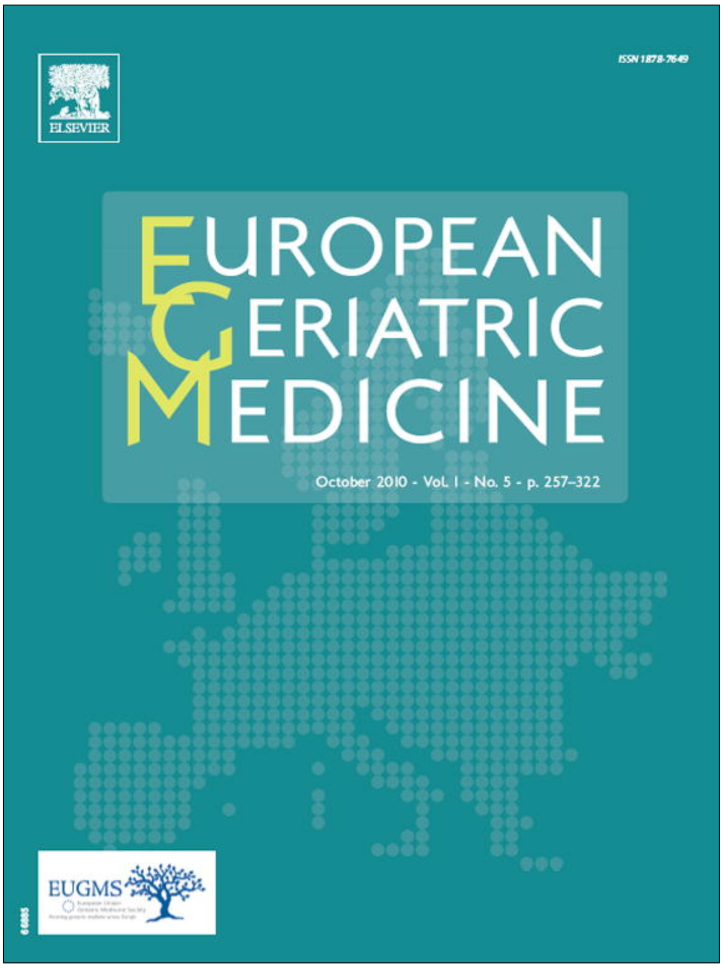
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Research paper

Exercise, fitness and cognition – A randomised controlled trial in older individuals: The DR's EXTRA study

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ABSTRACT

Background: Observational studies suggest that higher levels of physical activity and cardiorespiratory fitness associate with improved cognition. However, evidence from randomised controlled trials (RCT) is limited. We hypothesised that increased regular exercise improves cognition in older individuals. The trial is registered: ISRCTN45977199 (http://isrctn.org).
Methods: A population sample of 1335 men and women aged 57–78 years was randomised into aerobic exercise, resistance exercise, diet, combined aerobic exercise and diet, combined resistance exercise and diet or reference group for a 4-year intervention. Here, we report 2-year interim data. Exercise was assessed by a questionnaire and by maximal oxygen uptake (VO_{2max}), an objective measure of exercise, and cognition using Consortium to establish a registry for Alzheimer's disease (CERAD) neuropsychological tests.
Findings: In the intention to treat analyses, regular exercise increased in exercise groups, but remained unchanged in reference and diet only groups ($P < 0.001$ between groups). VO_{2max} remained unchanged in exercise groups, but decreased in reference and diet only groups ($P < 0.001$ between groups). There were between group differences neither in cognition, nor in the association of VO_{2max} to cognition during the first 2 years of intervention. In secondary analyses, improved VO_{2max} was associated with improved immediate memory in aerobic ($\beta = 0.11$, $P = 0.001$), resistance ($\beta = 0.08$, $P = 0.018$), diet ($\beta = 0.09$, $P = 0.029$) and combined aerobic and diet groups ($\beta = 0.09$, $P = 0.013$), with improved delayed memory in diet group ($\beta = 0.08$, $P = 0.015$) and with verbal performance in aerobic group ($\beta = 0.14$, $P = 0.044$). Those who were in the upper gender-specific VO_{2max} tertile had a 66.0% (95% confidence interval [CI] 34.2–82.4%, $P = 0.001$) lower, and those in the middle tertile a 56.4% (95% CI 22.6–75.4%, $P = 0.005$) lower risk of developing impaired delayed memory compared to those in the lower VO_{2max} tertile, after adjusting for potential confounders.
Conclusions: Present data from a large RCT among older individuals failed to show between group differences on the effects of regular exercise on cognition. However, secondary analyses suggest that higher levels of fitness may potentially mitigate memory impairment.

