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Original Article

Identifying the optimal combinations of modifiable dementia risk factors to target in multidomain intervention – Three-year longitudinal findings from the Canadian longitudinal study on aging

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A R T I C L E I N F O

Keywords:
Dementia prevention
Modifiable risk factors
Hearing loss
Physical inactivity
CLSA

A B S T R A C T

Background: Recent multidomain prevention trials for dementia have shifted toward more targeted approaches, focusing on specific combinations of risk factors and interventions at certain times. However, the optimal combinations of modifiable risk factors that can be targeted to maximize intervention effect remain unclear. Identifying risk factor combinations with the highest prevalence and largest effect sizes can enhance efficiency of trial design.
Objectives: To identify risk factor combinations that are both highly prevalent and have the most detrimental effect on cognition, and to assess their interaction effect and synergism.
Design: Longitudinal analysis of Canadian Longitudinal Study on Aging (CLSA).
Setting: Community.
Participants: 30,097 adults aged 45 to 85 at baseline
Measurements: The five most prevalent dyad, triad, and tetrad combinations of 12 modifiable risk factors were identified. Cognition was assessed with a composite Z-score from a neuropsychological test battery. Linear mixed effect models were used to examine the association between the identified combinations and 3-year cognitive changes. Interaction was assessed on additive scale, and synergism was explored.
Results: The combinations that were both highly prevalent and had the most detrimental effect on global cognition were: hearing loss and physical inactivity for the dyad (mean difference in change score = -0.07 SD; 95 % CI: -0.09 to -0.06; $p < 0.001$; effect size = -0.28), hearing loss, physical inactivity, and hypertension for the triad (mean difference in change score = -0.07; 95 % CI: -0.09 to -0.06; $p < 0.001$; effect size = -0.28), and hearing loss, physical inactivity, hypertension, and sleep disturbance for the tetrad (mean difference in change score = -0.05; 95 % CI: -0.07 to -0.03; $p < 0.001$; effect size = -0.20). Similar patterns were observed for memory and executive function. A significant synergistic interaction was observed between hearing loss and physical inactivity for global cognition ($p = 0.005$).
Conclusions: The combined effect of multiple risk factors varied by its combinations. The combination of hearing loss and physical inactivity offers a greater potential benefit than other dyad combinations. Hypertension and sleep disturbance can be further included for triad and tetrad combinations. Auditory health and exercise should be prioritized for multidomain interventions.

1. Introduction

The global prevalence of dementia is projected to increase from 55 million to 139 million by 2050 [1]. To combat this burden effectively, identifying efficacious prevention and risk reduction strategies has been suggested as a growing public health priority [2,3].

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The potential for dementia prevention and risk reduction through risk factor management has been emphasized in both observational studies and clinical trials. While age and apolipoprotein E genotype are the strongest known risk factors for dementia [4], the Lancet Commission Reports on Dementia have estimated that 40 to 45 % of dementia cases worldwide are attributable to 12 to 14 modifiable risk factors [5,6]. Furthermore, multidomain interventions addressing several lifestyle and cardiometabolic risk factors have shown to improve cognition and dementia risk score [7–9]. The importance of managing these risk factors at both individual and population/policy levels has been further reinforced by the World Health Organization's guideline on risk reduction for cognitive decline and dementia, which are evidence-based recommendations primarily derived from clinical trials [10].

Nevertheless, the modest effects observed in multidomain intervention trials have led researchers to refocus on methodological issues of trial design, target population eligibility, interventions, outcome measures and trial duration to produce greater benefits [11,12]. Current evidence recommends more targeted approaches that focus on specific combinations of risk factors and interventions tailored to particular populations at certain times [11]. However, assessing the most effective combination is challenging in most multidomain intervention trials, as they target a wide range of risk factors in one study arm [7–9,12,13]. While multi-arm or factorial designs could address this challenge [8,13], implementing such trial designs is not always feasible as they require a large sample size [13,14].

Exposure to multiple risk factors can have cumulative and interactive effects that may modify a risk factor's effect on dementia risk [15,16]. Yet, limited evidence exists regarding the combined effects of particular combinations of risk factors [12,16]. Additionally, dementia risk factors are inter-related, and multiple risk factors can benefit from a single intervention. For instance, exercise can help improve physical inactivity, obesity, hypertension, and sleep disturbance. Understanding the combined effects and interactions among risk factor combinations has been suggested not only to help identify at-risk populations who are likely to benefit the most but also to identify risk factor combinations that are most effective to target [12,16,17].

Although interventions with relatively small effect sizes can benefit many people in a large population, their impact would be even greater if the targeted risk factors are highly prevalent. Furthermore, risk factor combinations that are both highly prevalent and strongly associated with cognition can still be targeted in factorial trials. High prevalence can help overcome a key practical limitation of such trials – recruiting a sufficiently large number of participants with all targeted risk factors to achieve adequate power to detect interactions. Nonetheless, evidence on exploring the risk factor combinations in terms of their prevalence and combined potential for preventing cognitive decline is lacking. Additionally, combinations of common risk factors may differ by demographic characteristics and culture, and their association with cognition could also differ by sex and life stage.

Using data from the Canadian Longitudinal Study on Aging (CLSA), the present study aimed to estimate: i) the cumulative effect of co-occurring risk factors, ii) the pooled effect of specific combinations of highly prevalent risk factors, and iii) explore their individual and joint effects on cognitive change over 3 years. Identifying risk factor combinations that are both highly prevalent and strongly associated with cognitive change may allow us to inform future prevention trials with the specific combinations of risk factor that can be targeted to preserve cognition the most.

2. Methods

2.1. Study design and participants

The CLSA is a longitudinal cohort study that collects detailed data on various aspects of health and aging by following a national, stratified sample of 51,338 men and women aged 45–85 years at recruitment, for at least 20 years [18]. Participants were enrolled in either the tracking or comprehensive cohort, with the comprehensive cohort designed to collect more extensive data, as described elsewhere [18]. The present analysis uses data from the comprehensive cohort, which included a full neuropsychological test battery (NTB), audiometry, and physical assessments. The comprehensive cohort comprised 30,097 participants randomly sampled by age and sex strata within 25–50 km of 11 data collection sites across seven provinces in Canada. Sampling was conducted using sampling frames from provincial health registries, random-digit dialing, and the Quebec Longitudinal Study on Nutrition and Aging (NuAge) [18,19]. Full-time members of the Armed Forces, residents of First Nations reserves, territories, or long-term care institutions providing 24 hours of nurse care, and those who could not respond in English or French at recruitment were ineligible [18]. Additionally, individuals who were deemed to have cognitive impairment during face-to-face or telephone-administered cognitive screening were also excluded [18]. Baseline data were collected from 2010 to 2015, and the first follow-up was completed from 2015 to 2018 [18]. At the first follow up, 2332 participants (7.8 %) were lost to follow-up. Due to incomplete cognitive assessments for 3622 participants (12.0 %) at the first follow-up, the final analytical sample consisted of 24,143 participants.

