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SHORT REPORT

Alzheimer's disease genetic risk score and neuroimaging in the FINGER lifestyle trial

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Abstract

INTRODUCTION: We assessed a genetic risk score for Alzheimer's disease (AD-GRS) and apolipoprotein E (*APOE4*) in an exploratory neuroimaging substudy of the FINGER trial.

METHODS: 1260 at-risk older individuals without dementia were randomized to multidomain lifestyle intervention or health advice. $N = 126$ participants underwent magnetic resonance imaging (MRI), and $N = 47$ positron emission tomography (PET) scans (Pittsburgh Compound B [PiB], Fluorodeoxyglucose) at baseline; $N = 107$ and $N = 38$ had repeated 2-year scans.

RESULTS: The *APOE4* allele, but not AD-GRS, was associated with baseline lower hippocampus volume ($\beta = -0.27$, $p = 0.001$), greater amyloid deposition ($\beta = 0.48$, $p = 0.001$), 2-year decline in hippocampus ($\beta = -0.27$, $p = 0.01$), total gray matter volume ($\beta = -0.25$, $p = 0.01$), and cortical thickness ($\beta = -0.28$, $p = 0.003$). In analyses

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stratified by AD-GRS (below vs above median), the PiB composite score increased less in intervention versus control in the higher AD-GRS group ($\beta = -0.60$, $p = 0.03$).
DISCUSSION: AD-GRS and *APOE4* may have different impacts on potential intervention effects on amyloid, that is, less accumulation in the higher-risk group (AD-GRS) versus lower-risk group (*APOE*).

KEYWORDS
Alzheimer's disease, APOE4, clinical trial, dementia, genetic risk score, neuroimaging biomarker

Highlights

- First study of neuroimaging and AD genetics in a multidomain lifestyle intervention.
- Possible intervention effect on brain amyloid deposition may rely on genetic risk.
- AD-GRS and APOE4 allele may have different impacts on amyloid during intervention.

1 | INTRODUCTION

Apolipoprotein E (*APOE*) ε4 allele is the strongest known genetic risk factor for Alzheimer's disease (AD).[1–3] A comprehensive genetic risk score for Alzheimer's disease (AD-GRS) excluding *APOE* was recently developed based on 83 genome-wide significant variants.[4] The AD-GRS was linked to amyloid and tau accumulation on positron emission tomography (PET) scans in an observational cohort[5] but has not been investigated in intervention trials or at-risk individuals without substantial impairment. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (ClinicalTrials.gov identifier: NCT01041989) was the first 2-year randomized controlled trial (RCT) to report significant beneficial effects on cognition and other related health outcomes for a multidomain lifestyle intervention compared with regular health advice in an older general population at risk of dementia.[6] This study examined associations of AD-GRS and *APOE4* with neuroimaging measures (structural brain magnetic resonance imaging [MRI], Pittsburgh Compound B [PiB]-PET, and Fluorodeoxyglucose [FDG]-PET) in the FINGER. We also investigated the potential impact of AD-GRS and *APOE4* on the intervention effect on neuroimaging measures.

2 | METHODS

The FINGER trial protocol,[7] population characteristics,[8] primary findings,[6] and neuroimaging substudy[9,10] were described in detail previously. Briefly, 1260 participants were recruited. Inclusion criteria were as follows: age 60 to 77 years, Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) Dementia Risk Score ≥6 points, and cognitive performance at the mean level or slightly lower than expected for age (Finnish population norms for Consortium to Establish a Registry for Alzheimer's Disease [CERAD] neuropsychological battery).[11] Dementia and substantial cognitive impairment were excluded. Individuals were randomized 1:1 to a multidomain lifestyle intervention (combination of nutrition advice, exercise, cognitive training, and social activities and vascular risk monitoring) or control group (regular health advice).[6] FINGER was approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa. Written informed consents were obtained from participants.

The exploratory neuroimaging substudy including population characteristics was previously described.[9,10] Briefly, brain MRI scans and PiB-PET scans were conducted in connection with both baseline and 2-year visits. Participants were the most recently recruited individuals at the time when neuroimaging resources became available at each site (three MRI sites and one MRI and PET site), and with no contraindications. The MRI/PET population did not differ significantly from the population without MRI/PET at the neuroimaging sites. However, the neuroimaging population was slightly older than the rest of the FINGER population. MRI (1.5 T Avanto Siemens scanner at two sites, 3T Ingenuity Philips scanner at one site) and genome-wide association studies (GWAS) were available in $N = 126$ participants at baseline and $N = 107$ after 2 years. PET (Philips Ingenuity TF PET/MR scanner for PiB-PET, GE Advance PET scanner for FDG-PET) and GWAS were available in $N = 47$ participants at baseline and $N = 38$ after 2 years.

