control). Randomization was done at each study site by the study nurse using computerized allocation in blocks of four (two participants randomized to each group). Outcome assessors were masked to the group allocation and did not participate in intervention implementation. Participants were not actively informed about their group allocation.

## Procedures

The intervention group was provided with four different domains of intervention: nutrition, physical exercise, cognitive training and management of metabolic and vascular risk factors (described in Supplementary Table 2, the Supplementary material and the trial protocol[5]). Social engagement was promoted through group meetings of the other intervention domains. The control group received standard health guidance.

## Outcomes

The study psychologist administered an extended version of the Neuropsychological Test Battery (NTB) to assess participants' cognition at the beginning, after 12 months, and subsequently after 24 months. The primary outcome was change in the NTB total score derived from 14 tests, with higher scores indicating better performance (calculated as z-scores, standardized to the baseline mean and standard deviation). The secondary outcomes encompassed change in composite z-scores for memory, executive functioning and processing speed. *Post hoc* analyses included an abbreviated memory domain based on a subset of memory tests requiring more complex processing.

To address skewed distributions, a log transformation with zero skewness was applied to NTB components. The z-scores for the test results at each time point were standardized based on the mean and standard deviation at the baseline assessment. The NTB total score and domain scores for executive functioning, processing speed and memory were derived by calculating the mean of the individual NTB component z-scores.

## Genome-wide association study

The genomic DNA was extracted from venous blood samples using magnetic bead-based extraction techniques conducted with the PerkinElmer Chemagic MSM1 system. AD-GRS was calculated in accordance with the approach described by Bellenguez *et al.*[13] To summarize the process, it entailed assessing the genotype dosage of each risk allele for all 83 documented variants and subsequently multiplying them by their associated weights, which were derived from the effect sizes found in their meta-GWAS. The GRS is the cumulative sum of these products across all the variants. CAD-GRS selection[16] and calculation are described in Supplementary Table 4. *APOE4* genotyping was performed as previously described.[20]

## Statistical analysis

The present study is an exploratory analysis based on GWAS conducted on existing DNA samples during 2022–23. To ensure consistency, AD-GRS and CAD-GRS were standardized based on their respective means and standard deviations. Before standardization, zero-skewness log-transformation was applied to the CAD-GRS to correct skewness. Comparisons of baseline characteristics between intervention and control groups, females and males, and by GWAS data availability were done using *t*-tests or $\chi^2$ tests as appropriate.

Mixed effects regression models with maximum likelihood estimation were used to analyse change in cognitive scores as a function of randomization group, time, continuous GRS (AD-GRS or CAD-GRS), and their interactions (Group × Time, Group × GRS, Time × GRS, Group × Time × GRS). Analyses were adjusted for study site, baseline age, gender, and their effect on change in cognition (Age × Time, Gender × Time). As AD-GRS excludes *APOE*, AD-GRS analyses were additionally adjusted for *APOE4* carrier status and *APOE4* × Time. This was not done for CAD-GRS, which includes *APOE* genotype. We report the Group × Time × GRS interaction as the main result. To facilitate interpretation of three-way interactions, we also show forest plots of the Group × Time interaction (i.e. mean difference between intervention and control in cognitive change per year) from analyses stratified by GRS above versus below the median. For comparison, previously reported FINGER trial results for *APOE4* carrier status[20] are included in the figures.

Potential gender differences were investigated using mixed effects regression models with maximum likelihood estimation where change in cognitive scores were analysed as a function of randomization group, time, continuous GRS (AD-GRS or CAD-GRS), gender, and their interactions (Group × Time, Group × GRS, Group × Gender, Time × GRS, Gender × GRS, Gender × Time; Group × Time × GRS, Group × Time × Gender, Group × GRS × Gender, Time × GRS × Gender; and Group × Time × GRS × Gender). Analyses were adjusted for study site, age, Age × Time, and (for AD-GRS) *APOE4* carrier status and *APOE4* × Time. We report the Group × Time × GRS × Gender interaction as the main result, and also forest plots of the Group × Time interactions from analyses stratified by females and males, and GRS above versus below the median.

