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ASSOCIATIONS BETWEEN MULTIDOMAIN LIFESTYLE INTERVENTIONS AND INTRINSIC CAPACITY DOMAINS DURING AGING: A NARRATIVE REVIEW

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Abstract: *Background:* Recently, the World Health Organization defined five domains of intrinsic capacity (IC), composed of physical and mental capacities linked to body functions, and that contribute to healthy aging: locomotion, cognition, psychological, vitality and sensorial. In the past decade, studies investigating the effects of concomitant lifestyle interventions (also called multidomain interventions) on one or several IC domains have been developed. The aim of this study is to synthetize the scientific literature about the associations between multidomain lifestyle interventions and IC domains. *Methods:* We conducted a narrative review of randomized controlled trials examining the effects of multidomain lifestyle interventions on at least one IC domain among older people. Multidomain intervention was defined as the presence of at least two of the following lifestyle interventions: physical activity/exercise, nutrition, cognitive stimulation, and management of cardiovascular risk factors (eg, smoking, alcohol consumption). *Results:* Multidomain interventions were associated with improvements on locomotion (as measured by performance-based tests of lower-limb function) and vitality (as measured by handgrip strength); benefits on cognitive function were also found, in particular among populations at increased risk of dementia and when operationalizing strong multidomain interventions (eg, using regular exercise training instead of physical activity advices). No study investigated the effects of multidomain lifestyle interventions on the sensorial domain (hearing and/or vision). The modalities composing the multidomain interventions and intervention length, as well as study population, substantially varied across studies; the most common combination of interventions was physical activity- and nutritional-related interventions. *Conclusion:* Available evidence is still limited, but literature suggests a positive effect of multidomain lifestyle interventions on IC domains, in particular locomotion. Further studies are still needed on this topic, in particular, studies exploring the effects of multidomain lifestyle interventions on the sensorial domain, as well as on a composite measurement of all IC domains.

Key words: Intrinsic capacity, aging, multidomain intervention, locomotion, cognition, psychological, vitality, vision, hearing.

Abbreviations: ADL: Activity of Daily Living; CAIDE: Cardiovascular Risk Factors, Aging, and Incidence of Dementia; FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; FIT: Frailty Intervention Trial; IADL: Instrumental Activities of Daily Living; IC: Intrinsic Capacity; MAPT: Multidomain Alzheimer Preventive Trial; MDI: Multidomain Intervention pre; DIVA: Preventive of Dementia by Intensive Vascular care; RCT: Randomized Controlled Trial; SPPB: Short Physical Performance Battery; WHO: World Health Organization.

Introduction

Functional decline often occurs during aging. Recently, the World Health Organization (WHO) (1) supported the idea that healthy aging should not be defined as the absence of diseases, but as a process to develop and maintain functional abilities during aging. In this context, experts from WHO, in collaboration with academic researchers around the world, developed the theoretical framework of intrinsic capacity (IC) (2), ie, the combination of all physical and mental capacities of an individual. These experts proposed to divide IC through five domains that strongly contribute to healthy aging (1, 2): psychological, cognitive, locomotion, vitality and sensory. Therefore, developing strategies that benefit multiple domains of IC would probably lead to the promotion of healthy aging.

Several lifestyle interventions have been found to benefit specific domains of IC. Physical exercise improves locomotion (3) and may improve cognitive function (4, 5) as well as psychological outcomes, whereas cognitive training improves cognitive function6; nutritional aspects

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Table 1
Characteristic of the included studies