1. Introduction

Increasing longevity multiplies the number of individuals with mild cognitive impairment that often results in dementia. Memory impairment is a sensitive predictor for the development of Alzheimer's disease [1]. Observational studies suggest that higher levels of physical activity improve memory and attention [2], delay decline in global cognitive function [3,4] and diminish the risk of dementia [3,5–7]. However, as emphasized recently [8,9], there is a timely need for evidence-based data on the impact of physical activity and enhanced fitness on cognitive function. Two important recent randomised controlled trials have shown that exercise therapy improves cognitive function in individuals at high risk of cognitive decline and dementia [10] and in healthy women [11]. The focus in the present interim report of our ongoing 4-year randomised controlled trial in a relatively large population sample

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of mainly cognitively intact older individuals is to investigate the impact of regular, individually prescribed moderate intensity exercise, aerobic or resistance, on immediate memory, delayed memory, verbal performance, visual performance and Mini-Mental State Examination (MMSE).

2. Methods

2.1. Study setting and participants

We used 2-year interim data of the Dose Responses to Exercise Training (DR's EXTRA) Study, which is an ongoing 4-year randomised controlled trial on the health effects of regular physical exercise and diet (ISRCTN45977199, http://isrctn.org). The target population was a representative sample of men and women who lived in the city of Kuopio in Finland and who were 55–74 years of age in 2002, when they were randomly selected from the national population register (Fig. 1). Altogether, 1410 men and women who had no exclusion criteria, including diseases or conditions that inhibit participation in the examinations and interventions, were randomised into the six study groups after baseline measurements (April 5, 2005 – October 4, 2006) (Fig. 1). Of them, 1292 subjects participated in the examinations 2 years later (May 22, 2007 – December 17, 2008). After excluding individuals with missing or insufficient data on VO_{2max} ($n = 57$), diet ($n = 13$), both ($n = 4$) or cognitive function ($n = 1$), the final study sample consisted of 1335 subjects 57–78 years of age at baseline. Complete baseline and 2-year data were available from 1230 subjects, except that maximal oxygen uptake (VO_{2max}) data were available from 1142 subjects. The study protocol was approved by the joint Ethics Committee of the Kuopio University and University Hospital and conducted according to Declaraton of Helsinki. All participants gave a written informed consent.

2.2. Randomisation

Randomisation was done under surveillance of the principal investigator, and was done by blocks of 180 subjects so that 30 subjects were randomised into each of the six study groups. The subjects were asked to choose one of the identical sealed opaque envelopes that were in a mixed order and contained the group assignment. At this time, participants were re-informed, in detail, of the study design and procedure. In the aerobic and resistance exercise groups and the diet group, the second randomisation was carried out after 6 months of intervention (see chapter Interventions). Due to the nature of the intervention, participants were not blinded to group membership. Experienced research personnel who carried out CERAD tests were blinded both to the group assignment as well as baseline cognitive tests. We are not aware of any breaches of intervention protocol during the trial.

2.3. Interventions

The reference group was orally informed about general public health advice on diet and physical activity [12]. *The aerobic exercise group* was prescribed an individualised program that consisted of aerobic exercise at intensity corresponding to 55–65% of VO_{2max}. The frequency, duration and intensity were gradually increased during the first 6 months. Thereafter, the subjects were randomised into two subgroups with the energy expenditure of 1000–1500 kcal/week (5×60 min/week) or > 1500 kcal/week (5×90 min/week). Participants carried out the aerobic training programs on their own. The subjects in *the resistance exercise group* were prescribed an individualised strength-training program, based on measurement of one repetition maximum. The frequency, duration and intensity of the supervised programs were gradually increased during the first 6 months. Thereafter, the subjects were randomised into two subgroups with the energy expenditure of 1000–1500 kcal/week (two sessions/week) or > 1500 kcal/week (three sessions/week). In each session, 10–14 muscle groups were trained at an intensity of 60% of maximum (two sets, 15 repetitions/set). The loads were checked 1, 3, 4 and 6 months after baseline and every 6 month thereafter. The training program was written on a personal smart card, which controlled the exercise device (HUR Ltd, Finland) and stored the data. In addition, the subjects were advised to do aerobic exercise 150 or 180 minutes/week, respectively. *The diet group* received counselling by nutritionists. During the first 6 months, the subjects were given instructions based on the Finnish Nutrition Recommendations (FNR). The main goals were to substitute unsaturated for saturated fat and to increase the intake of fibre and antioxidants. After 6 months, the subjects were randomly allocated into the FNR group or the special nutrition (SN) group. The SN group was instructed, in addition to FNR, to increase the intake of vegetables, fruits, berries, chicken, nuts and almonds as well as to decrease the intake of red meat. The instructions were individually tailored by the nutritionists. *The combined diet and exercise groups* followed the aerobic (5×60 min/week) or resistance (two sessions/week) exercise program, respectively, and were given personal dietary counselling based on FNR. In all groups, the intervention included five individualised counselling sessions by the exercise physiologists or nutritionists during the 1st year and every 6 month thereafter.