2.2. Modifiable risk factors

A total of 12 modifiable risk factors – less education, hearing loss, traumatic brain injury, hypertension, excessive alcohol consumption, obesity, smoking, depression, social isolation, physical inactivity, diabetes, and sleep disturbance – were identified. Definitions for each are provided in Supplementary Method Table 1. These 12 modifiable risk factors were selected based on the 2020 Lancet Commission Report on Dementia [6], which was the most comprehensive analysis and review of dementia risk factors available at the time of our study. Although sleep disturbance was excluded from the Lancet Commission Reports due to insufficient evidence, it was included in our study as it is frequently targeted in multidomain intervention trials and has recently been incorporated into the Lifestyle for BRAin Health (LIBRA) dementia risk score [9,20]. Each risk factor was treated as a binary variable, indicating the presence of each risk factor. The total number of co-occurring risk factors for each individual was calculated by summing the presence of the 12 risk factors, resulting in a range from 0 to 12.

2.3. Selection of risk factor combination

The five most prevalent dyad, triad, and tetrad combinations were identified from the 66 possible dyads, 220 triads, and 495 tetrads formed from the 12 risk factors.

2.4. Cognitive performance

The CLSA's NTB comprises of nine tests measuring memory, executive function, and processing speed. All tests were standardized and administered by trained research staff with double data entry. However, due to administration issues or highly skewed distributions [21], only the following six tests were included in the present analysis: the Modified Rey Auditory Verbal Learning Test (RAVLT) – Immediate and Delayed Recall; the Controlled Oral Word Association Test – Category Fluency Test; the Animal Fluency Test – lenient score; the Mental Alteration test [22]; and the Victoria Stroop Test [23,24] – the total number of seconds to say the colour of ink. Log transformation was applied to the skewed NTB components. All scores were standardized to the baseline mean and standard deviation of each test. Individual test Z-scores were then averaged to compute the composite NTB Z score, representing global cognition. The domain-specific score for memory was calculated by averaging the Z-scores of RAVLT – Immediate and Delayed Recall, while the executive function score was based on the

Table 1
Baseline participant characteristics by loss to follow-up status at Year 3.

	All participants (N = 30097)	Completed Year 3 follow-up (N = 24143)	Missing Year 3 follow-up (N = 5954)	p-value
Age, mean (SD) years	59.74 (10.30)	59.28 (10.12)	61.27 (10.76)	<0.001
45–54	7595 (39 %)	6394 (41 %)	1201 (33 %)	<0.001
55–64	9856 (31 %)	8056 (31 %)	1800 (30 %)	
65–74	7362 (18 %)	5786 (17 %)	1576 (21 %)	
75–85	5284 (12 %)	3907 (11 %)	1377 (15 %)	
Sex				<0.001
Women	15,320 (52 %)	12,060 (51 %)	3260 (57 %)	
Men	14,777 (48 %)	12,083 (49 %)	2694 (43 %)	
Ethnicity				0.013
Non-white	1326 (6.2 %)	992 (5.8 %)	334 (7.6 %)	
White	28,771 (94 %)	23,151 (94 %)	5620 (92 %)	
Education				<0.001
Less than secondary	1643 (17 %)	1166 (15 %)	477 (24 %)	
Secondary but no post-secondary	2839 (12 %)	2151 (11 %)	688 (13 %)	
Some post-secondary	2238 (9.1 %)	1764 (9.5 %)	474 (7.6 %)	
Post-secondary	23,327 (62 %)	19,024 (64 %)	4303 (55 %)	
Marital status				<0.001
Single or never married	2654 (8.7 %)	2106 (8.5 %)	548 (9.6 %)	
Married	20,651 (74 %)	16,898 (75 %)	3753 (70 %)	
Divorced, divorced or separated	6784 (17 %)	5133 (16 %)	1651 (20 %)	
Income				<0.001
<$20,000	1566 (6.9 %)	1093 (5.8 %)	473 (11 %)	
$20,000 to $50,000	6360 (23 %)	4785 (21 %)	1575 (28 %)	
$50,000 to $100,000	9907 (33 %)	8012 (33 %)	1895 (34 %)	
$100,000 to 150,000	5524 (20 %)	4609 (21 %)	915 (16 %)	
$150,000+	4799 (17 %)	4190 (19 %)	609 (11 %)	
Rurality				0.005
Rural	2424 (5.2 %)	1836 (4.8 %)	588 (6.5 %)	
Urban	26,461 (90 %)	21,378 (91 %)	5083 (89 %)	
Peri-urban	1212 (4.3 %)	929 (4.2 %)	283 (4.6 %)	
Less education	3315 (14 %)	2357 (12 %)	958 (20 %)	<0.001
Hearing loss	11,454 (34 %)	8808 (33 %)	2646 (39 %)	<0.001
Traumatic brain injury	4074 (14 %)	3325 (14 %)	749 (13 %)	0.4
Hypertension	12,560 (37 %)	9803 (36 %)	2757 (42 %)	<0.001
Excessive alcohol use	3603 (11 %)	2926 (11 %)	677 (12 %)	0.7
Obesity	8793 (31 %)	7008 (30 %)	1785 (33 %)	0.03
Smoking	2567 (12 %)	1905 (10 %)	662 (15 %)	<0.001
Depression	4919 (17 %)	3838 (16 %)	1081 (19 %)	0.008
Social isolation	399 (1.7 %)	313 (1.6 %)	86 (2.1 %)	0.3
Physical inactivity	22,167 (77 %)	18,153 (76 %)	4014 (82 %)	<0.001
Diabetes	2785 (8.8 %)	2098 (8.1 %)	687 (11 %)	<0.001
Sleep disturbance	12,838 (43 %)	10,252 (43 %)	2586 (45 %)	0.12
Number of risk factors, mean (SD)	2.95 (1.64)	2.88 (1.63)	3.16 (1.66)	<0.001
0	1273 (4.7 %)	1059 (5.0 %)	214 (3.5 %)	<0.001
1	4388 (15 %)	3663 (16 %)	725 (12 %)	
2	6914 (23 %)	5585 (23 %)	1329 (22 %)	
3	6950 (23 %)	5577 (23 %)	1373 (23 %)	
4	5369 (18 %)	4258 (17 %)	1111 (19 %)	
5	3111 (10.0 %)	2410 (9.6 %)	701 (11 %)	
6	1439 (4.5 %)	1116 (4.1 %)	323 (6.0 %)	
7+	653 (2.5 %)	475 (2.3 %)	178 (3.2 %)	
REY immediate recall score	5.77 (1.90)	5.87 (1.89)	5.43 (1.89)	<0.001
REY delayed recall score	4.05 (2.14)	4.15 (2.14)	3.70 (2.13)	<0.001
Mental alternation test	26.23 (9.07)	26.74 (8.85)	24.50 (9.56)	<0.001
Victoria Stroop Test (seconds)[a]	2.13 (0.76)	2.12 (0.71)	2.16 (0.91)	0.2
Animal fluency test	21.15 (6.53)	21.47 (6.49)	20.02 (6.51)	<0.001
Letter word naming test	37.99 (12.79)	38.50 (12.68)	36.26 (13.00)	<0.001
NTB global Z score	−0.03 (0.66)	0.01 (0.65)	−0.18 (0.68)	<0.001
NTB memory Z score	−0.02 (0.92)	0.03 (0.91)	−0.19 (0.92)	<0.001
NTB executive function Z score	−0.03 (0.70)	0.01 (0.69)	−0.15 (0.71)	<0.001