Study	Country	Population	Age	Sex (% women)
Ng and al. (17)	SGP[a]	Frail or pre-frail people. Community-residents	65 years and older	61%
Kim and al. (18)	JPN[b]	Frail older women. Community-dwelling.	75 years and older	100%
Chan and al. (19)	TWN[c]	Frail and pre-frail people. Community-dwelling	65 – 79 years	59%
Kwon and al. (20)	JPN	Pre-frail women. Community-dwelling.	70 years and older	100%
Rydwick and al. (21)	SWE[d]	Frail elderly people. Community-dwelling.	75 years and older	60%
Luger and al. (22)	AUT[e]	Frail and pre-frail older adults. Community-dwelling.	65 years and older	84%
Cameron and al. (15, 16) Fairhall and al. (34)	AUS[f]	Frail older people. Community-dwelling.	70 years and older.	68%
Ngaudu and al. (27) Stephen and al. (28) Kulmala and al. (35)	FIN[g]	Elderly people with cognitive decline risk	60-77 years	46%
Chhetri and al. (25) Tabue-Teguo and al. (26) Andrieu and al. (24) Rolland and al. (32) Maltais and al. (33) Giudici and al. (38)	FRA[h]	Elderly people with subjective memory complaint. Community-dwelling	70 years and older	63%
Moll van Charante and al. (29) Van Middelaar and al. (30)	NLD[i]	Elderly participants. Community-dwelling.	70-78 years	54%
Berggren and al. (23)	SWE	Patients with femoral neck fractures	70 years and older	74%
Lee and al. (37)	KOR[j]	Community-dwelling older adults	60 years and older	78%
Barnes and al. (36)	USA	Elderly people with memory complaint	65 years and older	62%

a. Singapore; b. Japan; c. Taïwan; d. Sweden; e. Austria; f. Australia; g. Finland; h. France; i. Holland; j. Korea;

are also associated with different IC domains (7, 8). From the observation that different lifestyle interventions may lead to improvements in different clinical outcomes, the benefits of the combination of different lifestyle interventions, the so-called "multidomain intervention", have been recently explored. Multidomain lifestyle interventions would potentially have synergistic and positive effects on IC domains. However, as far as we know, no study gathered the available scientific evidence of the effects of multidomain lifestyle interventions on the five domains of IC. Moreover, the best combination of lifestyle interventions to improve older adults' function remains to be elucidated.

This narrative review aimed to synthetize the scientific findings regarding the effects of randomized controlled trials (RCT) of multidomain lifestyle interventions on the domains of IC among older adults.

Methods

Eligibility criteria

Articles were eligible for this review if they were written in English or French; reported the results of a RCT regarding the effects of multidomain lifestyle interventions on one or several IC domains; included older adults (participants' minimum age or the mean age of the study population ≥ 60 years). Multidomain lifestyle intervention was defined as the concomitant presence of at least two of the following lifestyle interventions: physical activity/exercise, nutrition, cognitive stimulation, and management of cardiovascular risk factors (eg, smoking, alcohol consumption).

The domains of IC were defined as follows:

1. Locomotion. Measured using the Short Physical Performance Battery9 (SPPB) or gait speed.
2. Cognition. Measured using a validated neuropsychological test or a battery of tests for older adults.
3. Psychological. Measured using a validated scale of depressive symptoms for the elderly (such as the Geriatric Depression Scale – GDS).
4. Vitality. A consensual way of measuring the concept of vitality is not yet established10. We opted to operationalize this domain by using the handgrip strength10, which is a vital sign during aging11 and is associated to nutritional status12.
5. Sensory. Measured using validated tests for vision (eg, near/distance visual acuity) and hearing (eg, audiometry, Whisper test) capacities in older people.

The exclusion criteria comprised studies using a single lifestyle intervention or comparing different types of lifestyle interventions without assessing the effects of the combination of at least two interventions; mean age of the