2.4. Primary outcome measure

Cognitive function was assessed using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological tests (Appendix A) [13] at baseline and after 2 intervention years. Sum scores were calculated for five cognitive domains; *immediate memory* (sum from three trials of Word List Memory Test), *delayed memory* (sum from Word List Recall Test, number of correctly identified words from Word List Recognition Test and delayed Constructional Praxis Test), *verbal performance* (sum from Verbal Fluency Test and Modified Boston Naming Test), *visual performance* (sum from Constructional Praxis Test and Clock Drawing Test) and *MMSE*. The subject was defined to have impaired immediate memory, delayed memory, verbal performance or visual performance if he/she was in the lowest quartile of the corresponding cognitive domain, or to have a low MMSE score if it was < 25.

2.5. Other measurements

Physical exercise was assessed by a 12-month questionnaire [14]. The participants recorded the duration, frequency and mean intensity of different physical activities during the previous 12 months. The intensity of physical exercise was based on age and gender specific metabolic equivalent (MET) values given for each mode of physical activity. One MET refers to the resting metabolic rate and corresponds to oxygen consumption of 3.5 mL/kg per minute. As a practical example, 1 hour walking at a speed of 3 km/h corresponds to 2,3 MET hours (138 MET minutes) equalling to an energy expenditure of 180 kcal in a person with body weight of 75 kg. For the statistical analyses moderate and heavy physical exercise were combined as "moderate-to-heavy". Cardiorespiratory fitness was assessed as VO_{2max} by a respiratory gas analysis in a symptom-limited maximal exercise stress test on an electrically braked cycle ergometer (Ergoline, Bitz, Germany) [15]. The standardised testing protocol included a warm-up of 3 minutes at a workload of 20 W, followed by 20 W increments every minute until exhaustion. A total of 98% of the subjects achieved the

