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Systematic Review

Gender-Specific Design and Effectiveness of Non-Pharmacological Interventions against Cognitive Decline – Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

BACKGROUND: The number of people living with dementia worldwide is increasing rapidly. Preventive approaches constitute a promising strategy to counter the dementia epidemic, and growing numbers of lifestyle interventions are conducted around the globe. Gender differences with respect to modifiable risk factors for dementia have been reported, however, little is known about gender-specific effectiveness of lifestyle trials against cognitive decline and dementia. A systematic review and meta-analysis was conducted to assess evidence on gender-specific design and effectiveness of randomized controlled trials against cognitive decline.

METHODS: Systematic literature searches were conducted in MEDLINE, PsycINFO, Web of Science, Cochrane Central and ALOIS. Studies assessing global and/or domain-specific cognitive function in older adults free from dementia were eligible for the systematic review. We assessed between-group effect sizes using random-effects meta-analysis. Methodological quality of included studies was assessed using the Scottish Intercollegiate Guidelines Network (SIGN)-checklist.

RESULTS: The systematic review and meta-analysis included 34 and 31 studies, respectively. Effects of lifestyle-interventions on global cognition were non-significant overall (g = .27; 95% CI: -.01; .56) and in male subsamples (g = -.05; 95% CI: -.55; .45), and small for female subsamples (g = .38; 95% CI: .05; .72). Small beneficial effects were found for memory (overall: g = .38; 95% CI = .17; .59). Stratified by gender, significant effects were observed only in women (g = .39; 95% CI = .13; .65; men: g = .37; 95% CI: .00; .73). Aspects of gender in study design and conduct were discussed in a small minority of studies. Comparable results were observed for executive function and verbal fluency. Methodological quality was deemed high in 17.6% of studies, acceptable and low quality in 52.9% and 29.4%, respectively.

DISCUSSION: We found evidence for small differences in the effectiveness of lifestyle interventions on global cognition and memory in favor of women. However, small numbers of trials 1) targeting men and 2) reporting gender-specific results for older adults with mild cognitive impairment warrant further attention. Assessing differences in modifiable risk factors for dementia in men and women and systematically addressing aspects of gender in trial conduction and recruitment in future studies might increase knowledge on gender-specific effectiveness of lifestyle trials against cognitive decline.

Key words: Dementia, cognition, gender, lifestyle, prevention, systematic review, meta-analysis.

Abbreviations: AD: Alzheimer's disease; APOE: Apolipoprotein; AVLT: Auditory Verbal Learning Test; BDNF: Brain-derived neurotrophic factor; BL: baseline; CANTAB: Cambridge neuropsychological test automated Subscale; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CI: confidence interval; Coeff: coefficient; CPT: Continuous Performance Test; DKEFS: Delis-Kaplan Executive Function System; DSC: Digit Symbol Coding; DSST: Digit Symbol Substitution Test; FCRST: Free and Cued Selective Reminding Test; FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; GMLT: Groton Maze Learning Test; HVLT: Hopkins Verbal Learning Test; LNS: Letter-Number Sequencing; MCI: mild cognitive impairment; MCSA: Mayo Clinic Study of Aging; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; NTB: neuropsychological test battery; OCL: One-card learning; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RBMT: Rivermead Behavioural Memory Test; RAVLT: Rey Auditory Verbal Learning Test; RCT: randomized controlled trial; Ref: reference; REML: restricted maximum likelihood; RPM: Raven's progressive matrices; SCD: subjective cognitive decline; SCWT: Stroop Colour Word Test; SE: standard error; SES: socioeconomic status; SIGN: Scottish Intercollegiate Guidelines Network; TMT: Trail Making Test; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition; WCST: Wisconsin Card Sorting Test; WW-FINGERS: World-Wide FINGERS

Introduction

Today, 55 million people worldwide are living with dementia, with projected increases to 78 million by 2030 due to growth of the ageing population (1). Available treatments are able to improve cognitive function and neuropsychiatric symptoms to a small extent and over limited periods of time, but still provide no cure (3). Evidence on potentially modifiable risk factors has been accumulating rapidly, pointing out the possibility of prevention (4). Twelve potentially modifiable risk factors have been established to date: low education in early life, hypertension and obesity in

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midlife, diabetes mellitus, smoking, excessive alcohol consumption, physical inactivity, depression, social isolation, hearing loss, traumatic brain injury and air pollution (5). Together, these risk factors are estimated to account for 40% of dementia cases. Declining incidence rates of dementia observed in several high-income countries have been linked to increased levels of education and improved management of cardiovascular diseases, indicating the potential of dementia prevention by targeting modifiable risk factors (6, 7).

Incidence and prevalence of dementia is higher in women, owing in part to differences in life expectancy (8), although this gap has been declining in developed countries. Certain lifestyle risk factors for dementia are distributed unequally by gender, however, it is not fully understood whether these risk factors impact dementia risk differently in men and women. In women, but not men, hypertension was found to increase risk for memory decline (9), incident mild cognitive impairment (MCI) (10) and dementia (11–13). Depression is associated with increased risk for incident MCI (14) and conversion from MCI to dementia (14, 15) more strongly for women than for men. Studies reported that diabetes mellitus is linked to greater cognitive decline (16), incident MCI (10) and risk for dementia (13, 17) for women than for men. Associations between history of stroke and higher risk for dementia (13) and cognitive decline (9) were observed only in men in some studies, while others reported higher risk for incident MCI (10) and dementia (18) after stroke for both men and women. Low education has been reported to increase memory decline (19) and risk for dementia (13) especially in women and incident MCI for both men and women (10). Smoking increased memory decline only in men in some studies (9, 20), while others reported higher risk for dementia for both genders (18). Growing evidence on prevention potential for dementia has resulted in a large number of randomized controlled trials (RCTs) targeting modifiable risk factors, with the most promising results observed in multi-domain trials which simultaneously target multiple risk factors (22–25). Recent meta-analyses reported small but significant beneficial effects of multi-domain interventions on risk for dementia (23) and cognitive composite scores (22). The pioneer multi-domain intervention trial, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)-study, is currently being adapted in numerous countries and settings worldwide, resulting in the global WORLD-WIDE FINGERs (WW-FINGERS) network (26).

Regarding potential benefits of interventions to protect cognitive function in older age, little is known about whether men and women respond differently to interventions (13, 27). Knowledge on possible differential effects of interventions between genders might benefit the design of future studies targeting older men and women, but also aide the implementation of the respective interventions in real world-settings (27). Recent reviews have highlighted the need for more targeted intervention designs in dementia prevention which take into account different needs of specific subgroups of older people, depending on cultural or geographic background and further personal characteristics and dementia risk profiles (25, 28, 29). In the face of many trials reporting small or non-significant effects on cognitive function and risk for dementia, consideration of these differences might increase intervention effectiveness (27). This includes the consideration of possible differences in intervention effectiveness according to gender. Against this background, we conducted a systematic review and meta-analysis to assess aspects of gender in design and effectiveness of non-pharmacological RCTs targeting modifiable risk factors for cognitive decline and dementia.