Table 2
Summary of Interventions and Results of the included studies

Study	Outcomes	Duration of intervention	Intervention groups	Intervention	Results
Ng and al (17)	1st outcome: frailty score, reduction of frailty, measures of frailty components. 2nd outcome: self-reported hospitalizations, self-reported falls, IADL[k] and ADL[l]	24 weeks	Physical training Nutritional Intervention Cognition Combination Intervention Control group	Strength and Balance training Nutritional Supplement Cognitive Training Physical, Cognitive and Nutritional Intervention Standard care and placebo nutritional supplements	Frailty status and score over 12 months were reduced in all groups, including control group, but were significant higher in nutritional, cognition, physical and combination groups. This effects were observed at 3 and 6 months and were maintained at 12 months. Improvements in physical frailty domains were most evident for knee strength (physical, cognitive, and combination treatment), physical activity (nutritional intervention), gait speed (physical intervention), and energy (combination intervention). No differences in secondary outcomes.
Kim and al (18)	Frailty status, Frailty reversal rate, frailty criterion, personal medical history, body composition assessment, grip strength, isometric knee extension, walking speed, haematological parameters	12 weeks	Exercise Milk Fat Globule Membrane (MFGM) supplementation Exercise and MFGM Placebo	Strength, balance and gait training MFGM supplementation Exercise training and MFGM supplementation Milk powder supplementation	Significant group and time interaction were observed for waking speed and timed up and go. Several frailty components were reversal (weight loss, low physical activity, slow walking speed) but low muscle strength did not significantly change. Ex+MFGM group had a significantly higher frailty reversal rate than MFGM or placebo groups at post-operation, and the reversal frailty was significantly greater in the Ex+MFGM than Ex+placebo groups or placebo group at the follow-up.
Chan and al (19)	1st outcome: improvement of CHS_PCF by at least one category. 2nd outcome: the 5 indicators of CHS_PCF, MMSE[m] , PRIME-MD[n] , Bartel Index, health care resource utilization, EQ-5D, BMI[o], FFM[p], BMD[q], left one-leg-stand, dominant leg extension power and 25(OH) Vitamin D.	12 weeks	Exercise and Nutrition No Exercise and Nutrition Problem Solving Therapy No Problem Solving Therapy	Nutritional consultation, exercise training program and guidebook Pedagogic guide with nutritional and physical activity advices Guidebook and problem solving therapy Pedagogic guide with nutritional and physical activity advices	The Exercise and Nutrition intervention resulted in 3 months of frailty status improvement and 12 months on BMD and serum vitamin D.
Kwon and al (20)	1st outcome: muscle strength, balance, walking speed. 2nd outcome: Handgrip, SF-36, skeletal muscle mass and dietary variety score (DVS)	12 weeks	Exercise and Nutrition Physical Activity Control	Strength and balance training. Alimentation education. Products used enriched with vitamins D and protein Strength and balance training. General Health intervention.	The combined intervention had positive effects on several domains of HRQOL and handgrip strength in pre-frail elderly woman.
Rydwick and al (21)	Physical performance: Muscle strength, Balance, Walking speed, Personal activities of daily living, IADL. Nutritional measures: Body composition, IBM, FFM, Energy Intake.	12 weeks	Nutritional Physical Training Combined intervention Control	Individual advices on alimentary intake. Food regime if necessary. Aerobic, Strength and Balance training Physical and nutritional intervention General advices.	The combined nutritional and physical intervention showed positive effects on muscle strength only at the first follow-up (3 months). No significate difference for nutritional measures.
Luger and al (22)	Nutritional Status: Mini Assessment long form Frailty Status: Fried criteria (exhaustion, loss of appetite, weakness (ie.handgrip strength), slowness, and low physical activity).	12 weeks	Physical and Nutritional Intervention Social Support	Guidebook. Without supplement. Home-based physical training focus on muscular strength. Discussion on topics of interest except on nutritional and physical habits.	The combined nutritional, physical and social program can compensate malnutrition and frailty in community-dwelling older persons.
Berggren and al (23)	Morbidity, mortality and occurrence of falls, MMSE, the modified OBS[s] , GDS-15[t] , ADL, S-COVS[u], chair stand test and Berg's balance scale.	Hospitalization	Intervention Group Control Group	Nutrition: consultation with dietician. Meals enriched on proteins during 4 days minimum. Supplementation on calcium and D vitamins. Physical rehabilitation: Functional retraining focus on fall risk factor. Health Education: active prevention on fall risk factor. Normal postoperative routines	No significant effects on the portion of fallers, numbers of fallers, fractures or mortality could be detected after discharge from hospital. No statistically significant effects of intervention on depressive symptoms, and cognitive function.

