Effect of a Multidomain Lifestyle Intervention on Estimated Dementia Risk

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Abstract. We investigated the effect of a multidomain lifestyle intervention on the risk of dementia estimated using the validated CAIDE risk score (\textit{post-hoc} analysis). The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is a 2-year randomized controlled trial among 1,260 at-risk older adults (60–77 years). Difference in the estimated mean change in CAIDE score at 2 years in the intervention compared to the control group was −0.16 (95\% CI −0.31 to 0.00) (\emph{p} = 0.013), corresponding to a relative dementia risk reduction between 6.04–6.50\%. This could be interpreted as a reflection of the prevention potential of the intervention.

Keywords: Clinical trial, dementia, dementia risk score, lifestyle intervention, prevention

INTRODUCTION

Preventing dementia is a major public health priority\cite{1}. Early identification of at-risk individuals is essential for effective preventive strategies. Several dementia risk algorithms have been developed based on various combinations of risk factors, often...
non-modifiable (e.g., age, sex, genetics) [2]. However, in addition to quantifying dementia risk, it is important to estimate prevention potential, i.e. the “room for risk reduction” with preventive interventions. Risk scores including modifiable factors (e.g., lifestyle, vascular, or metabolic) may be particularly useful for this purpose.

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was the first large, longer-term randomized controlled trial to report significant benefits on cognition [3], health-related quality of life [4], disability [5], and multimorbidity [6] for a 2-year multidomain lifestyle intervention among 1,260 older individuals with elevated dementia risk. Here we report post-hoc analyses of intervention effects on change in the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Dementia Risk Score. The CAIDE score is a validated tool for estimating dementia risk based on age, sex, education, systolic blood pressure, body mass index, serum total cholesterol, and physical activity [7, 8], and it was used to select at-risk participants to the FINGER trial.

METHODS

The FINGER trial (ClinicalTrials.gov NCT 01041989) protocol [9], recruitment [10], and primary results [3] have been previously reported. FINGER is a multicenter study conducted in 6 centers in Finland. It was approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa. Participants gave written informed consent.

Participants were recruited from previous population-based observational studies [10]. Eligibility criteria were: age 60–77 years; CAIDE Dementia Risk Score ≥ 6 points (for screening purpose calculated based on data from previous surveys, up to 40 years before the trial); and at least one cognitive test criterion: the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) [11, 12] Word List Memory task (10 words x3) ≤19 words, or CERAD Word List Recall ≤ 75%, or Mini-Mental State Examination (MMSE) [13] ≤ 26/30 points. Exclusion criteria were: dementia; MMSE < 20 points; conditions affecting safe participation or preventing co-operation; and coincident participation in another trial.

Between September 7, 2009 and November 24, 2011, 2,654 individuals were screened for eligibility, and 1,260 were randomized 1:1 into the intensive multidomain intervention or regular health advice (i.e., control) group. Computer-generated randomization was done in blocks of four individuals at each site. Outcome assessors were blinded to allocation and not involved in the intervention. The control group received regular health advice. The intervention group received nutritional advice (individual and group sessions led by study nutritionists), physical exercise program supervised by study physiotherapists at the gym, cognitive training (individual computer-based training, and group sessions led by study psychologists), and management of metabolic and vascular risk factors [9]. The intervention was completed in February 2014.

Risk factors included in the CAIDE score are based on data from population register (age, sex), self-reported questionnaires (education, physical activity), measurements by the study nurse (systolic blood pressure, body mass index), and laboratory analyses (serum total cholesterol). The scoring system has been reported and validated previously [7, 8]. CAIDE Dementia Risk Score was calculated using data from the FINGER baseline, 12- and 24-month visits. In addition, APOE ε genotype was assessed [14]. T-test or χ² test was used for baseline comparisons between intervention and control groups. Mixed effects regression models with maximum likelihood estimation were used to analyze change in CAIDE score as a function of randomization group, time, and group x time interaction. All participants with CAIDE score available from at least one time point were included in the main analysis (intention-to-treat) (n = 1,254, 99.5%). Sensitivity analyses were conducted including only participants with CAIDE score data at all time points (n = 1,030). Potential effect modification by other variables (baseline age, continuous; sex; or presence of at least one APOE ε4 allele) was investigated by adding the group x time x variable interaction to the model, together with the main variable effect and variable x time and variable x group interactions.