Materials and methods

Eligibility criteria

Studies were eligible for the systematic review if they fulfilled the following criteria: 1) the study design was a randomized-controlled trial; pilot studies were eligible if a randomized allocation of participants was conducted; 2) a lifestyle-intervention was applied, targeting either diet, physical activity, social activity, cognitive activity, smoking, alcohol consumption, or psychoeducation; 3) participants were free from dementia at baseline; 4) a standardized measure of cognitive function (global or domain-specific) was applied at baseline and post-intervention; 5) the study reported gender-specific outcomes or indicated that gender-specific outcomes were assessed. Where the retrieved article did not report gender-specific outcomes but indicated to have conducted respective analyses, authors were contacted to obtain the additional data; 6) the article was published in English or German. Where necessary data for the meta-analysis could not be obtained, the respective studies were reported narratively but were excluded from the meta-analysis.

Exclusion criteria

Studies were excluded if 1) the interventions were targeted at people with dementia; 2) the study did not address age-related cognitive decline, e.g. studies on post-operative cognitive function; 3) a pharmacological intervention was applied; 4) the study focused on subjects with severe pre-existing conditions affecting risk for cognitive decline and dementia, e.g. myocardial infarction, cancer, stroke, or major depression.

Registration, protocol and guidelines

Our review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) guidelines (30). The review was registered prospectively in PROSPERO (registration number: CRD42021235281) and the review protocol outlining the rationale, eligibility criteria and strategy for data analysis has been published (31).

Search strategy and study selection

We conducted a database search using a comprehensive search strategy for MEDLINE (PubMed interface), Cochrane Central Register of Controlled Trials, PsycINFO, Web of Science (Web of Science interface) and ALOIS without restriction on date or publication status. The full search strategy is provided in Additional File 1.

In a first step, titles and abstracts were screened of all database returns by two researchers independently (AZ, FW). Thereafter, studies were checked according to the eligibility criteria outlined above by full-text analysis.

Data extraction

Data from included studies were extracted independently by two investigators (FW, AZ) using a standardized data extraction form. Discrepancies at each stage of the selection process were resolved by discussion with inclusion of a third researcher (ML). The following data were extracted: study characteristics: first author, year of publication, country, numbers of participants randomized to intervention(s) and control group, cognitive outcome(s), type of intervention, type of control condition, intervention duration.; participant's characteristics: mean age, gender (distribution), cognitive function at baseline (cognitively healthy/SCD/MCI).

Quality assessment

Quality of included studies was assessed by two reviewers (AZ, FW) independently, using the SIGN (Scottish Intercollegiate Guidelines Network)-checklist for RCTs. This instrument covers information on internal validity (randomization, blinding, allocation concealment, drop-out rates, use of intention-to-treat-analysis) and general criteria for rating the quality of the study. As blinding of participants is hardly feasible in lifestyle intervention trials, a point for "blinding of subjects and investigators" was given if studies indicated that statisticians or other researchers involved in the study had been blinded. Disagreements between reviewers were resolved by discussion. Studies were judged as high quality if none of the aspects covered in the quality criteria was addressed insufficiently. If one to three criteria were not fulfilled or not adequately addressed, the study was considered to be of acceptable quality. Studies not fulfilling more than three quality criteria were scored as low-quality (32).

Effect sizes and meta-analytical procedures

Effect sizes of included studies, measuring change in cognitive function between baseline/pre-intervention and post-intervention (i.e. treatment effects) were obtained using sample sizes, means and standard deviations of included trials. We calculated effect sizes as between-group effect sizes per outcome, using data from intention-to-treat-analyses, where possible. If no intention-to-treat-data were available, we used estimators of per-protocol-analyses. Studies testing more than one intervention against a control group contributed data from all relevant intervention groups. Standardized mean group differences within included studies and a pooled overall effect size for the respective outcomes across studies were estimated using Hedge's g to account for heterogeneity in sample sizes across studies. Values of Hedge's g should be interpreted as follows: $g < 0.5$: small effect; $g = 0.5$-0.8: moderate effect; $g > 0.8$: strong effect (33). Further, we assessed heterogeneity by inspecting forest plots and by applying I^2-statistics. In addition, we used Egger's regression test to evaluate publication bias, and conducted a non-parametric trim-and-fill analysis to investigate the possible impact of publication bias (34). In order to assess potential determinants of the pooled effect sizes, we conducted random effects meta-regression analyses including the variables cognitive function at baseline, mean age at baseline, type of intervention, gender, number of intervention sessions/intensity, duration of intervention, and outcome assessment. The restricted maximum likelihood (REML) estimator was used to model the between-study variance in both the pooled effect size analyses and the meta-regression analyses. All analyses were conducted using Stata/SE 16.0 (StataCorp, College Station/TX).

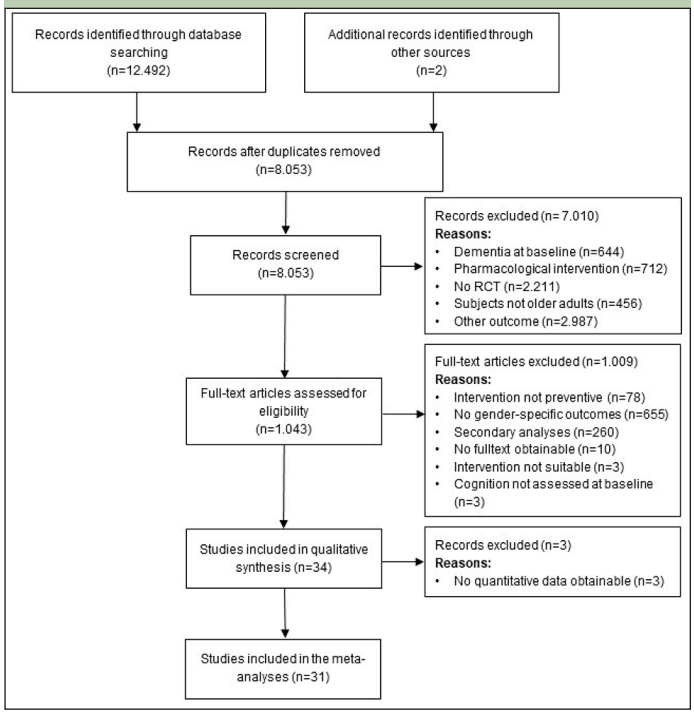
Results

Study selection

We identified 12.492 studies through literature searches in the databases PubMed, Web of Science, Cochrane, PsycInfo and ALOIS, of which 4.439 were duplicates and therefore removed. Two additional studies were identified screening the reference lists of current reviews. After screening titles and abstracts, 7.010 of articles were removed, the most common reasons being: study investigated no cognitive outcome (n=2.987), study was no RCT (n=2.211) or tested a pharmacological intervention (n=712), leaving 1.043 full-texts which were screened for eligibility. No studies were excluded due to language of publication. At this stage, the most common reasons for exclusion were trials not reporting gender-specific results (n=655), studies reporting secondary outcomes of trials already screened (n=260) or interventions not aimed at prevention (n=78). Finally, n=34 studies were included in the systematic review. If

an article did not report pre- and post-measures (mean, SD) of cognitive outcomes, corresponding authors were contacted to obtain the respective values. In cases were no information on pre- and post-intervention values of cognitive outcomes could not be obtained (n=3), the article was included in the systematic review but was not considered for the meta-analysis. The process of study selection is described in Figure 1.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the study selection process



Description of included articles

A full description of study characteristics is provided in Table 1.Studies included in the systematic review were conducted across a range of geographical regions, including the USA and Canada (1-6; 26-29), Brazil (7-12), Europe (13-20, 30, 31), Australia (21), Asia (22-24, 32, 33) and Iran (25, 34).