Table 2 (continued)
Summary of Interventions and Results of the included studies

Study	Outcomes	Duration of intervention	Intervention groups	Intervention	Results
Lee and al. (37)	1st outcome: MMSE 2nd outcome: change of measures in participants' physical, cognitive and social activities.	18 months	Group A Group B Group C Group D Group E	Usual Care Bimonthly telephonic care management based on the manual. Monthly telephonic care management and educational materials. Bimonthly health worker-initiated counseling visits. Bimonthly counseling-visits in addition to rewards for good behavior (ie. Gold medals)	Engaging in cognitive activities, in combination with positive health behaviors, may be most beneficial in preserving cognitive abilities in community-dwelling older adults.
			The Mental Activity and Exercise (MAX) Trial		
Barnes and al. (36)	Cognition: verbal learning and memory, verbal fluency, processing speed, executive function, mental flexibility, inhibition, and visuospatial function, composite cognitive score.	12 weeks	Mental Activity-Intervention[v] (MA-I) Mental Activity-Control[w] (MA-C) Exercise intervention[x] (EX-I) Exercise Control[y] EX-C)	Videogames on computer designed to enhance the speed and accuracy of visual and auditory processing. DVDs of educational lectures on art, history and sciences. 10 min of warm-up, 30 min of aerobic exercise, 5 min of cooldown, 10 min of strength training, 5 min of stretching and relaxation.	Composite cognitive score improved significantly over time but did not differ between groups (MA-I vs. MA-C; EX-I vs EX-C or across all 4 groups).
			Frailty intervention Trail Study (FIT study)		
Cameron and al (15)	1st outcome: frailty, mobility (SPPB). 2nd outcome: falls, mood (GDS), health related quality of life (EQ-5D), mobility related disability (Goal attainment Scale and Life Space Assessment), and activity limitation (gait speed, and activity measure for post acute care)	12 months	Intervention Group	Nutrition: Meals delivered at home or food supplements. Psychological: follow-up with psychologist or psychiatrist if necessary. Physical: WEBB program with physiotherapists.	The intervention showed an improvement of SPPB, gait speed, and life space (people mobilised in the home and community; covered distance, degree of independence) at 12 months in intervention group versus control group. The combined intervention also resulted in a lower prevalence of frailty in the intervention group compared with the control group. No benefits were observed for GDS score and EQ-5D (quality of life and mood).
Cameron and al. (16)	1st outcome: Frailty and mobility 2nd outcome: hospitalizations and admissions to nursing care facilities, disability (Barthel Index), Quality of Life (EQ-5D), Psychological status (GDS) and deaths	12 months	Control Group	Usual care	The intervention resulted in a lower prevalence of frailty at 12 months in the intervention group. Parameters of mobility were relatively stable in the intervention group whereas they declined in control group. No major differences were observed to the secondary outcomes between groups.
Fairhall and al. (34)	Risk factor for falling (SPPB and 4m walk test) and fall rate (PPA[z]).	12 months			SPPB score and gait speed were significantly improved at 12 months but not at 3 months in the intervention group compared with the control group.
			Finnish Geriatric Intervention Study to prevent cognitive impairment and disability (FINGER study)		
Ngaudu and.al. (27)	1st outcome: change in cognitive performance measured with composite cognitive score. 2nd outcome: z score of neuropsychological domain for executive functioning, processing speed, and memory.	24 months	Intervention Group	Nutrition: food regime adapted in individual sessions and advices. Physical activity: strength and aerobic training. Cognition: computed-based cognitive training.	Intervention had positive effects on global composite cognitive score, composite score of executive function and processing speed, BMI, dietary habits and physical activity. No benefits were observed on composite memory score, except especially on complex memory tasks.
Kulmala and al. (35)	Activities of Daily Living Disability: BADL[aa], IADL. Physical performance: SPPB	24 months			The ADL score increased in control group whereas it was relatively stable in intervention group at 12 and 24 months.
Stephen and al. (28)	Cognitive outcome: change of composite neuropsychological score. Composite score of executive functioning, processing speed, and memory score. MRI: Regional brain volumes and cortical thincknesses, WML volume	24 months	Control group	Regular health advice	The FINGER MRI sub-study did not show significant differences on change in regional brain volumes, regional cortical thicknesses or WML volume between both groups after 2 years in at general risk (cardiovascular, metabolic and dementia) elderly adults.