Analyses were adjusted by study site. Level of significance was set to p = 0.05 in all analyses; we also report three-way interactions with p < 0.10. Stata software version 14 was used.

RESULTS

Intervention and control groups were not significantly different in sociodemographic characteristics,
Table 1

| Baseline characteristics | Number of participants | Intervention group (N=631) | Control group (N=629) | p |
|--------------------------|------------------------|---------------------------|-----------------------|---|
| Age at baseline, y       | 1260                   | 69.5 (4.7)                | 69.2 (4.7)            | 0.26 |
| Women, N (%)             | 1260                   | 286 (45.3)                | 302 (48.0)            | 0.34 |
| Education, y             | 1258                   | 10.0 (3.5)                | 10.0 (3.4)            | 0.94 |
| Body mass index          | 1251                   | 28.3 (4.5)                | 28.1 (4.9)            | 0.44 |
| Systolic blood pressure, mmHg | 1251 | 140.2 (16.6)           | 140.0 (15.7)          | 0.77 |
| Physical inactivity, N (%) | 1247 | 189 (30.2)             | 175 (28.1)            | 0.41 |
| APOE4 carrier, N (%)     | 1175                   | 189 (32.0)                | 200 (34.2)            | 0.43 |
| Baseline CAIDE score     | 1233                   | 7.9 (1.8)                 | 7.8 (1.9)             | 0.69 |

Values are mean (SD) or N (%). The CAIDE Dementia Risk Score was calculated based on a combination of age, sex, education, systolic blood pressure, body mass index, total cholesterol and physical activity, as previously described [7].

vascular and lifestyle factors, medical history, cognitive performance (as previously described [3]), or CAIDE score (Table 1) at baseline. 1,254 (99.5%) participants had CAIDE score data from at least one trial visit.

The estimated mean change in CAIDE score in the intervention and control group during the trial is shown in Fig. 1. Between-group difference was significant ($p = 0.013$ for the group×time interaction). Estimated mean change in CAIDE score at 2 years was $-0.15$ (95% CI $-0.26$ to $-0.04$) in the control and $-0.31$ (95% CI $-0.42$ to $-0.20$) in the intervention group, with between-group difference $-0.16$ (95% CI $-0.31$ to $0.00$). The estimated between group difference in mean change in CAIDE score at year 1 was $-0.22$ (95% CI $-0.37$ to $-0.07$). Results remained unchanged in sensitivity analysis (participants with CAIDE score data at all 3 time points).

The intervention benefit on CAIDE score change tended to be more pronounced among women than men ($p = 0.098$ for the randomization group x time x sex interaction). The 2-year estimated between-group difference for men was $-0.03$ (95% CI $-0.24$ to $0.19$) and for women $-0.31$ (95% CI $-0.54$ to $-0.08$). There were no differences in attrition between men and women.

No significant differences were found by age or APOE ε4 carrier status ($p>0.32$).

To translate the intervention-related change in CAIDE score into estimates of dementia risk reduction, we used a previously reported formula for calculating 20-year dementia risk in middle-aged individuals [7]:

$$P(dementia) = \frac{e^{(-7.406 + 0.796 + 0.401 \times \text{SCORE})}}{1 + e^{(-7.406 + 0.796 + 0.401 \times \text{SCORE})}}$$

where \(\text{SCORE}_{control}\) was the baseline CAIDE score (mean 7.86 for all participants) minus 1 point for age to reflect a middle-aged population; and \(\text{SCORE}_{intervention}\) was \(\text{SCORE}_{control}\) minus 0.16 (estimated 2-year intervention-related decrease in CAIDE score). With a control group 20-year risk of 2.07%, and an intervention group risk of 2.07%, their ratio was 0.94. This indicated a relative risk reduction of 6.09%. Without the age adjustment, the relative risk reduction was 6.04%. Similar calculations using the observed 2-year difference in CAIDE score change between intervention and control groups ($-0.17$) with and without age adjustment resulted in a relative risk reduction between 6.44% and 6.50%.