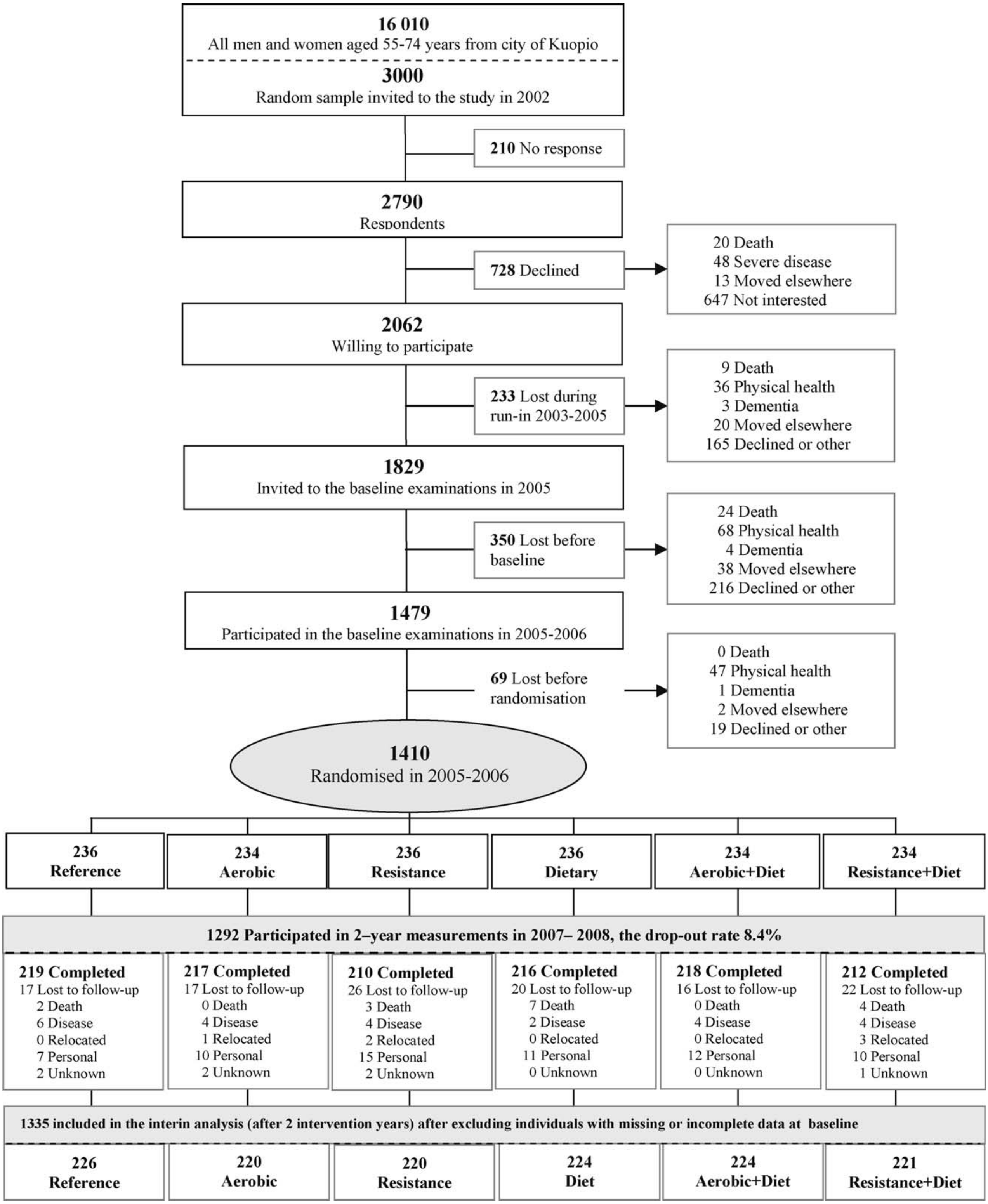

Fig. 1. The Consolidated Standards of Reporting Trials (CONSORT) flowchart of the DR's EXTRA study including the reference group, four exercise groups and the diet group.

respiratory exchange ratio of ≥ 1.1 at baseline and 99% achieved it at follow-up. Dietary intake was calculated by a four-day food record including 3 weekdays and 1 weekend day. Data from the food record were analysed using the MicroNutrica® nutrient calculation software. The assessments of background and medical history have been described previously [16]. Glucose tolerance status was defined by the WHO criteria. The symptoms of depression were assessed by the Center for Epidemiological Studies Depression Scale [17]. All measurements were performed at baseline and after 2 intervention years.

2.6. Statistical analysis

The analyses were conducted using SPSS for Windows, Release 14.0 (SPSS, Chicago, IL). P-value < 0.05 was defined as significant. Differences in the characteristics were analysed using Anova or

χ^2-test as appropriate. Linear mixed model analysis was used to study age and gender adjusted changes in physical exercise, VO_{2max} and cognition. In linear mixed models, study group, measurement time and their interaction were used as fixed factors and VO_{2max} was defined as a time-varying covariate. Repeated measures from the same subject were accounted for by specifying subject as a random effect. Logistic regression analysis was used to analyse the relative risk of developing cognitive impairment during 2 years across VO_{2max} tertiles at baseline. Analyses were adjusted for baseline age, gender, education, depression, cardiovascular disease (coronary heart disease, cardiac insufficiency, arrhythmias, stroke, transient ischemic attack, lower extremity peripheral artery disease), antihypertensive and lipid lowering medication, intake of saturated and polyunsaturated fatty acids, alcohol consumption, smoking, corresponding measure of cognition (as appropriate), and the study groups. Data were further adjusted for body weight and glucose status.

3. Results

3.1. Baseline characteristics

Baseline characteristics according to experimental group assignment were similar (Table 1). Those men and women ($n = 118$; 8%) who did not participate in 2-year examinations were older ($P = 0.001$) and less educated ($P = 0.008$), had lower VO_{2max} ($P < 0.001$), worse immediate memory ($P < 0.001$), delayed memory ($P < 0.001$), verbal performance ($P < 0.001$), visual performance ($P < 0.001$) and MMSE ($P = 0.001$) at baseline, compared to the participants. Of the non-participants, 59 (8%) were men and 59 (8%) were women ($P = 0.89$).