Weighted N was 3812085 for all sample, 2941950 for those who completed Year 3 follow-up, and 870135 for those who were missing at Year 3.
t-test adapted to complex survey samples; chi-squared test with Rao & Scott's second-order correction.
[a] higher score indicates poor performance.

average of the other four tests. The global composite Z score was calculated when at least three test scores were available, while domain-specific scores required at least two tests. Test results were recoded when appropriate so that lower scores indicated poorer cognitive performance.

2.5. Statistical analysis

Participant characteristics at baseline were summarized by loss to follow-up status at the first follow-up (Year 3) using descriptive statistics and compared with independent sample *t*-test or chi-square test, as appropriate. A series of pre-planned linear mixed effect models were used to estimate the association between risk factors and changes in cognition, measured in standard deviation (SD) units of cognitive scores. Multicollinearity between risk factors was checked using a variance inflation factor (VIF) <10. In all models, cognitive score was fitted as the dependent variable, while the main effect variables differed according to the specific research aim, as described below.

The cumulative effect of comorbid risk factors on cognitive performance was assessed by fitting the number of comorbid risk factors and its interaction with time.

The effect of each risk factor combination was examined using two different modeling strategies. To assess the pooled effect of each risk factor combinations on cognitive change, models included a single binary indicator for the presence or absence of the combination and an interaction between the combination and time. The regression coefficient of the interaction term represents the mean difference in 3-year cognitive change between participants with the combination versus those without it. A negative mean difference indicates attenuated cognitive improvement or greater cognitive decline, depending on the trend of cognitive change, while a positive mean difference suggests greater cognitive improvement or reduced cognitive decline.

To evaluate whether the joint effect of risk factor combinations over time are greater than the sum of individual effects, each risk factor in a given combination was fitted as an individual main effect variable along with the interaction terms between all the risk factors and time (i.e. a three-way interaction for dyads, four-way for triads, and five-way for tetrad). The primary interest was the statistical significance of the highest-order interaction terms, which indicate the presence of interaction on an additive scale. Marginal means for both individual and joint effects were estimated to assess synergistic interaction. All regression models were adjusted for age, sex, and other modifiable risk factors that were included in the study but not part of the specific combination being analyzed. For example, the model for the dyad of hearing loss and physical inactivity was adjusted for age, sex, and the remaining ten modifiable risk factors.

To further explore how the impact of risk factor combinations differs by sex and life stages (midlife vs. later life), the above analyses were stratified by sex and by two age groups (45–64 vs. 65–85 years). For all models, marginal means were estimated and interpreted as cognitive change over three years, with positive differences indicating improvement in cognition. Cohen's effect size was estimated by dividing the estimated marginal mean by the root mean square error (RMSE).

The five most prevalent risk factor combinations may slightly differ by sex and the two age groups. As a sensitivity analysis, we identified the five most prevalent combinations for each sex and age group, and repeated the above analyses for the risk factor combinations that ranked among the top five within a specific sex or age group but not in the overall participants.

All descriptive statistics were weighted using inflation weights, and regression models were weighted using analytic weights to account for differences in selection probabilities [19]. Analyses were performed using the *survey* [25], *lme4* [26], and *emmeans*[27] packages in R Version 4.2.0. Further details on statistical analysis can be found in the Supplementary Method.

3. Results

3.1. Participant characteristics

Participant characteristics at baseline are shown in Table 1. A total of 24143 participants (80 %) completed the first follow-up (Year 3) and their mean age was 59.3 years (SD = 10.1), with 51 % being women and 75 % married. Most participants (95 %) had one or more risk factors, and 80 % of them had two or more risk factors. Compared to those who missed the follow-up assessment, participants who completed the follow-up were younger, more likely to be men, had higher education or income, had better cognition, and were less likely to have risk factors at baseline. Overall, global cognition and memory slightly improved over the three years of follow-up, while executive function showed no change (Supplementary Figure 1).

3.2. Cumulative effect of number of comorbid risk factors

The improvement in cognition was inversely associated with the increasing number of comorbid risk factors, as shown in Fig. 1 and Supplementary Table 2. Compared to having no risk factors, cognitive improvement started to significantly diminish with three risk factors for global cognition, two risk factors for memory, and one risk factor for executive function. Conversely, a decline in executive function became notable with seven or more comorbid risk factors.

3.3. Pooled effect of risk factor combination

Table 2 shows the prevalence and pooled effects of the five most prevalent dyad, triad, and tetrad combination of risk factors on three-year cognitive change. Overall, individuals with these risk factor combinations tended to have lower cognition at baseline, and their cognitive improvement was less pronounced than those without the risk factor combinations. For the dyad combinations, the strongest pooled effect was seen with the combination of physical inactivity and hearing loss. The estimated mean change in global score was 0.06 SD (95 % CI: 0.05 to 0.07) for those with physical inactivity and hearing loss, compared to 0.13 SD (95 % CI: 0.13 to 0.14) in those without physical inactivity and hearing loss. The mean difference in change in global score between the two groups was −0.07 SD (95 % CI: −0.09 to −0.06; $p < 0.001$; ES= −0.28). Similar findings were observed for memory (mean difference = −0.15 SD; 95 % CI: −0.17 to −0.12; $p < 0.001$; ES = −0.29) and executive function (mean difference = −0.03 SD; 95 % CI: −0.04 to −0.01; $p < 0.001$; ES = −0.12).

Among the triad combination, the combination of physical inactivity, hearing loss, and hypertension was associated with the largest pooled effect on global cognition (mean difference = −0.07 SD; 95 % CI: −0.09 to −0.06; $p < 0.001$; ES = −0.28), memory (mean difference = −0.14 SD; 95 % CI: −0.17 to −0.11; $p < 0.001$; ES = −0.27), and executive function (mean difference = −0.03 SD; 95 % CI: −0.04 to −0.01; $p = 0.001$; ES = −0.12). The estimated mean change scores for individuals with these three risk factors was 0.05 SD (95 % CI: 0.03 to 0.07) for global, 0.20 SD (95 % CI: 0.16 to 0.24) for memory, and −0.01 SD (95 % CI: −0.03 to 0.01) for executive function. The estimated mean change scores for individuals without these three risk factors was 0.13 SD (95 % CI: 0.12 to 0.13) for global, 0.34 SD (95 % CI: 0.33 to 0.36) for memory, and 0.02 SD (95 % CI: 0.01 to 0.03) for executive function.