**DISCUSSION**

In the FINGER trial, there was a significant beneficial intervention effect on reducing estimated dementia risk measured by the CAIDE score. This
effect tended to be more pronounced in women. As
the intervention was more intensive during the first
year, the reduction in CAIDE score was also more
pronounced during the first year followed by main-
tenance of the risk score reduction during the second
year.

These post-hoc analyses could be interpreted as
a reflection of the prevention potential of the inter-
vention. The FINGER intervention was started early,
in at-risk individuals without substantial cognitive
impairment [3], and therefore incident dementia was
not a feasible outcome after 2 years. For several rea-
sions, the estimates presented here may not reflect
the actual magnitude of dementia risk reduction:
The CAIDE Dementia Risk Score is based on sim-
ple cut-offs for risk factors, restricting its sensitivity
to change over time. While it also includes non-
modifiable risk factors, the intervention effect is less
likely to be overestimated since risk estimates are
adjusted for such factors. Also, the CAIDE score
was developed as the first midlife risk score for esti-
mating dementia risk 20 years later and was used to
select FINGER participants based on pre-trial
midlife data. In addition, the FINGER control group
received a program of regular general health advice
as per national guidelines, leading to more conserva-
tive intervention effect estimates than a “do-nothing”
control group. Although the CAIDE score was also
reduced in the control group (a benefit that may at
least partly be explained by “trial effect”, regression
to the mean or other factors) [15, 16], the reduction
was significantly greater in the intervention group.

The intervention effect on the CAIDE score tended
to be more pronounced among women, although the
test of interaction was not significant. Given the lim-
ited sample size it is not possible to provide reliable
estimates separately for men and women. Hopefully
larger trials and joint analyses across multidomain
lifestyle trials will allow more detailed subgroup
analyses in the future, including analyses of sex dif-
fences in intervention efficacy and adherence.

We based our estimates of change in dementia risk
on data from the middle-aged observational cohort
originally used to develop the CAIDE score [7].
This is because dementia risk estimates in observa-
tional studies of older populations may be influenced
by reverse causation, i.e., vascular/metabolic factors
may be affected by “silent” disease processes. How-
ever, because the CAIDE risk score was developed
and validated in a midlife population, the estimated
risk of dementia is most likely an underestimation
in this population of older adults. Ongoing FINGER
extended follow-up will provide data on observed
dementia incidence, and more accurate risk reduc-
tion estimates and evaluation of the CAIDE score
as a potential surrogate outcome in lifestyle-based
dementia prevention trials [17].

As FINGER targeted at-risk participants from the
general population, the importance of potential risk
reduction should be interpreted in a public health
context. There is currently no direct evidence of cost-
efficacy of dementia prevention interventions, but
previous modelling studies have suggested that rela-
tively small risk reductions (0.6–3.2%) may already
be cost-effective [18].

The FINGER participants were recruited from
previous population-based studies and they are well-
representative of at-risk older adults in Finland [10].
The CAIDE score has been validated in, e.g., diverse
population in the US, and therefore also our results
may be at least to some extent generalizable to
other older at-risk populations. However, the rela-
tive importance of modifiable risk factors may differ
across populations and over time. In an early preven-
tion trial it is still difficult to estimate the potential
clinical significance of the findings. CAIDE risk score
can be used as a tool to communicate dementia risk,
and to select persons that may benefit from lifestyle
interventions. Based on the current results, it can per-
haps also be used to track risk factor changes. Novel
biomarker assays as well as additional lifestyle and
clinical measures may contribute to further develop-
ment of more sensitive risk scores.

In conclusion, an important area for future develop-
ments in dementia prevention would be multifactorial
algorithms that estimate both dementia risk and pre-
vention potential and are highly sensitive to capturing
change in various risk factors over time. Establish-
ishing risk models as surrogate outcomes for dementia
clinical significance of the findings. CAIDE risk score
as a potential surrogate outcome in lifestyle-based
dementia prevention trials [17].

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