Control conditions varied between passive, e.g. waitlist control design or no intervention (1, 3, 5, 7, 8, 10, 11, 13, 18, 19, 21, 23, 34), health education (2, 17, 20, 27), placebo or versions of the interventions at reduced intensity (4, 6, 9, 12, 14-16, 22, 26, 28-33) and alternative activities (crafting (24); informal social gatherings (25)).

Studies including men and women with unimpaired cognitive function

Among the included trials, n = 25 were aimed at older men and women with unimpaired cognitive function (1-25). Of these studies, five (1, 2, 4, 14, 20) included both men and women; five trials (7, 9, 13, 22, 25) targeted men only, while 15 trials (3-6, 8, 10, 12, 15, 16, 18, 19, 21, 23, 24) included exclusively female samples.

Studies including men and women with unimpaired cognitive function mainly tested physical activity-interventions (1-11, 13, 16, 17, 21, 22), while three trials combined physical and cognitive training (12, 14, 25). Study (23) applied an intervention to increase cognitive activity. In study (18), participants took part in either a physical or cognitive training. Two studies were single-domain interventions targeting nutrition (15, 19). Study (20) described gender-specific effects of the FINGER-multi-domain-lifestyle intervention, comprising physical, cognitive and social activity, optimization of nutrition and management of cardiovascular risk factors.

Sample sizes of trials investigating men and women with unimpaired cognitive function ranged from n = 19 (13) to n = 1.635 (2), with a mean of n = 195 participants. Duration of trials ranged from 4 weeks (25) to 24 months (2; 20).

Studies targeted at older individuals with MCI

A total of n = 9 studies were targeted at men or women with MCI (26). Of these, three trials included both men and women (26, 27, 30), while the remaining trials were conducted with female samples (28, 29, 31-34). No trials targeting older adults with MCI were conducted in exclusively male samples. We found no trial targeting men or women with subjective cognitive decline at baseline. Two studies (28, 29) covered the same trial and sample, but reported different cognitive outcomes and were, therefore, both included in the review.

Trials targeted at older men and women with MCI mostly applied physical activity interventions, e.g. aerobic or resistance training or combinations thereof (26-31, 33). Study (34) investigated the effectiveness of either physical or cognitive training or a combined intervention, while study (32) tested the effect of a nutritional intervention, i.e. controlled consumption of mold-fermented cheese.

Several trials tested interventions against an active control group, e.g. a light exercise condition (26, 28, 29, 31, 33) or similar foods with different nutritional properties than those in the intervention group (32). One trial applied a waitlist control-design (34), while the control group of (27) included regular care and health education. Sample sizes of trials targeted at older individuals with MCI ranged from n = 28 (31) to n = 152 (30); mean: n = 71). Duration of interventions ranged from 8 weeks (31, 34) to one year (30).

Three trials (20, 26, 28) did not report the necessary data to be included in the meta-analysis and did not respond to several attempts to contact the corresponding authors and principal investigators. Results of the respective trials are briefly described below.

Study (26) found beneficial effects of a high-intensity aerobic intervention on cognition in older men and women with MCI when compared to a stretching

Table 1. Study characteristics

Study ID	Study	Country	Participants randomized (n)	% female	Age at BL (mean, SD)	Intervention	Control	Outcomes, assessments	Duration
Cognitively unimpaired at baseline									
1	Blumenthal et al. (1989) (52)	USA	101 (33 / 34 / 34)	50.5	67.0 (4.9)	Aerobic, Yoga	Wait list	Digit span; TMT-B; digit symbol, Stroop test, verbal fluency	4 months
2	Sink et. al. 2015 (38)	USA	1635 (818 / 817)	68	78.9 (5.2)	Physical activity	Health education	DSC; HVLT-R; executive function composite score; global cognitive function composite score	24 months
3	Stonnington et al. 2020 (53)	USA	53 (30 / 23)	100	63.3 (6.3)	Zumba	Maintenance of habitual exercise	GMLT; DKEFS; TMT-B; OCL	6 months
4	Voss et al. 2020 (54)	USA	34 (22 / 11)	100	67.1 (4.3)	Aerobic exercise	Passive cycling	MMSE; MoCA	3 months
5	Williams & Lord 1997 (55)	USA	187 (94 / 93)	100	71.7 (5.4)	Aerobic exercise, balance and strengthening	Passive	WAIS-R Digit Span, WAIS-R Picture Arrangement, Cattel's matrices	42 weeks
6	Liu-Ambrose et al. 2010 (56)	Canada	154 (52 / 54 / 49)	100	69.6 (2.9)	Aerobic exercise and Resistance training	Balance-and-tone training	Stroop test; TMT B-A; Digit span test; change in whole-brain volume	12 months
7	Antunes et al. 2015a (57)	Brazil	46 (23 / 23)	0.00	65.9 (3.8)	Physical fitness program	Normal everyday activities	Picture arrangement; corsi block-tapping, verbal paired associates, free word recall	6 months
8	Antunes et al. 2015b (58)	Brazil	51 (23 / 11 / 17)	100	64.7 (3.6)	Physical exercise	Everyday activity	Digit span; WCST; digit symbols, Toulouse-Pieron, MMSE, Letter fluency; RPM	6 months
9	Cassilhas et al. 2007 (59)	Brazil	62 (19 / 20 / 23)	0.00	68.1 (0.8)	Resistance exercise	Exercise at reduced intensity	Digit span, corsis block-tapping, Toulouse-Pieron, Rey Osterrieth figure	6 months
10	Coelho-Júnior et al. 2020 (60)	Brazil	45 (15 / 15 / 15)	100	66.7 (5.2)	Traditional resistance training and power training	Passive	MMSE; short-term memory test	22 weeks
11	Moreira et al. 2018 (61)	Brazil	45 (24 / 21)	100	83.7 (3.7)	Multisensory exercise program	Wait list	MoCA	4 months
12	Moreira et al. 2021 (62)	Brazil	66 (32 / 34)	100	70.8 (5.1)	Exergaming training	Multicomponent training	MMSE; TMT-A & B	4 months
13	Kleinloog et al. 2019 (63)	Netherlands	19 (9 / 10)	0.00	67 (2)	Aerobic Exercise	Crossover after 8 weeks	CANTAB	30 weeks (8 weeks; 12-week washout; 8 weeks
14	Sipilä et. al. 2021 (64)	Finland	314 (155 / 159)	59.97	74.5 (3.8)	Physical activity and cognitive training	Physical training	Stroop test; TMT-A; TMT-B; letter fluenc; CERAD	12 months
15	Beauchet et al. 2019 (44)	France	40 (20 / 20)	100	71.2 (4.4)	Vitamin D and Calcium	Same without Vitamin D and lower dose of Calcium	MMSE	3 months
16	Carral et al. 2007 (65)	Spain	62 (31 / 31)	100	68.4 (3.4)	Water exercise combined with strengths	Water exercise and calisthenic exercise	MMSE	5 months
17	García-Garro et al. 2020 (66)	Spain	110 (55 / 55)	100	68.2 (8.4)	Pilates	Everyday activities + guidelines for physical activity	MMSE, Isaac test; TMT-A&B	3 months
18	Klusmann et al. 2010 [67]	Germany	259 (91 / 91 / 76)	100	73.6 (4.2)	Mental and physical activity	Habitual lifestyle	RBMT, FCSRT, semantic verbal fluency, Stroop test; TMT B/A	6 months
19	Prehn et al. 2017 (42)	Germany	53 (28 / 25)	100	61 (5)	Low-caloric diet	Normal diet	MMSE, TMT-A & B; strooptest verbal flexibility, VLMT	4 months