3.2. Primary analyses

There was a mean increase in moderate-to-heavy physical exercise in the four exercise groups, but no change in the reference and diet only groups ($P < 0.001$ between groups, Table 2). Of all participants, 705 (62%) had an increase in moderate-to-heavy physical exercise (average 9.2 METh/wk, standard deviation [SD] 9.9). Of them, 14% were in the reference group, 19% in the aerobic exercise group, 17% in the resistance exercise group, 15% in the diet group, 18% in the combined aerobic exercise and diet group and 17% in the combined resistance exercise and diet group. Of the 437 (38%) participants who experienced a decrease in moderate-to-heavy physical exercise (average −8.4 METh/wk, SD 10.3), the corresponding proportions were 22, 13, 16, 19, 16 and 14%.

VO_{2max} remained unchanged in the groups that included aerobic or resistance exercise, but decreased in the reference and the diet groups ($P < 0.001$ between groups, Table 2). Of all participants, 510 (45%) had an increase in VO_{2max} (average 2.4 ml/kg/min, SD 2.1). Of them, 17% were in the reference group, 17% in the aerobic exercise group, 18% in the resistance exercise group, 12% in the diet group, 18% in the combined aerobic exercise and diet group and 18% in the combined resistance exercise and diet group. Of the 632 (55%) participants who experienced a decrease in VO_{2max} (average −2.5 ml/kg/min, SD 1.9), the corresponding proportions were 18, 16, 15, 20, 16 and 15%.

There were no statistically significant differences in 2-year changes in immediate memory, delayed memory, verbal performance, visual performance or MMSE across the study groups (Table 2).

Table 1
Baseline characteristics of the 1335 subjects in the study groups.

	Reference ($n = 226$)	Aerobic ($n = 220$)	Resistance ($n = 220$)	Diet ($n = 224$)	Aerobic + Diet ($n = 224$)	Resistance + Diet ($n = 221$)	P-value
Age, years	66.0 (5.3)	66.9 (5.2)	66.5 (5.4)	66.8 (5.5)	66.2 (5.3)	65.6 (5.4)	0.10
Education, years	11.3 (3.9)	11.4 (4.0)	11.3 (3.9)	11.3 (3.7)	11.4 (4.1)	10.7 (3.7)	0.43
Immediate memory[a]	21.9 (3.6)	21.8 (3.8)	21.9 (3.5)	21.7 (3.6)	21.7 (3.6)	22.0 (3.8)	0.97
Delayed memory[a]	35.5 (3.6)	35.3 (3.5)	35.7 (3.5)	35.6 (3.3)	35.5 (3.0)	35.5 (3.7)	0.93
Verbal performance[a]	37.2 (7.2)	37.9 (6.9)	37.6 (7.1)	36.8 (7.3)	37.2 (6.9)	37.5 (7.8)	0.70
Visual performance[a]	15.0 (1.5)	14.9 (1.6)	14.9 (1.6)	15.1 (1.5)	15.0 (1.4)	15.0 (1.6)	0.70
MMSE[a] score	27.6 (2.2)	27.5 (1.9)	27.6 (1.9)	27.7 (1.7)	27.5 (1.8)	27.5 (2.1)	0.71
Body mass index	27.7 (4.3)	28.3 (4.5)	27.2 (4.1)	27.3 (4.3)	28.0 (4.8)	27.3 (4.6)	0.04
Waist circumference, cm	94.5 (12.9)	94.8 (12.7)	92.8 (12.6)	93.0 (12.4)	94.7 (14.3)	92.8 (13.7)	0.29
VO_{2max}, ml/kg/min	24.1 (6.2)	23.0 (6.4)	24.0 (6.4)	24.4 (6.5)	23.0 (5.9)	23.6 (5.9)	0.12
Serum LDL cholesterol, mmol/l	3.2 (0.8)	3.1 (0.9)	3.2 (0.9)	3.3 (0.8)	3.2 (0.9)	3.2 (0.9)	0.43
Serum HDL cholesterol, mmol/l	1.7 (0.5)	1.7 (0.5)	1.7 (0.5)	1.7 (0.5)	1.7 (0.5)	1.7 (0.5)	0.84
Systolic blood pressure, mmHg	147.2 (20.4)	149.5 (20.5)	147.2 (20.8)	148.8 (19.0)	147.2 (19.7)	147.0 (20.5)	0.68
Diastolic blood pressure, mmHg	83.1 (9.5)	83.7 (8.8)	82.6 (9.2)	83.3 (9.7)	83.7 (9.8)	83.5 (8.6)	0.82
Glucose tolerance status, %							0.85
NGT[a] / IGR[a] / Type 2 diabetes	69/19/12	62/25/13	67/23/10	65/20/15	67/21/12	66/21/13	
Prevalent hypertension, %	43	51	45	42	48	48	0.31
Prevalent cardiovascular diseases, %	40	35	36	29	39	36	0.14
History of stroke, %	4	3	4	2	4	7	0.15
Prevalent depressive symptoms, %	12	14	12	10	16	13	0.56
Use of sex hormones, %	25	27	27	25	28	28	0.97
Use of antihypertensive medication, %	39	47	42	39	41	42	0.49
Use of lipid lowering medication, %	34	39	31	35	33	37	0.52
Saturated fatty acid, E%	11.8 (3.3)	11.5 (2.9)	11.8 (3.3)	11.3 (2.9)	11.2 (2.9)	11.2 (2.7)	0.07
Polyunsaturated fatty acid, E%	5.6 (1.5)	5.4 (1.6)	5.6 (1.5)	5.6 (1.5)	5.6 (1.6)	5.4 (1.4)	0.36
Moderate-to-heavy physical exercise, METh/week	12.2 (12.6)	12.0 (11.5)	14.0 (12.8)	13.3 (13.6)	12.6 (13.1)	13.4 (16.2)	0.57
Alcohol consumption, doses/week	4.7 (6.5)	4.3 (6.2)	4.3 (7.0)	4.6 (6.9)	4.6 (8.5)	3.6 (6.2)	0.61
Smoking status, %							0.10
Never / Former / Current	46/43/11	57/34/9	60/28/12	57/33/10	57/33/10	50/38/12	