For the tetrad combination, individuals with hearing loss, hypertension, physical inactivity, and sleep disturbance exhibited the largest pooled effect on cognitive change (mean difference = −0.05 SD; 95 % CI: −0.07 to −0.03; $p < 0.001$; ES = −0.20 for global; mean difference = −0.10 SD; 95 % CI: −0.14 to −0.06; $p < 0.001$; ES = −0.19 for memory; and mean difference = −0.03 SD; 95 % CI: −0.05 to −0.001; $p = 0.02$; ES = −0.12 for executive function).

3.4. Interaction effect of risk factor combination

For simplicity, the estimated marginal means for having none of the risk factors, only one risk factor, and having all risk factors in the combination are depicted in Supplementary Tables 3–5. Overall, participants with all risk factors had the lowest cognition at baseline, and their improvement in cognition was more modest than those with none or only one risk factor.

There was a significant synergistic interaction effect between hearing loss and physical inactivity over three years for global cognition ($p = 0.005$; Fig. 2). The estimated mean change in global cognition was 0.14 SD (95 % CI: 0.12 to 0.16) for those with neither hearing loss nor physical inactivity (Supplementary Table 3). Individuals with hearing

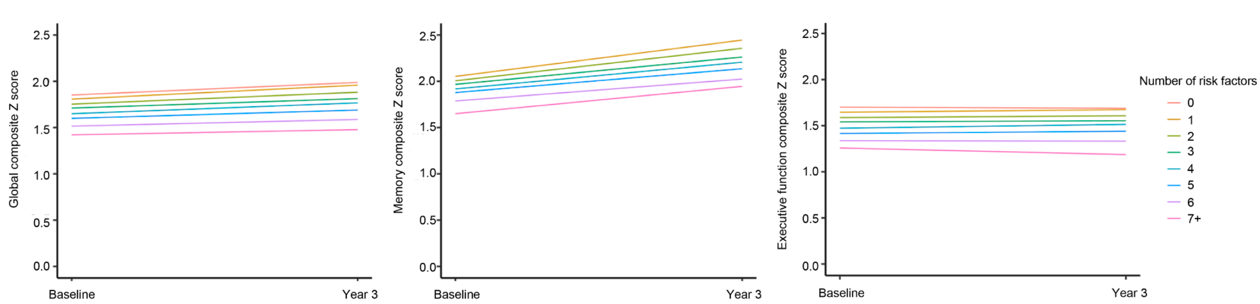

Fig. 1. Cumulative effect of number of comorbid risk factors on change in cognition over 3 years.

Table 2

Pooled effect of the five most prevalent dyad, triad, and tetrad combination on change in cognition over 3 years.

	Prevalence	Global				Memory				Executive function			
	n (%)	Mean difference Y3-Y0	(95 % CI)	p	ES	Mean difference Y3 – T0	(95 % CI)	p	ES	Mean difference Y3 – Y0	(95 % CI)	p	ES
Dyad													
Physical inactivity + Sleep disturbance	9889 (35 %)												
No		0.11	(0.10, 0.12)	–	–	0.32	(0.31, 0.34)	–	–	0.01	(0.004, 0.02)	–	–
Yes		0.12	(0.11, 0.13)	–	–	0.32	(0.29, 0.34)	–	–	0.02	(0.01, 0.04)	–	–
Yes vs. No (Ref.)		0.01	(−0.01, 0.02)	0.42	0.04	−0.01	(−0.03, 0.02)	0.66	−0.02	0.01	(−0.001, 0.02)	0.06	0.04
Hypertension + Physical inactivity	9770 (30 %)												
No		0.13	(0.12, 0.13)	–	–	0.34	(0.32, 0.36)			0.02	(0.01, 0.03)	–	–
Yes		0.09	(0.08, 0.11)	–	–	0.28	(0.26, 0.31)			0.01	(−0.004, 0.02)	–	–
Yes vs. No (Ref.)		−0.03	(−0.04, −0.02)	<0.001	−0.12	−0.06	(−0.08, −0.03)	<0.001	−0.11	−0.01	(−0.02, 0.0002)	0.06	−0.04
Hearing loss + Physical inactivity	8800 (27 %)												
No		0.13	(0.13, 0.14)	–	–	0.36	(0.34, 0.38)	–	–	0.02	(0.02, 0.03)	–	–
Yes		0.06	(0.05, 0.07)	–	–	0.21	(0.19, 0.24)	–	–	−0.003	(−0.02, 0.01)	–	–
Yes vs. No (Ref.)		−0.07	(−0.09, −0.06)	<0.001	−0.28	−0.15	(−0.17, −0.12)	<0.001	−0.29	−0.03	(−0.04, −0.01)	<0.001	−0.12
Obesity + Physical inactivity	7010 (25 %)												
No		0.11	(0.10, 0.12)	–	–	0.32	(0.30, 0.33)	–	–	0.01	(0.002, 0.02)	–	–
Yes		0.13	(0.12, 0.14)	–	–	0.34	(0.31, 0.36)	–	–	0.04	(0.02, 0.05)	–	–
Yes vs. No (Ref.)		0.02	(0.01, 0.03)	0.001	0.08	0.02	(−0.004, 0.04)	0.11	0.04	0.02	(0.01, 0.04)	<0.001	0.08
Hypertension + Sleep disturbance	5840 (18 %)												
No		0.12	(0.11, 0.13)	–	–	0.33	(0.31, 0.34)	–	–	0.02	(0.01, 0.03)	–	–
Yes		0.11	(0.09, 0.12)	–	–	0.29	(0.26, 0.32)	–	–	0.02	(−0.0005, 0.03)	–	–
Yes vs. No (Ref.)		−0.01	(−0.03, 0.002)	0.09	−0.04	−0.04	(−0.07, −0.01)	0.005	−0.08	−0.001	(−0.01, 0.01)	0.9	−0.002
Triad													
Hypertension + Physical inactivity + Sleep disturbance	4713 (15 %)												
No		0.12	(0.11, 0.12)	–	–	0.33	(0.31, 0.34)	–	–	0.02	(0.01, 0.03)	–	–
Yes		0.11	(0.09, 0.12)	–	–	0.3	(0.26, 0.33)	–	–	0.02	(−0.004, 0.03)	–	–
Yes vs. No (Ref.)		−0.01	(−0.02, 0.004)	0.16	−0.04	−0.03	(−0.05, 0.002)	0.07	−0.06	−0.01	(−0.02, 0.01)	0.76	−0.04
Hearing loss + Hypertension + Physical inactivity	4715 (14 %)												
No		0.13	(0.12, 0.13)	–	–	0.34	(0.33, 0.36)	–	–	0.02	(0.01, 0.03)	–	–
Yes		0.05	(0.03, 0.07)	–	–	0.2	(0.16, 0.24)	–	–	−0.01	(−0.03, 0.01)	–	–
Yes vs. No (Ref.)		−0.07	(−0.09, −0.06)	<0.001	−0.28	−0.14	(−0.17, −0.11)	<0.001	−0.27	−0.03	(−0.04, −0.01)	0.001	−0.12
Hypertension + Obesity + Physical inactivity	4202 (14 %)												
No		0.12	(0.11, 0.12)	–	–	0.32	(0.31, 0.34)	–	–	0.02	(0.01, 0.03)	–	–
Yes		0.11	(0.10, 0.13)	–	–	0.32	(0.28, 0.35)	–	–	0.02	(−0.0005, 0.04)	–	–