Additional analyses were conducted to investigate if AD-GRS and CAD-GRS were related to cognition at baseline and overall change in cognition over time (irrespective of randomization group). Mixed effects regression models with maximum likelihood estimation were used to analyse change in cognitive scores as a function of continuous GRS (AD-GRS or CAD-GRS), time and GRS × Time interaction, adjusted for randomization group, Group × Time interaction, study site, baseline age, Age × Time, gender, Gender × Time, and (for AD-GRS) *APOE4* carrier status and *APOE4* × Time. We report estimates (95% CI) for continuous GRS, indicating cross-sectional associations with cognition at baseline, and for GRS × Time, indicating longitudinal associations with cognitive change.

The level of significance was set to $P < 0.05$ in all analyses, and STATA software, version 14 (STATACorp), was used. The FINGER trial was registered on ClinicalTrials.gov, identifier NCT01041989.

## Results

In total 2654 individuals were screened between 7 September 2009 and 24 November 2011, and 1260 were assigned randomly to the intervention group ($n = 631$) or control group ($n = 629$; 628 after one individual withdrew consent; Supplementary Fig. 1). There were 1177 participants (585 control, 592 intervention) with available GWAS data, and 1112 of them had *APOE4* carrier status, assessed separately.[20] At baseline, there were no differences in age, gender distribution, *APOE4* carrier status, AD-GRS, CAD-GRS or cognitive performance between the control and intervention groups (Table 1). Participants with or without available GWAS data were not significantly different (Supplementary Table 5).

The intervention effect on the primary cognitive outcome by genetic risk level is shown in Fig. 1 and Supplementary Tables 6 and 7. The Randomization group × Time × Continuous GRS interactions were not statistically significant: $P = 0.46$ for AD-GRS and $P = 0.65$ for CAD-GRS, similar to the previously reported Group × Time × *APOE4* interaction, $P = 0.30$.[20] Stratified analysis by genetic risk level showed similar patterns for all three genetic risk measures. The intervention had a beneficial effect on primary cognitive outcome among participants with AD-GRS above the median (estimate = 0.032, 95% CI = 0.002 to 0.063, $P = 0.038$; Supplementary Table 6) and those with CAD-GRS above the median (estimate = 0.031, 95% CI = 0.002 to 0.059, $P = 0.031$; Supplementary Table 7), similar to *APOE4* carriers (estimate = 0.037, 95% CI = 0.001 to 0.073, $P = 0.045$).[20] The intervention-control difference, although favouring intervention, was not statistically significant among people with lower genetic risk levels (Fig. 1).

The intervention effects on NTB memory, abbreviated memory, executive function and processing speed scores by genetic risk level are shown in Fig. 2 and Supplementary Tables 6 and 7. Neither Randomization group × Time × Continuous GRS interactions, nor previously reported Group × Time × *APOE4* interactions were statistically significant. Stratified analysis by CAD-GRS level showed a significant difference between intervention and control groups, favouring intervention in processing speed (estimate = 0.045, 95% CI = 0.007 to 0.083, $P = 0.021$), with a similar trend for executive function (estimate = 0.035, 95% CI = −0.001 to 0.072, $P = 0.056$) among participants with CAD-GRS above the median. This was not observed for memory scores. For processing speed, but not other cognitive domains, there was a trend favouring intervention in participants with AD-GRS below the median (estimate = 0.038, 95% CI = −0.002 to 0.077, $P = 0.061$). In comparison, there was a significant intervention-control difference among *APOE4* carriers for abbreviated memory (estimate = 0.070, 95% CI = 0.006 to 0.135, $P = 0.03$), with a similar trend for executive functioning (estimate = 0.045, 95% CI = −0.002 to 0.091, $P = 0.059$), but not other cognitive domains.