Table 1 (continued). Study characteristics

Study ID	Study	Country	Participants randomized (n)	% female	Age at BL (mean, SD)	Intervention	Control	Outcomes, assessments	Duration
20	Sindi et al. (13)	Finland	1260 (591 / 599)	46.67	69.4 (4.7)	Optimization of nutrition, physical activity, cognitive training, social activity, management of cardiovascular risk factors	Regular health advice	NTB total score; subscores for executive function, memory, processing speed	24 months
21	Vaughan et al. 2014 (68)	Australia	49 (25 / 24)	100	68.9 (3.3)	Multimodal exercise proram on neurocognitive and physical functioning	Wait list	TMT-A & B; LNS; Coast; Cowat	4 months
22	Tsai et al. 2017 (69)	Taiwan	69 (23 / 23 / 23)	0.00	66.3 (4.4)	Skill exercise	Balance and stretching program	MMSE; memory depth	6 months
23	Adriani et al. 2020 (70)	Indonesia	64 (32 / 32)	100	65.1 (4.4)	Brain Gym exercise	Passive	MMSE	3 months
24	Lu et al. 2016 (71)	China	31 (15 / 16)	100	70.0 (6.6)	Tai Chi training	Series of music, English, handicrafts and fall prevention class	Auditory stroop test	4 months
25	Norouzi et al. 2019 (72)	Iran	60 (20 / 20 / 20)	0.00	68.3 (3.8)	Dual-task training	Informal meetings	N-back task	1 months
Mild cognitive impairment at baseline									
26	Baker et al. 2010 (48)	USA	33 (23 / 10)	51.5	69.5 (8.3)	Aerobic exercise	Stretching	TMT; Strooptest; verbal fluency, symbol digit modalities	6 months
27	Barha et al. 2017 (39)	Canada	71 (36 / 35)	52.1	73.8 (4.9)	Aerobic exercise	Usual care education group	TMT B-A; strooptest; digit span	6 months
28	Nagamatsu et al. 2012 (73)	Canada	86 (28 / 30 / 28)	100	74.9 (5.1)	Resistance & Aerobic Training	Balance-and-tone training	MoCA; MMSE; Stroop Test; TMT-A&B; Digit span	6 months
29	Ten Brinke et al. 201 (74)	Canada	86 (30 / 28 / 28)	100	75.2 (3.7)	Aerobic training & Resistance training	Balance-and-tone training	MMSE; MoCA; RAVLT	6 months
30	Van Uffelen et al. 2008 (51)	Netherlands	152 (77 / 75)	44.1	75.0 (2.8)	Walking	Placebo activity program	MMSE; AVLT; SCWT; DSST; verbal fluency test	12 months
31	Jurakic et al. 2017 (75)	Croatia	28 (14 / 14)	100	70.4 (3.9)	Balance and core resistance training	Pilates	MoCA	2 months
32	Suzuki et al. 2019 (43)	Japan	71 (36 / 35)	100	79.4 (4.8)	Mold fermented cheese	Non-mold fermented cheese	MMSE	3 months
33	Yoon et al. 2017 (76)	Korea	58 (19 / 19 / 20)	100	76 (1.0)	Elastic band-based high-speed power training	Balance-and-tone training	MMSE; MoCA	3 months
34	Damirchi et al. 2018	Iran	54 (11 / 11 / 14 / 9)	100	68.3 (4.3)	Mental training, physical training, both combined	Wait list	Working Memory, Processing speed	2 months

AVLT, Auditory-Verbal Learning Test; BDNF, Brain-derived neurotrophic factor; BL: baseline; CANTAB, Cambridge neuropsychological test automated Subscale; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CPT, Continuous Performance Test ; DKEFS, Delis-Kaplan Executive Function System; DSC, Digit Symbol Coding; DSST, Digit Symbol Substitution Test; FCRST, Free and Cued Selective Remind¬ing Test; GMLT, Groton Maze Learning Test; HVLT-R, Hopkins Verbal Learning Test–Revised; LNS, Letter-Number Sequencing; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NTB: neuropsychological test battery; OCL, One-card learning; RAVLT, Rey Auditory Verbal Learning Test; RBMT, Rivermead Behavioural Memory Test; RPM, Raven's progressive matrices; SCWT, Stroop Colour Word Test; TMT, Trail Making Test; WCST, WAIS-R: Wechsler Adult Intelligence Scale, revised version; Wisconsin Card Sorting Test

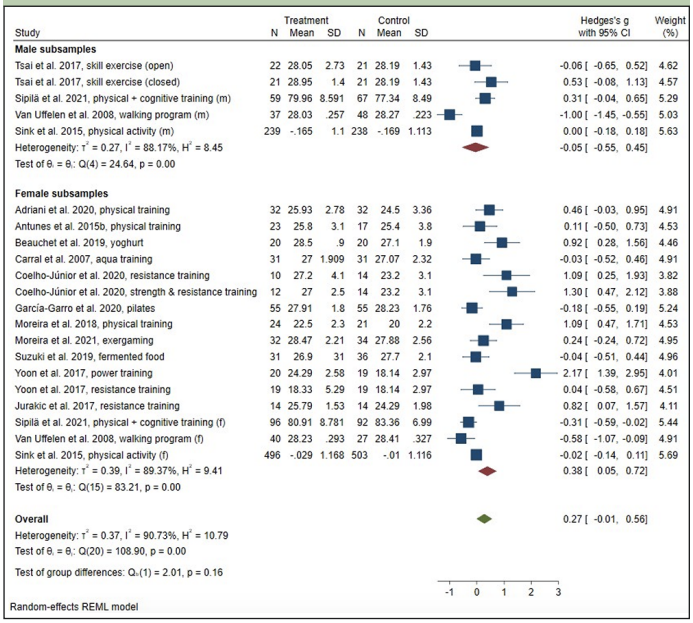
exercise-control group. Six months of aerobic exercise improved several measures of executive function and verbal fluency in women and revealed favourable effects on executive function (Trail Making Test B) in men. Intervention effects were more pronounced in women than in men across all cognitive tests. Study (28) reported beneficial effects of six months of resistance training in older women with MCI. Resistance training improved measures of selective attention and associative memory, while an aerobic exercise intervention showed beneficial effects on physical, but not cognitive functioning. The FINGER-multi-domain intervention (physical, cognitive, social activity, optimization of nutrition, management of cardiovascular risk factors; study (20) improved global

cognitive function, processing speed, memory and executive function, without differences in effectiveness between men and women.