Values are means (±SD) from Anova or percentages from χ^2-test as appropriate, P-value denotes difference between groups.
[a] Immediate memory: sum from three trials of Word List Memory Test; delayed memory: sum of Word List Recall Test, correctly identified Words from Word List Recognition Test and Delayed Constructional Praxis Test; verbal performance: sum of Verbal Fluency Test and Modified Boston Naming Test; visual performance: sum of Constructional Praxis Test and Clock Drawing Test; MMSE: Mini-Mental State Examination; NGT: normal glucose tolerance; IGR: impaired glucose regulation.

Table 2
Changes in physical exercise, cardiorespiratory fitness and cognitive function in the study groups during 2 years.

	Reference (n = 226)		Aerobic exercise (n = 220)		Resistance exercise (n = 220)		Diet (n = 224)		Aerobic + Diet (n = 224)		Resistance + Diet (n = 221)	
	Change	P-value	Change	P-value	Change	P-value	Change	P-value	Change	P-value	Change	P-value
Moderate-to-heavy exercise, METh/week	0.59	0.503	5.08	< 0.001	4.00	< 0.001	0.14	0.881	2.10	0.018	2.16	0.017
VO_{2max}, ml/kg/min	−0.53	0.016	−0.01	0.977	0.10	0.664	−1.33	< 0.001	−0.01	0.976	0.21	0.361
Immediate memory	0.12	0.565	0.24	0.245	0.20	0.333	0.28	0.172	0.33	0.100	−0.03	0.895
Delayed memory	−0.07	0.688	0.18	0.325	0.31	0.095	−0.04	0.816	0.19	0.291	−0.21	0.256
Verbal performance	0.95	0.014	0.78	0.046	0.91	0.021	0.60	0.125	1.46	< 0.001	1.07	0.007
Visual performance	−0.34	0.001	−0.11	0.307	−0.24	0.031	−0.20	0.067	−0.18	0.094	−0.14	0.208
MMSE	−0.18	0.188	−0.12	0.377	−0.18	0.211	−0.15	0.276	−0.14	0.297	−0.23	0.100

Data are expressed as mean difference and derived from mixed model analysis adjusted for baseline age and gender.
P-values for 2-year change within the study groups are presented.

3.3. Secondary analyses

One unit improvement in VO_{2max} was associated with better immediate memory in the aerobic ($\beta = 0.11$, $P = 0.001$), the resistance ($\beta = 0.08$, $P = 0.018$), the diet ($\beta = 0.09$, $p = 0.029$) and the combined aerobic and diet group ($\beta = 0.09$, $P = 0.013$). Similarly, increased VO_{2max} was associated with improved delayed memory in the diet group ($\beta = 0.08$, $P = 0.015$) and verbal performance in the aerobic group ($\beta = 0.14$, $P = 0.044$) after potential adjustments.