(*continued on next page*)

Table 2 (*continued*)

	Prevalence	Global				Memory				Executive function			
	n (%)	Mean difference Y3-Y0	(95 % CI)	p	ES	Mean difference Y3 – T0	(95 % CI)	p	ES	Mean difference Y3 – Y0	(95 % CI)	p	ES
Yes vs. No (Ref.)		−0.01	(−0.02, 0.01)	0.86	−0.04	−0.01	(−0.03, 0.03)	0.84	−0.02	0.01	(−0.01, 0.02)	0.83	0.04
Obesity + Physical inactivity + Sleep disturbance	3772 (14 %)												
No		0.11	(0.10, 0.12)	–	–	0.32	(0.30, 0.33)	–	–	0.01	(0.01, 0.02)	–	–
Yes		0.14	(0.12, 0.16)	–	–	0.35	(0.32, 0.39)	–	–	0.03	(0.01, 0.05)	–	–
Yes vs. No (Ref.)		0.03	(0.01, 0.04)	0.001	0.12	0.04	(0.01, 0.07)	0.02	0.08	0.02	(0.004, 0.04)	0.02	0.08
Hearing loss + Physical inactivity + Sleep disturbance	3951 (12 %)												
No		0.12	(0.11, 0.13)	–	–	0.33	(0.32, 0.35)	–	–	0.02	(0.01, 0.03)	–	–
Yes		0.07	(0.05, 0.09)	–	–	0.23	(0.19, 0.27)	–	–	−0.001	(−0.02,0.02)	–	–
Yes vs. No (Ref.)		−0.05	(−0.07, −0.04)	<0.001	−0.2	−0.11	(−0.14, −0.08)	<0.001	−0.21	−0.02	(−0.04, −0.004)	0.02	−0.08
Tetrad													
Hypertension + Obesity + Physical inactivity + Sleep disturbance	2353 (7.9 %)												
No		0.11	(0.11, 0.12)	–	–	0.32	(0.31, 0.34)	–	–	0.02	(0.01, 0.03)	–	–
Yes		0.12	(0.10, 0.15)	–	–	0.33	(0.28, 0.38)	–	–	0.02	(−0.01, 0.04)	–	–
Yes vs. No (Ref.)		0.01	(−0.01, 0.02)	0.55	0.04	0.01	(−0.03, 0.04)	0.73	0.02	−0.01	(−0.02, 0.02)	0.93	−0.04
Hearing loss + Hypertension + Physical inactivity + Sleep disturbance	2254 (6.8 %)												
No		0.12	(0.11, 0.13)	–	–	0.33	(0.31, 0.34)	–	–	0.02	(0.01, 0.03)	–	–
Yes		0.07	(0.04, 0.09)	–	–	0.23	(0.18, 0.28)	–	–	−0.01	(−0.04, 0.02)	–	–
Yes vs. No (Ref.)		−0.05	(−0.07, −0.03)	<0.001	−0.2	−0.1	(−0.14, −0.06)	<0.001	−0.19	−0.03	(−0.05, −0.001)	0.02	−0.12
Hearing loss + Hypertension + Obesity + Physical inactivity	1868 (5.9 %)												
No		0.12	(0.11, 0.12)	–	–	0.33	(0.31, 0.34)	–	–	0.02	(0.01, 0.03)	–	–
Yes		0.09	(0.06, 0.12)	–	–	0.27	(0.21, 0.32)	–	–	−0.003	(−0.03,0.03)	–	–
Yes vs. No (Ref.)		−0.03	(−0.05, −0.01)	0.007	−0.12	−0.06	(−0.10, −0.01)	0.01	−0.11	−0.02	(−0.04, 0.01)	0.22	−0.08
Hearing loss + Obesity + Physical inactivity + Sleep disturbance	1508 (5.1 %)												
No		0.12	(0.11, 0.12)	–	–	0.32	(0.31, 0.34)	–	–	0.02	(0.01, 0.03)	–	–
Yes		0.09	(0.06, 0.12)	–	–	0.28	(0.22, 0.34)	–	–	−0.004	(−0.03, 0.04)	–	–
Yes vs. No (Ref.)		−0.03	(−0.05, −0.002)	0.03	−0.12	−0.04	(−0.09, 0.01)	0.09	−0.08	−0.01	(−0.04, 0.01)	0.29	−0.04
Hearing loss + Hypertension + Obesity + Sleep disturbance	1243 (3.8 %)												
No		0.12	(0.11, 0.12)	–	–	0.32	(0.31, 0.34)	–	–	0.02	(0.01, 0.03)	–	–
Yes		0.09	(0.06, 0.13)	–	–	0.29	(0.22, 0.36)	–	–	−0.005	(−0.04, 0.03)	–	–
Yes vs. No (Ref.)		−0.02	(−0.05, 0.004)	0.09	−0.08	−0.03	(−0.09, 0.02)	0.22	−0.06	−0.02	(−0.05, 0.01)	0.12	−0.08

MD, mean difference in 3-year changes in Z scores; ES, effect size; Ref. Reference group.
Adjusted for other risk factors, sex, and age in years.
Effect size was calculated as regression coefficient / root mean squared error.