There was some evidence for potential gender differences for the impact of AD-GRS on the intervention effect on NTB total score and memory: Randomization group × Time × Continuous AD-GRS × Gender interaction, $P = 0.024$ for NTB total score and $P = 0.089$ for memory (Fig. 3 and Supplementary Table 8). For all cognitive domains, the Group × Time × AD-GRS interaction consistently showed positive estimates for females and negative estimates for males in analyses stratified by gender. This was not observed for CAD-GRS or *APOE4* (Supplementary Tables 9 and 10). Baseline population characteristics by gender are shown in Supplementary Table 11. Females were

**Table 1 Baseline characteristics of the FINGER population with available genetic data**

| Characteristics | *n* | Control | Intervention | P |
|---|---|---|---|---|
| Age, years | 1177 | 68.8 (4.74) | 68.9 (4.68) | 0.63 |
| Female, *n* (%) | 1177 | 275 (47.0) | 261 (44.1) | 0.31 |
| Education, years | 1175 | 9.99 (3.44) | 9.98 (3.50) | 0.96 |
| *APOE4* carriers, *n* (%) | 1112 | 184 (33.1) | 174 (31.3) | 0.52 |
| AD-GRS | 1177 | 0.01 (0.97) | −0.01 (1.03) | 0.75 |
| CAD-GRS | 1177 | 0.01 (0.98) | −0.01 (1.02) | 0.65 |
| NTB-Total score | 1176 | 0.02 (0.59) | −0.03 (0.56) | 0.13 |
| NTB-Memory | 1176 | 0.02 (0.66) | −0.04 (0.69) | 0.12 |
| NTB-Abbreviated memory | 1155 | 0.02 (0.74) | −0.03 (0.78) | 0.20 |
| NTB-Executive functioning | 1175 | 0.01 (0.70) | −0.03 (0.66) | 0.42 |
| NTB-Processing speed | 1176 | 0.03 (0.84) | −0.03 (0.78) | 0.16 |

Values are means (standard deviation) unless otherwise specified. All values for AD-GRS, CAD-GRS and cognitive scores are shown as z-scores. *APOE4* = Apolipoprotein ϵ4 allele; AD-GRS = Alzheimer's disease genetic risk score; CAD-GRS = coronary artery disease genetic risk score; FINGER = Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability randomized controlled trial; NTB = Neuropsychological Test Battery.

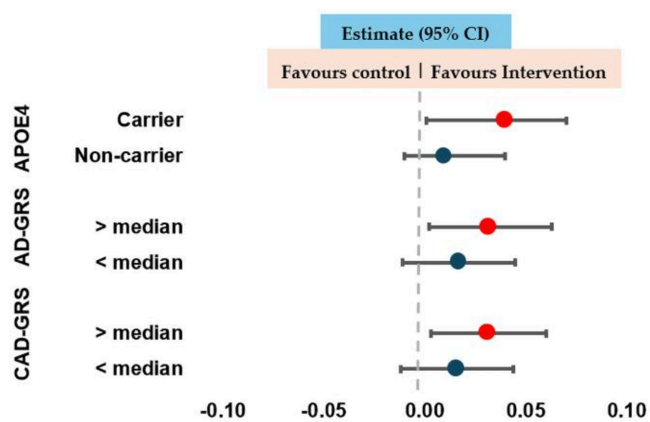


**Figure 1 Intervention effect on the primary cognitive outcome stratified by genetic risk.** Mixed-model repeated-measures analyses were used to investigate whether AD-GRS or CAD-GRS influenced intervention effects on cognitive performance (Group × Time × Continuous GRS interactions). To determine estimates for the difference between intervention and control groups per year, analyses were stratified by GRS above versus below the median. A positive value of the estimate for the difference between intervention and control groups indicates that the effect is in favour of the intervention group. Estimates for groups with higher genetic risk (APOE4 carriers, GRS above the median) are shown in red. Estimates for groups with lower genetic risk (APOE4 non-carriers, GRS below the median) are shown in blue. Estimates from Solomon *et al.*[20] for APOE are shown for comparison. The 95% confidence intervals indicate statistical significance for within-group effects (all three-way interactions were not statistically significant). APOE4 = Apolipoprotein ϵ4 allele; AD-GRS = Alzheimer's disease genetic risk score; CAD-GRS = coronary artery disease genetic risk score; GRS = genetic risk score.