Effect sizes

To increase comparability of results and facilitate interpretation of findings, we decided to focus on global cognitive function, and, additionally, on a selection of cognitive outcomes which are of high relevance for independence in daily functioning and exhibit high sensitivity to age-related decline and neurodegenerative diseases, i.e. executive function, memory and verbal fluency (35–37). This constitutes a clarification of processes outlined in the review protocol. All modifications and clarifications of procedures described in the review protocol are outlined in Additional File 2.

Figure 2. Effects of lifestyle interventions on global cognition, stratified by gender



Intervention effects for global cognitive function, memory, executive function and verbal fluency are described using forest plots, providing information on overall-effect sizes and effectiveness by gender. The forest plot of between-group effect sizes for global cognitive function is displayed in Figure 2. Overall, 15 individual studies targeting global cognitive function were analysed meta-analytically, comprising 18 interventions. One study (33) assessed global cognitive function with two tests, respectively, i.e. the MMSE and the MoCA. Due to its higher sensitivity, the MoCA was chosen as outcome for this study. The meta-analysis revealed no effect of lifestyle-interventions on measures of global cognition in the overall study sample (g = .27, 95% CI: -.01; .56), displaying a high level of heterogeneity (I^2 = 90.73%). Stratified analyses by gender revealed a small intervention effect for women (g = .38, 95% CI: .05; .72) and a high level of heterogeneity (I^2 = 89.37%). Intervention effects were non-significant in male subsamples (g = -.05; 95% CI: -.55; .45), with high levels of heterogeneity (I^2 = 88.17%).

Only one study (30) investigated intervention effects in a sample of older adults with MCI at baseline, therefore, we did not stratify meta-analyses by baseline cognitive function. Random effects meta-regression revealed no effect of the considered determinants on the pooled effect sizes for the overall-sample (Table 2). We found evidence for possible small-study effects, as indicated be Egger's test (p = .044). The results of the non-parametric trim-and-fill analysis indicated no difference in effect size due to potentially unpublished studies.

Meta-analysis for memory (19 studies, testing 27 interventions) revealed a small beneficial overall effect (g = .38, 95% CI = .17; .59; Figure 3), with high levels of heterogeneity (I^2 = 85.47%). Stratifying results by gender, we observed significant small effects only in women (g = .39, 95% CI = .13; .65; men: g = .37, 95% CI = .00; .73), with high levels of heterogeneity in male (I^2 = 84.08%) and female subsamples (I^2 = 86.26%), respectively.

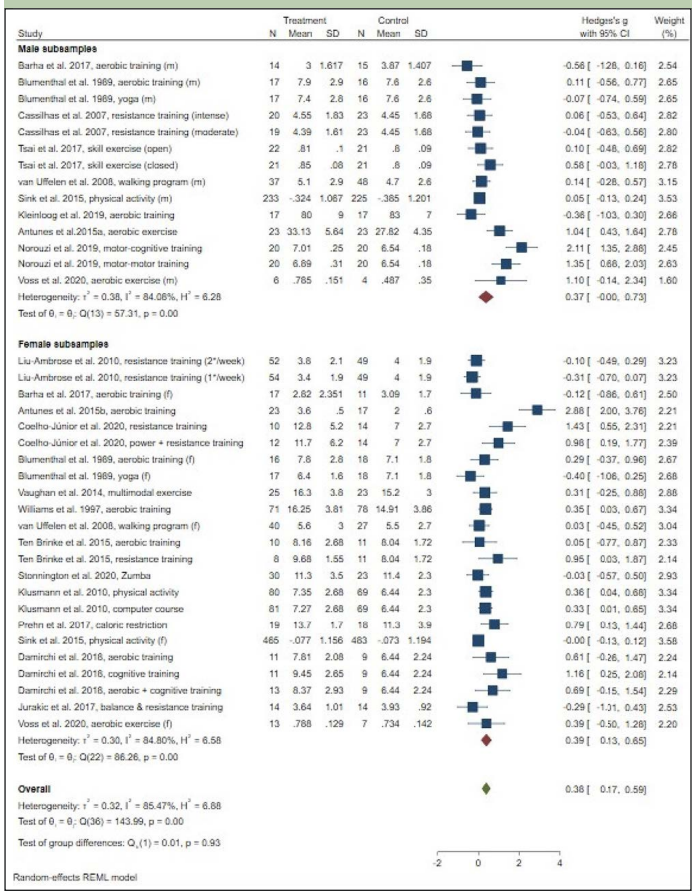
Table 2. Random effects meta-regression analysis for global cognitive function

	Coeff.	SE	95% CI
Female sex	.07	.41	-.72; .86
MCI at baseline (ref.: cognitively unimpaired)	-.67	.68	-2.00; .66
Type of intervention (ref.: physical activity intervention)			
Nutritional intervention	1.06	1.03	-.05; 3.69
Physical + cognitive intervention	.33	1.02	-1.67; 2.33
Assessment instrument (ref.: MMSE)			
MoCA	1.82	.95	-.05; 3.69
CERAD	-.58	1.72	-3.95; 2.79
Composite score#	-.40	2.43	-5.17; 4.37
Number of sessions	.00	.01	-.01; .01
Intervention duration (weeks)	.01	.03	-.05; .06
Mean age of participants (years)	-.08	.09	-.27; .10

CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CI: confidence interval; Coeff.: coefficient; MCI: mild cognitive impairment; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; SE: standard error; #: standardized composite score as applied in [38], consisting of Digit Symbol Coding task, revised Hopkins Verbal Learning Test immediate and delayed recall, n-back task, reaction time on task switching and Flanker task.

Random effects meta-regression revealed no influence of considered determinants on the pooled effect sizes for memory (Table 3). Egger's test indicated possible small-study effects (p = .007). Publication bias was suspected as suggested by trim-and-fill analysis, with an adjusted effect size of g = .09 (95% CI: -.18; .36) in the absence of publication bias (eight studies imputed).

Figure 3. Effects of lifestyle interventions on memory, stratified by gender



Results for executive function and verbal fluency are displayed in Additional File 3. A total of 17 studies, comprising 21 interventions, targeted executive function. A non-significant overall-effect size of g = -.16 (95% CI = -.31; .00) was detected, whereas negative values indicated positive intervention effects. Level of heterogeneity was moderate (I^2 = 70.98%). Stratified analysis by gender revealed a non-significant effect size of g = .01 (95% CI = -.21; .23) for men and a small but significant effect (g = -.24; 95% CI = -.43; -.04) for women, with moderate and considerable levels of heterogeneity for men (I^2 = 39.17%) and women (I^2 = 76.34%), respectively. Egger's test did not suggest influence of small-study effects (p = .275). Publication bias was suspected as indicated by trim-and-fill analysis, with an adjusted effect size of g = -.11 (95% CI: -.29; .07) if one further study was imputed.