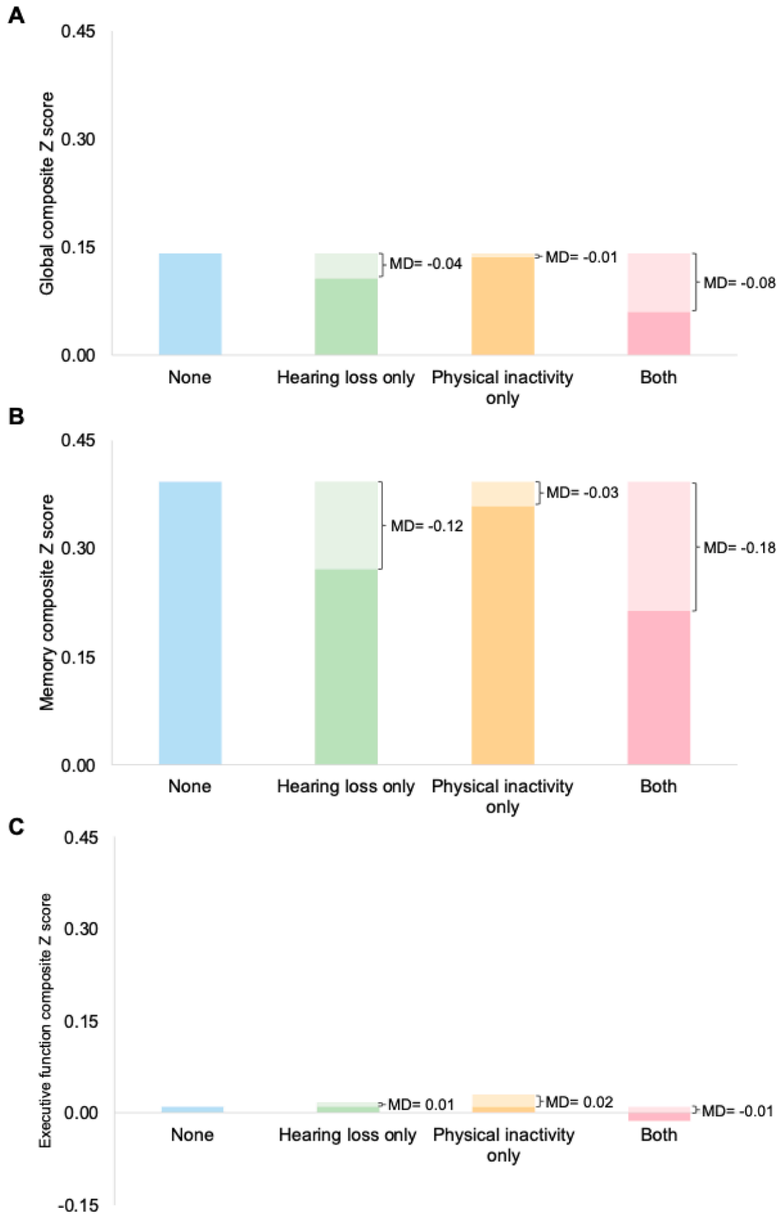

Fig. 2. Individual and joint effect of hearing loss and physical inactivity on changes in cognition over 3 years
p-value of 3-way interaction term (Hearing loss x Physical inactivity x Time) was A) Global cognition: $p = 0.005$; B) Memory: $p = 0.39$; and C) Executive function: $p = 0.009$
MD, mean difference in change in cognition over 3 years, compared to individuals without both hearing loss and physical inactivity (none).

loss only had a mean change of 0.11 SD (95 % CI: 0.07 to 0.14), while those with physical inactivity only had a mean change of 0.14 SD (95 % CI: 0.13 to 0.15). The mean change for having both hearing loss and physical inactivity was 0.06 SD (95 % CI: 0.05 to 0.08), suggesting the least improvement on global cognition compared to the individual effects. The observed joint effect of hearing loss and physical inactivity on improvement in global cognition (mean difference = −0.08) was larger than the expected joint effect of hearing loss and physical inactivity (mean difference = −0.05; Fig. 2). We did not observe any synergistic interaction effects for triad (Supplementary Table 4) and tetrad combinations (Supplementary Table 5).

A significant antagonistic interaction effect was observed with the dyad of obesity and physical inactivity ($p = 0.007$ for global cognition; and $p = 0.001$ for memory; Supplementary Figure 2), the dyad of hypertension and physical inactivity ($p = 0.001$ for memory; and $p = 0.003$ for executive function; Supplementary Figure 3), and the triad of hypertension, obesity, and physical inactivity ($p = 0.03$ for memory; Supplementary Figure 4). Their observed joint effect was less than the expected joint effect.

3.5. Sex- and age-stratified analyses for risk factor combinations – pooled effect

The prevalence of the five most prevalent combinations by sex and age groups are shown in Supplementary Table 6. The pooled effects of risk factor combinations on cognitive change, stratified by sex and age groups, are presented in Supplementary Tables 7–10. A similar pattern to that observed in the overall sample was observed across both sexes and age groups. However, the improvement was more modest in later life compared to midlife.

The same dyad (hearing loss and physical inactivity) and triad (hearing loss, hypertension, and physical inactivity) combinations were associated with the greatest deleterious effect in both sexes (Supplementary Tables 7 and 8) and two age groups (Supplementary Tables 9 and 10). However, the magnitude of the observed effect was stronger in women than in men, whereas it was similar between midlife and later life. For the tetrad, the greatest negative impact on cognitive improvement was seen with hearing loss, hypertension, physical inactivity, and sleep disturbance, but it was statistically significant in women only for global cognition ($p < 0.001$) and memory ($p < 0.001$; Supplementary Table 8). Regardless of statistical significance, the tetrad combinations either had no effect or a protective effect in later life (Supplementary Table 10).

3.6. Sex- and age-stratified analyses for risk factor combinations – interaction effect

A synergistic interaction between hearing loss and physical inactivity was observed for global cognition in men ($p = 0.03$) and in midlife ($p = 0.006$). Men and those in midlife with both hearing loss and physical inactivity experienced the least improvement in cognition compared to those with only one or neither of these risk factors. The observed joint effect in these groups was greater than the expected joint effect (data not shown).

3.7. Sensitivity analyses

The top five most prevalent combinations of risk factors, stratified by sex and age groups, are listed in Supplementary Tables 11–13. Most of the sex- and age-specific prevalent combinations were the same combinations as those observed in the overall participants. Nonetheless, considering the pooled effects of the sex- and age-specific combinations did not change the dyad and triad combinations with the largest pooled effect (Supplementary Tables 14–16). However, this was not the case for tetrad combinations. The largest pooled effect was observed with the combination of hypertension, depression, physical inactivity, and sleep disturbance (mean difference = −0.06; 95 % CI: −0.09 to −0.02; $p = 0.002$ for global; mean difference = −0.12; 95 % CI: −0.20 to −0.05; $p = 0.001$ for memory) in midlife (Supplementary Table 15), and with less education, hearing loss, hypertension, and physical inactivity (mean difference = −0.07; 95 % CI: −0.12 to −0.01; $p = 0.03$ for memory) in later life (Supplementary Table 16).

4. Discussion

This study identified combinations of risk factors for dementia with the highest prevalence and with largest effect sizes on cogntive changes, which can be targeted in future dementia prevention trials. Focusing on highly prevalent combinations with large effect sizes helps identify target populations that are more likely to respond to multidomain interventions intended to treat their combined risk factors. Our study confirms that a higher number of comorbid risk factors is associated with worst longitudinal cognitive changes in a dose-response relationship. The novelty of this study is related to the risk factor combinations associated with the strongest detrimental effects, which were: hearing loss with physical inactivity for the dyad; physical inactivity, hearing loss, and hypertension for the triad; and hearing loss, hypertension, physical inactivity, and sleep disturbance for the tetrad. The combination of hearing loss and physical inactivity was the only combination showing a synergistic interaction with the strongest detrimental effect on cogntive changes. These findings suggest that targeting hearing loss and physical inactivity may offer the greatest potential to reduce dementia risk compared to other combinations.