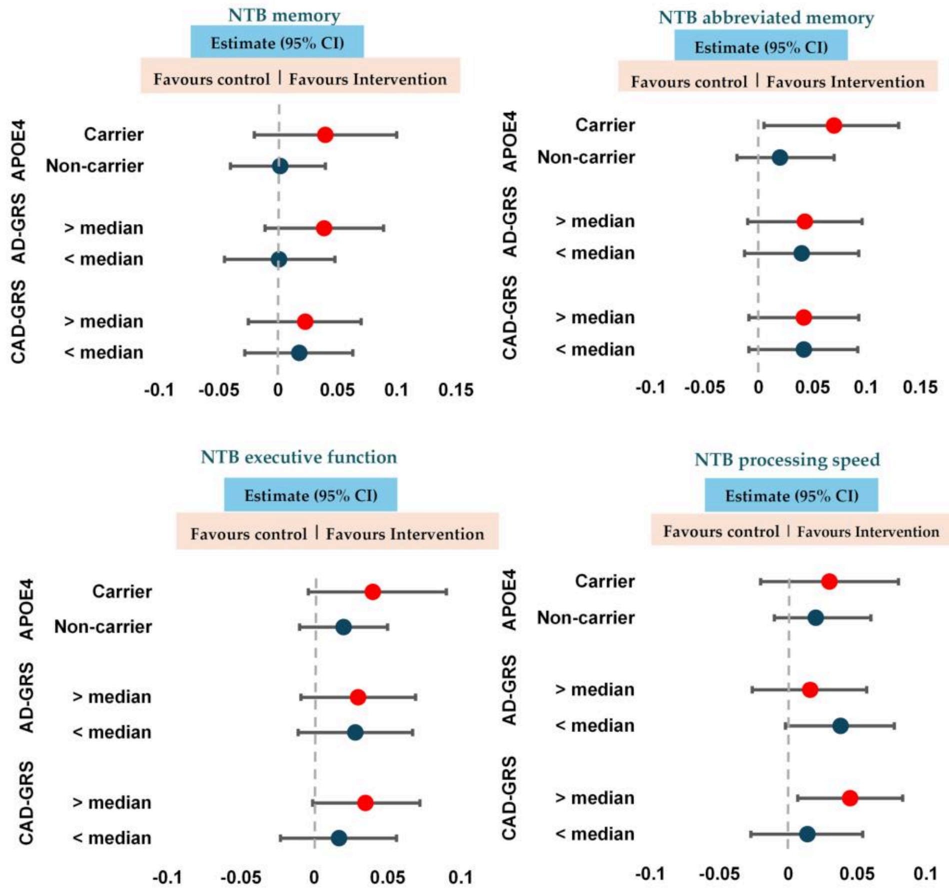


**Figure 2 Intervention effect on the secondary cognitive outcomes stratified by genetic risk.** Mixed-model repeated-measures analyses were used to investigate whether AD-GRS or CAD-GRS influenced intervention effects on cognitive performance (Group × Time × Continuous GRS interactions). To determine estimates for the difference between intervention and control groups per year, analyses were stratified by GRS above versus below the median. A positive value of the estimate for the difference between intervention and control groups indicates that the effect is in favour of the intervention group. Estimates for groups with higher genetic risk (APOE4 carriers, GRS above the median) are shown in red. Estimates for groups with lower genetic risk (APOE4 non-carriers, GRS below the median) are shown in blue. Estimates from Solomon *et al.*[20] for APOE are shown for comparison. The 95% confidence intervals indicate statistical significance for within-group effects (all three-way interactions were not statistically significant). APOE4 = apolipoprotein ϵ4 allele; AD-GRS = Alzheimer's disease genetic risk score; CAD-GRS = coronary artery disease genetic risk score; GRS = genetic risk score; NTB = Neuropsychological Test Battery.

somewhat older, had slightly lower education level and better performance in NTB total, memory, abbreviated memory and processing speed but worse performance on executive function compared with males.

Cross-sectional and longitudinal associations of AD-GRS and CAD-GRS with cognition (irrespective of randomization group) are shown in Supplementary Table 12. Higher AD-GRS was significantly associated with lower baseline memory ($P = 0.033$) and abbreviated memory ($P = 0.050$) but not other cognitive domains or change in cognition over time. CAD-GRS was not associated with baseline cognition, but higher CAD-GRS showed a trend for association with an increase in abbreviated memory ($P = 0.079$) and processing speed ($P = 0.056$) over time.