Figure 4. Methodological quality of studies (Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist for randomized controlled trials)

Study ID, authors	Internal validity										Overall quality		
	Appropriate and clearly focused question	Randomized assignment of subjects	Adequate concealment method	Blinding of subjects and investigators*	Treatment and control groups similar at the start of the trial	The only difference between groups is the treatment under investigation	Outcomes are measured in a standard, valid and reliable way	Drop out rate(s) (%)	Use of intention to treat analysis	If multiple study sites: results comparable across sites?	How well was the study done to minimise bias?	Certainty that the overall effect is due to the study intervention?	Results of study directly applicable to the targeted patient group?
1) Blumenthal et al. 1989	Y	Y	N	N	Y	Y	Y	I: 6.1 I: 0.0 C: 5.9	N	N.A.	+	Y	Y
2) Sink et al. 2015	Y	Y	?	Y	Y	N	Y	I: 10.1 C: 9.3	Y	Y	+	Y	Y
3) Stonnington et al. 2020	Y	?	N	Y	Y	N	Y	I: 16.7 C: 36.1	N	N.A.	-	Y	Y
4) Voss et al. 2020	Y	Y	N	?	Y	Y	Y	I: 2.9 C: 0.0	N	N.A.	+	Y	Y
5) Williams & Lord 1997	Y	Y	N	?	Y	Y	Y	I: 24.5 C: 16.1	N	N.A.	+	Y	Y
6) Liu-Ambrose et al. 2010	Y	Y	Y	Y	Y	Y	Y	I: 11.5 I: 13.0 C: 14.3	Y	N.A.	++	Y	Y
7) Antunes et al. 2015a	Y	?	N	?	Y	Y	Y	I: 0.0 C: 0.0	Y	N.A.	+	Y	Y
8) Antunes et al. 2015b	Y	Y	N	Y	N	N	Y	I: 0.0 C: 0.0	?	N.A.	-	U	Y
9) Cassilhas et al. 2007	Y	?	N	?	Y	Y	Y	I: 0.0 C: 0.0	Y	N.A.	+	Y	Y
10) Coelho-Junior et al. 2020	Y	Y	?	N	Y	N	Y	I: 33.0 I: 20.0 C: 6.7	N	N.A.	-	Y	Y
11) Moreira et al. 2018	Y	?	N	Y	Y	Y	Y	I: 0.0 C: 0.0	Y	N.A.	+	Y	Y
12) Moreira et al. 2021	Y	Y	N	N	Y	Y	Y	I: 34.7 C: 32.0	N	N.A.	-	Y	Y
13) Kleinloog et al. 2019	Y	Y	N	Y	Y	Y	Y	I: 20.0 C: 0.0	N	N.A.	+	Y	Y
14) Sipilä et al. 2021	Y	Y	?	Y	Y	Y	Y	I: 7.7 C: 6.9	Y	N.A.	++	Y	Y
15) Beauchet et al. 2019	Y	Y	Y	Y	Y	Y	Y	I: 5.0 C: 10.0	Y	N.A.	++	Y	Y
16) Carral & Pérez 2007	Y	?	N	N	Y	Y	Y	I: 12.9 C: 6.5	N	N.A.	-	N	Y
17) García-Garro et al. 2020	Y	Y	?	Y	Y	Y	Y	I: 5.5 C: 0.0	N	N.A.	+	Y	Y
18) Klusmann et al. 2010	Y	Y	?	Y	Y	Y	Y	I: 12.1 I: 12.0 C: 9.2	N	N.A.	+	Y	Y
19) Prehn et al. 2017	Y	?	N	Y	Y	Y	Y	I: 33.3 C: 26.9	N	N.A.	+	Y	Y
20) Sindi et al. 2021	Y	Y	Y	Y	Y	Y	Y	I: 14.0 C: 11.0	Y	?	++	Y	Y
21) Vaughan et al. 2014	Y	Y	Y	Y	Y	Y	Y	I: 0.0 C: 4.2	Y	N.A.	++	Y	Y
22) Tsai et al. 2017	Y	Y	N	Y	Y	N	Y	I: 4.5 I: 8.7 C: 8.7	N	N.A.	+	Y	Y
23) Adriani et al. 2020	Y	?	N	N	Y	Y	Y	I: 0.0 C: 18.8	N	?	-	U	Y
24) Lu et al. 2016	Y	Y	N	Y	Y	N	Y	I: 13.1 C: 12.5	Y	N.A.	+	Y	Y
25) Norouzi et al. 2019	Y	?	N	N	Y	Y	Y	I: 0.0 C: 0.0	Y	N.A.	+	Y	Y
26) Baker et al. 2010	Y	?	N	Y	Y	Y	Y	I: 17.0 C: 0.0	N	N.A.	+	Y	Y
27) Barha et al. 2017b	Y	Y	Y	Y	Y	Y	Y	I: 13.9 C: 22.9	N	N.A.	+	Y	Y
28) Nagamatsu et al. 2012	Y	?	N	?	Y	Y	Y	I: 7.1 I: 20.0 C: 3.6	?	N.A.	-	Y	Y
29) Ten Brinke et al. 2015	Y	Y	Y	Y	Y	Y	Y	I: 20.0 I: 3.6 C: 7.1	Y	N.A.	++	Y	Y
30) Van Uffelen et al. 2008	Y	Y	N	Y	Y	Y	Y	I: 10.5 I: 19.4	N	N.A.	+	Y	Y
31) Jurakic et al. 2017	Y	?	N	N	Y	N	Y	I: 7.1 C: 14.3	Y	?	-	Y	Y
32) Suzuki et al. 2019	Y	Y	N	?	Y	Y	Y	I: 0.0 C: 11.4	N	N.A.	+	Y	Y
33) Yoon et al. 2016	Y	?	N	?	?	?	Y	I: 63.0 I: 52.0 C: 30.0	N	N.A.	-	Y	Y
34) Damirchi et al. 2018	Y	?	N	?	Y	Y	Y	I: 20.0 I: 0.0 I: 0.0 C: 53.3	N	N.A.	-	Y	Y

* Scored "yes" if statistician or other researchers were blinded; N: no (red); N.A.: not applicable (no color); Y: yes (green); ?: can't say (yellow); ++: high quality; +: acceptable; -: low quality; CMP: complete sample; I: intervention group; C: control group; U: unsure

Table 3. Random effects meta-regression for memory

	Coeff.	SE	95% CI
Female sex	.22	.33	-.42; .86
MCI at baseline (ref.: cognitively unimpaired)	-.15	1.02	-2.16; 1.85
Type of intervention (ref.: physical activity intervention)			
Nutritional intervention	-.18	1.10	-2.33; 1.97
Physical + cognitive intervention	.84	.64	-.42; 2.09
Cognitive intervention	.43	.66	-.88; 1.73
Assessment instrument (ref.: digit span test)			
Picture memory test	.89	.60	-.28; 2.06
n-back-test	.54	.43	-.30; 1.38
letter-number-sequencing test	-.01	.77	-1.51; 1.50
AVLT	.26	.54	-.80; 1.33
RBMT	-.15	1.02	-2.15; 1.84
HVLT	.05	2.71	-5.27; 5.37
Delayed match-to-sample-test	-.59	.80	-2.15; .97
WAIS-III memory subscore	.12	1.07	-1.97; 2.21
Free word recall test	.87	.75	-.61; 2.35
MoCA subscore "memory"	-.54	1.03	-2.55; 1.48
Number of sessions	.00	.01	-.02; .03
Intervention duration (weeks)	-.02	.02	-.06; .03
Mean age of participants (years)	-.01	.11	-.23; .20