Regional cortical thickness and brain volumes on MRI were measured using Freesurfer version 5.3. Cortical thickness in AD signature regions was calculated as the mean of entorhinal, middle temporal, inferior temporal, and fusiform regions. The volume of white matter lesions was quantified on T1 and fluid attenuated inversion recovery images. Composite scores for PiB and FDG uptake on PET scans were calculated as the mean of the prefrontal, parietal, lateral temporal, precuneus, anterior cingulate, and posterior cingulate regions.[12]

The GRSs were calculated as described in Bellenguez et al.[4] In brief, they were generated by multiplying the genotype dosage of each risk allele for each of the 83 reported variants by its respective weight, that

is, effect sizes obtained in their meta-GWAS, and then summing across all variants.

Statistical analyses were conducted using STATA version 14. Linear regression was used to assess associations between AD-GRS, *APOE4* allele, and imaging outcomes, adjusted for age, and sex (PET analyses), and additionally site and estimated intracranial volume (MRI analyses). Changes in imaging outcomes were calculated as (follow-up − baseline)/baseline × 100. Longitudinal analyses were additionally adjusted for the randomization group. Skewed imaging outcomes were log-transformed. We additionally investigated whether AD-GRS or *APOE4* allele had an impact on the intervention effect on change in imaging outcomes by adding AD-GRS × group or *APOE4* × group interactions in the longitudinal models.

3 | RESULTS

There were no significant baseline differences between the intervention and control groups, except for a slightly higher FDG composite score in the control group ($p = 0.03$, Table 1). The *APOE4* allele was significantly associated with lower hippocampus volume (Table 2, $\beta = -0.27$, $p = 0.001$) and higher PiB composite score ($\beta = 0.48$, $p = 0.001$). Higher AD-GRS showed a trend toward association with lower hippocampus volume ($\beta = -0.15$, $p = 0.07$) and lower FDG composite score ($\beta = -0.23$, $p = 0.08$) at baseline. *APOE4* also showed a significant association with longitudinal decline in hippocampus volume ($\beta = -0.27$, $p = 0.01$), total gray matter volume ($\beta = -0.25$, $p = 0.01$), and AD cortical thickness ($\beta = -0.28$, $p = 0.003$).

Interactions of *APOE4* or AD-GRS with the randomization group were not statistically significant (Table 3). In analyses stratified by genetic risk, there was less increase in PiB composite score in intervention versus control group among participants with AD-GRS above the median ($\beta = -0.60$, $p = 0.03$). There was also a trend favoring the intervention group for less increase in PiB composite score among *APOE4* non-carriers ($\beta = -0.38$, $p = 0.08$), and for less decline in FDG composite score among participants with AD-GRS below the median ($\beta = 0.41$, $p = 0.08$).

4 | DISCUSSION

It has been hypothesized that *APOE4* and other AD genetic risk factors contribute to disease risk in mechanistically different ways; for example, *APOE4* increases the risk of amyloid deposition, while other genetic risk factors may act after amyloid deposition has started, thereby increasing the risk of dementia development.[13] In this exploratory FINGER study, the *APOE4* allele was consistently linked to several neuroimaging measures. Higher AD-GRSs had weaker associations with lower hippocampus volume and FDG composite scores and a non-significant association with higher PiB-PET score at baseline. This may be due to, for example, a smaller sample size and/or focus on at-risk individuals without substantial impairment. One previous observational study that also included people with mild cognitive impairment (MCI) and dementia reported that a higher AD-GRS was associated with higher rates of tau-PET accumulation, especially with higher amyloid-PET accumulation. Associations of AD-GRS with amyloid-PET have been reported mainly in cohorts including MCI and dementia. However, they have not been studied specifically in at-risk participants without substantial impairment.[5,14,15]

The interplay between lifestyle and genetic factors in relation to amyloid deposition has so far not been investigated in RCTs. Our exploratory results suggest that there may be some intervention benefit on amyloid deposition, especially in participants with higher compared to lower AD-GRS and in *APOE4* non-carriers compared to carriers. This suggests that adopting healthier lifestyle habits may not affect the amyloid deposition process driven by *APOE4* but may at least partly counteract the subsequent impact of non-*APOE* polygenic risk. The pathogenesis of AD has been linked to multiple pathways beyond amyloid, such as inflammation-related pathways, innate immunity, microglial activation, and lipid metabolism, which are relevant for the AD-GRS used in this study.[4] Whether such non-amyloid-related pathways can be influenced by the FINGER multidomain lifestyle intervention remains to be determined. Alternatively, the intervention may need to start at an earlier age or earlier pathology development stage to impact amyloid accumulation.