Additional analyses controlling for education and Education × Time interactions did not significantly change any of the results (results not shown). Analyses of CAD-GRS without APOE showed results nearly identical to the original CAD-GRS (Supplementary Tables 7, 10 and 12).

## Discussion

This study provides the first RCT-based evidence that a multidomain lifestyle intervention can have cognitive benefits in older adults with lifestyle/vascular risk for dementia, regardless of their overall genetic risk level for Alzheimer's disease or coronary artery disease. In the 2-year FINGER RCT, a comprehensive AD-GRS[13] or CAD-GRS[16] did not show a statistically significant impact (test of interaction) on the previously reported intervention benefits on cognition.[5] However, within-group findings by polygenic risk level above versus below the median showed beneficial intervention effects on the overall cognitive performance (primary outcome NTB total score), particularly among participants with higher Alzheimer's disease or coronary artery disease risk. Within-group findings for specific cognitive domains (secondary outcomes) suggested intervention benefits on executive function and processing speed, but not memory, particularly in the higher CAD-GRS risk group. There did not seem to be a consistent pattern for AD-GRS risk groups in relation to overall intervention effects on secondary cognitive outcomes. Interestingly, the results suggested potential gender differences regarding AD-GRS (but not APOE4 or CAD-GRS), with more pronounced intervention benefits on the NTB total score and memory among females with higher AD-GRS.

A key question regarding dementia risk reduction strategies is whether people with genetic susceptibility can still benefit from

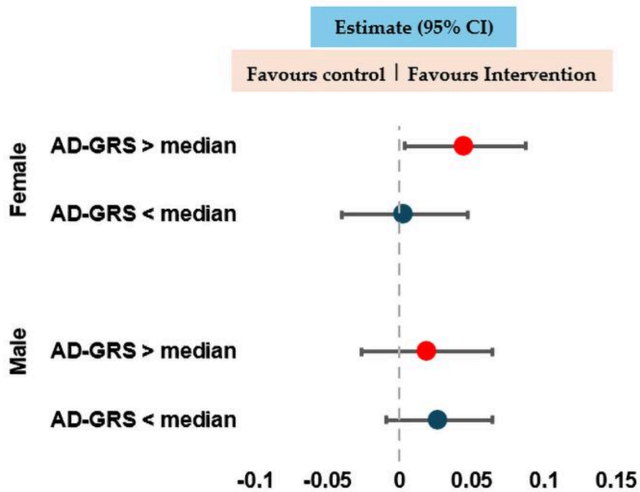


**Figure 3 Intervention effect on the primary cognitive outcomes stratified by AD-GRS risk in males and females.** Mixed-model repeated-measures analyses were used to investigate whether AD-GRS influenced intervention effects on cognitive performance differently by gender (Group × Time ×Continuous AD-GRS × Gender interactions). To determine estimates for the difference between the intervention and control groups per year, analyses were stratified by GRS above versus below the median, as well as by males versus females. A positive value of the estimate for the difference between intervention and control groups indicates that the effect is in favour of the intervention group. Estimates for groups with AD-GRS above the median are shown in red. Estimates for groups with AD-GRS below the median are shown in blue. The 95% confidence intervals indicate statistical significance for within-group effects (four-way interaction was statistically significant). AD-GRS = Alzheimer's disease genetic risk score; GRS = genetic risk score.

lifestyle intervention. The first evidence that *APOE4* carriers may have more cognitive benefit from multidomain lifestyle interventions compared with non-carriers was provided by a meta-analysis combining the FINGER and MAPT trials.[11] The FINGER-based Japanese J-Mint trial has also recently reported cognitive benefits in APOE4 carriers.[21] While the *APOE4* allele is widely recognized as the main genetic risk factor for sporadic Alzheimer's disease, it has been estimated that the full Alzheimer's disease genetic risk may be explained by up to 100 causal common genetic variants.[14] Thus, our findings have positive implications for lifestyle-based dementia risk reduction, because having a higher genetic risk for AD did not seem to hinder the intervention benefits on cognition even after adjusting for *APOE4*.