Table 2 (continued)
Summary of Interventions and Results of the included studies

Study	Outcomes	Duration of intervention	Intervention groups	Intervention	Results
			Multidomain Alzheimer Preventive Trial (MAPT study)		
Chhetri and al. (25)	Cardiovascular risk factors: CAIDE score Cognitive Tests: FCSRT[bb], MMSE, DSST[cc], TMT[dd], CNT[ee], COWAT[ff].	3 years	Omega-3 polyunsaturated fatty acid supplement (omega-3 PUFA)	Docosahexaenoic acid (DHA) supplementation. Nutritional advices.	Multidomain intervention with omega-3 PUFA showed significant improvement in the FCSRT and MMSE orientation at 36 months compared to the placebo group. High-risk subjects for dementia screened with CAIDE dementia score might benefit from multidomain intervention strategies, particularly in the MMSE orientation and delayed recall capacity.
Tabue-Teguo and al. (26)	Cognition: FCSRT, MMSE, DSST, COWAT, CNT, TMT	3 years	Multidomain Intervention (MI)	Cognition: Reasonning processing, and memory. Physical activity: 150 minutes per week. Booster session at 1 and 2 years.	The multidomain intervention with omega-3 PUFA did not show significant effects on cognitive function in frail older adults with memory complains.
Andrieu and al. (24)	1st outcome: change of composite neuropsychological score (including FCSRT, MMSE orientation, DSST, CNT) 2nd outcome: score on cognitive tests: MMSE, TMT, COWAT, visual analogue scale, SPPB, IADL, CDR, GDS. Amyloïd pet-scan. Blood sample, death.	3 years	MI with omega-3 PUFA	MI with omega-3 PUFA supplement. ation	The multidomain intervention with omega-3 supplementation did not significantly reduce cognitive decline over 3 years compared with placebo.
Rolland and al. (32)	1st outcome. Muscle strength: Handgrip and repeated chair stand test. 2nd outcome: walking speed, balance test, SPPB.	3 years	Control group	Placebo	Low dose of omega-3 PUFA, either alone or combined with multidomain lifestyle intervention, had no significant effect on muscle strength over 3 years in older adults.
Maltais and al. (33)	Physical activity: Minnesota leisure Time Activities.	3 years			Physical Activity Level were associated with some components of biological aging, especially in terms of neurodegeneration
Giudici and al. (38)	Body composition: FFM, TFM[gg], handgrip Cognition: MMSE, Brain volume				IC Z-score decreased among all groups, but no significant difference was found between groups.
			PreDIVA		
Moll van Charante and al. (29)	1st outcome: all cause of dementia according to the DSM IV[hh]. 2nd outcome: MMSE and VAT[ii]	6-8 years	IVC group	Consultation with practice nurse every 4 months to evaluate life style habits.	A modifiable dementia risk score did not identify heterogeneity in treatment effect of a multidomain intervention to prevent dementia or cognitive decline, in community-dwelling older adults.
Van Middelaar and al. (30)	1st outcome: ADLs. 2nd outcome: incident cardiovascular disease, cardiovascular, and all cause mortality. MMSE and VAT, GDS-15, blood pressure, BMI, blood lipid concentrations and glucose concentrations.	6-8 years	Control group	Intervention if necessary and personalized Usual care	The intervention comprising a long term nurse led vascular care did not show reduction in incidence of all-cause dementia, disability, or mortality

k. Instrumental Activity of Daily Living; l. Activity of Daily Living; m. Mini Mental State Examination; n. Primary Care Evaluation of Mental Disorders; o. Body Mass Index; p. Fat Free Mass; q. Bone Mineral Density; r. x2 factorial design; s. The modified organic Brain Syndrome Scale; t. Geriatric depression Scale 15 items; u. Swedish version of the clinical outcome variables; v. MA-I : Mental activity Intervention; w. MA-C: Mental Activity Control; x. EX-I : Exercise intervention; y. EX-C : Exercise Control; z. Physiological Profile Assessment; aa. Basic activities of daily living; bb. Further stratified into free recall; cc. Digital Substitution Symbol Test; dd. Trail Making test; ee. Categorical Naming Test; ff. Controlled Oral World Association Test;; gg. Trunk Fat Mass; hh. Diagnotic and Statistical manuel of Mental Disorders IV; ii. Visual Association test

study population< 60 years; and samples of participants specifically presenting MCI or dementia.

Search strategy

Potentially eligible studies were searched on PubMed database from November 2019 to July 2020, and in the reference lists of previous literature reviews and other publications (13, 14), as well as authors' personal files. For the search, key-words related to the population (eg, elderly), the intervention (eg, multidomain), and the study design (eg, random) were used. All the search terms are summarized in Supplementary Table 1.

Data extraction

One author extracted the information of selected publications on: study population characteristics, intervention, IC domains investigated, and findings of the effects of multidomain lifestyle intervention on the IC domain. This review included 23 articles. Characteristics of key articles/studies and interventions are, respectively, presented in Table 1 and Table 2 (15–38).