Interestingly, there seemed to be some intervention benefit on FDG-PET (glucose hypometabolism considered a neurodegeneration marker) in participants with lower GRSs. Although the analysis accounted for baseline FDG-PET (lower in intervention compared with

RESEARCH IN CONTEXT

1. **Systematic review:** Traditional sources (eg, PubMed and Google Scholar) were used to review the literature. Little is known about the dynamics of Alzheimer's disease (AD) neuroimaging biomarkers in relation to AD polygenic risk beyond the *APOE4* allele. We investigated how a genetic risk score for AD (AD-GRS) and *APOE4* allele relate to neuroimaging measures in a 2-year multidomain lifestyle randomized controlled trial in older individuals at risk of dementia (FINGER neuroimaging substudy).
2. **Interpretation:** This exploratory substudy suggests potential intervention benefits on brain amyloid deposition, particularly in individuals with higher compared to lower AD-GRS, and in *APOE4* non-carriers compared to carriers.
3. **Future directions:** These exploratory findings need to be verified in larger studies. Potential underlying mechanisms should be further investigated as these results indicate that, while adopting healthier lifestyle habits may not directly impact *APOE4*-related amyloid deposition, it may partially counteract the effects of non-*APOE* polygenic risk.

TABLE 1 Characteristics of FINGER neuroimaging population with available AD-GRS data.

MRI population				
Characteristics	***N* (Control/ intervention)**	**Control**	**Intervention**	***p***
Age	126 (60/66)	69.4 (4.49)	69.8 (4.81)	.69
Women, *N* (%)	126 (60/66)	30 (50.0)	27 (40.9)	.31
APOE4 carriers, *N* (%)	126 (60/66)	19 (31.67)	18 (27.27)	.59
AD-GRS	126 (60/66)	55.2 (3.32)	55.9 (2.86)	.21
NTB total score at baseline	126 (60/66)	−0.03 (0.54)	−0.13 (0.50)	.28
NTB total score at 2 years	105 (50/55)	0.06 (0.69)	0.10 (0.67)	.75
Baseline MRI measures				
Total Hippocampus volume, ml	126 (60/66)	7.2 (0.84)	7.43 (0.94)	.16
Total gray matter volume, ml	126 (60/66)	559.25 (53.8)	564.42 (47)	.57
AD cortical thickness, mm	126 (60/66)	2.76 (0.14)	2.75 (0.13)	.60
White matter lesion volume, ml	95 (44/51)	11.5 (14.9)	12.1 (13.3)	.82
2-year MRI measures				
Total hippocampus volume, ml	107 (50/57)	6.82 (0.90)	7.04 (1.02)	.26
Total gray matter volume, ml	107 (50/57)	556.42 (54.8)	569.54 (50.1)	.20
AD cortical thickness, mm	107 (50/57)	2.75 (0.16)	2.73 (0.12)	.48
White matter lesion volume, ml	95 (45/50)	12.7 (2.51)	13.9 (15.6)	.71
PET population				
Age	47 (23/24)	70 (4.64)	70.8 (5.41)	.61
Women, *N* (%)	47 (23/24)	12 (52.2)	9 (37.5)	.31
APOE4 carriers, *N* (%)	47 (23/24)	7 (30.4)	8 (33.3)	.83
AD-GRS	47 (23/24)	55.1 (3.18)	55.4 (2.45)	.71
NTB total score at baseline	47 (23/24)	0.02 (0.55)	−0.05 (0.53)	.69
NTB total score at 2 years	38 (20/18)	0.08 (0.67)	−0.10 (0.82)	.47
Baseline PET measures				
PiB Composite score	47 (23/24)	1.57 (0.37)	1.46 (0.38)	.31
FDG Composite score	45 (23/22)	1.24 (0.08)	1.19 (0.02)	**.03**
2-year PET measures				
PiB Composite score	38 (20/18)	1.73 (0.39)	1.63 (0.50)	.52
FDG Composite score	38 (20/18)	1.20 (0.10)	1.19 (0.06)	.63