AVLT: Auditory Verbal Learning Test; CI: confidence interval; Coeff.: coefficient; HVLT: Hopkins Verbal Learning Test; MCI: mild cognitive impairment; MoCA: Montreal Cognitive Assessment; RBMT: Rivermead Behavioural Memory Test; SE: standard error; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition

Interventions targeted at verbal fluency (n = 8 studies, testing 10 interventions) revealed an overall effect size of g = .12 (95% CI = .01; .24), with low levels of heterogeneity (I^2 = 0.00%). We observed non-significant effects in male subsamples (g = .01; 95% CI: -.28; .25), with low levels of heterogeneity (I^2 = 17.40%). Investigating female subsamples revealed an effect size of g = .16 (95% CI: .02; .29), with low levels of heterogeneity (I^2 = 0.00%). We found no indication of small study effect, as suggested by Egger's test (P = .735). Trim-and-fill analysis suggested an adjusted effect size of g = .11 (95% CI: .00; .22) if one further study had been available for analysis.

Gender-specific aspects in design and effectiveness of included trials

In addition to gender-specific effectiveness, we assessed whether aspects of gender were discussed in the study design, interpretation of results and respective conclusions of included trials. Study (26), which included both men and women, found evidence for gender-specific effects of physical activity on cognition, with beneficial effects on three measures of executive function in women but only on one measure in men. While no gender differences regarding effectiveness of the FINGER-intervention were detected, study (20) provides evidence for different risk profiles in older men and women at increased risk for dementia. Regarding adherence to the intervention and participant feedback, no gender differences were observed. However, more men than women (49% vs. 39%, p = .008) in the intervention group believed they had been part of the control group, i.e. these participants did not perceive themselves as having taken part in an intensive lifestyle intervention (13). Study (27) reports gender differences in effectiveness of an aerobic training intervention, with greater improvement on the TMT-B in women. However, no differences were observed for the outcomes Stroop and Digit Span Test. The authors report that baseline levels of physical activity were lower in women than in men, leaving greater room for improvement (39). No gender differences regarding intervention effectiveness were reported in studies (1, 2, 14).

Regarding included trials with gender-homogenous samples, n = 18 did not state reasons for recruiting only one gender (3-5, 7-11, 16, 17, 19, 24, 25, 28, 31-34). Studies (6, 13, 15, 21, 22, 29, 34) stated that a gender-homogenous sample was recruited in order to eliminate a potential influence of gender as an effect modifier. Studies (12) and (23) reported that trial participation was open to both men and women in their respective studies, however, only women were recruited into the trials. The authors provide no further information on possible underlying reasons or how this might have influenced their findings. Study (18), which tested both an intensive physical and cognitive intervention (i.e. computer course), stated that

use of advanced technology might still be less common in older women than in older men. Therefore, a guided course for use of computers might be more challenging and provide more pronounced effects on cognition in older women.

Methodological quality

Of all included studies in the systematic review, 21 (61.8%) provided sufficient information on randomization technique; the remaining studies were randomized trials but failed to provide information on randomization method. Six studies (17.6%) applied an adequate concealment measure, while allocation was not concealed in 22 studies (66.7%) and insufficiently described in six (17.6%) studies. Intention-to-treat-analyses were applied in 12 studies (35.3%). Overall, 17.6% (n = 6) of studies were deemed "high quality", n = 18 (52.9%) were judged as "acceptable" and n = 10 (29.4%) as being of "low quality". The results of the methodological quality assessment, providing information on internal validity and overall-quality of studies, is displayed in Figure 4. Quality assessments for individual studies are provided in Additional File 4.

Discussion

Our study is the first attempt to systematically assess gender aspects in the design and effectiveness of a broad variety of non-pharmacological RCTs against cognitive decline in older adults free from dementia. Effects of lifestyle interventions on global cognition were non-significant in the overall-sample, whereas a small effect was detected in female subsamples. When investigating intervention effects on memory and verbal fluency, small effect sizes were observed, which were mostly due to effectiveness of interventions in female subsamples. For executive function, small effects sizes were observed only in female samples. The results were unaffected by type of intervention (e.g. physical, cognitive activity or nutrition), as indicated by meta-regression results. Most interventions were tested in female samples and included participants with unimpaired cognitive function at baseline, complicating statements on intervention effectiveness in men and older adults with MCI. However, random effects meta-regression did not reveal effects of baseline cognitive function on the observed estimates, aligning with results from a recent review reporting no interaction effect of baseline cognitive function and intervention in multi-domain lifestyle trials (22). Our findings are in line with previous reviews examining effects of physical activity interventions on cognitive function, reporting more pronounced effects in studies with larger proportions of women (40, 41). Only few included trials applied interventions targeted at nutrition or cognitive activity, while other potentially beneficial domains like e.g. social activity were not applied in identified trials. Likely due to ethical reasons prohibiting a non-active control group, no intervention trials targeted at tobacco or alcohol consumption were identified. Moreover, identified studies aimed at cognitive activity and nutrition applied very heterogeneous approaches (e.g. caloric restriction in study (19) (42) vs. consumption of specific foods in studies (15) and (32) (43, 44) as nutritional interventions). The majority of trials included in our study applied physical activity or exercise interventions, either as single-domain interventions or in combination with cognitive activity.

The meta-analyses focused on specific domains of cognitive function known to be sensitive to age-related decline. Choice of outcomes and availability of data across identified trials might, however, have influenced the findings: Several studies report a general advantage of older women in verbal fluency and memory (45, 46) which is preserved over the lifespan even despite increased pathology for AD (27). This could have lead to the slightly larger intervention effects observed in female samples regarding the respective domains. Men, on the other hand, have been reported to show better performance in tasks of visuospatial abilities (46), a measure for which insufficient amounts of data were available in the current study.

The observed differences between men and women might partly be explained by gender differences in education and occupational history. Older women, especially in less recent trials including earlier birth cohorts, might have been less likely to have been employed generally and, more specifically, in higher-ranking occupations which have been found to contribute to better cognitive function in older age (27, 47). These differences due to interactions of socio-economic status and gender might imply greater room for improvement of cognitive function brought about by lifestyle interventions. However, due to large heterogeneity between included samples and limited numbers of trials investigating men and women simultaneously, this line of thought should be interpreted with caution.

Another line of thought points to baseline differences in health and cardiovascular risk factors between older men and women. Single trials reported differences in body fat and fitness (48), BMI, total and high-density lipoprotein cholesterol (13) and physical activity (39) between male and female participants in favor of men, leaving more room for improvement in cardiovascular risk factors for dementia in women. On the other hand, more favorable dietary habits (regular intake of fruit and vegetables, fish, little or no alcohol consumption) were observed in women in single trials (13). Due to a limited number of studies assessing respective risk profiles by gender, this explanation could not be further assessed in the current review and demands further attention. Numerous trials following the FINGER-model are currently conducted around the globe (25), likely improving knowledge on the impact of baseline dementia

risk factors on intervention effectiveness in men and women.