Results

The articles/studies were performed in Japan (18, 20), Australia (15, 16), Korea (37), Singapore (17), Taiwan (19), Austria (22), Finland (21, 27, 28, 35), France (24–26, 32, 33, 38), the Netherlands (29, 30), the United States (36) and Sweden (21, 23). The sample size varied from 80 to 1680 participants across studies, with a mean age higher than 65 years old for all studies. Intervention length varied from 2 months to 6 years. The most used multidomain lifestyle intervention was a combination of physical activity, nutritional and cognitive interventions (17, 24–28, 35, 38); a combination of physical activity and nutritional intervention (18–21) or individually-tailored multifactorial interventions (including exercise, nutritional and psychological interventions depending on individual's needs) (15, 16, 34). A combination of physical activity and cognitive intervention (36) or physical activity, nutritional intervention and health education (22, 23); as well as assessments of cardiovascular risk factor and adapted advice were also observed (29, 30). Thus, the advices and encouragement in physical, cognitive and social activities, in combination with rewards for good health behaviours (37) were included.

About the IC domains investigated, locomotion (15–18, 20, 21, 24, 27, 34, 35) and cognition (23–30, 36, 37) capacities were the most frequent IC domains investigated, followed by the vitality domain (as measured by handgrip strength) (16, 18–20, 22, 32), and then the psychological domain (15, 16, 19, 23, 27, 33). One study has investigated the effects of a multidomain lifestyle intervention on a composite score of IC (38.) This analysis, using data of the MAPT study, has included the following four IC domains: locomotion, cognition, psychological and vitality.

No study has assessed the effects of multidomain lifestyle interventions on a valid measurement of vision or hearing capacities (sensorial domain).

Effects of multidomain lifestyle intervention on IC domains in elderly persons

IC Z-score

Recently, one study from MAPT38 has investigated the effects of a multidomain lifestyle intervention (composed by physical activity advices, nutritional counselling, and cognitive training), with or without omega-3 supplementation, on an IC Z-score including four domains (ie. locomotion, psychology, cognition and vitality). After three years, the IC Z-score decreased among all groups, but no significant difference was found between groups.

This article was the first to study the effects of a multidomain lifestyle intervention on a composite score of intrinsic capacity. Further studies are needed in order to be able to conclude on this topic.

Locomotion

Some publications (15–18, 20, 21, 24, 27, 34, 35) evaluated the effects of multidomain lifestyle interventions on locomotion. Regarding gait speed, results of at least three articles (15, 18, 34) showed an improvement of gait speed in the multidomain intervention group. This significant increase was observed in particular among participants with slow gait speed and participants with higher levels of frailty. Besides, the combined physical, nutritional and psychological intervention (15) showed also an improvement of gait speed in frailty older adults. However, other studies (17, 20, 21, 24) did not find any effects of multidomain intervention on walking speed.

At least five articles (15, 16, 24, 34, 35) used the SPPB score in order to measure the mobility of participants. The multidomain approach composed of individually-tailored interventions (including exercise, nutritional, and psychosocial support depending on individual's needs) described in three publications (15, 16, 34) had positive effects on the SPPB score after 12 months, but not at 3 months of follow-up. Additionally, the combination of physical activity, nutritional counselling, cognitive training, social activities and management of metabolic and vascular risk in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (35) showed a protective effect of physical decline for chair rise test, but no effects were observed for SPPB score (27). However, another study with an intervention composed by physical activity, nutritional counselling and cognitive training, with or without omega-3 polyunsaturated fatty acid supplementation, had

no effects on the SPPB score (24).

Overall, despite still limited findings, part of the currently scientific evidence about SPPB supports a positive effect of multidomain lifestyle intervention. In contrast, concerning gait speed, most of the included studies found no effects of multidomain lifestyle intervention.

Cognition

Several articles (23–30, 36, 37) assessed cognitive capacity after a multidomain intervention. The assessment of cognitive function varied across studies. Executive function was an outcome in two studies (26, 27), and was improved in one of them (27). In the FINGER Study (27), both intervention and control groups (usual health advice) had an increase on cognitive function (executive function and processing speed), but this improvement was significantly higher in the intervention group after 24 months. Despite using magnetic resonance imaging (MRI) (28), authors were unable to explain the effects of this multidomain intervention on global cognitive function by some structural brain mechanisms. One study (37) proposing bimonthly counseling-visits with rewards for good behavior showed superior cognitive function (ie. improvement of MMSE score) compared to the control group (ie. standards and usual care), identifying participation at cognitive activities as a protector factor against cognitive decline. The Mental Activity and eXercise (MAX) Trial (36) enrolled inactive older adults with cognitive complaints in home-based mental activity and class-based physical activity for 12 weeks, and found an improvement of global cognitive scores over time but with no differences between intervention and active control groups, what may suggest that, for this population, the amount of activity would be more important than its type.