We observed an improvement in global cognition and memory over time in our study participants, while their executive function either remained unchanged or slightly declined over three years. Notably, although cognitive improvement was observed overall, clinical significance was only reached for the combinations with the largest detrimental effects (ES $\geq$ 0.2). A similar trend has been reported in other studies using CLSA data that assessed the relationship between dementia risk factors and changes in memory and executive function over three years and even six years of follow-up [28–32]. The improvements in memory align with learning and the practice effect phenomenon that are likely to occur with repeated memory testing, but less likely with executive function testing [33,34]. By excluding individuals with cognitive impairment at baseline, the CLSA cohort is composted of relatively healthy adults who maintained their capacity to learn over time. Another reason could be attrition or dropout bias. Individuals who did not complete the first follow-up assessment were more likely to be older and have lower socioeconomic status. Most importantly, their baseline cognitive scores were lower than those who completed the follow-up assessment. Additionally, the minimal observed effect on executive function further suggests that our findings on global cognition are primarily driven by memory, despite the memory domain consisting of fewer tests than executive function domain. Nevertheless, the combinations with the largest detrimental effects still showed statistically significant effects on executive function.

Interestingly, the observed cognitive improvement in our study aligns with what is seen in multidomain dementia prevention trials that targeted older adults at risk, including the FINGER and US POINTER trials [35,36]. In both trials, benefits were also seen in the control groups; thus, our results can help mutltidomain prevention trial designs by estimating the potential cognitive changes over time in control groups. Differences in outcome measures and their interpretation are among the reasons for translational gaps between observational studies and clinical trials. Observational studies mostly focus on cognitive decline, while prevention trials aim to improve or preserve cognition. As such, prevention trial outcomes targeting population at risk are interpreted based on relative improvements rather than comparing decline. The cognitive improvement observed in our observational study, thereby, strengthens the relevance of our findings in the context of intervention and prevention.

The dose-response gradient between the number of comorbid risk factors and the strength of the associations observed in our study has also been consistently reported in other studies. A systematic review and meta-analysis of 18 studies including over 40000 participants found that the risk of dementia associated with risk factors increased from 20 % for one risk factor to 65 % for two risk factors, and 220 % for three or more risk factors [16]. This cumulative effect of modifiable risk factors on cognitive change and dementia risk reinforces the importance of addressing multiple risk factors to delay and prevent cognitive impairment. In our study sample, the majority of participants had multiple risk factors, with four in five participants had more than two risk factors, over half had at least three risk factors, more than one-third had at least four risk factors, and one in five had five or more. Furthermore, the detrimental effect became evident with two risk factors for memory and three risk factors for global cognition. A considerable decrease in the prevalence of having five or more risk factors supports our focus on exploring risk factor combinations of up to four factors.

The degree to which combined risk factors affected cognitive improvement varied by the specific combination of risk factors. In the pooled effect analyses of the five most prevalent dyad combinations, the combination of hearing loss and physical inactivity exhibited the largest attenuated improvement. Likewise, the attenuated improvement was also observed for physical inactivity with hypertension and hypertension with sleep disturbance. Nevertheless, a synergistic interaction effect on cognitive change was only found between hearing loss and physical inactivity. The literature on whether particular combinations of risk factors are associated with greater cognitive decline or dementia risk than other combinations is sparse. Previous studies examining the combined effect of risk factors are based on index scores, such as Cardiovascular Risk Factors, Aging and Dementia (CAIDE), or LIBRA scores, implying a cumulative effect of number of risk factors rather than the effect of particular combinations [16]. Despite the fact that few studies have examined the interaction effect between some risk factors [37–39], the interactions between physical inactivity and hearing loss has not been previously studied. The joint effect of physical inactivity with hypertension or obesity was not greater than the sum of their individual effect in spite of their detrimental pooled effect. This observed antagonistic effect on the additive scale could be due to shared pathological mechanisms.

With respect to triad combinations, the combination of hearing loss, physical inactivity, and hypertension had the strongest mitigating effect on cognitive improvement, followed by the combination of hearing loss, physical inactivity, and sleep disturbance. Concerning tetrad combinations, the strongest diminished effect was observed with the combination of hearing loss, hypertension, physical inactivity, and sleep disturbance. Nonetheless, none of the triad and tetrad combinations demonstrated a synergistic interaction effect. This suggests that although having the above combinations can attenuate cognitive improvement, they do not have an above-additive effect. We could not compare our findings of triad and tetrad combinations to the previous literature due to the scarcity of studies exploring the combined effect of three or four particular risk factors on cognition or dementia risk.

Our sex-stratified analyses revealed that the effects of risk factor combinations were stronger in women than in men for all dyad, triad, and tetrad combinations. In age-stratified analyses, similar effects of dyad combinations of risk factors were observed across midlife and later life, whereas the triad and tetrad combinations tended to show no effects or protective effects in later life. One possible explanation for this is differential attrition or survival bias, particularly in later life and among those with a greater number of risk factors [40,41].

In terms of the risk factor combination with the strongest effect on cognitive change, we did not observe sex and age differences for dyad and triad combinations. This indicates that the combination with the strongest effect was hearing loss and physical inactivity for dyad, and hearing loss, physical inactivity, and hypertension for triad in both sexes and age groups. For tetrad combination, only women had the risk factor combination that was significantly associated with the largest detrimental effect, which was the combination of hearing loss, hypertension, physical inactivity, and sleep disturbance. None of the tetrad combinations demonstrated significant detrimental effect in men, and across two age groups. The stronger association observed in women is consistent with multidomain intervention trials reporting a greater benefit in women. Secondary analyses of the FINGER trial reported more pronounced benefit of multidomain lifestyle intervention on dementia risk, as measured with the CAIDE score [42], and improvement in processing speed among women [43]. However, men showed greater improvement in executive function, and effect modification by sex was not detected for any cognitive domain [43].

Noteworthily, a synergistic interaction effect on cognitive improvement was observed between hearing loss and physical inactivity in men and in midlife. Although few combinations demonstrated significant interactions between risk factors across sex and age groups, most of them indicated exposure-based antagonism. Further, more triad and tetrad combinations exhibited significant interactions in the sex- and age-stratified analysis than in the overall sample, particularly in women and in later life. This could be due to confounding and warrants further investigation.

Sensitivity analysis did not affect the risk factor combination that was associated with the strongest pooled effect in men and women. Similarly, considering age-specific prevalent combinations did not change the dyad and triad risk factor combinations that were linked to the strongest pooled effect in midlife and later life. However, the sensitivity analysis revealed that the tetrad combinations demonstrating the largest pooled effects were the combination of hypertension, depression, physical inactivity, and sleep disturbance for midlife, and less education, hearing loss, hypertension, and physical inactivity for later life. This highlights the importance of understanding risk factor combinations across different ages to tailor intervention strategies.