The majority of trials included in our review and meta-analyses tested interventions against an active control group, which might have resulted in a possible underestimation of the true effect sizes observed in included studies. Further, most included studies assessed intervention effects using single measures of global or domain-specific cognitive function, while composite scores and comprehensive neurocognitive assessment batteries have been pointed out to provide higher reliability than single tests (22). Therefore, choice of outcome measures and design of control groups might have impacted our results.

We identified only few studies with mixed samples reporting intervention effects for men and women separately. Trials investigating either men or women commonly explained this recruitment strategy by possible differences in brain structure and hormonal influences in women and men. To date, this has resulted in an underrepresentation of men in prevention trials against cognitive decline which has been observed in earlier reviews (41), highlighting the need for increased efforts in targeting older men. Two studies, however, were by design open to both men and women but failed to include both genders without discussing possible reasons for gender imbalance. This raises the question whether different interventions, e.g. physical activity or optimization of nutrition, might appeal differently to older men and women and whether needs and expectations towards lifestyle interventions differ by gender. Future trials might counteract this by discussing aspects of gender in early stages of study design, e.g. feasibility of intervention components for men and women, and by cooperation with relevant interest groups, e.g. older men and women in the community or health service practitioners with close contact to the targeted groups. The presented results align with previous reviews and guidelines, suggesting a mismatch between evidence from observational studies and intervention trials (22, 28, 49). While epidemiological cohort studies provide evidence for several potentially modifiable risk factors impacting on cognitive function in older age, results from randomized controlled trials are still inconclusive, (50). Existing studies often exhibit low or moderate methodological quality and suffer from small sample sizes and lack of statistical power, a limitation addressed already in previous reviews (50). Substantial differences between trials in study- and intervention design, as observed in the trials included for our review, resulted in high levels of heterogeneity, as observed in earlier reviews (28). Identifying and addressing populations with increased risk for dementia, assessed e.g. using biomarkers, cardiovascular risk factors or validated dementia risk scores has been highlighted as a promising strategy for future trials (28). As insufficient data on baseline dementia risk factors were available, we cannot rule out possible influences of baseline dementia risk on the respective findings. Tailoring interventions to at-risk-populations and reporting on baseline dementia risk factors in future trials might further increase knowledge on intervention effectiveness in older men and women, as first trials have reported different risk profiles between male and female trial participants (13, 39).

Strengths and limitations

To the best of our knowledge, our study is the first to describe gender differences in the effectiveness of a broad range of lifestyle interventions against cognitive decline, therefore contributing to the growing field of research on prevention of dementia. Further, while much of current evidence on lifestyle factors and cognitive function in older age stems from observational studies, our review relies on data from randomized controlled trials, therefore providing a higher quality of evidence regarding effectiveness of lifestyle changes against cognitive decline. Our review solely included studies using standardized objective measures of cognitive function, therefore allowing for differentiated statements on effectiveness of interventions on cognition and avoiding risk of self-report bias by excluding subjective measures of cognitive function. Where possible, we stratified analyses by cognitive function at baseline, as subjects with MCI might likely differ from cognitively unimpaired older adults in ability to participate in ambitious intervention trials. Due to the small number of eligible studies investigating men and women with MCI, however, further studies are warranted to ascertain these findings and provide evidence for possible gender differences. Exclusion of clinical samples and differentiation for various cognitive outcomes should improve comparability of reported results. Lastly, our study assessed methodological quality of included trials using a standardized, objective quality assessment.

This review has several limitations. Due to the focus on gender-specific aspects, many published studies reporting effectiveness of lifestyle trials for cognition had to be excluded from the initial search results if studies did not investigate results stratified by gender. Especially, only a limited number of trials including male (sub)samples or older adults with MCI was identified or provided the necessary data, therefore prohibiting stratified meta-analyses by gender and MCI for several outcomes. Further, only few included studies tested interventions targeting nutrition or cognitive activity or applied the same outcome measures across studies, prohibiting subgroup analyses of intervention effectiveness by type of intervention. Although we took great efforts to maximize the number of studies to include in the meta-analysis, several suitable articles could only be presented narratively due to non-reported data and non-response of corresponding authors to our inquiry. Most trials included in our review covered rather small samples, and possibility of small-study-effects was

confirmed in the meta-analyses. This might have led to an underestimation of effect sizes and points towards the need for large-scale lifestyle intervention trials providing gender-specific results. Although we investigated possible determinants of intervention effectiveness by applying a meta-regression analyses, certain potential covariates which were not reported across all studies might have impacted on the pooled effect sizes, e.g. adherence to the intervention protocol, which certain trials reported to be important predictors of intervention effects (51). Lastly, due to high heterogeneity between studies regarding choice and assessment of outcome(s), it was decided to limit the number of cognitive outcomes covered in the meta-analysis. Heterogeneity in methodology and outcome assessment has been recognized as a problematic feature in lifestyle trials targeting cognitive function in older age and attempts at data harmonizing in current trials in order to increase comparability of findings have been launched (26).

Conclusion

Our systematic review found evidence for small differences in the effectiveness of lifestyle interventions on cognition in favour of women. However, we were able to point out several weaknesses and knowledge gaps in the growing field of lifestyle interventions against cognitive decline. Despite growing numbers of RCTs aiming at prevention of cognitive decline around the globe, questions of gender are only seldom addressed in trial design and interpretation of results to date, limiting our knowledge on intervention effectiveness especially in men and older adults with MCI. Future studies investigating mixed-gender samples and reporting stratified results by gender are highly warranted to improve our understanding of the effectiveness of lifestyle interventions in older adults. Applying a greater variety of recruitment strategies and discussing aspects of study design with older men and women from the respective target population might likely contribute to more gender-balanced samples in future trials.

Growing numbers of multi-domain lifestyle trials with large sample sizes are currently being conducted, which will increase the evidence base for effectiveness of lifestyle interventions against cognitive decline in men and women. Many of these trials follow the FINGER-approach of targeting at-risk-individuals based on modifiable risk factors for dementia, allowing for the investigation of the impact of baseline risk factors on intervention effectiveness in men and women, respectively. In addition to cognitive function, future studies are encouraged to assess intervention effects on surrogate outcomes, e.g. dementia risk scores or changes in risk behaviour for men and women, as respective effects might lead to reduced risk for cognitive decline and dementia in the long run.

Lastly, harmonization of outcome assessments and trial conduct constitutes another aim for future research, as highlighted by expert consortia in the field. Beyond that, enabling active participation of older men and women in the design and implementation of future interventions may constitute a promising approach to conduct tailored, individualized interventions in the future. The potential of lifestyle interventions against cognitive decline and dementia has been shown. Addressing gender differences in trial design and effectiveness will enhance precision and personalization of interventions, which might thereby improve effectiveness.

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Availability of data and materials: The data generated for this study are available from the corresponding author upon request.

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