There may be similar positive implications for people with higher cardiovascular genetic risk who adopt healthier lifestyles. This is important because the FINGER multidomain lifestyle intervention simultaneously addressed several modifiable factors previously linked to the risk for both dementia and coronary artery disease. Alzheimer's disease and coronary artery disease are complex multifactorial diseases, with overlapping vascular/metabolic and lifestyle-related factors. *APOE* is a pleiotropic gene impacting both diseases, with *APOE4* increasing the risk of Alzheimer's disease and coronary artery disease, *APOE2* being associated with a potentially beneficial impact and APOE3 falling somewhat in the middle.[22] Although *APOE4* has much less impact on coronary artery disease than on Alzheimer's disease risk,[23] and the two conditions have limited genetic overlap beyond *APOE* genotype, a significant overlap has been described in the mechanistic pathways affected by risk genes. An extensively studied example is lipid dysregulation, which increases the risk for both Alzheimer's disease and coronary artery disease. For example, oxysterols such as 27-hydroxycholesterol, which showed reduction during the FINGER intervention related to cognitive improvement,[24] have been identified as a missing link between peripheral and brain cholesterol. The exact mechanisms underlying the cognitive benefits from intervention in people with higher CAD-GRS need to be further studied. This is important because higher coronary artery disease polygenic risk, although not directly related to dementia risk, has been shown to impact the association between clinically manifest cardiovascular conditions and dementia.[25]

It is currently unclear whether individuals with higher AD-GRS or CAD-GRS may benefit more from a multidomain lifestyle intervention compared with those with lower AD-GRS or CAD-GRS. Reporting guidelines for RCTs emphasize tests of interaction as most appropriate for investigating whether the effects of interventions vary between individuals based on specific characteristics.[26] However, few single trials are sufficiently powered to detect significant interactions. Regarding the example of *APOE* genotype, tests of interaction in the FINGER trial (1260 participants) or MAPT trial (1680 participants) did not initially show significant differences in intervention benefits on cognition between *APOE4* carriers and non-carriers. However, combining the results from the two trials in a meta-analysis resulted in increased statistical power to detect a greater cognitive benefit in carriers compared with non-carriers.[11] The impact of polygenic risk for Alzheimer's disease or coronary artery disease will thus need to be further tested in joint analyses from multiple lifestyle RCTs. For example, several FINGER-based RCTs are currently ongoing as part of World-Wide FINGERS, the first global network of multidomain lifestyle-based dementia prevention trials (currently >60 member countries, https://fbhi.se/world-wide-fingers-network). The inclusion of genetically diverse populations is particularly important in this context, as the predictive performance of polygenic risk scores generally varies between populations with different ancestries.[16]

Although we also report analyses stratified by AD-GRS or CAD-GRS above versus below the median, these within-group findings are primarily presented for descriptive purposes to facilitate the interpretation of complex three-way interactions involving continuous polygenic scores. Reporting guidelines for RCTs caution against over-interpretation of within-group analyses, i.e. heterogeneity of intervention effects should not be assumed based only on significant within-group results. Dividing the trial population into smaller groups can also limit statistical power for detecting significant intervention-control differences and may lead to non-significant results, e.g. it should not be assumed that individuals with lower genetic risk do not benefit from the intervention.

Within-group findings for the primary cognitive outcome showed a similar pattern of intervention benefit for all high-risk groups, i.e. *APOE4* carriers, and AD-GRS or CAD-GRS above the median. However, within-group findings for secondary cognitive outcomes did not show a consistent pattern for AD-GRS compared with *APOE4* carrier status. *APOE4* and other genetic risk factors may contribute to disease risk in mechanistically different ways, e.g. APOE4 mainly via amyloid-related pathways and other genetic factors mainly via non-amyloid-related pathways.[27] For CAD-GRS, although the intervention effects on memory outcomes did not vary by genetic risk level, within-group findings suggested intervention benefits on executive function and processing speed in the higher genetic risk group. This is interesting because executive function and processing speed domains are commonly affected in vascular conditions.[28] However, the present study cannot clarify the potential underlying mechanisms and to what extent they are related to Alzheimer's disease and/or vascular pathophysiological processes.