Note: Values are mean ± SD unless otherwise specified; ttest or chi-squared tests were used to compare characteristics between control and intervention groups. Significant between-group differences ($p < 0.05$) are marked in bold. Higher AD-GRS indicates higher AD polygenic risk. For PET measures, a higher PiB composite score indicates more amyloid accumulation, while a higher FDG composite score indicates less neurodegeneration.

control group), we cannot fully exclude the possibility that this may have affected the results. Since participants with higher AD-GRSs were also more likely to have lower FDG-PET composite scores at baseline, this finding may reflect more intervention benefit in people with less neurodegeneration. It is also possible that people with lower GRSs have a different, non-genetic driver of neurodegeneration that may be more responsive to the FINGER intervention. The change in FDG-PET was not related to *APOE*.

This is the first study investigating both *APOE4* and the most comprehensive AD-GRS to date in relation to neuroimaging outcomes in a multidomain lifestyle RCT targeting an at-risk population without substantial impairment. Given the small sample size limiting statistical power, the study is exploratory in nature. Also, while a 2-year duration is now relatively common for RCTs, this may not be long enough to detect AD-related changes in early prevention trials. These findings will need to be validated in larger trials and ongoing initiatives such as the World-Wide FINGERS network of multidomain lifestyle RCTs building on the FINGER intervention model.

In conclusion, *APOE4* and AD-GRS may reflect different aspects of genetic AD risk. Our findings on potential intervention benefit for amyloid accumulation and/or neurodegeneration in people with different risk levels according to AD-GRS or *APOE* genotype may have implications for interventions aimed at individuals at risk of AD.

TABLE 2 Associations between AD-GRS, APOE, and neuroimaging measures.

Neuroimaging measures	AD-GRS	AD-GRS adjusted for APOE	APOE
Baseline			
Hippocampus	*−0.15 (0.07)*	*−0.15 (0.06)*	**−0.27 (0.001)**
Total gray matter	−0.06 (0.25)	−0.06 (0.25)	0.02 (0.77)
White matter lesion	−0.12 (0.24)	−0.12 (0.24)	−0.04 (0.69)
AD cortical thickness	0.04 (0.64)	0.04 (0.64)	−0.06 (0.49)
PiB composite score	0.21 (0.17)	0.19 (0.16)	**0.48 (0.001)**
FDG composite score	*−0.23 (0.08)*	*−0.23 (0.09)*	−0.08 (0.57)
Change in 2 years			
Hippocampus	−0.03 (0.74)	−0.04 (0.69)	**−0.27 (0.01)**
Total gray matter	0.13 (0.19)	0.13 (0.20)	**−0.25 (0.01)**
White matter lesion	0.04 (0.70)	0.04 (0.70)	−0.03 (0.75)
AD cortical thickness	0.002 (0.98)	−0.003 (0.97)	**−0.28 (0.003)**
PiB composite score	−0.03 (0.86)	−0.03 (0.84)	0.23 (0.17)
FDG composite score	0.07 (0.69)	0.07 (0.71)	−0.07 (0.67)

Note: Values are standardized β coefficients (p values) from linear regressions. Significant results ($p < 0.05$) are marked in bold. Results with $p < 0.1$ are marked in italic.

TABLE 3 Impact of AD-GRS on multidomain lifestyle intervention effect on PET measures.

Change in PET measures	AD-GRS	Difference in 2-year change between intervention and control groups β (p value)	Intervention × AD-GRS interaction p value	APOE4 carrier status	Difference in 2-year change between intervention and control groups β (p value)	Intervention × APOE4 interaction p value
PiB composite score	<median	0.04 (.86)	0.27	Non-carrier	*−0.38 (.08)*	0.24
	>median	**−0.60 (.03)**		Carrier	0.05 (.90)	
FDG composite score	<median	*0.41 (.08)*	0.25	Non-carrier	0.06 (.79)	0.44
	>median	−0.22 (.46)		Carrier	0.22 (.47)	

Note: Values are standardized β coefficients (p values) from linear regressions stratified by AD-GRS above versus below the median, or APOE4 carrier status, and p values for the interaction between randomization group and AD-GRS or APOE4. Negative β coefficients indicate less increase and positive β coefficients indicate more increase in PET composite scores over 2 years in the intervention group compared with the control group. Significant results ($p < 0.05$) are marked in bold. Results with $p < 0.1$ are marked in italic. There were no statistically significant findings for MRI measures (all $p > 0.1$, results not shown).

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CONFLICTS OF INTEREST STATEMENT

The authors report no conflicts of Interest. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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