The findings of our study have important implications for the next generation of multidomain intervention trials and population level strategies for dementia risk reduction. The strongest pooled and synergistic effect observed between hearing loss and physical inactivity suggests that future prevention trials and strategies should prioritize addressing this combination.

Second, although no synergistic benefits were found for the triad and tetrad combinations with the strongest pooled effect – hearing loss, physical inactivity, and hypertension for the triad, and hearing loss, physical inactivity, hypertension, and sleep disturbance for the tetrad – interventions focusing on hearing and exercise can still address all these risk factors given that exercise can also improve hypertension and sleep disturbance. As such, targeting hearing and exercise could be considered as essential components of a multidomain intervention to produce greater effect. However, -the effect of targeting auditory health and physical inactivity should be tested in intervention trials to confirm whether modifying these factors leads to clinically meaningful improvements in cognition, preferably using a factorial trial design to estimate synergistic effects. Since our study focused on risk factor combinations with high prevalence, such a factorial trial would likely have sufficient power to test both main effect and interaction effects.

Third, our findings emphasize that women are more likely to benefit from multidomain interventions, and that individuals in midlife are just as likely to benefit as those in later life. Therefore, the present study supports the recent global recommendation that public health prevention strategies and intervention trials should begin early, from midlife, rather than later life, for a greater prevention potential [44,45]. One of our notable findings was that the risk factor combinations with the strongest associations were similar across both sexes and age groups, with the exception of the tetrad combinations, which varied by age group. This suggests that sex does not need to be a design factor for multidomain intervention strategies, while age does, particularly when designing multidomain interventions targeting four risk factors. This is an important consideration for precision prevention approaches [46].

Strengths of this study include its large sample size, which enabled the assessment of high-order interaction terms that require a much larger sample size to achieve the same statistical power as main effects [47]. Beginning the analysis from age 45 allowed us to capture risk factor associations from a life-course perspective and to identify when these risk factors have the greatest effect on cognition. Furthermore, by including risk factors that require population-level intervention approaches, such as less education, in identifying the prevalent risk factor combinations, our findings have implications for both individual-level and population-level risk reduction approaches [48].

Although our study is the first to demonstrate which particular combinations of risk factors have the greatest effects on cognition, there are several limitations to be noted. A first limitation could be from information bias. Self-reported data were used to define most of the risk factors, and some risk factors may have been misclassified. Although individuals with noticeable cognitive decline may have a more positive recall of risk factors, the exclusion of those with severe cognitive impairment and the trend of cognitive improvement over follow-up suggests that the misclassification of risk factors is likely to be non-differential in the present study. All risk factors were dichotomized, which potentially resulted in a loss of information. Moreover, we did not account for risk factor changes over time, and some risk factors, such as sleep disturbance and social isolation, were operationalized using a proxy of the true etiologic risk factor we aimed to estimate. A second limitation could arise from selection bias which resulted from differential attrition as individuals with poor cognition or cognitive decline are less likely to complete the follow-up. Consequently, our study estimates may be conservative because they may underestimate the true association in the general population. A third limitation could be related to residual confounding, as risk factor specific covariates were not adjusted for in regression analyses. A fourth limitation is related to the recent update of the Lancet Commission Report on Dementia, which identified vision loss and high LDL cholesterol as new risk factors that were not included in this study. Fifth, our standardised cognitive scores were not adjusted for age, sex, education, and language (English or French). Use of standardized normed scores could have provided more precise results. Sixth, despite the large sample size, sex- and age-stratification as well as sensitivity analyses may suffer from a small number of participants with all risk factors being tested for high-order interaction terms. This could underpower the interaction analyses and lead to overestimation. Seventh, our findings may not be generalizable to the general population, as our sample predominantly consisted of White and highly educated Canadians who are also likely to be healthier. Eighth we considered this study as hypothesis-generating, with the primary aim of identifying combinations with the strongest association, so multiple testing correction was not performed. In light of these limitations, our findings should be replicated in other observational studies with longer follow-up and using methods such as latent curve analysis to incorporate changes in risk factors over time.

The most frequently targeted lifestyle risk factors in multidomain interventions are physical activity followed by diet and cognitive training, while no trials have addressed hearing [9]. This highlights the need of incorporating hearing health in current multidomain framework to promote greater risk reduction. The beneficial effect of hearing aids on dementia risk, observed in epidemiological studies, has recently been tested in clinical trials, with notable benefits observed in cohorts with more dementia risk factors but not in the total cohort [49]. The main challenge associated with hearing intervention is that the available interventions, such as hearing aids, focus on treating the hearing impairments, rather than preventing hearing loss, and they are not financially feasible for everyone. Nonetheless, incorporating education on hearing health may help prevent further hearing loss. Moreover, trials can target individuals with hearing loss, as they showed the most detrimental cognitive effects, suggesting greater potential for improvement. More studies are needed to identify effective hearing care interventions that are also feasible and practical in both clinical and community settings.

Taken together, hearing loss and physical inactivity were the most prevalent and smallest risk factor combination with the largest expected effect size. For three factor combinations, hearing loss, physical inactivity, and hypertension were the most prevalent with the largest pooled effect, while the combination of hearing loss, physical inactivity, hypertension, and sleep disturbance had the largest pooled effect among four-factor combinations. However, given that the synergistic benefit was observed only between hearing loss and physical inactivity and considering that exercise can also benefit hypertension and sleep disturbance, future interventions should prioritize addressing auditory health and exercise levels. The similar magnitude of association observed in midlife and later life supports the recommendation that risk reduction should begin in midlife.

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Declaration of generative AI and AI-assisted technologies in the writing process

This manuscript did not use AI at all.

Data availability

Data are available from the Canadian Longitudinal Study on Aging (w ww.clsa-elcv.ca) for researchers who meet the criteria for access to de-identified CLSA data.

CRediT authorship contribution statement

Surim Son: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mark Speechley:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Conceptualization. **Guangyong Zou:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Manuel Montero-Odasso:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

MMO reports receiving support through grants for his program in Gait and Brain Health from the Canadian Institutes of Health Research, the Ontario Ministry of Research and Innovation, the Ontario Neurodegenerative Diseases Research Initiative, the Canadian Consortium on Neurodegeneration in Aging, the Weston Family Foundation, and the Department of Medicine Program of Experimental Medicine Research Award, Western University. He is President and member of the executive of the Canadian Geriatrics Society (CGS) and of the World Falls Prevention Society, member of the Advisory Board of the CIHR Institute of Aging, Member of the Research Executive Committee of the Canadian Consortium on Neurodegeneration in Aging (CCNA) and Associate Editor of the Journal of Alzheimer's Disease, the Journal Gerontology Medical Sciences and Geriatrics, and holds the Wolfe Research Professorship in Aging. SS, MS, and GZ report no conflict of interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100321.

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Further reading

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