Previous studies have reported that genetic risk factors may have a different impact in females versus males, e.g. females with at least one *APOE-ϵ4* allele have higher Alzheimer's disease risk, earlier disease onset, and faster cognitive decline and disease progression compared with males.[18] Gender differences have also been described for genetic factors related to coronary artery disease,[17] which has a higher incidence in males than in females at all ages.[29] We thus investigated whether the impact of *APOE4* carrier status, AD-GRS or CAD-GRS on the intervention-related cognitive benefits was different between females and males. This has not previously been studied in multidomain lifestyle RCTs for dementia risk reduction. Results suggested potential gender differences regarding AD-GRS but not *APOE4* or CAD-GRS. Because these analyses include complex four-way interactions, they are, by default, low in power and highly exploratory, i.e. this study cannot provide definitive evidence on gender differences related to genetic factors for Alzheimer's disease or coronary artery disease. However, the consistently different patterns observed for AD-GRS in females versus males across all cognitive outcomes represent an intriguing signal worth exploring across multiple multidomain lifestyle-based intervention RCTs. This is particularly relevant for dementia prevention strategies since our findings suggest that females with higher AD-GRS, i.e. the highest Alzheimer's disease risk group, may have the most significant intervention-related cognitive benefits. Importantly, these results should not be interpreted to indicate a lack of intervention benefit among males with higher AD-GRS. Regarding CAD-GRS, if the benefit is indeed similar for females and males, irrespective of coronary artery disease polygenic risk level, this is also relevant because the higher coronary artery disease incidence in males has been linked to cognitive decline with brain microvascular lesions.[29]

Adherence to the FINGER lifestyle intervention was previously shown to be similar for females compared with males.[30] Participants were not aware of their genetic risks for either Alzheimer's disease or coronary artery disease, i.e. this knowledge did not impact their participation in the lifestyle-related activities. The overall intervention benefits on cognition were also not significantly different between females and males.[30] Although the intervention and control groups did not differ in baseline age, education, cognitive measures, AD-GRS or CAD-GRS, there were baseline differences in age, education and cognitive measures (but not AD-GRS and CAD-GRS) between females and males in the GWAS population. Females were on average slightly older, had somewhat lower education and better cognitive performance, except for executive function. It is unclear if these differences are random or suggest that females may be in earlier risk/disease stages and may benefit more due to an early start of intervention. While this study cannot determine potential mechanisms, previous studies have reported faster progression of Alzheimer's disease-related pathology in cognitively normal females compared with males.[31]

The key strengths of this study include its randomized controlled design with a thoroughly conducted 2-year multidomain lifestyle intervention that addressed multiple modifiable risk factors simultaneously and comprehensive assessment of genetic risk factors for both Alzheimer's disease and coronary artery disease. Nonetheless, there are several limitations. The study focused on at-risk older individuals from the general population who did not have dementia or significant cognitive decline (cognitive performance <0.5 standard deviations of the mean for the cognitively normal Finnish population). This is an early intervention, i.e. we cannot determine how genetic factors may influence the intervention effect on dementia incidence. Our findings may not necessarily apply to interventions conducted in individuals who already have cognitive impairment. The FINGER 11-year extended follow-up will provide more data on longer-term intervention effects, as well as the shorter- versus longer-term influences of genetic factors. Since all analyses in this study were exploratory, and statistical power was limited for interaction analyses, the results should be considered exploratory, and further validation through larger-scale studies is required. Owing to statistical power limitations, it was not possible to investigate potential interactions between the AD-GRS and CAD-GRS in relation to cognitive outcomes. The mechanisms behind potential gender differences and the benefit observed, especially in females with higher AD-GRS, could not be determined.