Independent of the intervention group assignment, delayed memory increased by 0.28 points in the 510 individuals whose VO_{2max} increased or was maintained, but decreased by 0.19 points in the 632 individuals whose VO_{2max} decreased, adjusted for age and gender ($P = 0.003$ for difference between groups). Verbal performance increased by 1.32 points in those whose VO_{2max} increased or was maintained, and by 0.68 points in those whose VO_{2max} decreased ($P = 0.05$ for difference between groups).

After excluding participants with impaired immediate memory, ($n = 330$), delayed memory ($n = 310$), verbal performance ($n = 337$), visual performance ($n = 217$) or MMSE score < 25 ($n = 95$) at baseline, the incidence of cognitive impairment in the remaining subjects was 5.6% in immediate memory, 10.4% in delayed memory, 7.5% in verbal performance, 10.7% in visual performance and 5.5% in MMSE. After excluding participants with impaired delayed memory at baseline, those who were in the upper gender-specific VO_{2max} tertile had a 66.0% (95% confidence interval [CI] 34.2–82.4%, $P = 0.001$) lower, and those in the middle tertile a 56.4% (95% CI 22.6–75.4%, $P = 0.005$) lower risk of developing impaired delayed memory compared to those in the lower VO_{2max} tertile, after adjusting for potential confounders. Two individuals were diagnosed for dementia during 2 years.

3.4. Adverse events

Five adverse events were recorded during the 2 years (one angina pectoris during a cycle ergometer test, one angina pectoris and three light-headedness episodes during muscle strength training). In medical examination, physicians judged that it was unlikely any of these events were directly caused by the interventions, and these events did not lead to exclusion of the participants.

4. Discussion

The present data give additional sound support for the current public health recommendations for physical exercise in the elderly [18]. While the primary analyses failed to show significant effects of exercise on the primary outcome, secondary analyses suggest that cardiorespiratory fitness predicts a lower incidence of impaired memory.

In addition to the design, the DR's EXTRA trial has several strengths. The very low drop-out rate, showing excellent retention to interventions, earns additional merit keeping in mind that subjects are a randomly selected population-based sample, who were not paid for their participations. The CERAD battery is a sensitive measure of cognitive domains that are vulnerable in early and preclinical stages of Alzheimer's disease and to have substantial interrater and test-retest reliabilities [13]. We used an objective measure of cardiorespiratory fitness that mainly reflects habitual physical activity, although age and genes play a role as well [19], and is a stronger predictor of many health outcomes than physical activity assessed by questionnaires [20]. Self-reported physical activity may reflect other factors, such as generally healthy lifestyle or social engagement which have been suggested to protect against cognitive impairment [21]. Multifaceted statistical analyses with careful controlling for potential confounders allowed us to investigate the independent relation of VO_{2max} with specific cognitive domains. In our study, dramatic changes in life circumstances due to incident neurodegenerative diseases of next of kin appeared to be a significant limiting factor for participation in the intervention program. Due to the large sample size, we were unable to organise the aerobic exercise training under supervision. On the other hand, the study design corresponds closely to real-life circumstances. Other weaknesses include lack of state-of-the art neuro-imaging examinations to screen for cerebrovascular problems, such as stroke, at baseline other than by history. The message of the public health recommendations regarding regular exercise and healthy diet has penetrated the population and nowadays, the awareness of the importance of lifestyle factors has reached a large fraction of the adult population. This is also seen in the present study, as there were approximately 15% of the subjects in the reference and diet groups who improved their cardiorespiratory fitness. All these reasons may explain missing effect of intervention on cognition between the study groups during the first 2 years. Also, keeping in mind the rather low intensity exercise level prescribed for the aerobic exercise, it may well be that longer time is needed to see the difference between the study groups in this mainly cognitively intact study population.

Several mechanisms may potentially explain the relation between cardiorespiratory fitness and cognition. In healthy ageing individuals, higher levels of cardiorespiratory fitness have been associated with an increased white and gray tissue density in the frontal, parietal and temporal cortices [22], the areas most vulnerable to ageing and further mild cognitive impairment. Physical activity may increase circulating brain-derived neurotrophic factor (BDNF) expression [23], which plays a key role in brain plasticity [24]. In turn, low levels of circulating BDNF are linked to cardiovascular risk factors [25], which are known to predict cognitive impairment and dementia. In our study, the association between cardiorespiratory fitness and cognition remained significant after adjusting for various vascular risk factors or disorders. However, it is still possible that disorders such as endothelial dysfunction or silent brain infarct, common in general population of elderly people have affected these results.