Moreover, analysis of the effects of interventions in the Multidomain Alzheimer Preventive Trial (MAPT study) (25) restricted to the subgroup of older adults with higher risk of dementia due to cardiovascular risk factors (CAIDE dementia risk score) showed an improvement of the cognitive function in multidomain groups; similar results were found in the subgroup with high β-amyloid load in the brain (24). However, it is important to highlight that in the full sample of the MAPT study (24) as well as in the Preventive of Dementia by Intensive Vascular care (preDIVA) (29, 30) no effects were observed on cognitive function, including among those with an increased dementia risk score. Besides, the addition of rewards for good behaviours at the combined nutritional and cognitive activities (23) did not show beneficial effect on cognitive function.

Therefore, the effects of multidomain lifestyle intervention on cognitive function are not a consensus. On the one hand, two studies presented positive effects for this type of intervention. These results corroborate with those of another study comparing the effects of physical activity, cognitive training and the combination of both with a control group (39). On the other hand, two cohorts did not find any results on cognitive function (24, 25, 29, 30). Thus, the effectiveness of multidomain lifestyle interventions on cognitive function still demands further exploring.

Psychological

Only few studies (15, 16, 19, 23, 27, 33) tested the effects of multidomain interventions on psychological function among elderly subjects. The results of these studies (15, 16, 19, 23, 27, 33) revealed no effects of multidomain interventions on depressive symptoms (measured by the GDS or the Center for Epidemiologic Studies Depression Scale – CES-D) in elderly people with frailty, memory complains or at risk of cognitive decline, after follow-ups varying from 3 months to 3 years.

So far, the available scientific evidence did not support any effects of multidomain intervention on the psychological domain of IC among older adults.

Vitality

Some studies of multidomain RCT (16, 18–20, 22, 32) evaluated the effects of the intervention on handgrip strength. At least three studies showed significant positive effects of interventions – including individually-tailored interventions (physical activity, nutritional intervention, psycho-social support according to participants' needs) (16); exercise and cognitive intervention (19); and exercise associated with nutritional intervention (22) – on handgrip strength. Effects were significant in follow-ups of 12 months or over.

We found two studies that showed no improvement from the multidomain intervention (including exercise training and nutritional supplementation of milk fat globule membrane (18); or physical activity, nutritional counselling, and cognitive training (32)) on handgrip strength. However, one study (20) comprising nutritional and physical intervention showed a decline in handgrip during post-intervention follow-up, after maintenance during the combined intervention.

In summary, effects of multidomain lifestyle intervention on handgrip strength in older adults are still mixed. Twos studies found positive effects, other two studies found no effects on vitality domain and one study did not find significant benefits on handgrip during intervention but showed a significant decline post-intervention. Thus, it is not possible to conclude on the effectiveness of multidomain lifestyle interventions on handgrip measure.

Final considerations

This is the first review focused on current evidence of the effects of multidomain lifestyle interventions on IC among elderly people. One of the findings revealed herein is the complete absence of studies considering the sensory domain (hearing and vision) as an outcome. Although positive effects of multidomain interventions on locomotion, cognition and vitality (handgrip strength) were observed, findings were globally mixed. Another important finding of this review is that, as far as we know, only one study investigated the effects of the multidomain intervention on a global IC score, operationalized by considering four of the five domains of IC, except the sensory domain (38). The limited evidence about this topic does not allow us to conclude whether or not multidomain interventions would globally affect intrinsic capacity. Further studies operationalizing IC are therefore necessary.