In conclusion, people with genetic susceptibility for Alzheimer's disease/dementia or coronary artery disease can benefit from lifestyle-based preventive interventions. Whether the previously reported pattern of higher cognitive benefits in *APOE4* carriers compared with non-carriers may also apply to higher versus lower Alzheimer's disease or coronary artery disease polygenic risk needs to be further tested across several multidomain lifestyle trials to ensure adequate statistical power and inclusion of genetically diverse populations. Although exploratory, this study provides the first preliminary evidence on how genetic factors for both Alzheimer's disease and coronary artery disease interact with lifestyle interventions in the context of cognitive decline prevention. Precision prevention strategies addressing modifiable risk factors shared by dementia and cardiovascular diseases, and their interplay with genetic factors, may ultimately contribute to reducing the burden of multimorbidity that is increasingly common in older populations.

## Data availability

Public deposition of the de-identified dataset is not possible due to legal and ethical reasons, and complete de-identification is not possible, as this investigation is part of an ongoing study. The study participants gave informed consent, which includes data use only under a confidentiality agreement. The data contain sensitive information, and public data deposition may pose privacy concerns. Data relevant to the present study can be shared upon request by addressing requests to the Finnish Institute for Health and Welfare: kirjaamo@thl.fi. Pseudonymized personal data relevant to the present study can be made available only to those fulfilling the requirements for viewing confidential data as required by Finnish law and the Finnish Institute for Health and Welfare. Data will be made available only for the purpose of research that is in alignment with informed consent, with investigator support and after approval of a proposal and completion of a material transfer agreement.

## Acknowledgements

The authors would like to thank the participants, researchers and clinicians involved in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study.

## Funding

M.C.D. received funding from the Research Council of Argentina (CONICET), Hospital El Cruce (HEC), National University Arturo Jaretche (UNAJ). M.H. received funding from the following sources:

Research Council of Finland, grant 338182; Sigrid Juselius Foundation; Strategic Neuroscience Funding of the University of Eastern Finland (Itä-Suomen Yliopisto); Alzheimer's Association, ADSF-24-1284326-C. F.M. received funding from Innovative Health Initiative Joint Undertaking (IHI JU), grant agreement no. 101132933 AD-RIDDLE; ERA PerMed Pattern-Cog grant; Region Stockholm (ALF, Sweden). R.S. received funding from the Finnish Cultural Foundation (Suomen Kulttuurirahasto), Wilhelm och Else Stockmanns Stiftelse (Finland). T.N. received funding from the EU Joint Programme—Neurodegenerative Disease Research (JPND), EURO-FINGERS grant; Research Council of Finland, Sigrid Jusélius Foundation; Juho Vainio Foundation; NordForsk, NJ-FINGERS grant; Alzheimer's Research and Prevention Foundation; Päivikki and Sakari Sohlberg Foundation; Finnish Cultural Foundation (Finland); Janssen Pharmaceutica. M.K. received funding from EU the Joint Programme—Neurodegenerative Disease Research (JPND) EURO-FINGERS grant; NordForsk NJ-FINGERS grant; Alzheimer's Drug Discovery Foundation (USA); EU Innovative Health Initiative Joint Undertaking (IHI JU) AD-RIDDLE, under grant agreement No. 101132933; Region Stockholm (ALF, Sweden); Center for Innovative Medicine (CIMED) at Karolinska Institute (Sweden); Stiftelsen Stockholms sjukhem (Sweden); Knut och Alice Wallenbergs Stiftels (Sweden); Swedish Research Council for Health, Working Life and Welfare (FORTE); Juho Vainio Foundation (Finland); Kela (Finland); Research Council of Finland. A.S. received funding from the European Research Council [grant 804371]; EU Joint Programme—Neurodegenerative Disease Research (JPND), Multi-MeMo grant; EU Innovative Health Initiative Joint Undertaking (IHI JU) AD-RIDDLE, under grant agreement No. 101132933; Alzheimerfonden (Sweden); Juho Vainio Foundation (Finland); Finnish Cultural Foundation (Finland); Yrjö Jahnsson Foundation (Finland). The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

## Competing interests

F.M. received personal honoraria for advisory boards and a Lilly honorarium for advisory board. M.K. received honoraria for lectures, presentations (Eisai, Nestle, Nutricia) and for participation on advisory boards (Combinostics, Eisai, BioArtic, Nestle, Eli Lilly).

## Supplementary material

Supplementary material is available at *Brain* online.

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