Experimental studies among animals suggest that physical activity increases neurogenesis in the hippocampus [26]. Aerobic exercise increases capillary density in the cerebellum, and increased levels of cardiorespiratory fitness associate with enhanced cortical high-affinity choline uptake, increased dopamine receptor density in the brain and the number of new cells in the hippocampus [27]. Exercise may even reduce Alzheimer's disease related amyloid burden in the brain [28].

Prior evidence indicates that improved cardiorespiratory fitness has the strongest effect on executive processes [27]. In line with a 6-year follow-up study [29], in our study cardiorespiratory fitness associated with specific cognitive domains, but, most strongly with memory. Memory impairment is the hallmark feature of Alzheimer's disease and it's precursor "mild cognitive impairment" [1], whereas impairment in executive functioning is considered as an indicator of vascular cognitive impairment and vascular dementia [30]. However, it is well-known that there is a considerable overlap in risk factors, symptomatology and pathophysiology of Alzheimer's disease and vascular dementia. Moreover, the recent NIH State-of-the-Science Conference Statement highlights the absence of highly reliable consensus-based diagnostic criteria for cognitive decline, mild cognitive impairment and Alzheimer's disease, and the available criteria have not been uniformly applied [9]. For these issues, we focused on multiple cognitive domains on specific neuropsychological tests.

In conclusion, the present data show the feasibility and safety of exercise as a treatment modality among older individuals. Data suggest that higher levels of cardiorespiratory fitness, which can be achieved by regular physical exercise, may potentially mitigate memory impairment.

Additional contributions

We thank the participants and research staff of the DR's EXTRA study.

Author contributions

All authors had full access to all of the data, and approved the manuscript to submit for publication.

Study concept and design: Komulainen, Kivipelto, Lakka, Rauramaa.

Acquisition of data: Komulainen, Savonen, Hassinen, Rauramaa.

Analysis and interpretation of data: Komulainen, Kivipelto, Lakka, Savonen, Hassinen, Kiviniemi, Hänninen, Rauramaa.

Drafting of the manuscript: Komulainen.

Critical revision of the manuscript for important intellectual content: Komulainen, Kivipelto, Lakka, Savonen, Hassinen, Kiviniemi, Hänninen, Rauramaa.

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Study supervision: Rauramaa, the PI of the study.

Conflicts of interest

There are no conflicts of interest.

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Appendix A. Individual tests in the order of administration within the CERAD battery

Test	Object	Instruction and score
Verbal Fluency Test	To measure semantic memory, verbal production and language	The subjects were asked to name as many animals (animal category) as possible in 1 minute. The score is the total number of different animals named
Modified Boston Naming Test	To measure visual naming	The subjects were asked to name 15 objects. The items are stratified into three groups of five items each, the names having high, medium, and low frequency of occurrence in the Finnish language. The maximum score is 15
Mini-Mental State Examination	To measure global cognitive function including orientation, language, memory, concentration and constructional praxis	The maximum score is 30
Word List Memory	To measure ability to remember newly learned information	The subjects are presented 10 unrelated items to remember on printed cards. The subjects are instructed to read aloud each word as it is presented. Immediately following presentation of each 10 words, the subject is asked to recall as many items as possible. On each of three learning trials, the 10 words are presented in a different order. The maximum score on each trial is 10. The maximum total score is 30
Constructional Praxis	To measure visuospatial and constructional ability	Four line drawings of figures of increasing complexity (circle, diamond, overlapping rectangles and cube) are presented to the subject for copying. At the end of the session, the subject is asked to make a mental note of the objects, because later, they will be asked to draw them without model. The maximum score is 11. For each subject, a saving score can be calculated and is presented as a percentage reflecting the delayed ability to draw the objects without model ([copy from object/delayed drawing]* 100)
Word List Recall	To measure delayed memory	After 5 minutes for the Word List Memory task, the subject is asked to remind as many words as possible. A maximum of 90 seconds is allowed. A maximum number of correct responses is 10. For each subject, a saving score can be calculated and is presented as a percentage reflecting the relative amount of verbal information retained over the delay interval ([delayed words/Trial 3 words from Word list memory]* 100)
Word List Recognition	To measure correctly recognized words presented in the Word list memory task	The words are presented among 10 distracting words. The number of correctly identified distracting words is also counted. The maximum score for each is 10
Clock Drawing	To measure executive function	The subject is asked to draw a clock with all the numbers, and set the hands at ten past eleven. The maximum score is 6

CERAD; the Consortium to establish a registry for Alzheimer's disease neuropsychological test battery.

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