The absence of multidomain RCT examining intervention effects on the sensorial IC domain is understandable given the nature of this domain: improving vision and hearing would not be expected with nutritional counselling or stimulating physical activity, for example. However, it is possible that multidomain interventions could contribute to preventing sensorial impairments, in particular for vision, through the prevention and control of cardiovascular and metabolic conditions, such as hypertension and diabetes. The well-known associations of physical activity/exercise and the prevention/management of cardiovascular and metabolic diseases are well-established (40–42). In addition, studies including antioxidant supplementations (43, 44), or multidomain lifestyle intervention (including Mediterranean diet, physical activity, avoided smoking and sedentary behaviours) (45) suggested positive effects on the progress and prevalence of aging related macular degeneration. It can also be noted that in MAPT Study, preventive consultations (which were part of the multidomain intervention) included evaluation of vision and hearing deficits, with recommendations for management where necessary (46).

Although still limited, available evidence supports an effect of multidomain interventions on locomotion when exercise training is present. SPPB was improved in multidomain RCTs that operationalized exercise sessions (not only advices on physical activity), even though other trials with exercise sessions found no effects on locomotion outcomes. It is possible that multidomain interventions have an effect on global locomotion (SPPB) only when a comprehensive exercise training, with strength but also balance exercises, is comprised in the intervention; indeed, a multidomain trial (34), including exercise training with strength and balance exercises, had positive effects on SPPB, in particular among frail participants and those who were more compliant with the intervention.

Multidomain lifestyle interventions improved cognition among older adults when operationalizing strong interventions (27) or for subpopulation of individuals at increased risk of cognitive decline (25, 47). Indeed, the FINGER trial (27) had supervised strength and aerobic training, compared to other RCTs that restricted the physical part of the intervention to counselling (24). Moreover, FINGER (27) and MAPT (24), this latter showing positive effects of the multidomain intervention on cognition among people at high risk for dementia (ie, high both CAIDE dementia score and amyloid load in the brain), had strong cognitive training and were among the largest (well-powered) and longest multidomain RCTs. Therefore, it is possible that lifestyle multidomain interventions should have strong components for both cognitive and exercise training to increase cognitive function. Multidomain interventions may still benefit cognition with a less strong physical component in subpopulations at increased risk for clinically meaningful cognitive decline.

For the psychological IC domain, we did not find improvements of multidomain interventions on depressive symptoms (15, 19, 23, 33). It is possible that in order to improve the psychological domain of IC, an intervention with more important psychological content (eg, group-based activities focusing on social support) would be needed. It is also plausible to think, as it seems to occur for the cognitive IC domain, that multidomain lifestyle interventions would be more effective in a subpopulation at increased risk for depression.

The handgrip strength, composing the vitality domain, was improved in three studies (16, 19, 22), but not in two others trials (18, 32); therefore, literature on this topic is mixed. One major point regards the non-consensual definition of vitality: although we opted to operationalise this IC domain using handgrip strength, as in previous publications (10), another operational definition using nutritional status is attracting further attention, including the World Health Organization (48). Although handgrip is associated with nutritional status (12), they are distinct measurements. It is thus possible that nutritional status would respond differently to a multidomain lifestyle intervention; this is still truer since a nutrition-related component is found in nearly all multidomain interventions operationalized to date.

Taken together, findings suggest that, in the long term, multidomain interventions can bring beneficial effects to health. The magnitude of these benefits will vary according to the modalities of intervention composing the multidomain approach. Globally, long-term (one year or over) and strong (eg, composed by exercise training instead of physical activity counselling) interventions lead to benefits on specific IC domains. It should be noted, however, that this review found an important variability across studies regarding the modalities of intervention composing the multidomain intervention. This variability makes it difficult to compare their findings and to generalize their results. Moreover, the

small quantity of studies with multidomain interventions in elderly people do not allow us to precisely define the more effective protocol to each IC domain. Such methodological differences may probably have contributed to the mixed findings gathered in the present work.

Conclusion

IC tend to decline during aging, reducing individuals' resilience and increasing their vulnerability to adverse health outcomes. Multidomain interventions are an interesting approach to optimize the effects of combined lifestyle interventions on the different IC domains. This review gathered heterogeneous findings on the effects of multidomain interventions on the different IC domains. Although still limited, the evidence suggest multidomain interventions may benefit locomotion and, to a lesser extent, cognition and vitality (handgrip strength). Developing strategies for preserving IC is crucial and of high clinical interest in the scenery of integrated care for older adults. Therefore, further investigating the links of multidomain interventions with each IC domain, but also with a global measurement of IC (combining all domains) would importantly contribute to the topic.

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